ACID-BASE PHYSIOLOGY

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Licensing

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CHAPTER OVERVIEW

1: Introduction

1.1: Overview

Approaches to understanding acid-base physiology

Traditional Approach

The discussion of acid-base physiology outlined in most of this book is the traditional empirical approach. The concepts and explanations of this approach are still the most common way that acid-base physiology is taught and understood by many clinicians.

But this is not the only approach.

Physico-chemical Approach

An alternative approach derived from physico-chemical principles was proposed by a Canadian physiologist, Peter Stewart in 1981. Alternative names for this approach are the "Stewart approach" and "Quantitative Acid-base Analysis"

The two approaches are very similar in the way that acid-base disorders are classified and measured. The major difference is in the explanation and interpretation of acid-base disorders and control mechanisms. Recent research has largely confirmed the correctness of the Stewart approach but it must be admitted that it will take quite some time for main-stream acid-base physiology teaching to catch up. Indeed, there has been some vitriolic resistance from the traditionalists.

The rest of this chapter discusses some introductory concepts.

What to expect in this book

Chapter 1 provides an introduction to basic concepts of acids & bases and the hydrogen ion . The reason why the extremely low hydrogen ion concentrations in the body have such major effects on body processes is discussed. The final part of this chapter is about the imidazole alpha-stat hypothesis and the pH-stat hypothesis.

Chapter 2 considers the control of acid-base balance, including:

- The acids produced by the body and the concept of balance, both internal and external
- Buffering and other aspects of the body's response to acid-base stress
- The major roles of the lungs and the kidneys in acid-base regulation
- The importance of the liver
- Regulation of intracellular pH.

Chapters 3 discusses the terminology of acid-base disorders. A distinction is made between primary processes which generate an acid-base disorder and the body's compensatory responses. The concepts of anion gap, delta ratio, urinary anion gap, and osmolar gap are useful in analysis of some acid-base disorders.

The 4 types of acid-base disorder - Chapter 4: Respiratory acidosis, Chapter 5: Metabolic acidosis, Chapter 6: Respiratory alkalosis, Chapter 7: Metabolic alkalosis - are each covered in a systematic way: definition, causes, maintenance, metabolic effects, compensation, correction, assessment, prevention.

Chapter 8 covers some of the major types of metabolic acidosis in more detail. In particular, attention is focussed on lactic acidosis, ketoacidosis, acidosis with renal failure, hyperchloraemic acidosis, renal tubular acidosis, and acidosis occurring with drugs and toxins. The place of sodium bicarbonate therapy is discussed.

Chapter 9 explains a structured approach to the assessment of acid-base disorders & includes numerous worked clinical examples. You can work through these examples yourself, then compare your results with my analysis. The approach to analysis used in this book is based on the 'Boston approach' so an introduction to the 'Great transatlantic acid-base debate' discusses why this approach is best.

Chapter 10 introduces quantitative acid-base analysis (or "the Stewart approach"). This is only an introductory treatment but will be enhanced as this method of analysis becomes more common in clinical use. Peter Stewart introduced an approach that leads to an improved understanding of acid-base control in the body. His landmark 1981 book ("**How to Understand Acid-Base**") has recently been placed online at http://www.AcidBase.org .

Chapter 11 considers several special areas including children & pregnancy.

The best way to learn analysis of acid-base results is to frequently practice what you have learned.

As a neophyte to acid-base analysis, you will generally consider this a pretty daunting topic. You will notice that arterial blood gas results are frequently ordered on ill patients but little comment is made on these in the patient record. It is certain that a lot of relevant clinical information is lost because of a lack of understanding of acid-base analysis. A particular aim of this book is to develop the subject gradually and systematically, and to lead you to a practical structured approach to analysis of blood gas results which you can use in your clinical practice. Because of the interaction of acid-base physiology with respiratory, cardiovascular, and renal systems and substrate metabolism, in particular, a set of blood-gas results can be a very useful teaching aid. The Blood Gas Archive contains a set of six (hopefully entertaining) simulated teaching exercises; this is constructed as a dialogue between a consultant and a registrar.

Some of the difficulties in learning acid-base physiology are outlined in the following quote.

Pertinent Quote

"Acid/base homeostasis is arguably one of the most difficult of the subdisciplines of physiology for veterinary and human medical students to master. There are several reasons for this. Typically, the approach to this material is highly quantitative and based on the physical characteristics and fundamental behaviors of acids and bases, which can be off-putting to veterinary and human medical students."
"Neophyte students are also often intimidated by acid/base physiology, because it is patently integrative. Students quickly realize that understanding the data in a blood gas panel requires an appreciation for not only acids and bases, but also ventilation, gas exchange, dynamics of electrolyte and water movement, plasma composition, respiratory control, and renal mechanisms of hydrogen ion, electrolyte, and water excretion."
"In addition, it is essential that the student develop an understanding of a host of other organ, metabolic, and structural dysfunctions that can potentially contribute acid or base loads to the extracellular fluid."
from: Rawson RE & Quinlan KM, Adv Physiol Educ 2002; 26: 85-97

Some additional materials on this web site provide examples of gas results worked through in a more integrative context.

1.2: Acids and Bases

What is an acid?

The term acid is derived from the Latin word *acidus* which means sour. Early chemists had a list of properties that were common to the substances that they considered to be acids or bases [eg acids had a sour taste, turned litmus red, reacted with some metals to produce a flammable gas (hydrogen) ..etc..]. They would assess a new substance as an acid or as a base (or as neither) by comparing the properties of the new substance against the list of properties.

The Arrhenius Theory

The first modern approach to acid-base chemistry was by Arrhenius in 1887. He defined an acid as a substance which was capable of dissociating in water solution to produce hydrogen ions. This definition identified most of the substances which were considered to be acids at that time. A base was defined as a substance which dissociated in water solution to produce hydroxide ions. The theory was not totally satisfactory for several reasons. For example, some substances which had acidic properties did not contain hydrogen and some bases did not contain hydroxide ions. The theory also applied only to aqueous solutions.

The Bronsted-Lowry Theory

The next development was the Bronsted-Lowry Theory (1923) and this is the approach which is generally accepted in biological and medical fields. An acid is defined as a substance which donates a hydrogen ion to another substance. This does not require an aqueous solution or dissociation into ions as in the Arrhenius definition. The substance which accepts the H^+ from the acid is called the conjugate base. This idea of conjugate acid-base pairs is an important part of the Bronsted-Lowry approach. Acid strength is defined in terms of the strength of the tendency to donate the hydrogen ion to the solvent (ie water in biological systems). A strong acid has a high tendency to donate a proton to water, so the $[H_3O^+]$ is high.

Other Approaches: Lewis and Usanovich

A more general definition of acids and bases is the approach of Lewis in 1923. The impetus here was the problem of substances which exhibited acidic properties in solution (eg CO_2) but did not contain an H^+. Lewis defined an acid as any compound that was a potential electron pair acceptor and a base as any compound that was a potential electron pair donor. In the Lewis scheme, H^+ itself is an acid.

Usanovich (1939) developed an even more general approach to acid-base theory that consolidated the differing approaches of the previous theories.

What Approach Should We Use?

From the medical and biological perspective, the Bronsted-Lowry theory is easy to understand and encompasses all the biological acids and bases encountered in aqueous solutions. It is the preferred approach.(CO_2 is not strictly an acid in the Bronsted-Lowry system as it has no hydrogen ion but it can be accommodated by considering carbonic acid (H_2CO_3) as the acid.)

In reality, most physicians have a basic knowledge of acids and bases which is somewhat of an combination of the Arrhenius approach (acid: H^+ in solution), the Bronsted-Lowry approach (acid = proton donor) and even the Lewis approach (eg CO_2 as an acid). This level of understanding is generally satisfactory for clinical purposes. The table below summarises the different approaches.

Basic Principles of the Various Theories of Acids and Bases	
Traditional approach	*Acid: a substance that has certain properties (eg sour taste, turns litmus red)*
Arrhenius	*Acid : H^+ in aqueous solution* *Base : OH^- in aqueous solution* *At neutrality: $[H^+] = [OH^-]$*
Bronsted-Lowry	*Acid : H^+ donor* *Base : H^+ acceptor* *Conjugate acid-base pairs* *No concept of neutrality*
Lewis	*Acid : a potential electron-pair acceptor* *Base : a potential electron-pair donor*

Usanovich	*Acid: a substance that donates a cation, or accepts an anion or an electron* *Base: a substance that donates an anion, or accepts a cation.*

1.3: The Hydrogen Ion

Hydrogen Ion in Solution

Bare protons (ie H^+) do not exist in solution. Protons are associated and react with surrounding water molecules. This is sometimes represented as H_3O^+ (the hydronium ion) but this one-to-one relationship is also inaccurate. Stewart suggests that the most accurate representation is $\{H:(H_2O)n\}^+$ to illustrate the reaction or interaction of H^+ with water molecules. This would be extremely inconvenient to use clinically so we continue to speak of the hydrogen ion (H^+) simply out of convenience. This is an acceptable convention but remember that H^+ is a symbol for a metaphor (Stewart) and does not exist in solutions in that form. This "metaphorical H^+" is extensively used and this convention is continued here.

Hydrogen Ion Activity

Chemists speak of ideal solutions which have certain predictable physicochemical properties. However, real solutions exhibit various degrees of non-ideal behaviour. This deviation from ideal behaviour is due to interactions between the molecules in the solution and includes both solvent-solute interactions and solute-solute interactions. The magnitude of this interaction (and the deviation from ideal behaviour) is higher with higher particle concentration in the solution and with ions as compared to non-charged species.

The idea of 'effective concentration' or 'activity' was introduced by Lewis to deal with this problem. Activity indicates how many particles seem to be present in the solution and is different from how many actually are present. Activity can be thought of as applying a correction factor to the concentration. Activity is related to concentration by the activity coefficient:

Definition: Definition of Activity

$$a_x = g \cdot [x] \tag{1.3.1}$$

where:

- a_x = activity of substance x in the solution
- g = activity coefficient of x
- $[x]$ = concentration of substance x in the solution

The activity coefficient of a solute is constant in any particular given solution but its value can change if the properties of the solution are changed (eg by changing the ionic strength or the temperature). If the relationship between concentration and activity is plotted on a graph, it is not linear. It depends on the type of solvent and the type and concentration of the various solutes present in the solution. In an ideal solution, the activity coefficient is one. The activity coefficient also approaches unity as non-ideal solutions become more and more dilute.

It is usual in discussions of acid-base balance to assume the activity coefficient of solutes is equal to one and use concentrations nstead of activities. This is obviously not correct but the errors introduced are usually small and not clinically relevant. Some measurement techniques (such as ion selective electrodes) measure activities and others measure concentration.

pH

The glass electrode for H^+ is an ion-selective electrode (ISE) widely used in clinical medicine. The potential that develops in this electrode is proportional to the log of the hydrogen ion activity in the test solution. The term used is pH which is now defined as:

Definition: pH

$$pH = -\log_{10} aH^+ \tag{1.3.2}$$

or

$$aH^+ = 10^{-pH} \tag{1.3.3}$$

where aH^+ is the activity of H^+

The term **pH** (in that exact form - lowercase p, uppercase H) was first used by WM Clark (inventor of the Clark oxygen electrode) in 1920. (see: Compact Oxford English Dictionary) However the concept was invented by the Danish chemist Soren Peter Sorensen in 1909 to refer to the negative log of hydrogen ion concentration; he used the term $\mathbf{P_H}$ in his original paper. He called it the **Wasserstoffionenexponent** (German for hydrogen ion exponent as hydrogen is "wasserstoff" in German).

There are several versions of what the 'p' means. In the common version, the p refers to the German word potenz (power in the sense of being an exponent) so pH means 'power of hydrogen'. The power referred to is the power of 10 used as the base for the log and not to the acid strength of the solution. Recent research suggests the 'p' was used as a result of how he arbitrarily labeled the 2 electrodes used in his experiment as 'p' and 'q', and the measurements derived from these electrodes included the letters p and q.

Note that the symbol p is used in two contexts in acid-base discussions:

- p meaning the negative log of as in pH, pK, pOH
- p meaning partial pressure as in pCO_2

pH is regarded as a 'dimensionless representation of the $[H^+]$' (Kellum, 2000) and is not itself a concentration. Because of this, pH does not have any units: it is just a number. There is a loose use of the term pH units as a device to assist explanation of some concepts. For example, the maximal pH gradient across the gastric mucosa is 6 pH units (ie 7.4 minus 1.4) representing a hydrogen ion concentration gradient of 10^6 (ie 1,000,000). By contrast, the hydrogen ion gradient across the renal collecting duct when maximally acidic urine (pH 4.5) is produced is about 3 pH units (ie gradient of 10^3). The term pH unit is considered to mean unit change in pH in most contexts. The term pH concentration is simply wrong and should never be used.

Theoretically, values of pH could range from -infinity to +infinity but the practical limits in aqueous solutions are from -1.2 to +15 reflecting $[H^+]$ varying from 15 to 10-15 moles/litre. Concentrated hydrochloric acid used by chemists has a pH of -1.1. Values in human fluids range from extremely acid (pH 0.87 for HCl secretion into the intracellular canaliculus of gastric parietal cells) to the alkaline values of bile and pancreatic juice. The reference range for arterial pH is 7.36 to 7.44 and the limits of survival cover a ten fold range of H^+ (from 160 to 16 nmoles/l which is pH 6.8 to 7.8).

Which is Best: pH or $[H^+]$?

There is a continuing discussion about the most appropriate symbol to represent the acidity of body fluids: pH or [H+]. In practical terms it is best to be most familiar with what is used in your local pathology laboratory. The current recommendation of the relevant international body (the IUCC) is to use pH.

The advantages of pH compared to $[H^+]$ are:

- It is the traditional symbol and remains in wide use
- It is related to the activity of H^+ (rather than concentration) or more specifically the log of H^+ activity and this is what physiological systems seem to respond to.
- It is what is measured by the pH electrode (ie activity of H^+)
- The alternative $[H^+]$ is not correct because the activity coefficient is ignored
- Free H^+ (ie bare protons) are not the form really present in solution anyway.

The disadvantages of pH are:

- It is a contrived symbol which represents a double non-linear transformation of $[H^+]$ (ie the log of a reciprocal)
- It is difficult to learn and understand
- It disguises the magnitude of changes in $[H^+]$

A Simple Way to Convert between pH and $[H^+]$

Changes in the $[H^+]$ by a factor of 2 cause a pH change of 0.3 -this provides us with a simple way to determine various pH-$[H^+]$ pairs of values if we know that pH 7.4 is 40 nmoles/l. For example: a $[H^+]$ of 80 nmoles/l is a pH of 7.1 - inspection of the table above shows a value of 79 so this simple method is pretty accurate. This useful relationship holds because log 2 is 0.3 so a doubling or a halving of $[H^+]$ means a change in pH by 0.3 either up or down.

Relationship between pH & $[H^+]$

pH	$[H^+]$ (nanomoles/l)
6.8	158

pH	$[H^+]$ (nanomoles/l)
6.9	125
7.0	100
7.1	79
7.2	63
7.3	50
7.4	40
7.5	31
7.6	25
7.7	20
7.8	15

This doesn't allow you to mentally calculate every pH and $[H^+]$ value but the 4 basic pairs which are useful and easy to memorise are:

- pH 7.4 is 40 nM
- pH 7.0 is 100 nM
- pH 7.36 is 44 nM
- pH 7.44 is 36 nM

The last two values above are the normal range of pH values which is easy to remember because the relationship between the $[H^+]$ and the decimal part of the pH (ie the normal range of 7.36 to 7.44 is a $[H^+]$ range of 44 to 36 nM. Now you can work out that a pH of 7.06 has a $[H^+]$ value of 88nm as this is double that at 7.36 (ie 44nM) - and so on.

References

1. Norby J. The origin and meaning of the little p in pH. Trends in Biochemical Sciences 2000; 25: 36-37.

1.4: Measurement of pH

Methods

The hydrogen gas platinum electrode was originally used for measuring [H^+] but is not useful for clinical pH analysis. The sample had to be fully saturated with hydrogen gas and all the oxygen eliminated. The method is not suitable for rapid automated analysis of blood samples. Current methods of pH measurement include:

- Colorimetric methods. Litmus paper is used to decide between acid or base but papers incorporating pH-sensitive dyes have been been designed to measure finer gradations of pH (eg urine pH is estimated by use of indicator dyes in dipsticks). Progress in colorimetric pH methods using indicator dyes (incl. fluorescent dyes) has lead to the development of accurate intravascular methods of pH measurement. The Paratrend 7+ is a commercially available system for measuring intra-arterial pH and blood gases.
- Glass electrodes. These are widely used in medical applications eg blood-gas machines.
- ISFET electrodes - using 'Ion-selective field effect transistors'. These are used mostly in industry but have beendeveloped for intravascular use.

The Glass pH Electrode

Cremer in 1906 discovered that a electrical potential developed across a glass membrane which was proportional to the pH difference across the membrane. Kerridge in 1925 developed the first glass electrode for analysis of blood samples.MacInnes & Dole in 1929 experimented with different types of glass to find the one which was most sensitive. This MacInnes-Dole glass (known as Corning 015 glass) consists of 72% silicon dioxide, 6% calcium oxide and 22% disodium oxide (Na_2O).

The pH electrode consists of 2 half cells: the glass electrode and a reference electrode (eg calomel electrode). This unit develops an electrical potential across the glass which is dependent on the difference in aH^+ across the glass membrane. This effectively allows measurement of the pH of the test solution because the pH in the solution on the other side of the membrane is constant. Other potentials develop in the pH electrode (eg liquid junction potential, asymmetry potential & diffusion potentials) and these are usually not quantified in a particular electrode. The problem is overcome by standardisation and calibration. Standardisation refers to the process of requiring that these potentials are the same when measuring the sample solution and when measuring the calibrating solutions. In particular, the liquid junction potential must remain unchanged. The calibrating solutions are chemical standard buffer solutions with a known pH. Many of the components of the electrode (eg the calomel reference cell) are very temperature sensitive. The temperature of the measurement must be precisely controlled: usually at 37°C.

Temperature Correction

If required, modern blood gas machines will report the pH value for actual patient temperature but this corrected value is calculated mathematically from the pH measured at 37°C in the machine. The change in pH with temperature is almost linear and 'anaerobic cooling' of a blood sample (ie cooling in a closed system) causes the pH to rise. The Rosenthal correction factor is recommended for clinical use.

Rosenthal Correction Factor

Change in pH = 0.015 pH units per degree C change in temperature
Example
If the measured pH is 7.360 at a blood gas electrode temperature of 37°C, then the pH at a patient temperature of 34°C is calculated as follows:
$pH = 7.360 + (37 - 34) \cdot (0.015) = 7.405$

The potential generated in the pH electrode is about 61.5 mV/pH unit. The electrode has a high internal resistance so the measuring apparatus has to have a very high (10^{11} Ohms) impedance to avoid drawing current from the cell and changing the potential.

1.5: pH and Cellular Metabolism

Why is pH so important?

The Davis Hypothesis & Ion trapping

What is the role of pH in the body and why does H^+ have an importance which seems out of keeping with its incredibly low concentration?

An insight can be gained from the findings of Davis (1958). He surveyed all known metabolic pathways and looked at the structural features of the compounds in each of these pathways. He found that nearly every biosynthetic intermediate has at least one group that would be largely ionised at physiological pH, whether it is an acid or a base. The only few exceptions he could find amongst hundreds of compounds were some macromolecules, some water-insoluble lipids and end-products of metabolism (eg waste compounds).

In summary, he found that:
all the known low molecular weight and water soluble biosynthetic intermediates possess groups that are essentially completely ionised at neutral pH.

These groups are phosphate, ammonium and carboxylic acid groups.

The Davis hypothesis is that the advantage to the cell of this pH-dependent ionisation was the efficient trapping of these ionised compounds within the cell and its organelles.

What about the exceptions to this generalisation?

There are some compounds that are seeming exceptions to the generalisation. So we need to ask this question: Does the existence of the exceptions that Davis found render his whole theory of ion trapping invalid?

Let's look at the 3 groups of possible exceptions:

Some macromolecules

It could be argued that these large molecules do not need to be charged for their distribution to be restricted to the intracellular environment. They could be trapped within the cell because of their size. However, size-trapping is not particularly effective *if* the macromolecule is very hydrophobic as such molecules would tend to move into lipid membranes. But most macromolecules in ther cell (eg proteins) are charged or are polar molecules and it is this that effectively traps them within the cell (unless there is a specific pathway for their excretion from the cell).

Lipids

Lipids are not ionised and cross cell membranes easily. But some lipids are 'trapped' within the cell despite not being ionised. These lipids which are not charged are trapped within the cell by another mechanism: by being protein-bound. So lipids that are necessary for intracellular purposes are trapped by an alternative means.

Metabolic precursors & waste products

These compounds need to be able to cross the membrane for ease of uptake (precursors like glucose) or excretion (waste products) from the cell. It is an advantage if they are not charged and not trapped. The first reaction that precursors undergo when they enter a cell is a reaction that places a charged group on the molecule. An example is glucose which is converted to glucose-6-phosphate which is charged at intracellular pH and thereby trapped within the cell. Clearly any reaction pathway that had noncharged or non-bound intermediates would have strong evolutionary pressures against it because of the diffusional loss of these intermediates from the cell.

So these exceptions do not invalidate the Davis hypothesis but instead add to it.

The importance of H^+ is clearly not related to its concentration per se because this is incredibly small. Its importance derives from the fact even though its concentration is extremely low, an alteration in this concentration has major effects on the relative concentrations of every conjugate acid and base of all the weak electrolytes. One major consequence as discussed above is that at 'neutral pH' metabolic intermediates are present only in the charged form and effectively trapped within the cell.

It is not just the small molecules of intermediary metabolism that are affected. The other critically important aspect of the importance of pH involves proteins. The net protein charge is dependent on the pH and the function of proteins is dependent of this charge because it determines the 3-D shape of the molecule and its binding characteristics (eg ionic bonding). (See 'Importance of Intracellular pH')

1.6: Alphastat Hypothesis

1.6.1 Beyond Davis : the Alphastat Hypothesis

Reeves[1] and Rahn[2] extended the conclusions reached by Davis[3] by considering the dissociation constants (pK) for these metabolic intermediates. They found that the pK for all the acid intermediates was less than 4.6 and the pK of all the basic intermediates was greater than 9.2 . The degree of dissociation of all these compounds at a pH around neutrality was 1.0 (ie fully ionised). The intermediates are all charged and trapped within the lipid cell membrane.

They suggested looking at acid-base physiology from the point of view of the *intracellular* environment instead of the usual clinical extracellular approach. They first posed the following question:

What is the ideal intracellular pH?

The work of Davis and the findings concerning pK values suggested that the ideal state for intermediary metabolism is **the state of neutrality** because maximal ionisation with consequent intracellular trapping of metabolic intermediates occurs at this pH.

First Hypothesis: pH(ICF) = pN

If theoretically, it is clear that the ideal ICF pH should be the pH of neutrality (pN)[see 4], then the next step is to ask the question:

Is the actual intracellular pH as predicted?

According to Rahn, measurements confirmed that the mean intracellular pH of man is 6.8 at 37°C which is indeed the pH of neutrality (pN) at that temperature!

Before going further we need to understand:

What is meant by 'neutrality'?

Neutrality is defined, for aqueous systems, as the state when $[H^+] = [OH^-]$. (This definition derives from the Arrhenius acid-base theory and it is noted in passing that a criticism of the Bronsted-Lowry theory is that it has no definition of neutrality.)

By the Law of Mass Action applied to the dissociation of water (see Section 10.4), then:

$pN = 0.05 \times pKw$ where pKw is the ion product for water[4]

Consideration of this equation is important as it provides us with a way to test the Davis, Reeves and Rahn hypothesis that intracellular pH equals pN (with consequent biological advantage of intracellular trapping of metabolic intermediates. *The clue is that pKw'is very temperature dependent*.

So pN is temperature dependent and if the hypothesis (ICF pH = pN) is correct then intracellular pH should change with change in temperature to maintain the predicted relationship.

An intracellular pH at about pN must surely apply to other animals (with body temperatures other than 37°C) as there is no reason to believe that humans at 37°C alone should be in a unique position. If this predicted change with temperature does occur, it would lend very strong support to the theory. So, the next question is:

Does intracellular pH change with temperature in order to remain equal to pN at each temperature? (And if so: How does this happen?)

Measurements of intracellular pH in skeletal muscles have been carried out in several ectothermic animals which have been acclimatised at temperatures ranging from 5°C to 31°C. These all show the expected pH change: **intracellular pH is maintained at about pN with change in temperature!!**

It has been calculated that for the body to have this temperature-pH relationship requires certain things. There must be a buffer system with a pK which is approximately one-half that of water (because a buffer is most effective close to its pK) and which changes its pK so that it maintains this relationship as temperature changes. The buffer must be present in sufficient concentration and have certain chemical properties (eg ΔH = 7 kcals per mole). For this system to work optimally, it also requires a constant CO_2 content.

Experimental work has shown that protein buffering, largely due to the imidazole group of histidine is responsible for maintaining this temperature-pH relationship (aided by phosphate and bicarbonate buffering). Of all the protein-dissociable groups that are

available, **it is only the imidazole of histidine that has the correct pK and whose pK changes with temperature in the appropriate way.**

The imidazole has a degree of dissociation (referred to as alpha) of 0.55 in the intracellular compartment and this remains constant despite changes in temperature (ie the pK is changing with change in temperature). This theory about the constancy of the imidazole alpha value as proposed by Reeves and Rahn has been termed the imidazole alphastat hypothesis.

Alphastat Hypothesis

The degree of ionisation (alpha) of the imidazole groups of intracellular proteins remains constant despite change in temperature.

The other necessary condition for maintaining imidazole alpha constant is that the CO_2 content in blood must be kept constant at different body temperatures. This means that ventilation must be regulated to maintain the imidazole alpha in the blood. It has been found experimentally that this regulation to maintain imidazole alpha constant in blood will result in imidazole alpha being maintained in other compartments (eg intracellular fluid) as well. The respiratory control that adjusts ventilation probably involves proteins whose activity is altered in an appropriate direction by an alphastat mechanism. Adjustment of ECF pCO_2 is necessary as this maintains a constant relative alkalinity of the ECF relative to the ICF so there is constancy of the gradient for H^+ across the cell membrane. In reality this does not mean that ventilation has to increase markedly with decrease in temperature because the reduced metabolic rate will automatically result in decreased CO_2 production.

Shouldn't neutral pH be 7.0?

Many people have a belief that a pH of 7.0 is the 'neutral pH' and consequently have trouble understanding how the change in pN with temperature can be possible.
By definition, neutrality is when the solution has $[H^+] = [OH^-]$. At a temperature of 25°C, this condition does indeed occur in pure water when pH is 7.0 and this is the basis of the common high-school teaching. But, as indicated in the calculations in Section 10.4, this condition of $[H^+] = [OH^-]$ is based on the amount that water dissociates and occurs when pH = 0.5 x pKw. This pH (the pN) is dependent *only* on the ion product of water pKw' (which indicates how much water dissociates); the value of this term is very temperature dependent. At a higher temperature, water still dissociates to produce equal amounts of H^+ and OH^- (the neutral condition) but there is *more* dissociation so the $[H^+]$ is higher (i.e. pH is lower). At 37°C, pN is 6.8

Alpha-stat versus pH-stat

The alternative theory is the **pH-stat hypothesis**: this argues that the pH should be kept constant despite changes in temperature. This is the same as saying that ECF pH should be kept at 7.4 whether the temperature is 20°C or 25°C or whatever it is.

Blood gas results: To temperature correct or not?

The **pH-stat approach** is also implicitly the approach used by anyone who temperature corrects blood gas results to the patient's temperature but interprets the values against the reference range relevant to 37°C. No reference range is available for temperatures other than 37°C but the pH-stat approach is that the reference range for 37°C is valid at all temperatures.
The alpha-stat approach is to never temperature correct blood gas results.
Do not report the patient's temperature on the request form, or if doing the gases yourself, only enter the temperature as 37°C no matter what the patient's actual temperature. The results from the blood gas machine must then be those as measured in the machine at 37°C. The reference range for 37°C is obviously the correct one to apply when assessing these results.
You should be careful because if you or a colleague indicate the patient's actual temperature on the blood-gas request form, the lab technician will enter this temperature into the blood-gas machine and the printed report will have the values calculated for this patient temperature (i.e. the 'corrected' values).
Note that whatever the actual patient temperature, the machine is always thermostatted to 37°C and all measurements are consequently performed at 37°C. For other patient temperatures, the computer in the machine uses various correction formulae to calculate what the values for the parameters would be at the patient's actual temperature. The pH correction used in most machines is the Rosenthal correction factor. The manual for the blood gas machine has a complete listing of the formulae it uses for all calculated values.

This controversy over whether the alpha-stat or the pH-stat theory is *correct* does have practical anaesthetic relevance in patients who are rendered hypothermic (eg while on cardiopulmonary bypass). What is the pH level to aim for in these patients? It seems that the alpha-stat theory is now widely accepted. This is probably related to the intellectual attraction of the theoretical arguments because major differences in outcome between groups of patients managed by the pH-stat or the alpha-stat technique have not been clear. Cells are capable of functioning despite the presence of a certain level of perturbation. Clinical studies have concentrated on which approach is best for the heart (myocardial outcome) and/or which approach is best for the brain (neurological outcome). The pH-stat aim to maintain a pH of 7.4 at the lower temperatures of hypothermic cardiac bypass is achieved by having a pCO_2 level which is higher than that required for alpha-stat management. This means that from the alphastat point of view, pH-stat management results in a respiratory acidosis at the lower temperature. One effect is that the cerebral blood flow is higher at a given temperature with pH-stat management than it is with alphastat management. (See section 1.6.3)

The alphastat hypothesis is about maintaining alpha which means that the net charge on all proteins is kept constant despite changes in temperature. This ensures that all proteins can function optimally despite temperature changes. The importance of pH is not just about intracellular trapping of metabolic intermediates (small molecule effect) but also about protein function (large molecule effect). This affects all proteins, though enzymes usually figure prominently as examples. So, to answer the question about why pH is so important in metabolism involves these two reasons.

Summary: The two reasons why pH is so important for metabolism

- **Effect on small molecules**: Intracellular trapping of intermediary metabolites (iethe Davis hypothesis)
- **Effect on large molecules (proteins)**: Maintaining optimal protein function both intracellularly and extracellularly.
- Consequently, the body regulates pH very tightly

A final point: According to chemists, the situation concerning pH and temperature is actually quite complex: for example, the thermodynamic basis of pH measurement includes a term for the ground state potential which must be arbitrarily defined at every temperature. This means that the absolute value of measured potential at any particular temperature cannot be precisely determined and thus that pH values obtained at different temperatures, strictly speaking, cannot be compared. This really is not a concern to the clinician.

Example: Alphastat Management during Induced Hypothermia

As an example, consider the management of a patient who is cooled during open heart surgery.

A patient is cooled to 20°C for cardiac surgery while on cardiac bypass. Imagine an arterial sample was drawn and analysed at 20°C and showed pH 7.65 and pCO_2 18 mmHg. Now if this same sample was analysed at 37°C then at that temperature, the values would be pH 7.4 and pCO_2 40 mmHg. *So which value do you want reported to you?*

The values for 37°C can be interpreted against the known reference values for 37°C and they would be considered to be normal. This is the alphastat approach and is equivalent to assessing the results against the appropriate reference range for 20°C but without having to know what it is.

The values for 20°C could also be interpreted against the reference values for 37°C. [Actually the blood gas machine measures at 37°C then applies the correction formulae and reports what the values would be if measured at 20°C]. This is the pH-stat approach (ie the idea is that the pH must be kept at the semi-magical 7.4 value at every temperature).

By the pH-stat approach then, it would be decided that this patient had a significant respiratory alkalosis and measures would be taken to correct this.

Clearly, the two approaches can result in quite different therapies being applied.

Summary of important aspects of Chapter One

- The approach discussed in the majority of this book is the traditional approach to acid-base physiology as this is still almost the only approach discussed in physiology texts. An alternative approach is the Stewart quantitative approach which is derived from basic physicochemical principles - though now well supported by evidence this approach is more difficult to use in everyday clinical practice - this approach is discussed in Chapter 10.

- The Bronsted-Lowry acid-base theory is normally used in biology.
  Definitions: - An acid is a proton donor & a base is a proton acceptor
- Hydrogen ions (ie protons) do not exist free in solution but are linked to adjacent water molecules by hydrogen bonds. Because of this interaction it is the activity (or effective concentration) of hydrogen ions rather than the actual concentration that is important for biological effects
- pH is the quantity used to assess the acidity or alkalinity of a solution. It is defined as the negative log of the hydrogen ion activity. It is measured using an ion-selective glass electrode
- pH is typically 7.4 in plasma ($[H^+]$ about 40 nmol/l) but lower values of pH are found intracellularly.
- $[H^+]$ in the body is tightly regulated. The physiological advantages principally involve providing conditions for optimal intracellular function, particularly:
  - intracellular trapping of metabolite intermediates is maximised at an intracellular pH of neutrality
  - activity of all proteins (incl enzymes) is optimised because their net charge is kept constant
- In the body, the intracellular pH changes with temperature such that the intracellular pH remains at or close to pH of neutrality. This is achieved by appropriate temperature-induced changes in the pK of the imidazole group of histidine. The idea that the degree of dissociation (known as alpha) of imidazole remains constant despite changes in temperature is known as the **alpha-stat hypothesis**. This has implications for clinical practice (e.g. management of hypothermia during cardiopulmonary bypass; and not temperature-correcting values in ABG reports.)

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CHAPTER OVERVIEW

2: Control of Acid-Base Balance

2.1: Acid-Base Balance

Each day there is *always* a production of acid by the body's metabolic processes and to maintain balance, these acids need to be excreted or metabolised. The various acids produced by the body are classified as respiratory (or volatile) acids and as metabolic (or fixed) acids. The body normally can respond very effectively to perturbations in acid or base production.

Respiratory Acid

The acid is more correctly carbonic acid (H_2CO_3) but the term 'respiratory acid' is usually used to mean carbon dioxide. But CO_2 itself is not an acid in the Bronsted-Lowry system as it does not contain a hydrogen so cannot be a proton donor. However, CO_2 can instead be thought of as representing a potential to create an equivalent amount of carbonic acid. Carbon dioxide is the end-product of complete oxidation of carbohydrates and fatty acids. It is called a volatile acid meaning in this context it can be excreted via the lungs. Of necessity, considering the amounts involved there must be an efficient system to rapidly excrete CO_2.

The amount of CO_2 produced each day is huge compared to the amount of production of fixed acids. Basal CO_2 production is typically quoted at 12,000 to 13,000 mmols/day.

Basal Carbon Dioxide Production

Consider a resting adult with an oxygen consumption of 250 mls/min and a CO_2 production of 200 mls/min (Respiratory quotient 0.8):

Daily CO_2 production

$$= \frac{0.2 \times 60 \times 24 \text{litres/day}}{22.4 \text{litres/mole}}$$

$$= 12,857 \text{mmoles/day}$$

Increased levels of activity will increase oxygen consumption and carbon dioxide production so that actual daily CO_2production is usually significantly more than the oft-quoted basal level. [Different texts quote different figures usually in the range of 12,000 to 24,000 mmoles/day but the actual figure simply depends on the level of metabolic activity and whether you quote basal or typical figures.]

Daily CO_2 production can also be calculated from the daily metabolic water production. The complete oxidation of glucose produces equal amounts of CO_2 and H_20. The complete oxidation of fat produces approximately equal amounts of $CO_2$and H_2O also. These two processes account for all the body's CO_2 production. Typically, this metabolic water is about 400 mls per day which is 22.2 moles (ie 400/18) of water. The daily typical CO_2 production must also be about 22,200 mmoles.

Metabolic Acids

This term covers all the acids the body produces which are non-volatile. Because they are not excreted by the lungs they are said to be fixed in the body and hence the alternative term **fixed acids**. All acids other then H_2CO_3 are fixed acids.

These acids are usually referred to by their anion (eg lactate, phosphate, sulphate, acetoacetate or b-hydroxybutyrate). This seems strange at first because the anion is, after all, the *base* and not itself the acid. This useage is acceptable in most circumstances because the dissociation of the acid must have produced one hydrogen ion for every anion so the amount of anions present accurately reflects the number of H^+ that must have been produced in the original dissociation.

Another potentially confusing aspect is that carbon dioxide is produced as an end-product of metabolism but is not a metabolic acid according to the usual definition. This inconsistency causes some confusion: it is simplest to be aware of this and accept the established convention.

Net production of fixed acids is about 1 to 1.5 mmoles of H^+ per kilogram per day: about 70 to 100 mmoles of H^+ per day in an adult. This non-volatile acid load is excreted by the kidney. Fixed acids are produced due to incomplete metabolism of carbohydrates (eg lactate), fats (eg ketones) and protein (eg sulphate, phosphate).

The above total for net fixed acid production excludes the lactate produced by the body each day as the majority of the lactate produced is metabolised and is not excreted so there is no net lactate requiring excretion from the body.

For acid-base balance, the amount of acid excreted per day must equal the amount produced per day.

The routes of excretion are the lungs (for CO_2) and the kidneys (for the fixed acids). Each molecule of CO_2 excreted via the lungs results from the reaction of one molecule of bicarbonate with one molecule of H^+. The H^+ remains in the body as H_2O.

Response to an Acid-Base Perturbation

The body's response[1] to a change in acid-base status has three components:

- First defence: Buffering
- Second defence: Respiratory : alteration in arterial pCO_2
- Third defence: Renal : alteration in HCO_3^- excretion

The word 'defence' is used because these are the three ways that the body 'defends' itself against acid-base disturbances. This is not the complete picture as it neglects some metabolic responses (eg changes in metabolic pathways) that occur.

This response can be considered by looking at how the components affect the $\frac{[HCO_3^-]}{pCO_2}$ ratio in the Henderson-Hasselbalch equation. The 3 components of the response are summarised below.

The Immediate Response : Buffering

Buffering is a rapid physico-chemical phenomenon. The body has a large buffer capacity. The buffering of fixed acids by bicarbonate changes the $[HCO_3^-]$ numerator in the ratio (in the Henderson-Hasselbalch equation).

The Respiratory Response : Alteration in Ventilation

Adjustment of the denominator pCO_2 (in the Henderson-Hasselbalch equation) by alterations in ventilation is relatively rapid (minutes to hours). An increased CO_2 excretion due to hyperventilation will result in one of three acid-base outcomes:

- correction of a respiratory acidosis
- production of a respiratory alkalosis
- compensation for a metabolic acidosis.

Which of these three circumstances is present cannot be deduced merely from the observation of the presence of hyperventilation in a patient.

This respiratory response is particularly useful physiologically because of its effect on intracellular pH as well as extracellular pH. Carbon dioxide crosses cell membranes easily so changes in pCO2 affect intracellular pH rapidly and in a predictable direction.

The system has to be able to respond quickly and to have a high capacity because of the huge amounts of respiratory acid to be excreted.

The Renal Response : Alteration in Bicarbonate Excretion

This much slower process (several days to reach maximum capacity) involves adjustment of bicarbonate excretion by the kidney. This system is responsible for the excretion of the fixed acids and for compensatory changes in plasma $[HCO_3^-]$ in the presence of respiratory acid-base disorders.

Balance: Internal versus External

This refers to the difference between Hydrogen Ion Turnover in the body (or Internal Balance) versus Net H^+ Production & Excretion requiring excretion from the body (ie External Balance)

Most discussions of hydrogen ion balance refers to net production (which requires excretion from the body to maintain a stable body pH) rather than to turnover of hydrogen ions (where H^+ are produced and consumed in chemical reactions without any net production). Net production under basal conditions gives 12 moles of CO_2 and 0.1 moles of fixed acids.

The majority of the fixed acids are produced from proteins (sulphate from the three sulphur containing amino acids; phosphate from phosphoproteins) with a smaller contribution from metabolism of other phosphate compounds (eg phospholipids).

Key Fact: Turnover of hydrogen ions in the body is HUGE & very much larger then net acid excretion.

Turnover[2] includes:

- 1.5 moles/day from lactic acid turnover

- 80 moles/day from adenine dinucleotide turnover
- 120 moles/day from ATP turnover
- At least another 360 moles/day involved in mitochondrial membrane H+ movements (Johnston & Alberti).

Compared to the total of these huge turnover figures, the 12 moles/day of CO_2 produced looks small and the 0.1 mole/day of net fixed acid production looks positively puny. (Appearances of course can be deceptive). Because with turnover, these H^+ are produced and consumed without any net production requiring excretion, they are less relevant to this discussion where the emphasis is on external acid-base balance.

By definition, for acid-base equilibrium, the *net* acid production by the body must be excreted. This discussion of external acid-base balance also includes any acids or bases ingested or infused into the body. Acid-base balance means that the net production of acid is excreted from the body each day (ie 'external balance'). The internal turnover of H^+ is largely ignored (except for lactic acid) in the rest of this book.

References

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2.2: Buffering

Definition of a Buffer

A buffer is a solution containing substances which have the ability to minimise changes in pH when an acid or base is added to it [1].

A buffer typically consists of a solution which contains a weak acid HA mixed with the salt of that acid & a strong base e.g. NaA. The principle is that the salt provides a reservoir of A^- to replenish $[A^-]$ when A^- is removed by reaction with H^+.

Buffers in the Body

The body has a very large buffer capacity.

This can be illustrated by considering an old experiment (see below) where dilute hydrochloric acid was infused into a dog.

Swan & Pitts Experiment [2]

In this experiment, dogs received an infusion of 14 mmols H^+ per litre of body water. This caused a drop in pH from 7.44 ($[H^+] = 36$ nmoles/l) or a pH of 7.14 ($[H^+] = 72$ nmoles/l). That is, a rise in $[H^+]$ of only 36 nmoles/l.

If you just looked at the change in $[H^+]$ then you would only notice an increase of 36 nmoles/l and you would have to wonder what had happened to the other 13,999,964 nmoles/l that were infused.

Where did the missing H^+ go?

They were hidden on buffers and so these hydrogen ions were hidden from view.

Before we proceed, lets just make sure we appreciate what this experiment reveals [3]. The dogs were infused with 14,000,000 nmoles/l of H^+ but the plasma $[H^+]$ only changed by a bit over 0.002%. By any analysis, this is a system which **powerfully resists change in $[H^+]$**. (My personal analogy on appreciating the magnitude of this is to use the analogy of depositing $14,000,000 in the bank, but then finding that after 'bank charges' my account only went up by $36.)

The conclusion is that the body has:

- a HUGE buffering capacity, *and*
- this system is essentially IMMEDIATE in effect.

For these 2 reasons, physicochemical buffering provides a powerful first defence against acid-base perturbations.

Buffering hides from view the real change in H^+ that occurs.

This huge buffer capacity has another not immediately obvious implication for how we think about the severity of an acid-base disorder. You would think that the magnitude of an acid-base disturbance could be quantified merely by looking at the change in $[H^+]$ - BUT this is not so.

Because of the large buffering capacity, the actual change in $[H^+]$ is so small it can be ignored in any quantitative assessment, and instead, the magnitude of a disorder has to be estimated indirectly from the decrease in the total concentration of the anions involved in the buffering. The buffer anions, represented as A^-, decrease because they combine stoichiometrically with H^+ to produce HA. A decrease in A^- by 1 mmol/l represents a 1,000,000 nano-mol/l amount of H^+ that is hidden from view and this is several orders of magnitude higher than the visible few nanomoles/l change in $[H^+]$ that is visible.) - As noted above in the comments about the Swan & Pitts experiment, 13,999,994 out of 14,000,000 nano-moles/l of H^+ were hidden on buffers and just to count the 36 that were on view would give a false impression of the magnitude of the disorder.

The Major Body Buffer Systems

Site	***Buffer System***	***Comment***
ISF	*Bicarbonate*	*For metabolic acids*
	Phosphate	*Not important because concentration too low*

	Protein	*Not important because concentration too low*
Blood	*Bicarbonate*	*Important for metabolic acids*
	Haemoglobin	*Important for carbon dioxide*
	Plasma protein	*Minor buffer*
	Phosphate	*Concentration too low*
ICF	*Proteins*	*Important buffer*
	Phosphates	*Important buffer*
Urine	*Phosphate*	*Responsible for most of 'Titratable Acidity'*
	Ammonia	*Important - formation of NH_4^+*
Bone	*Ca carbonate*	*Important in prolonged metabolic acidosis*

The Bicarbonate Buffer System

The major buffer system in the ECF is the CO_2-bicarbonate buffer system. This is responsible for about 80% of extracellular buffering. It is the most important ECF buffer for metabolic acids but it cannot buffer respiratory acid-base disorders.

The components are easily measured and are related to each other by the Henderson-Hasselbalch equation.

Henderson-Hasselbalch Equation

$$pH = pKa + \log_{10}\left(\frac{[HCO_3]}{0.03}\right) \times pCO_2 \tag{2.2.2}$$

The pKa value is dependent on the temperature, $[H^+]$ and the ionic concentration of the solution. It has a value of 6.099 at a temperature of 37C and a plasma pH of 7.4. At a temperature of 30C and pH of 7.0, it has a value of 6.148. For practical purposes, a value of 6.1 is generally assumed and corrections for temperature, pH of plasma, and ionic strength are not used except in precise experimental work.

A note on terminology: Ka is the equilibrium constant for acid dissociation reaction. pKa is the negative log (to base 10) of Ka.

The pKa is derived from the Ka value of the following reaction:

$$CO_2 + H_2O \Leftrightarrow H_2CO_3 \Leftrightarrow H^+ + HCO_3^- \tag{2.2.3}$$

(where CO_2 refers to dissolved CO_2)

The concentration of carbonic acid is very low compared to the other components so the above equation is usually simplified to:

$$CO_2 + H_2O \Leftrightarrow H^+ + HCO_3^- \tag{2.2.4}$$

By the Law of Mass Action:

$$K_a = \frac{[H^+] \cdot [HCO_3^-]}{[CO_2] \cdot [H_2O]} \tag{2.2.5}$$

The concentration of H_2O is so incredibly large (55.5M or 55,500 mmol/l) compared to the other components, the small loss of water due to this reaction changes its concentration by only an extremely small amount. To get an idea of what this means, imagine that you have 100 million dollars in the bank, and you give away $1. The amount your bank account has changed relative to the total amount is so incredibly small that you still have a $100 million dollars in the bank. Thus back to the situation with water, the dissociation is so incredibly small that $[H_2O]$ is effectively constant. This allows further simplification as the two constants (Ka and $[H_2O]$) can be combined into a new constant K'a.

$$K'_a = K_a \times [H_2O] = [H^+] \cdot \frac{[HCO_3^-]}{[CO_2]} \tag{2.2.6}$$

Substituting in the equation using:

$$K'_a = 800 nmol/L \text{ (value for plasma at } 37^\circ \text{C)} \tag{2.2.7}$$

$$[CO_2] = 0.03 \times pCO_2 \text{(by Henry's Law) [where 0.03 is the solubility coefficient]} \tag{2.2.8}$$

gives the form known as the **Henderson Equation**:

$$[H^+] = (800 \times 0.03) \cdot \frac{pCO_2}{HCO_3^-} \tag{2.2.9}$$

$$[H^+] = 24 \times \frac{pCO_2}{[HCO_3^-]} nmol/l \tag{2.2.10}$$

Now this equation can be converted into another form using the following information (where [H^+] is in mol/l) and the standard rules of algebra and logs:

$$pH = \log_{10}[H^+] \tag{2.2.11}$$

$$pK'_a = -\log_{10} K'_a = \log_{10}(800 \times 10^{-9}) = 6.1 \tag{2.2.12}$$

Thus, the **Henderson-Hasselbalch equation**

$$-\log_{10}[H^+] = -\log_{10}(800 \times 10^{-9}) + \log \frac{[HCO_3^-]}{0.03 pCO_2} \tag{2.2.13}$$

$$pH = pK'_a + \log \frac{[HCO_3^-]}{0.03 pCO_2} \tag{2.2.14}$$

$$pH = 6.1 + \log \frac{[HCO_3^-]}{0.03 pCO_2} \tag{2.2.15}$$

Note

The distinction between pKa and p'Ka is usually forgotten and the Henderson-Hasselbalch equation is always written with pKa

On chemical grounds, a substance with a pKa of 6.1 should not be a good buffer at a pH of 7.4 if it were a simple buffer. The system is more complex as it is *open at both ends* (meaning both [HCO_3^-] and pCO_2 can be adjusted) and this greatly increases the buffering effectiveness of this system. The excretion of CO_2 via the lungs is the key thing because of the rapidity of the response. The adjustment of pCO_2 by change in alveolar ventilation has been referred to as *physiological buffering*.

Note: This use of the word *buffering* is in the broader sense of something that resists change in a property, and is different from the definition of buffering (or 'physiological buffering') given at the top of this page. This shift in meaning of buffering can be confusing because the word buffering is mostly used in speech and in articles without the qualification of either 'physicochemical' or 'physiological' (or some qualifying word).

The bicarbonate buffer system is an effective buffer system despite having a low pKa because the body also controls pCO_2

Other Buffers

The other buffer systems in the blood are the protein and phosphate buffer systems.

These are the only blood buffer systems capable of buffering respiratory acid-base disturbances as the bicarbonate system is ineffective in buffering changes in H^+ produced by itself.

The phosphate buffer system is NOT an important blood buffer as its concentration is too low

The concentration of phosphate in the blood is so low that it is quantitatively unimportant. Phosphates are important buffers intracellularly and in urine where their concentration is higher.

Phosphoric acid is triprotic weak acid and has a pKa value for each of the three dissociations:

	$pK_{a1} = 2$		$pK_{a2} = 6.8$		$pK_{a3} = 12$	
H_3PO_4	$\Leftrightarrow$	$H^+ + H_2PO_4^-$	$\Leftrightarrow$	$H^+ + HPO_4^{2-}$	$\Leftrightarrow$	$H^+ + PO_4^{3-}$

The three pKa values are sufficiently different so that at any one pH only the members of a single conjugate pair are present in significant concentrations.

At the prevailing pH values in most biological systems, monohydrogen phosphate (HPO_4^{-2}) and dihydrogen phosphate ($H_2PO_4^-$) are the two species present. The pKa2 is 6.8 and this makes the closed phosphate buffer system a good buffer intracellularly and in urine. The pH of glomerular ultrafiltrate is 7.4 and this means that phosphate will initially be predominantly in the monohydrogen form and so can combine with more H^+ in the renal tubules. This makes the phosphate buffer more effective in buffering against a drop in pH than a rise in pH.

Note

The pKa2 value is actually 7.2 if measured at zero ionic strength, but at the typical ionic strength found in the body its apparent value is 6.8. The other factor which makes phosphate a more effective buffer intracellularly and in urine is that its concentration in these two sites is much higher than in extracellular fluid.

Haemoglobin is an important blood buffer particularly for buffering CO_2

Protein buffers in blood include haemoglobin (150g/l) and plasma proteins (70g/l). Buffering is by the imidazole group of the histidine residues which has a pKa of about 6.8. This is suitable for effective buffering at physiological pH. Haemoglobin is quantitatively about 6 times more important then the plasma proteins as it is present in about twice the concentration and has about three times the number of histidine residues per molecule. For example if blood pH changed from 7.5 to 6.5, haemoglobin would buffer 27.5 mmol/l of H^+ and total plasma protein buffering would account for only 4.2 mmol/l of H^+.

Deoxyhaemoglobin is a more effective buffer than oxyhaemoglobin and this change in buffer capacity contributes about 30% of the Haldane effect. The major factor accounting for the Haldane effect in CO_2 transport is the much greater ability of deoxyhaemoglobin to form carbamino compounds.

Isohydric Principle

All buffer systems which participate in defence of acid-base changes are in equilibrium with each other. There is after all only one value for $[H^+]$ at any moment. This is known as the **Isohydric Principle**.

It means that an assessment of the concentrations of any one acid-base pair can be utilised to provide a picture of overall acid-base balance in the body. This is fortunate as the measurement of the concentrations of all the buffer pairs in the solution would be difficult. Conventionally, the components of the bicarbonate system (ie $[HCO_3^-]$ and pCO_2) alone are measured. They are accessible and easy to determine. Blood gas machines measure pH and pCO_2 directly and the $[HCO_3^-]$ is then calculated using the Henderson-Hasselbalch equation.

Buffering in different sites

Respiratory disorders are predominantly buffered in the intracellular compartment. Metabolic disorders have a larger buffering contribution from the extracellular fluid (eg ECF buffering of 40% for a metabolic acidosis and 70% for a metabolic alkalosis).

Various buffer systems exist in body fluids (see Table) to minimise the effects on pH of the addition or removal of acid from them.

In ECF, the bicarbonate system is quantitatively the most important for buffering metabolic acids. Its effectiveness is greatly increased by ventilatory changes which attempt to maintain a constant pCO_2 and by renal mechanisms which result in changes in plasma bicarbonate.

In blood, haemoglobin is the most important buffer for CO_2 because of its high concentration and its large number of histidine residues.

Deoxyhaemoglobin is a better buffer than oxyhaemoglobin

Another factor which makes haemoglobin an important buffer is the phenomemon of **isohydric exchange**. That is, the buffer system ($HHbO_2$-HbO_2^-) is converted to another more effective buffer (HHb-Hb^-) exactly at the site where an increased buffering capacity is required. More simply, this means that oxygen unloading increases the amount of deoxyhaemoglobin and this better

buffer is produced at exactly the place where additional H^+ are being produced because of bicarbonate production for CO_2 transport in the red cells.

Link between Intracellular & Extracellular Compartments

How are changes in [H^+] communicated between the ICF and ECF?

The two major processes involved are:

- Transfer of CO_2 across the cell membrane
- Ionic shifts (ie proton-cation exchange mechanisms)

Important points to note about CO_2 are:

- It is very lipid soluble and crosses cell membranes with ease causing acid-base changes due to formation of H^+ and HCO_3^-. Because of this ease of movement, CO_2 is not important in causing differences in pH on the two sides of the cell membrane.
- Extracellular buffering of CO_2 is limited by the inability of the major extracellular buffer (the bicarbonate system) to buffer changes in [H^+] produced from the reaction between CO_2 and water.

The result is that buffering for respiratory acid-base disorders is predominantly intracellular: 99% for respiratory acidosis and 97% for respiratory alkalosis.

The second major process which allows transfer of H^+ ions intracellularly is entry of H^+ in exchange for either K^+ or Na^+. This ionic exchange is necessary to maintain electroneutrality. This cation exchange is the mechanism which delivers H^+intracellularly for buffering of a metabolic disorder. In the cell, the protein and phosphates (organic and inorganic) buffer the H^+ delivered by this ion exchange mechanism.

Experiments in metabolic acidosis have shown that 57% of buffering occurs intracellularly and 43% occurs extracellularly. The processes involved in this buffering are:

Processes involved in Buffering	
ECF	43% (by bicarbonate & protein buffers)
ICF	57% (by protein phosphate and bicarbonate buffers) due to entry of H^+ by:
	• Na^+-H^+ exchange 36% • K^+-H^+ exchange 15% • Other 6%

(see Section 10.6 for a chemical explanation of how an exchange of Na^+ or K^+ for H^+ across a membrane can alter the pH by changing the *strong ion difference* or 'SID')

Thirty-two percent (32%) of the buffering of a metabolic alkalosis occurs intracellularly and Na^+-H^+ exchange is responsible for most of the transfer of H^+.

Role of Bone Buffering

The carbonate and phosphate salts in bone act as a long term supply of buffer especially during *prolonged* metabolic acidosis.

The important role of bone buffers is often omitted from discussions of acid-base physiology[4].

Bone consists of matrix within which specialised cells are dispersed. The matrix is composed of organic [collagen and other proteins in ground substance] and inorganic hydroxyapatite crystals: general formula $Ca_{10}(PO_4)_6(OH)_2$)] components. The hydroxyapatite crystals make up two-thirds of the total bone volume but they are extremely small and consequently have a huge total surface area. The crystals contain a large amount of carbonate (CO_3^{-2}) as this anion can be substituted for both phosphate and hydroxyl in the apatite crystals. Bone is the major CO_2 reservoir in the body and contains carbonate and bicarbonate equivalent to 5 moles of CO_2 out of a total body CO_2 store of 6 moles. (Compare this with the basal daily CO_2 production of 12 moles/day)

CO_2 in bone is in two forms: bicarbonate (HCO_3^-) and carbonate (CO_3^{-2}). The bicarbonate makes up a readily exchangeable pool because it is present in the bone water which makes up the hydration shell around each of the hydroxyapatite crystals. The

carbonate is present in the crystals and its release requires dissolution of the crystals. This is a much slower process but the amounts of buffer involved are much larger.

How does bone act as a buffer?

Two processes are involved:

- Ionic exchange
- Dissolution of bone crystal

Bone can take up H^+ in exchange for Ca^{2+}, Na^+ and K^+ (ionic exchange) or release of HCO_3^-, CO_3^- or HPO_4^{-2}. In acute metabolic acidosis uptake of H^+ by bone in exchange for Na^+ and K^+ is involved in buffering as this can occur rapidly without any bone breakdown. A part of the so-called 'intracellular buffering of acute metabolic disorders may represent some of this acute buffering by bone. In chronic metabolic acidosis, the major buffering mechanism by far is release of calcium carbonate from bone. The mechanism by which this dissolution of bone crystal occurs involves two processes:

- direct physicochemical breakdown of crystals in response to $[H^+]$
- osteoclastic reabsorption of bone.

The involvement of these processes in buffering is independent of parathyroid hormone. Intracellular acidosis in osteoclasts results in a decrease in intracellular Ca^{2+} and this stimulates these cells.

Bone is probably involved in providing some buffering for all acid-base disturbances. Little experimental evidence is available for respiratory disorders. Most research has been concerned with chronic metabolic acidoses as these conditions are associated with significant loss of bone mineral (osteomalacia, osteoporosis). In terms of duration only two types of metabolic acidosis are long-lasting enough to be associated with loss of bone mineral: renal tubular acidosis (RTA) and uraemic acidosis. Bone is an important buffer in these two conditions.

In uraemia, additional factors are more significant in causing the renal osteodystrophy as the loss of bone mineral cannot be explained by the acidosis alone. Changes in vitamin D metabolism, phosphate metabolism and secondary hyperparathyroidism are more important than the acidosis in causing loss of bone mineral in uraemic patients. The loss of bone mineral due to these other factors releases substantial amounts of buffer.

Summary

- Bone is an important source of buffer in chronic metabolic acidosis (ie renal tubular acidosis & uraemic acidosis)
- Bone is probably involved in providing some buffering (mostly by ionic exchange) in most acute acid-base disorders but this has been little studied.
- Release of calcium carbonate from bone is the most important buffering mechanism involved in chronic metabolic acidosis.
- Loss of bone crystal in uraemic acidosis is multifactorial and acidosis is only a minor factor
- BOTH the acidosis and the vitamin D3 changes are responsible for the osteomalacia that occurs with renal tubular acidosis.

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2.3: Respiratory Regulation of Acid-Base Balance

How is the Respiratory System Linked to Acid-base Changes?

Respiratory regulation refers to changes in pH due to pCO_2 changes from alterations in ventilation. This change in ventilation can occur rapidly with significant effects on pH. Carbon dioxide is lipid soluble and crosses cell membranes rapidly, so changes in pCO_2 result in rapid changes in $[H^+]$ in all body fluid compartments.

A quantitative appreciation of respiratory regulation requires knowledge of two relationships which provide the connection between alveolar ventilation and pH via pCO_2. These 2 relationships are:

- First equation - relates alveolar ventilation (V_A) and pCO_2
- Second equation - relates pCO_2 and pH.

The two key equations are outlined in the boxes below:

First Equation: Alveolar ventilation - Arterial pCO2 Relationship

Relationship: Changes in alveolar ventilation are inversely related to changes in arterial pCO_2 (& directly proportional to total body CO_2 production).

$paCO_2$ is proportional to **$[V_{CO2} / V_A]$**

where:

- $paCO_2$ = Arterial partial pressure of CO_2
- V_{CO2} = Carbon dioxide production by the body
- V_A = Alveolar ventilation

Alternatively, this formula can be expressed as:

$$paCO_2 = 0.863 \times \frac{V_{CO_2}}{V_A} \tag{2.3.1}$$

(if VCO_2 has units of mls/min at STP and VA has units of l/min at 37°C and at atmospheric pressure.)

Second Equation: Henderson-Hasselbalch Equation

Relationship: These changes in arterial pCO_2 cause changes in pH (as defined in the Henderson-Hasselbalch equation):

$$\boldsymbol{pH = pKa + \log \frac{[HCO_3^-]}{0.03 \times pCO_2}} \tag{2.3.2}$$

or more simply: **The Henderson equation:**

$$\boldsymbol{[H^+] = 24 \times \frac{pCO_2}{[HCO_3^-]}} \tag{2.3.3}$$

The key point is that these 2 equations can be used to calculate the effect on pH of a given change in ventilation provided of course the other variables in the equations (eg body's CO_2 production) are known.

The next question to consider is how all this is put together and controlled, that is, how does it work?

Control System for Respiratory Regulation

The control system for respiratory regulation of acid-base balance can be considered using the model of a simple servo control system. The components of such a simple model are a controlled variable which is monitored by a sensor, a central integrator which interprets the information from the sensor and an effector mechanism which can alter the controlled variable. The servo control means that the system works in such a way as to attempt to keep the controlled variable constant or at a particular set-point. This means that a negative feedback system is in operation and the elements of the system are connected in a loop.

Control systems in the body are generally much more complex than this simple model but it is still a very useful exercise to at first attempt such an analysis.

Control System for Respiratory Regulation of Acid-base Balance		
Control Element	**Physiological or Anatomical Correlate**	**Comment**
Controlled variable	Arterial pCO_2	A change in arterial pCO_2 alters arterial pH (as calculated by use of the Henderson-Hasselbalch Equation).
Sensors	Central and peripheral chemoreceptors	Both respond to changes in arterial pCO_2 (as well as some other factors)
Central integrator	The respiratory center in the medulla	
Effectors	The respiratory muscles	An increase in minute ventilation increases alveolar ventilation and thus decreases arterial pCO_2 (the controlled variable) as calculated from 'Equation 1'(discussed previously). The net result is of negative feedback which tends to restore the pCO_2 to the 'setpoint'.

2.4: Renal Regulation of Acid-Base Balance

Role of the Kidneys

The organs involved in regulation of external acid-base balance are the **lungs** are the **kidneys**.

The lungs are important for excretion of carbon dioxide (the respiratory acid) and there is a huge amount of this to be excreted: at least 12,000 to 13,000 mmols/day.

In contrast the kidneys are responsible for excretion of the fixed acids and this is also a critical role even though the amounts involved (70-100 mmols/day) are much smaller. The main reason for this renal importance is because there is no other way to excrete these acids and it should be appreciated that the amounts involved are still very large when compared to the plasma [H^+] of only 40 nanomoles/litre.

There is a second extremely important role that the kidneys play in acid-base balance, namely the reabsorption of the filtered bicarbonate. Bicarbonate is the predominant extracellular buffer against the fixed acids and it important that its plasma concentration should be defended against renal loss.

In acid-base balance, the kidney is responsible for 2 major activities:

- Reabsorption of filtered bicarbonate: 4,000 to 5,000 mmol/day
- Excretion of the fixed acids (acid anion and associated H^+): about 1 mmol/kg/day.

Both these processes involve secretion of H^+ into the lumen by the renal tubule cells but only the second leads to excretion of H^+ from the body.

The renal mechanisms involved in acid-base balance can be difficult to understand so as a *simplification* we will consider the processes occurring in the kidney as involving 2 aspects:

- Proximal tubular mechanism
- Distal tubular mechanism

Proximal Tubular Mechanism

The contributions of the proximal tubules to acid-base balance are:

- firstly, reabsorption of bicarbonate which is filtered at the glomerulus
- secondly, the production of ammonium

The next 2 sections explain these roles in more detail.

Bicarbonate Reabsorption

Daily filtered bicarbonate equals the product of the daily glomerular filtration rate (180 l/day) and the plasma bicarbonate concentration (24 mmol/l). This is 180 x 24 = 4320 mmols/day (or usually quoted as between 4000 to 5000 mmols/day).

About 85 to 90% of the filtered bicarbonate is reabsorbed in the proximal tubule and the rest is reabsorbed by the *intercalated cells* of the distal tubule and collecting ducts.

The reactions that occur are outlined in the diagram. Effectively, H^+ and HCO_3^- are formed from CO_2 and H_2O in a reaction catalysed by carbonic anhydrase. The actual reaction involved is probably formation of H^+ and OH^- from water, then reaction of OH^- with CO_2 (catalysed by carbonic anhydrase) to produce HCO_3^-. Either way, the end result is the same.

The H^+ leaves the proximal tubule cell and enters the PCT lumen by 2 mechanisms:

- Via a Na^+-H^+ antiporter (major route)
- Via H^+-ATPase (proton pump)

Filtered HCO_3^- cannot cross the apical membrane of the PCT cell. Instead it combines with the secreted H^+ (under the influence of brush border carbonic anhydrase) to produce CO_2 and H_2O. The CO_2 is lipid soluble and easily crosses into the cytoplasm of the PCT cell. In the cell, it combines with OH^- to produce bicarbonate. The HCO_3^- crosses the basolateral membrane via a Na^+-HCO_3^- symporter. This symporter is electrogenic as it transfers three HCO_3^- for every one Na^+. In comparison, the Na^+-H^+ antiporter in the apical membrane is not electrogenic because an equal amount of charge is transferred in both directions.

The basolateral membrane also has an active Na^+-K^+ ATPase (sodium pump) which transports 3 Na^+ out per 2 K^+ in. This pump is electrogenic in a direction opposite to that of the Na^+-HCO_3^- symporter. Also the sodium pump keeps intracellular Na^+ low which sets up the Na^+ concentration gradient required for the H^+-Na^+ antiport at the apical membrane. The H^+-Na^+ antiport is an example of *secondary active transport*.

The net effect is the reabsorption of one molecule of HCO_3 and one molecule of Na^+ from the tubular lumen into the blood stream for each molecule of H^+ secreted. This mechanism does not lead to the net excretion of any H^+ from the body as the H^+ is consumed in the reaction with the filtered bicarbonate in the tubular lumen.

Note

The differences in functional properties of the apical membrane from that of the basolateral membranes should be noted. This difference is maintained by the tight junctions which link adjacent proximal tubule cells.

These tight junctions have two extremely important functions:

Gate function: They limit access of luminal solutes to the intercellular space. This resistance can be altered and this paracellular pathway can be more open under some circumstances (ie the gate can be opened a little).

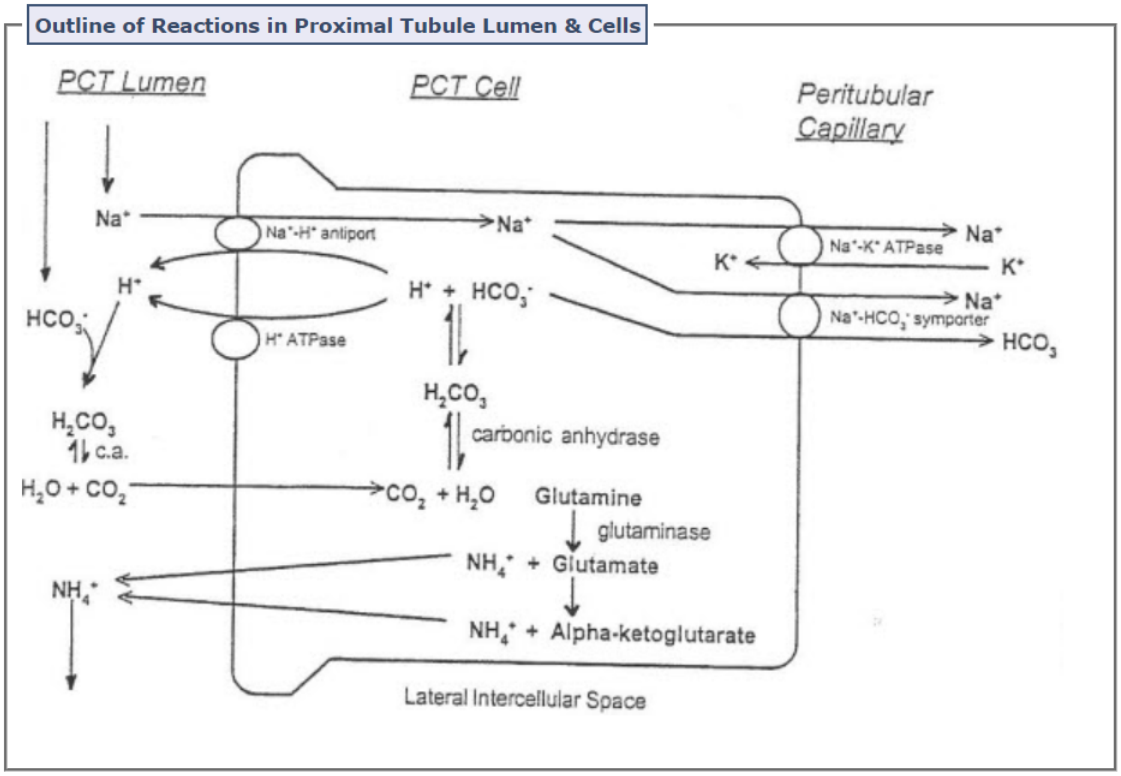
Fence function: The junctions maintain different distributions of some of the integral membrane proteins. For example they act as a fence to keep the Na^+-H^+ antiporter limited to the apical membrane, and keep the Na^+-K^+ ATPase limited to the basolateral membrane. The different distribution of such proteins is absolutely essential for cell function.]

The 4 major factors which control bicarbonate reabsorption are:

- Luminal HCO_3^- concentration
- Luminal flow rate
- Arterial pCO_2
- Angiotensin II (via decrease in cyclic AMP)

An increase in any of these four factors causes an increase in bicarbonate reabsorption. Parathyroid hormone also has an effect: an increase in hormone level increases cAMP and decreases bicarbonate reabsorption.

Outline of Reactions in Proximal Tubule Lumen & Cells



The mechanism for H^+ secretion in the proximal tubule is described as a high capacity, low gradient system:

The high capacity refers to the large amount (4000 to 5000 mmols) of H^+ that is secreted per day. (The actual amount of H^+ secretion is 85% of the filtered load of HCO_3^-).

The low gradient refers to the low pH gradient as tubular pH can be decreased from 7.4 down to 6.7-7.0 only.

Though no net excretion of H^+ from the body occurs, this proximal mechanism is extremely important in acid-base balance. Loss of bicarbonate is equivalent to an acidifying effect and the potential amounts of bicarbonate lost if this mechanism fails are very large.

Ammonium Production

Ammonium (NH_4) is produced predominantly within the proximal tubular cells. The major source is from glutamine which enters the cell from the peritubular capillaries (80%) and the filtrate (20%). Ammonium is produced from glutamine by the action of the enzyme glutaminase. Further ammonium is produced when the glutamate is metabolised to produce alpha-ketoglutarate. This molecule contains 2 negatively-charged carboxylate groups so further metabolism of it in the cell results in the production of 2 HCO_3^- anions. This occurs if it is oxidised to CO_2 or if it is metabolised to glucose.

The pKa for ammonium is so high (about 9.2) that both at extracellular and at intracellular pH, it is present entirely in the acid form NH_4^+. The previous idea that lipid soluble NH_3 is produced in the tubular cell, diffuses into the tubular fluid where it is converted to water soluble NH_4^+ which is now trapped in the tubule fluid is incorrect.

The subsequent situation with ammonium is complex. Most of the ammonium is involved in cycling within the medulla. About 75% of the proximally produced ammonium is removed from the tubular fluid in the medulla so that the amount of ammonium entering the distal tubule is small. The thick ascending limb of the loop of Henle is the important segment for removing ammonium. Some of the interstitial ammonium returns to the late proximal tubule and enters the medulla again (ie recycling occurs).

An overview of the situation so far is that:

- The ammonium level in the DCT fluid is low because of removal in the loop of Henle
- Ammonium levels in the medullary interstitium are high (and are kept high by the recycling process via the thick ascending limb and the late PCT)
- Tubule fluid entering the medullary collecting duct will have a low pH if there is an acid load to be excreted (and the phosphate buffer has been titrated down.

If H^+ secretion continues into the medullary collecting duct this would reduce the pH of the luminal fluid further. A low pH greatly augments transfer of ammonium from the medullary interstitium into the luminal fluid as it passes through the medulla. The lower the urine pH, the higher the ammonium excretion and this ammonium excretion is augmented further if an acidosis is present. This augmentation with acidosis is 'regulatory' as the increased ammonium excretion by the kidney tends to increase extracellular pH towards normal.

If the ammonium returns to the blood stream it is metabolised in the liver to urea (Krebs-Henseleit cycle) with net production of one hydrogen ion per ammonium molecule.

Note

Section 2.4.7 discusses the role of urinary ammonium excretion.

Distal Tubular Mechanism

This is a low capacity, high gradient system which accounts for the excretion of the daily fixed acid load of 70 mmols/day. The maximal capacity of this system is as much as 700 mmols/day but this is still low compared to the capacity of the proximal tubular mechanism to secrete H^+. It can however decrease the pH down to a limiting pH of about 4.5 : this represents a thousand-fold (ie 3 pH units) gradient for H^+ across the distal tubular cell. The maximal capacity of 700 mmols/day takes about 5 days to reach.

The processes involved are:-

- Formation of titratable acidity (TA)
- Addition of ammonium (NH_4^+) to luminal fluid
- Reabsorption of Remaining Bicarbonate

1. Titratable Acidity

H^+ is produced from CO_2 and H_2O (as in the proximal tubular cells) and actively transported into the distal tubular lumen via a H^+-ATPase pump. Titratable acidity represents the H^+ which is buffered mostly by phosphate which is present in significant concentration. Creatinine (pKa approx 5.0) may also contribute to TA. At the minimum urinary pH, it will account for some of the titratable acidity. If ketoacids are present, they also contribute to titratable acidity. In severe diabetic ketoacidosis, beta-hydroxybutyrate (pKa 4.8) is the major component of TA.

The TA can be measured in the urine from the amount of sodium hydroxide needed to titrate the urine pH back to 7.4 hence the term titratable acidity.

2. Addition of Ammonium

As discussed previously, ammonium is predominantly produced by proximal tubular cells. This is advantageous as the proximal cells have access to a high blood flow in the peritubular capillaries and to all of the filtrate and these are the two sources of the glutamine from which the ammonium is produced.

The medullary cycling maintains high medullary interstitial concentrations of ammonium and low concentrations of ammonium in the distal tubule fluid. The lower the urine pH, the more the amount of ammonium that is transferred from the medullary interstitium into the fluid in the lumen of the medullary collecting duct as it passes through the medulla to the renal pelvis. [Note: The medullary collecting duct is different from the distal convoluted tubule.]

The net effect of this is that the majority of the ammonium in the final urine was transferred from the medulla across the distal part of the tubule even though it was produced in the proximal tubule. [Simplistically but erroneously it is sometimes said that the ammonium in the urine is produced in the distal tubule cells.]

Ammonium is not measured as part of the titratable acidity because the high pK of ammonium means no H^+ is removed from NH_4^+ during titration to a pH of 7.4. Ammonium excretion in severe acidosis can reach 300 mmol/day in humans.

Ammonium excretion is extremely important in increasing acid excretion in systemic acidosis. The titratable acidity is mostly due to phosphate buffering and the amount of phosphate present is limited by the amount filtered (and thus the plasma concentration of phosphate). This cannot increase significantly in the presence of acidosis (though of course some additional phosphate could be released from bone) unless other anions with a suitable pKa are present. Ketoanions can contribute to a significant increase in titratable acidity but only in ketoacidosis when large amounts are present.

In comparison, the amount of ammonium excretion can and does increase markedly in acidosis. The ammonium excretion increases as urine pH falls and also this effect is markedly augmented in acidosis. Formation of ammonium prevents further fall in pH as the pKa of the reaction is so high.

In review

- Titratable acidity is an important part of excretion of fixed acids under normal circumstances but the amount of phosphate available cannot increase very much.
- Also as urine pH falls, the phosphate will be all in the dihyrogen form and buffering by phosphate will be at its maximum.
- A further fall in urine pH cannot increase titratable acidity (unless there are other anions such as keto-anions present in significant quantities)
- The above points mean that titratable acidity cannot increase very much (so cannot be important in acid-base regulation when the ability to increase or decrease renal H^+ excretion is required)
- In acidosis, ammonium excretion fills the regulatory role because its excretion can increase very markedly as urine pH falls.

A low urine pH itself cannot directly account for excretion of a significant amount of acid: for example, at the limiting urine pH of about 4.4, $[H^+]$ is a negligible 0.04 mmol/l. This is several orders of magnitude lower than H^+ accounted for by titratable acidity and ammonium excretion. (ie 0.04 mmol/l is insignificant in a net renal acid excretion of 70 mmols or more per day)

3. Reabsorption of Remaining Bicarbonate

On a typical Western diet all of the filtered load of bicarbonate is reabsorbed. The sites and percentages of filtered bicarbonate involved are:

- Proximal tubule 85%
- Thick ascending limb of Loop of Henle 10-15%
- Distal tubule 0-5%

The decrease in volume of the filtrate as further water is removed in the Loop of Henle causes an increase in $[HCO_3^-]$ in the remaining fluid. The process of HCO_3^- reabsorption in the thick ascending limb of the Loop of Henle is very similar to that in the proximal tubule (ie apical Na^+-H^+ antiport and basolateral Na^+-HCO_3^- symport and Na^+-K^+ ATPase). Bicarbonate reabsorption here is stimulated by the presence of luminal frusemide. The cells in this part of the tubule contain carbonic anhydrase.

Any small amount of bicarbonate which enters the distal tubule can also be reabsorbed. The distal tubule has only a limited capacity to reabsorb bicarbonate so if the filtered load is high and a large amount is delivered distally then there will be net bicarbonate excretion.

The process of bicarbonate reabsorption in the distal tubule is somewhat different from in the proximal tubule:

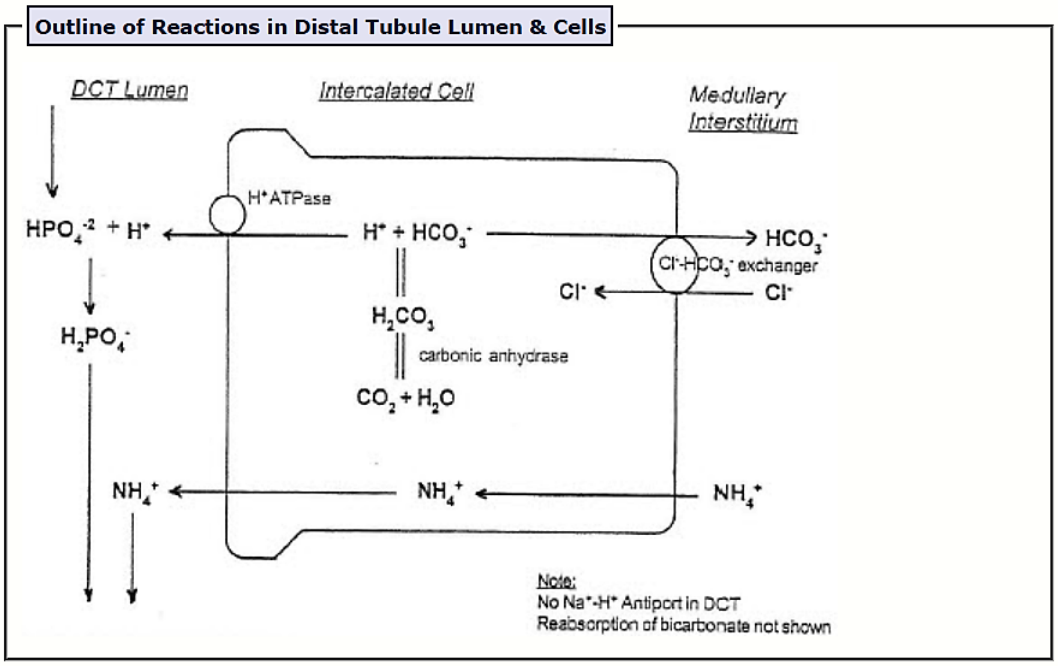
- H^+ secretion by the intercalated cells in DCT involves a H^+-ATPase (rather than a Na^+-H^+ antiport)
- HCO_3^- transfer across the basolateral membrane involves a HCO_3^- -Cl^- exchanger (rather than a Na^+-HCO_3^- symport)

The net effect of the excretion of one H^+ is the return of one HCO_3^- and one Na^+ to the blood stream. The HCO_3^-effectively replaces the acid anion which is excreted in the urine.

The net acid excretion in the urine is equal to the sum of the TA and $[NH_4^+]$ minus $[HCO_3^-]$ (if present in the urine). The $[H^+]$ accounts for only a very small amount of the H^+ excretion and is not usually considered in the equation (as mentioned earlier).

In metabolic alkalosis, the increased bicarbonate level will result in increased filtration of bicarbonate provided the GFR has not decreased. The kidney is normally extremely efficient at excreting excess bicarbonate but this capacity can be impaired in certain circumstances. (See Section 7.2 and 7.3)

Outline of Reactions in Distal Tubule Lumen & Cells



Regulation of Renal H^+ Excretion

The discussion above has described the mechanisms involved in renal acid excretion and mentioned some factors which regulate acid excretion.

The major factors which regulate renal bicarbonate reabsorption and acid excretion are:

1. Extracellular volume

Volume depletion is associated with Na^+ retention and this also enhances HCO_3^- reabsorption. Conversely, ECF volume expansion results in renal Na^+ excretion and secondary decrease in HCO_3^- reabsorption.

2. Arterial pCO_2

An increase in arterial pCO_2 results in increased renal H^+ secretion and increased bicarbonate reabsorption. The converse also applies. Hypercapnia results in an intracellular acidosis and this results in enhanced H^+ secretion. The cellular processes involved have not been clearly delineated. This renal bicarbonate retention is the renal compensation for a chronic respiratory acidosis.

3. Potassium & Chloride Deficiency

Potassium has a role in bicarbonate reabsorption. Low intracellular K^+ levels result in increased HCO_3^- reabsorption in the kidney. Chloride deficiency is extremely important in the maintenance of a metabolic alkalosis because it prevents excretion of the excess HCO_3^- (ie now the bicarbonate instead of chloride is reabsorbed with Na^+ to maintain electroneutrality). (See discussion in Section 7.3)

4. Aldosterone & cortisol (hydrocortisone)

Aldosterone at normal levels has no role in renal regulation of acid-base balance. Aldosterone depletion or excess does have indirect effects. High aldosterone levels result in increased Na^+ reabsorption and increased urinary excretion of $H^+$and K^+ resulting in a metabolic alkalosis. Conversely, it might be thought that hypoaldosteronism would be associated with a metabolic acidosis but this is very uncommon but may occur if there is coexistent significant interstitial renal disease.

5. Phosphate Excretion

Phosphate is the major component of titratable acidity. The amount of phosphate present in the distal tubule does not vary greatly. Consequently, changes in phosphate excretion do not have a significant regulatory role in response to an acid load.

6. Reduction in GFR

It has recently been established that a reduction in GFR is a very important mechanism responsible for the maintenance of a metabolic alkalosis. The filtered load of bicarbonate is reduced proportionately with a reduction in GFR.

7. Ammonium

The kidney responds to an acid load by increasing tubular production and urinary excretion of $N4H^+$. The mechanism involves an acidosis-stimulated enhancement of glutamine utilisation by the kidney resulting in increased production of NH_4^+ and HCO_3^- by the tubule cells. This is very important in increasing renal acid excretion during a chronic metabolic acidosis. There is a lag period: the increase in ammonium excretion takes several days to reach its maximum following an acute acid load. Ammonium excretion can increase up to about 300 mmol/day in a chronic metabolic acidosis so this is important in renal acid-base regulation in this situation. Ammonium excretion increases with decreases in urine pH and this relationship is markedly enhanced with acidosis.

What is the Role of Urinary Ammonium Excretion?

There are different views on the true role of NH_4^+ excretion in urine. How can the renal excretion of ammonium which has a pK of 9.2 represent H^+ excretion from the body?

One school says the production of ammonium from glutamine in the tubule cells results in production of alpha-ketoglutarate which is then metabolised in the tubule cell to new bicarbonate which is returned to the blood. The net effect is the return of one bicarbonate for each ammonium excreted in the urine. By this analysis, the excretion of ammonium is equivalent to the excretion of acid from the body as one plasma H^+ would be neutralised by one renal bicarbonate ion for each ammonium excreted. Thus an increase in ammonium excretion as occurs in metabolic acidosis is an appropriate response to excrete more acid.

The other school says this is not correct. The argument is that metabolism of alpha-ketogluarate in the proximal tubule cells to produce this new HCO_3^- merely represents regeneration of the HCO_3^- that was neutralised by the H^+produced when alpha-ketoglutarate was metabolised to glutamate in the liver originally so there can be no direct effect on net H^+ excretion. The key to understanding is said to lie in considering the role of the liver. Consider the following:

Every day protein turnover results in amino acid degradation which results in production of HCO_3^- and NH_3^+. For a typical 100g/day protein diet, this is a net production of 1,000mmol/day of HCO_3^- and 1,000mmol/day of NH_4^+. (These are produced in equal amounts by neutral amino acids as each contains one carboxylic acid group and one amino group.) The high pK of the ammonium means it cannot dissociate to produce one H^+ to neutralise the HCO_3^- so consequently amino acid metabolism is powerfully alkalinising to the body. The body now has two major problems:

- How to get rid of 1,000mmol/day of alkali?
- How to get rid of 1,000mmol/day of the highly toxic ammonium?

The solution is to react the two together and get rid of both at once. This process is hepatic urea synthesis (Krebs-Henseleit cycle). The cycle consumes significant energy but solves both problems. Indeed, the cycle in effect acts as a ATP-dependent pump that transfers H^+ from the very weak acid NH_4^+ to HCO_3^- . The overall reaction in urea synthesis is:

$$2NH_4^+ + 2HCO_3^- \Rightarrow urea + CO_2 + 3H_2O$$

The body has two ways in which it can remove NH_4^+:

- Urea synthesis in the liver
- Excretion of NH_4^+ by the kidney

The key thing here is that the acid-base implications of these 2 mechanisms are *different*.

For each ammonium converted to urea in the liver one bicarbonate is consumed. For each ammonium excreted in the urine, there is one bicarbonate that is not neutralised by it (during urea synthesis) in the liver. So overall, urinary excretion of ammonium is equivalent to net bicarbonate production -but by the liver! Indeed in a metabolic acidosis, an increase in urinary ammonium excretion results in an exactly equivalent net amount of hepatic bicarbonate (produced from amino acid degradation) available to the body. So the true role of renal ammonium excretion is to serve as an alternative route for nitrogen elinination that has a different acid-base effect from urea production.

The role of glutamine is to act as the non-toxic transport molecule to carry NH_4^+ to the kidney. The bicarbonates consumed in the production of glutamine and then released again with renal metabolism of ketoglutarate are not important as there is no net gain of bicarbonate.

Overall: renal NH_4^+ excretion results indirectly in an equivalent amount of net hepatic HCO_3^- production.

Other points are:

- Glutamate metabolism in the proximal tubule converts ADP to ATP and the low availability of ADP limits the maximal rate of NH_4^+ production in the proximal tubule cells. Further as most ATP is consumed in the reabsorption of Na^+, then it is ultimately the amount of Na^+ reabsorbed in the proximal tubule that sets the upper limit for NH_4^+production.
- The anion that is excreted with the NH_4^+ is also important. Excretion of beta-hydroxybutyrate (instead of chloride) with NH_4^+ in ketoacidosis leads to a loss of bicarbonate as this anion represents a potential bicarbonate.

Finally: The role of urine pH in situations of increased acid secretion is worth noting. The urine pH can fall to a minimum value of 4.4 to 4.6 but as mentioned previously this itself represents only a negligible amount of free H^+.

As pH falls, the 3 factors involved in increased H^+ excretion are:

1. Increased ammonium excretion (increases steadily with decrease in urine pH and this effect is augmented in acidosis) [This is the *major and regulatory factor* because it can be increased significantly].

2. Increased titratable acidity:

- Increased buffering by phosphate (but negligible further effect on H^+ excretion if pH < 5.5 as too far from pKa so minimal amounts of HPO_4^{2-} remaining)
- Increased buffering by other organic acids (if present) may be important at lower pH values as their pKa is lower (eg creatinine, ketoanions)

(As discussed also in section 2.5.4, increases in TA are limited and are not as important as increases in ammonium excretion)

3. Bicarbonate reabsorption is complete at low urinary pH so none is lost in the urine (Such loss would antagonise the effects of an increased TA or ammonium excretion on acid excretion.)

Comment

The above discussion focuses on the 'traditional' approach to acid-base balance and a short-coming of that approach is that the explanations are wrong. The Stewart approach (seeChapter 10) provides the explanations and the insights into what is occurring. For example, the focus on excretion of H^+ and excretion of NH_4^+ by the kidney is misleading. 'Acid handling' by the kidney is mostly mediated through changes in Cl^- balance. NH_4^+ is a weak anion that when excreted with Cl^- allows the body to retain the strong ions Na^+ and K^+. The urinary excretion of Cl^- without excretion of an equivalent amount of strong ion results in a change in the SID (or 'strong ion difference') and it is this change which causes the change in plasma pH. The explanatory focus should be on the excretion of Cl^- without strong ions and not on the excretion of NH_4^+. See Chapter 10 for an introduction to the Stewart approach.

2.5: Acid-Base Role of the Liver

The liver is important in acid-base physiology and this is often overlooked. It is important because it is a metabolically active organ which may be either a significant net producer or consumer of hydrogen ions. The amounts of acid involved may be very large. The acid-base roles of the liver may be considered under the following headings:

- Carbon dioxide production from complete oxidation of substrates
- Metabolism of organic acid anions (such as lactate, ketones and amino acids)
- Metabolism of ammonium
- Production of plasma proteins (esp albumin)

Substrate Oxidation

Complete oxidation of carbohydrates and fat which occurs in the liver produces carbon dioxide but no fixed acids. As the liver uses 20% of the body's oxygen consumption, this hepatic metabolism represents 20% of the body's carbon dioxide production also. The CO_2 diffuses out of the liver and reactions in red cells result in production of H^+ and HCO_3^-.

Acid Anions

The metabolism of various organic anions in the liver results in consumption of H^+ and regeneration of the extracellular bicarbonate buffer. These anions may be:

- Exogenous (eg citrate in blood transfusion, acetate and gluconate from Plasmalyte 148 solution, lactate from Hartmann's solution), or
- Endogenous (eg lactate from active glycolysis or anaerobic metabolism, keto-acids produced in the liver)

The term acid anion is used because they are anions produced by dissociation of an acid.

That is: $HA \rightarrow H^+ + A^-$ (where HA is the acid and A^- is the acid anion).

The anions are the conjugate base of the acid (Bronsted-Lowry system) and are not themselves acids. This is an important distinction to make because they are often referred to as though they were acids and this leads to confusion.

If the endogenous production of these anions is followed by later consumption in the liver then there is no net production of acid or base because the H^+ produced (from the dissociation of the acid) is consumed when the anion is subsequently metabolised by the liver.

When these organic anions are exogenously administered (eg in intravenous fluids), administration of the anion (the conjugate base) without any H^+ occurs because the cation involved is Na^+. Any subsequent metabolism of these anions in the liver will consume H^+ and result in excess bicarbonate production. As an example, a metabolic alkalosis can result after a massive blood transfusion when the citrate anticoagulant is metabolised to bicarbonate. (The alkalosis is only transitory as the kidney normally excretes it rapidly- see Section 7.3). The important point to note is how some of these anions (eg lactate, acetate) are used in IV crystalloid solutions as a bicarbonate source (though this is indirect of course as the bicarbonate is only produced when they are metabolised in the body).

The situation with lactate sometimes causes confusion to students. The key point to remember is that lactic acid is an acid but lactate is a base. The administration of lactate in Hartmann's solution can never result in a lactic acidosis because it is a base and not an acid. The solution contains sodium lactate and not lactic acid. The lactate anion is the conjugate base of lactic acid and represents potential bicarbonate and not potential H^+.

So does this mean that Hartmann's solution can be used for volume resuscitation in patients with lactic acidosis?

Firstly, consider the following points:

- Hartmann's solution has a high [Na^+] (which restricts the fluid to the ECF) so it is a useful ECF replacement solution. Infusion of an appropriate amount can correct an intravascular volume deficiency.
- Lactate cannot buffer H^+ (to form lactic acid) at physiological pH as the pKa (3.86) of the reaction is too low.
- Normally, lactate can be metabolised in the liver and this results in the consumption of H^+ (or equivalently: production of HCO_3^-)
- Patients with lactic acidosis have inadequate hepatic metabolism of lactate so the production of HCO_3^- from the infused lactate is impaired. (So until this problem with hepatic metabolism can be corrected then the infused lactate cannot act as a bicarbonate

source).

The serum lactate level is used as an index of the severity of the lactic acidosis as each lactate generally means that one H^+ has been produced. If sodium lactate in Hartmann's solution is now given then the lactate level is not as useful a guide as now not all the lactate implies the presence of an equivalent amount of H^+ that was produced with it in the body.

So: Hartmann's solution is an excellent ECF replacement solution to correct hypovolaemia. If the circulation improves and hepatic metabolism of lactate returns to normal then bicarbonate will be generated and the solution indirectly assists in correcting the lactic acidosis as well. (But of course if this happened then the body would also metabolise the endogenously produced lactate and this would be the major factor in correction of the acidosis.) However, if this hepatic metabolism does not happen, then the infused lactate just interferes with the usefulness of serial lactate measurements as an serial index of severity of the acidosis.

Overall then, it is generally not the preferred ECF replacement solution. If it is the only solution readily available then it can be used and the infused lactate (a base) cannot worsen the acidaemia. The 'official' recommendation is to not use Hartmann's solution in patients with lactic acidosis. (As a point of interest, you might like to consider whether normal saline which contains the non-metabolisable chloride as the anion could possibly be any better!)

Endogenous Lactate

Some excess lactate is normally produced in certain tissues and 'spills over' into the circulation. This lactate can be taken up and metabolised in various tissues (eg myocardium) to provide energy. Only in the liver and the kidney can the lactate can be converted back to glucose (gluconeogenesis) as an alternative to metabolism to carbon dioxide. The glucose may re-enter the blood and be taken up by cells (esp muscle cells). This glucose-lactate-glucose cycling between the tissues is known as the Cori cycle. Typically there is no net lactate production which is excreted from the body. The renal threshold for lactate is relatively high and normally all the filtered lactate is reabsorbed in the tubules.

The total amount of lactate involved is large (1,500 mmols/day) in comparison to the net fixed acid production (1 to 1.5 mmols/kg/day). The metabolism of lactate in the liver indirectly eliminates the H^+ produced subsequent to the tissue production of lactate. Lactic acidosis will result if this hepatic metabolism is not adequate. (See Lactic Acidosis).

Metabolism of lactate sourced from IV Hartmann's solution also results in a net consumption of H^+, but as this lactate was associated with Na^+, the overall result is a net bicarbonate production. Effectively, metabolism of this lactate results in generation of an equivalent amount of bicarbonate. The situation is similar with metabolism of citrate and gluconate in other IV fluids.

Ketones

Keto-acids such as acetoacetate are produced in hepatic mitochondria due to incomplete oxidation of fatty acids. The ketones are released into the blood stream and metabolised in the tissues (esp muscle). Hepatic production of ketoacids produces H^+ and the oxidation of the keto-anion in the tissues consumes H^+ and thereby regenerates the HCO_3^- which had buffered it in the blood stream. In severe diabetic ketoacidosis, the keto-acid production may exceed 1,200 mmols/day in an adult! In healthy individuals, a modest amount of excess ketones are produced only with significant fasting. (See also Section 8.2 Ketoacidosis)

Amino Acids

Amino acids are all dipolar ions (zwitterions) at physiological pH as they all have both COO^- and NH_3^+ groups. These are the groups that participate in formation of the peptide bond. As these groups are present on all amino acids, then the oxidation of these groups in all amino acids will result in a production of equal amounts of bicarbonate and ammonium: typically 1,000 mmol/day of each. This aspect and the acid-base implications has been covered in the previous section 2.4 and will not be repeated here.

Amino acids also have side chains and incomplete metabolism of some of these has acid-base effects - eg side chain metabolism can result in a net fixed acid production. Sulphuric acid is produced from metabolism of methionine and cysteine. This is a major component of the net fixed acid load.

Arginine, lysine and histidine have nitrogen in their side chains so their metabolism generates H^+ . Glutamate and aspartate have carboxylic acid groups (COO^-) in their side chains so their metabolism consumes H^+ (and therefore produces HCO_3^-). The balance of these reactions is a net daily production of H^+ and acid anions of 50 mmol/day (ie production of 210 mmols/day and consumption of 160 mmol/day). The liver is the major net producer of fixed acids.

Metabolism of Ammonium

See section 2.4 for details. The conversion of NH_4^+ to urea in the liver results in an equivalent production of H^+. Infusions of NH_4Cl have an acid loading effect because of this hepatic metabolism. H^+ cannot be released directly from NH_4^+ in the body because the high pKa of the reaction means that NH_3 is present in only minute quantities at pH 7.4.

Synthesis of Plasma Proteins

The liver is the major producer of plasma proteins as nearly all (except the immunoglobulins) are produced here. Albumin synthesis accounts for 50% of all hepatic protein synthesis. The acid-base roles of albumin are:

- it is the major unmeasured anion in the plasma which contributes to the normal value of the anion gap
- extracellular buffer for CO_2 and fixed acids
- abnormal levels can cause a metabolic acid-base disorder

Haemoglobin is more important than albumin for buffering H^+ produced from CO_2. Also, bicarbonate is more important than albumin as a buffer for fixed acids.

The role of low or high albumin levels in causing acid-base disorders is difficult to explain within the traditional framework of acid-base analysis. The role of albumin as the major non-volatile weak acid present in plasma and its significance in acid-base balance is discussed in Section 10. Hypoalbuminaemia causes a metabolic alkalosis.

Overview

Consideration of all these factors shows that the liver has an extremely important role in normal acid-base physiology. The traditional emphasis on the lung and kidney as the organs of acid-base regulation should be extended to a new concept of the importance of the lung-liver-kidney complex.

Hepatic disorders are often associated with acid-base disorders. The most common disturbances in chronic liver disease are respiratory alkalosis (most common) and metabolic alkalosis.

2.6: Regulation of Intracellular Hydrogen Ion Concentration

Importance of Intracellular [H^+]

The most important [H^+] for the body is the intracellular [H^+]

Why? Because of its profound effects on metabolism and other cell processes which occur due to the effects of [H^+] on the degree of ionisation of intracellular compounds. Specifically:

- **Small molecule effect**: Intracellular trapping function -due to the ionisation of metabolic intermediates.
- **Large molecule effect**: Effects on protein function: The function of many intracellular proteins (esp the activities of enzymes) is altered by effects on the ionisation of amino acid residues (esp histidine residues)

In assessment of acid-base disorders, the clinician is always looking from the outside in.

Why? For 2 reasons:

- Ease of sampling: Arterial blood is easy to sample. It is much more difficult to obtain an intracellular sample
- Arterial blood gives results which can be considered a sort of 'average value'. It would be more difficult to find an intracellular sample that could be considered to be 'representative' of all ICF.

The basis of the clinical approach is to use the extracellular results to make inferences about intracellular conditions.

Both carbon dioxide and the fixed acids are produced intracellularly and move down concentration gradients to the ECF. Carbon dioxide crosses cell membranes very easily and it is important to realise that CO_2 can move in or out depending on the gradient across the cell membrane.

In diabetic ketoacidosis (DKA), the ketoacids are produced in the liver and not in every cell in the body. The intracellular alkalinising effect of the compensatory hypocapnia that occurs will however affect every cell and not just the hepatocytes. Does this mean that DKA produces an extracellular rise in [H^+] but the opposite change in most tissues (excluding the liver) where the net effect is a fall in intracellular [H^+] due to the compensatory hypocapnia? Ketoacids can enter most cells and be used as an energy substrate and this would initially cause a fall in intracellular [H^+]. Intracellular pH may not be altered much once maximal respiratory compensation has been achieved because of these opposing effects. It is possible that though the maximal respiratory compensation does not fully correct the extracellular acidaemia, it may be sufficient to prevent much change in intracellular pH. This discussion is speculative and has not been fully investigated. The purpose here is merely to show that looking at acid-base disorders from the intracellular viewpoint can lead to ideas which are different from those of the conventional extracellular viewpoint.

The hypothesis of Rahn and coworkers (see section 1.6) is that the intracellular pH is maintained at about the pH of neutrality (pN) because this is the pH at which metabolite intermediates are all charged and trapped inside the cell. Extracellular pH is higher by 0.5 to 0.6 pH units and this represents about a fourfold gradient favouring the exit of hydrogen ion from the cell. Measurements of intracellular pH in a variety of mammalian skeletal muscle preparations have found pH values mostly in the 6.8 to 7.1 range. Values found in other tissues have sometimes been higher depending on the experimental arrangements. This value is a little higher then the pN (6.8 at 37°C) but is still able to effectively trap intermediates within the cell. A further complication is that intracellular pH is not uniform and measurements have been able to give only mean pH values for the whole intracellular compartment. These mean values may be misleading as there may be acidic and basic areas within different cell areas or organelles and it is this local pH which is important.

Because of the powerful effects of intracellular [H^+] on metabolism it is useful to consider the processes which attempt to maintain it at a stable value. This assists us in making inferences about intracellular events from an extracellular acid-base sample.

The processes responsible for maintaining a stable intracellular pH are:

- Intracellular buffering
- Adjustment of arterial pCO_2
- Loss of fixed acids from the cell into the extracellular fluid

Intracellular Buffering

This term refers to those rapid reversible processes occurring within the intracellular fluid which minimise changes in pH in response to an acid or alkali stress. The term buffering is used here in a much broader sense then that discussed in section 2.2 where it was used to refer to the process of physicochemical buffering alone. Intracellularly, there are other rapid and reversible processes which act to minimise acute changes in intracellular [H^+] and which can usefully be considered a form of buffering. Intracellular buffering includes the following processes:

- Physicochemical buffering
- Metabolic buffering
- Organellar buffering

Experiments have shown that these three processes can neutralise over 99.99% of any acid or alkali added acutely to the intracellular fluid! These processes provide rapid but temporary relief from acute intracellular acid-base changes.

Physicochemical buffering

In quantitative terms this is the most important process which resists change in intracellular [H^+]. (Physicochemical buffering is discussed in section 2.2.)

In the intracellular environment, **proteins** (particularly imidazole of histidine) and **phosphates** (organic and inorganic) are the most important buffers because they have a pK close to the normal intracellular pH and are present in the highest concentrations. The ICF is responsible for 97 to 99% of the body's total buffering of respiratory acid-base disorders. The intracellular contribution to buffering is less with metabolic disorders (60% for metabolic acidosis; 30% for metabolic alkalosis) but is still substantial. The bicarbonate system is present intracellularly and is involved in buffering for metabolic acidosis. Intracellular amino acids provide a small amount of the buffering. Free histidine has a pKa of about 6.0 which is lower than the average 6.8 value when it is incorporated into proteins. A small amount of H^+ is used up into producing alanine and glutamine.

Metabolic buffering

Metabolic (or biochemical) buffering refers to changes in the metabolism of acids within the cell which tend to oppose changes in [H^+].

Changes in intracellular pH affect the activity of enzymes. The net effect of differential changes in enzyme activity in various pathways (including the main glycolytic pathway) is an alteration in the levels of acidic metabolites in such a way that changes in [H^+] are minimised. For example, the metabolism of lactate to glucose or to water and CO_2 (which can readily leave the cell) will effectively remove H^+ from intracellular fluid. This is clearly not simply physicochemical buffering. Consider another example: If intracellular pCO_2 decreases due to acute hyperventilation, this produces a relative intracellular alkalosis. Changes in enzyme activities result in increased levels of lactate, pyruvate and other acidic intermediates. This occurs quickly, is reversible and tends to minimise the change in intracellular pH. Metabolic buffering can account for a hydrogen ion consumption up to half of that due to the process of physicochemical buffering within the cell.

Organellar buffering

This refers to the acute sequestration in or release of H^+ from intracellular organelles in a direction which opposes the change of intracellular pH.

The overall contribution of this process to intracellular buffering is not clear.

The energy released during the electron transfers in the respiratory chain in mitochondria is used to extrude hydrogen ions. The energy is stored as a proton gradient across the inner mitochondrial membrane. When the hydrogen ions re-enter via membrane-bound ATPase, the energy is released and used to produce ATP from ADP. Mitochondria extrude a total of six protons for every oxygen atom that is reduced to water. A rise in cytoplasmic [H^+] provides additional H^+which can enter the mitochondria. This will contribute to ATP formation via the inner membrane proton gradient and will buffer changes in cytoplasmic pH.

Lysosomes contain enzymes which have maximal activity at acidic pH. In some experiments, the internal pH of lysosomes increases when extracellular pH increases. This can be interpreted as a mechanism which assists in buffering changes in cytoplasmic pH. The overall significance of this process is not established.

Adjustment of Arterial pCO_2

Carbon dioxide is produced in huge quantities by cells: typically 12,000 (basally) to as much as 15,000 to 20,000 mmols/day with typical levels of activity. An efficient system exists for its removal. The arterial pCO_2 is of critical importance for intracellular acid-base balance because of both its potential to change rapidly and because of its effectiveness in altering intracellular $[H^+]$.

Carbon dioxide crosses cell membranes easily. A change in ventilation affects the arterial pCO_2 level and the intracellular pCO_2 throughout the body. The compensatory response to a metabolic acid-base disorder is to increase alveolar ventilation and thus decrease arterial pCO_2 levels. This changed pCO_2 will affect intracellular pH and this effect is rapid. For example an acute metabolic acidosis will be compensated by a fall in pCO_2 which will minimise the intracellular effects of the acidosis.

Fixed Acid Extrusion from Cells

Metabolism (an intracellular event) produces excess acid. In the long term, hydrogen ion balance within the cell is dependent on loss of these acids from the cell. The various buffering processes discussed previously are only short-term measures as the acid is not removed from the cell.

Experiments show that cells respond to an acute acid load (eg hypercapnia) by an initial fall in pH (minimised by intracellular buffering discussed above) but that the pH subsequently returns slowly towards normal despite the continued presence of the acid stress. This is due to net acid extrusion from the cell across the cell membrane. This process involves a coupled exchange of ions (H^+, HCO_3^-, Na^+ and Cl^-) across the membrane. The process does not affect the membrane potential so it must be electroneutral. Various models have been proposed but the relative importance of these in vertebrates has not been fully established. The response of cells to an alkaline load is much less developed and much less studied than the response to an acid load.

The movement of H^+ or HCO_3^- across the membrane is not important in changing $[H^+]$ (see discussion in section 10.6) but the movement of strong electrolytes (such as Na^+, Cl^-, lactate) will alter intracellular $[H^+]$. The important point is that it is the movement of the acid anion out of the cell (rather than hydrogen ion per se) that results in a net loss of fixed acid from the cell. A similar situation applies in the kidney: the emphasis should be on the urinary loss of the acid anions (with the H^+ buffered on phosphate of ammonium) rather than hydrogen ion itself. The traditional use of hydrogen ion in explanations must be quantitatively equivalent but does serve to disguise the true nature of the process.

In summary:

In experiments where cells are subjected to an acid load, they respond by an increase in the rate of acid extrusion from the cell. This returns intracellular $[H^+]$ towards normal. The response is not as rapid as the mechanisms involved in intracellular buffering.

CHAPTER OVERVIEW

3: Acid-Base Disorders

3.1: Terminology of Acid-Base Disorders

Definitions

The definitions of the terms used here to describe acid-base disorders are those suggested by the Ad-Hoc Committee of the New York Academy of Sciences in 1965. Though this is over 35 years ago, the definitions and discussion remain valid today.

Basic Definitions

- **Acidosis** - an abnormal process or condition which would lower arterial pH if there were no secondary changes in response to the primary aetiological factor.
- **Alkalosis** - an abnormal process or condition which would raise arterial pH if there were no secondary changes in response to the primary aetiological factor.
- **Simple (Acid-Base) Disorders** [1] are those in which there is a single primary aetiological acid-base disorder.
- **Mixed (acid-Base) Disorders** [2,3] are those in which two or more primary aetiological disorders are present simultaneously.
- **Acidaemia** - $Arterial\, pH < 7.36\ (ie\ [H^+] > 44nM)$
- **Alkalaemia** - $Arterial\, pH > 7.44\ (ie\ [H^+] < 36nM)$

The meaning of the terms acid, base, [H^+] and pH has been discussed previously in Sections 1.2 and 1.3.

An acidaemia of course must be due to an acidosis so is an indicator of the presence of this disorder. In mixed acid-base disorders, there may be co-existing disorders each having opposite effects on the ECF pH so a quick check of the arterial pH is insufficient to fully indicate all primary acid-base disorders. In mixed disorders, it does indicate in general terms the most severe disorder. That is, if the arterial pH is 7.2 (an acidaemia), there must be an acidosis present, and any alkalosis present must be of lesser magnitude. (This idea is the basis of an initial step in the systematic approach to analysis of arterial blood gas results).

The Disorders

The 4 simple acid-base disorders are:

- Respiratory acidosis
- Respiratory alkalosis
- Metabolic acidosis
- Metabolic alkalosis.

Respiratory disorders are caused by abnormal processes which tend to alter pH because of a primary change in pCO_2levels.

Metabolic disorders are caused by abnormal processes which tend to alter pH because of a primary change in [HCO_3^-].

Correct Terminology for Compensatory Responses

Secondary or compensatory responses should NOT be designated as acidosis or alkalosis.

The committee recommended the use of the adjectives secondary or compensatory to describe the change in the composition of the blood or the process (eg ventilation) but not to modify the nouns acidosis or alkalosis. This is the practice adopted here.

Many published articles refer to compensatory processes as though they were primary processes. This lazy and incorrect use of these terms is extremely confusing so caution must be exercised and ultimately one should not be too pedantic in insisting on correct terminology in others as the practice is widespread in the clinical literature.

For example: A patient with diabetic ketoacidosis and compensatory Kussmaul respirations should be described as having a 'metabolic acidosis with compensatory hyperventilation'.

The use of the term secondary respiratory alkalosis in this case would be wrong as the change is a compensatory one and not a primary process and so by definition then it cannot be an alkalosis.

It is possible that a patient such as this could have a mixed disorder with a respiratory acid-base disorder as well as the metabolic acidosis. The interpretation of these more complicated cases is discussed in Section 8.4.

The terms acidaemia and alkalaemia may be used to describe the net pH deviation in the blood but the *Ad-Hoc Committee* recommended the reporting of the actual pH value or the use of the terms low, high and normal as preferable.

Disorders are defined by their ECF Effects

The clinical acid-base disorders are defined by their effects in the extracellular fluid (or more specifically, in the arterial blood).

The disorder may arise because of changes intracellularly (eg excess lactate production) but the effect extracellularly is what is able to be easily measured.

Despite the definitions of acidosis and alkalosis above, it is common to speak of an 'intracellular acidosis' or an 'intracellular alkalosis'. This use is not consistent with the definitions above but as there are no other satisfactory terms available so this common practice is followed here.

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3.2: The Anion Gap

Definition & Clinical Use

The *anion gap* (AG) represents the concentration of all the unmeasured anions in the plasma. The negatively charged proteins account for about 10% of plasma anions and make up the majority of the unmeasured anion represented by the anion gap under normal circumstances. The acid anions (e.g., lactate, acetoacetate, sulfate) produced during a metabolic acidosis are not measured as part of the usual laboratory biochemical profile. The H^+ produced reacts with bicarbonate anions (buffering) and the CO_2 produced is excreted via the lungs (respiratory compensation). The net effect is a decrease in the concentration of measured anions (i.e., HCO_3^-) and an increase in the concentration of unmeasured anions (the acid anions) so the anion gap increases.

AG is calculated from the following formula:

$$\text{Anion Gap} = [Na^+] - [Cl^-] - [HCO_3^-] \tag{3.2.1}$$

Reference range is 8 to 16 mmol/l. An alternative formula which includes K^+ is sometimes used particularly by Nephrologists. In *Renal Units*, K^+ can vary over a wider range and have more effect on the measured Anion Gap. This alternative formula is:

$$AG = [Na^+] + [K^+] - [Cl^-] - [HCO_3^-] \tag{3.2.2}$$

The reference range is slightly higher with this alternative formula. The K^+ is low relative to the other three ions and it typically does not change much so omitting it from the equation does not have much clinical significance.

Major Clinical Uses of the Anion Gap

- To signal the presence of a metabolic acidosis and confirm other findings
- Help differentiate between causes of a metabolic acidosis: high anion gap versus normal anion gap metabolic acidosis. In an inorganic metabolic acidosis (eg due to HCl infusion), the infused Cl^- replaces HCO_3^- and the anion gap remains normal. In an organic acidosis, the lost bicarbonate is replaced by the acid anion which is not normally measured. This means that the AG is increased.
- To assist in assessing the biochemical severity of the acidosis and follow the response to treatment

The Anion Gap can be Misleading

It is determined from a calculation involving three other measured ions, so the error with an AG is much higher than that of a single electrolyte determination. The commonest cause of a low anion gap is laboratory error in the electrolyte determinations. The 95% error range for the AG is about +/- 5 mmol/l (i.e., a 10 mmols/l range!)

- If the AG is greater than 30 mmol/l, than it invariably means that a metabolic acidosis is present.
- If the AG is in the range 20 to 29 mmol/l, then about one third of these patients will not have a metabolic acidosis.

Other clinical guides should also be used in deciding on the presence and severity of a metabolic acidosis. Significant lactic acidosis may be associated with an anion gap which remains in the reference range. Lactate levels of 5 to 10 mmols/litre are associated with a high mortality if associated with sepsis, but the AG may be reported as within the reference range in as many as 50% of these cases! (Dorwart & Chalmers 1975) (See also discussion in Section 8.4 regarding lactate-chloride antiport.)

The anion gap is useful especially if very elevated or used to confirm other findings. Causes of a high anion gap acidosis can be sorted out more specifically by using other investigations in addition to the history and examination of the patient. Investigations which may be very useful are:

- Lactate
- Creatinine
- Plasma glucose
- Urine ketone test

Key Fact: Hypoalbuminaemia causes a low anion gap

Albumin is the major unmeasured anion and contributes almost the whole of the value of the anion gap. Every one gram decrease in albumin will decrease anion gap by 2.5 to 3 mmoles. A normally high anion gap acidosis in a patient with hypoalbuminaemia may appear as a normal anion gap acidosis. This is particularly relevant in Intensive Care patients where

lower albumin levels are common. A lactic acidosis in a hypoalbuminaemic ICU patient will commonly be associated with a normal anion gap.

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3.3: The Delta Ratio

Definition

This Delta Ratio is sometimes useful in the assessment of metabolic acidosis [1,2,3,4]. As this concept is related to the anion gap (AG) and buffering, it will be discussed here before a discussion of metabolic acidosis. The Delta Ratio is defined as:

$$\text{Delta Ratio} = \frac{\text{Increase in Anion Gap}}{\text{Decrease in bicarbonate}} \tag{3.3.1}$$

Others[5] have used the *delta gap* (defined as rise in AG minus the fall in bicarbonate), but this uses the same information as the delta ratio and has does not offer any advantage over it.

How is this useful?

In order to understand this, consider the following:

If one molecule of metabolic acid (HA) is added to the ECF and dissociates, the one H^+ released will react with one molecule of HCO_3^- to produce CO_2 and H_2O. This is the process of buffering. The net effect will be an increase in unmeasured anions by the one acid anion A^- (ie anion gap increases by one) and a decrease in the bicarbonate by one.

Now, if all the acid dissociated in the ECF and all the buffering was by bicarbonate, then the increase in the AG should be equal to the decrease in bicarbonate so the ratio between these two changes (which we call the delta ratio) should be equal to one. The delta ratio quantifies the relationship between the changes in these two quantities.

Example 3.3.1

If the AG was say 26 mmols/l (an increase of 14 from the average value of 12), it might be expected that the HCO_3^-would fall by the same amount from its usual value (ie 24 - 14 = 10mmols/l). If the actual HCO_3^- value was different from this it would be indirect evidence of the presence of certain other acid-base disorders (see Guidelines below).

Problem

A problem though: the above assumptions about all buffering occurring in the ECF and being totally by bicarbonate are not correct. Fifty to sixty percent of the buffering for a metabolic acidosis occurs intracellularly. This amount of H^+ from the metabolic acid (HA) does not react with extracellular HCO_3^- so the extracellular [HCO_3^-] will not fall as far as originally predicted. The acid anion (ie A^-) however is charged and tends to stay extracellularly so the increase in the anion gap in the plasma will tend to be as much as predicted.

Overall, this significant intracellular buffering with extracellular retention of the unmeasured acid anion will cause thevalue of the delta ratio to be greater than one in a high AG metabolic acidosis.

Caution

Inaccuracies can occur for several reasons, for example:

- Calculation requires measurement of 4 electrolytes, each with a measurement error
- Changes are assessed against 'standard' normal values for both anion gap and bicarbonate concentration.

Sometimes these errors combine to produce quite an incorrect value for the ratio. As an example, patients with hypoalbuminaemia have a lower 'normal' value for anion gap so using the standard value of 12 to compare against must lead to an error. Do not over-interpret your result and look for supportive evidence especially if the diagnosis is unexpected.

Guidelines for Use of the Delta Ratio

Some general guidelines for use of the delta ratio when assessing metabolic acid-base disorders in provided in the table below.

Delta Ratio	Assessment Guideline
< 0.4	Hyperchloraemic normal anion gap acidosis
0.4 - 0.8	Consider combined high AG & normal AG acidosis BUT note that the ratio is often <1 in acidosis associated with renal failure

Delta Ratio	Assessment Guideline
1 to 2	Usual for uncomplicated high-AG acidosis Lactic acidosis: average value 1.6 DKA more likely to have a ratio closer to 1 due to urine ketone loss (esp if patient not dehydrated)
> 2	Suggests a pre-existing elevated HCO_3 level so consider: • a concurrent metabolic alkalosis, or • a pre-existing compensated respiratory acidosis

Warning

Be very wary of over-interpretation - Always check for other evidence to support the diagnosis as an unexpected value without any other evidence should always be treated with great caution.

A high ratio

A high delta ratio can occur in the situation where the patient had quite an elevated bicarbonate value at the onset of the metabolic acidosis. Such an elevated level could be due to a pre-existing metabolic alkalosis, or to compensation for a pre-existing respiratory acidosis (ie compensated chronic respiratory acidosis). With onset of a metabolic acidosis, using the 'standard' value of 24 mmol/l as the reference value for comparison when determining the 'decrease in bicarbonate' will result in an odd result.

A low ratio

A low ratio occurs with hyperchloraemic (or normal anion gap) acidosis. The reason here is that the acid involved is effectively hydrochloric acid (HCl) and the rise in plasma [chloride] is accounted for in the calculation of anion gap (ie chloride is a 'measured anion'). The result is that the 'rise in anion gap' (the numerator in the delta ration calculation) does not occur but the 'decrease in bicarbonate' (the denominator) does rise in numerical value. The net of of both these changes then is to cause a marked drop in delta ratio, commonly to < 0.4

Lactic acidosis

In lactic acidosis, the average value of the delta ratio in patients has been found to be is 1.6 due to intracellular buffering with extracellular retention of the anion. As a general rule, in uncomplicated lactic acidosis, the rise in the AG should always exceed the fall in bicarbonate level.

Diabetic ketoacidosis

The situation with a pure diabetic ketoacidosis is a special case as the urinary loss of ketones decreases the anion gap and this returns the delta ratio downwards towards one. A further complication is that these patients are often fluid resuscitated with 'normal saline' solution which results in a increase in plasma chloride and a decrease in anion gap and development of a 'hyperchloraemic normal anion gap acidosis' superimposed on the ketoacidosis. The result is a further drop in the delta ratio.

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3.4: The Urinary Anion Gap

Definition

The cations normally present in urine are Na^+, K^+, NH_4^+, Ca^{2+} and Mg^{2+}. The anions normally present are Cl^-, HCO_3^-, sulfate, phosphate and some organic anions. Only Na^+, K^+ and Cl^- are commonly measured in urine so the other charged species are the unmeasured anions (UA) and cations (UC). Because of the requirement for macroscopic electroneutrality, total anion charge always equals total cation charge, so:

$$Cl^- + UA = Na^+ + K^+ + UC \tag{3.4.1}$$

Rearranging:

$$\text{Urinary Anion Gap} = (UA - UC) = [Na^+] + [K^+] - [Cl^-] \tag{3.4.2}$$

Clinical Use

Key Fact: The urinary anion gap can help to differentiate between GIT and renal causes of a hyperchloraemic metabolic acidosis.

It has been found experimentally that the *Urinary Anion Gap* (UAG) provides a rough index of urinary ammonium excretion. Ammonium is positively charged so a rise in its urinary concentration (ie increased unmeasured cations) will cause a fall in UAG as can be appreciated by inspection of the formula above.

How is this useful? Consider the following:

Step ONE: Metabolic acidosis can be divided into two groups based on the anion gap (AG):

- High anion gap acidosis
- Normal anion gap (or hyperchloraemic) acidosis.

It is easy to calculate the anion gap so this differentiation is easy and indeed clinically useful.

Step Two: Consider the hyperchloraemic group for further analysis. Hyperchloraemic acidosis can be caused by:

- Loss of base via the kidney (eg renal tubular acidosis)
- Loss of base via the bowel (eg diarrhoea).
- Gain of mineral acid (eg HCl infusion).

Step Three: Bowel or kidney as the cause?

Diagnosis between the above 3 groups of causes is usually clinically obvious, but occasionally it may be useful to have an extra aid to help in deciding between a loss of base via the kidneys or the bowel.

- If the acidosis is due to loss of base via the bowel then the kidneys can response appropriately by increasing ammonium excretion to cause a net loss of H^+ from the body. The UAG would tend to be decreased, That is: increased NH_4^+ (with presumably increased Cl^-) => increased UC =>decreased UAG.
- If the acidosis is due to loss of base via the kidney, then as the problem is with the kidney it is not able to increase ammonium excretion and the UAG will not be increased.

Does this work?

Experimentally, it has been found that patients with diarrhoea severe enough to cause hyperchloraemic acidosis have a negative UAG (average value -27 +/- 10 mmol/l) and patients with acidosis due to altered urinary acidification had a positive UAG. In many cases, the cause (gut or kidney) will be obvious, but occasionally calculation of the urinary anion gap can be useful.

Conclusion

In a patient with a hyperchloraemic metabolic acidosis:

- A negative UAG suggests GIT loss of bicarbonate (eg diarrhoea)
- A positive UAG suggests impaired renal distal acidification (ie renal tubular acidosis).

As a memory aid, remember neGUTive - negative UAG in bowel causes. For more details of the use of the UAG in differentiating causes of distal urinary acidification, see Batlle et al (1989).

Remember that is most cases the diagnosis may be clinically obvious (eg severe diarrhoea is hard to miss) and consideration of the urinary anion gap is not necessary.

3.5: Osmolar Gap

Note

'Osmolar gap' has several alternative names: 'osmol gap', 'osmole gap', 'osmolarity gap' & 'osmolal gap'; these all refer to the same thing. For consistency, the term "osmolar gap" is used exclusively through this book.

What is the 'osmolar gap'?

Definitions

- An **osmole** is the amount of a substance that yields, in ideal solution, that number of particles (Avogadro's number) that would depress the freezing point of the solvent by 1.86K
- **Osmolality** of a solution is the number of osmoles of solute per kilogram of solvent.
- **Osmolarity** of a solution is the number of osmoles of solute per litre of solution.

So osmolality is a measure of the number of particles present in a unit weight of solvent. It is independent of the size, shape or weight of the particles. It can only be measured by use of a property of the solution that is dependent on the particle concentration. These properties are collectively referred to as Colligative Properties. Osmolality is **measured** in the laboratory by machines called osmometers. The units of osmolality are mOsm/kg of solute

Osmolarity is **calculated** from a formula which represents the solutes which under ordinary circumstances contribute nearly all of the osmolality of the sample. There are many such formulae which have been used. One widely used formula for plasma which is used at my hospital is:

$$\text{Calculated osmolarity} = (1.86 \times [Na^+]) + [\text{glucose}] + [\text{urea}] + 9 \tag{3.5.1}$$

Regarding units

For the Equation 3.5.1, all concentrations are in mmol/l, and not mg/100mls. The result will then be in mOsm/l of solution. This equation is often expressed differently in North America where glucose & blood urea nitrogen (BUN) are reported in mg/dl. This version is essentially identical as it just includes conversion factors to convert mg/dl to mmol/l:

$$\text{Calculated osmolarity} = (1.86 \times [Na^+]) + \frac{\text{glucose}}{18} + \frac{BUN}{2.8} + 9 \tag{3.5.2}$$

This formula become popular after a study (by Dorwart & Chambers) comparing 13 different formulae found this one to yield the most accurate results.

What level of osmolar gap is "abnormal"?

An osmolar gap > 10 mOsm/l is often stated to be abnormal. The support for this contention is poor. One study (Hoffman RS et al, 1993) suggested the use of this formula:

$$\text{Calculated osmolarity} = (2 \times [Na^+]) + \frac{\text{glucose}}{18} + \frac{BUN}{18} + \frac{\text{ethanol}}{4.6} \tag{3.5.3}$$

They found a mean osmolar gap of 2.2 with SD 5.5 mOsm/l. The 95% range (mean +/- 2SD) was -14 to +10. This study is probably the basis for the >10 value as being abnormal. The range for normal values is very dependent on the particular formula that is used.

Osmolarity is easy to calculate because it only requires the measurement of 3 substances and these are routinely measured in every hospital biochemistry laboratory. Its calculation is usually programmed into the biochemistry autoanalyser and is routinely printed on the standard result sheet and is available to you even without having to ask.

The osmolar gap is the difference between the 2 values: the *osmolality* (which is measured) and the *osmolarity* (which is calculated from measured solute concentrations).

Osmolar gap = Osmolality - Osmolarity

In healthy persons, the osmolar gap is small as the osmolarity (calculated using the formula above) is a fairly good estimate of the osmolality. But in some conditions, there are significant amounts of abnormal substances present which contribute to the total osmolality and then the osmolarity will underestimate the osmolality. Consequently the osmolar gap will necessarily be increased. A given concentration of abnormal other solutes (in mg/dl) will contribute more particles (mOsm/kg) if they have a low molecular weight. It follows then that if the osmolar gap is significantly elevated, this provides indirect evidence that there must be a significant concentration of one or more low molecular substances present. It does not identify these abnormal solutes but alerts you to their presence.

A minor point for completeness: The units of osmolality (mOsm/kg) and osmolarity (mOsm/litre) are different so strictly they cannot be subtracted from one another. That said though, the value of the difference is clinically useful so this problem will be ignored.

Type of Osmometer

You MUST check the type of osmometer used by your hospital

The osmolality is measured in the pathology laboratory using an instrument called an osmometer which uses one of the colligative properties as the basis for its measurement.

Currently available osmometers fall into 2 groups:

- Those using the colligative property of freezing point depression
- Those using the colligative property of vapour pressure depression.

Only osmometers using freezing point depression method should be used

Why? Because they are the only type of osmometer that can detect all the volatile alcohols which can abnormally increase the osmolar gap. The other type of osmometer cannot do this. An explanation for this difference is:

"Vapor pressure osmometry, in contrast to osmometry using the freezing point depression method, requires an equilibrium between vapor and liquid phases and is unreliable when volatile chemicals such as ethanol and methanol are present because these chemicals tend to remain in the vapor phase" (from Glaser, 1996)

You must check what type your pathology laboratory is using otherwise you will be misled by spuriously normal osmolar gap results.

What is the meaning & usefulness of a high osmolar gap?

An elevated osmolar gap provides indirect evidence for the presence of an abnormal solute which is present in significant amounts. To have much effect on the osmolar gap, the substance needs to have a low molecular weight and be uncharged so it can be present in a concentration (measured in mmol/l) sufficient to elevate the osmolar gap.

Ethanol, methanol, ethylene glycol (used in anti-freeze solutions), isopropanol, and propylene glycol (used as a vehicle with some drugs e.g. lorazepam) are solutes that cause an elevated osmolar gap. If you suspect that your patient may have ingested one of these substances than, as a screening tool, you should determine the osmolar gap. (See Lynd et al, and Krasowski et al.) This testing is readily available in hospitals. Apart from ethanol levels, determination of the levels of other toxic glycols and alcohols is much less commonly available in pathology laboratories.

Main Use of Osmolar gap: Screening test for detecting abnormal low MW solutes

Ethylene glycol is used as an anti-freeze in car radiators.

Osmolar Gap: Use with Caution

Important reservations need to be made about the clinical utility of the osmolar gap, in particular:

- Its calculation depends on measurement of three substances and an osmolality measurement, so the error is the sum of the errors of all these measurements
- Many formulae are available to calculate osmolarity and the calculated value varies significantly depending on which one is used
- The osmolar gap has a wide normal range in the population
- The osmolar gap may be normal with ethylene glycol ingestion because of its higher MW (in comparison to methanol). The sensitivity of the test in detecting toxic ingestion of ethylene glycol is not high
- As ethylene glycol and methanol are metabolised, the osmolar gap decreases (and the anion gap increases) so a 'normal' value is more likely if the patient presents late.

Ethanol Cloaking: A Practical Problem

An elevated osmolar gap indicates an unknown solute but does not identify it. It is important to follow-up and determine what substance (or substances) is responsible. As an example, consider the following situation:

Consider a patient who has ingested ethanol as well as ethylene glycol or methanol. The ethanol will increase the osmolar gap and you can miss the presence of the more toxic substances if you make the assumption that the gap is due to the ethanol alone. This mistake could have serious adverse consequences for the patient.

Solution 1: For this reason, it is advisable to request an ethanol level whenever you request a measured osmolality. You can then correct the osmolar gap for any ethanol present and determine a 'corrected' osmolar gap. This approach is generally readily available in hospitals and has the advantage of indirectly detecting the presence of ANY other such low molecular weight toxin and not just ethanol. You won't know what this other solute is yet but your suspicions are raised and you can proceed to more specifc analyses.

Note

To convert ethanol levels in mg/dl to mmol/l divide by 4.6. For example, an ethanol level of 0.05% is 50mg/dl. Divide by 4.6 gives 10.9mmols/l

Solution 2: Another way to sort this out is if there is clinical suspicion AND your laboratory has the facilities, is to request specific assays for methanol or ethylene glycol. However, depending on the technique your laboratory uses, you may or may not detect other rare ingestions. You can miss the specific toxins that you are trying to measure if time has passed and they have already been extensively metabolised to their toxic products. In this latter case, you would be misled as to the toxic potential lurking in your patient.

The problem with this solution is that many laboratories do not measure these levels so your specimen may need to be sent to a distant large laboratory. The method used in our referring lab is a gas chromatographic separation followed by a mass spectroscopic detection. This is labour intensive and time consuming so the laboratory adds an additional layer of the need to discuss the case with a chemical pathologist before the analysis is agreed to. Only about 15% of requests get through this step in our local experience.

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CHAPTER OVERVIEW

4: Respiratory Acidosis

4.1: Definition

A respiratory acidosis is a primary acid-base disorder in which arterial pCO_2 rises to a level higher than expected.

At onset, the acidosis is designated as an '**acute respiratory acidosis**'. The body's initial compensatory response is limited during this phase.

As the body's renal compensatory response increases over the next few days, the pH returns towards the normal value and the condition is now a '**chronic respiratory acidosis**'.

The differentiation between acute and chronic is determined by time but occurs because of the renal compensatory response (which is slow).

4.2: Causes

The arterial pCO_2 is normally maintained at a level of about 40 mmHg by a balance between production of CO_2 by the body and its removal by alveolar ventilation. If the inspired gas contains no CO_2 then this relationship can be expressed by:

$paCO_2$ *is proportional to* $\frac{V_{CO_2}}{V_A}$

where:
V_{CO2} is CO_2 production by the body
V_A is Alveolar ventilation

An increase in arterial pCO_2 can occur by one of three possible mechanisms:

- Presence of excess CO_2 in the inspired gas
- Decreased alveolar ventilation
- Increased production of CO_2 by the body

CO_2 gas can be added to the inspired gas or it may be present because of rebreathing : Anaesthetists are familiar with both these mechanisms. In these situations, hypercapnia can be induced even in the presence of normal alveolar ventilation and normal carbon dioxide production by the body.

An adult at rest produces about 200mls of CO_2 per minute: this is excreted via the lungs and the arterial pCO_2 remains constant. An increased production of CO_2 would lead to a respiratory acidosis if ventilation remained constant. The system controlling arterial pCO_2 is very efficient (ie rapid and effective) and any increase in pCO_2 very promptly results in a large increase in ventilation. The result is that increased CO_2 production almost never results in respiratory acidosis. It is only in situations where ventilation is fixed that increased production will cause respiratory acidosis. Examples of this would be a ventilated patient who develops acute malignant hyperthermia: the arterial pCO_2 will rise unless the alveolar ventilation is substantially increased.

Most cases of respiratory acidosis are due to decreased alveolar ventilation.

The defect leading to this can occur at any level in the respiratory control mechanism. This provides a convenient way to classify causes that is used in the following table.

Alveolar hypoventilation may impair oxygen uptake.

The degree of arterial hypoxaemia will be related to the amount of hypoventilation. Increasing the percent of oxygen in the inspired gas can completely correct the hypoxaemia if hypoventilation is the only factor involved. If pulmonary disease leading to shunt or ventilation-perfusion mismatch is present, then the hypoxaemia will not be so easily corrected. The following list classifies causes by the mechanism or site causing the respiratory acidosis.

Causes of Respiratory Acidosis (classified by Mechanism)
A: Inadequate Alveolar Ventilation
Central Respiratory Depression & Other CNS Problems
• Drug depression of resp. center (eg by opiates, sedatives, anaesthetics) • CNS trauma, infarct, haemorrhage or tumour • Hypoventilation of obesity (eg Pickwickian syndrome) • Cervical cord trauma or lesions (at or above C4 level) • High central neural blockade • Poliomyelitis • Tetanus • Cardiac arrest with cerebral hypoxia
Nerve or Muscle Disorders

• Guillain-Barre syndrome • Myasthenia gravis • Muscle relaxant drugs • Toxins eg organophosphates, snake venom • Various myopathies
Lung or Chest Wall Defects
• Acute on COAD • Chest trauma -flail chest, contusion, haemothorax • Pneumothorax • Diaphragmatic paralysis or splinting • Pulmonary oedema • Adult respiratory distress syndrome • Restrictive lung disease • Aspiration
Airway Disorders
• Upper Airway obstruction • Laryngospasm • Bronchospasm/Asthma
External Factors
• Inadequate mechanical ventilation
B: Over-production of Carbon Dioxide
Hypercatabolic Disorders
• Malignant Hyperthermia
C: Increased Intake of Carbon Dioxide
Rebreathing of CO_2-containing expired gas
Addition of CO_2 to inspired gas
Insufflation of CO_2 into body cavity (eg for laparoscopic surgery)

The generalisation made in this section is that though there are three possible distinct mechanisms that can result in a respiratory acidosis, ***in clinical practice, nearly all cases are due to inadequate alveolar ventilation***. This is a very important point. Nevertheless the rare causes should be considered especially in Anaesthetic and Intensive Care practice where patients are often intubated and connected to circuits. Particular issues here include:

- Malignant hyperthermia (MH) is an extremely rare but potentially fatal condition which occurs almost exclusively in Anaesthetised patients exposed to certain drugs
- Various circuit misconnections & malfunctions, or soda lime exhaustion, can result in significant rebreathing of expired carbon dioxide
- Patients who are paralysed and on controlled ventilation cannot increase their alveolar ventilation to excrete any increased amounts of CO_2 produced by the body (eg in hypercatabolic states such as sepsis or MH)
- Exogenous carbon dioxide is introduced into the body in certain procedures (eg laparoscopy) and this increases the amount of carbon dioxide to be excreted by the lungs
- Adding CO_2 to the inspired gas as a respiratory stimulant has resulted, albeit rarely, in adverse outcomes in the past. (This practice is now abandoned in modern Anaesthetic practice)

Continuous capnography monitoring is now mandatory in Anaesthetic practice.

4.3: Maintenance

Key Fact: A rise in arterial pCO_2 is a potent stimulus to ventilation so a respiratory acidosis will rapidly correct unless some abnormal factor is maintaining the hypoventilation.

This feedback mechanism is responsible for the normal tight control of arterial pCO_2. The factor causing the disorder is also the factor maintaining it. The prevailing arterial pCO_2 represents the balance between the effects of the primary cause and the respiratory stimulation due to the increased pCO_2.

Other then by ventilatory assistance, the pCO_2 will return to normal only by correction of the cause of the decreased alveolar ventilation.

An extremely high arterial pCO_2 has direct anaesthetic effects and this will lead to a worsening of the situation either by central depression of ventilation or as a result of loss of airway patency or protection.

4.4: Metabolic Effects

Depression of Intracellular Metabolism

As CO_2 rapidly and easily crosses lipid barriers, a respiratory acidosis has rapid & generally depressing effects on intracellular metabolism.

Hypercapnia will rapidly cause an intracellular acidosis in all cells in the body. The clinical picture will be affected by the arterial hypoxaemia that is usually present. The effects described below are the metabolic effects of hypercapnia rather than respiratory acidosis. Patients with respiratory acidosis can be hypocapnic if a severe metabolic acidosis is also present.

Important effects of Hypercapnia

- Stimulation of ventilation via both central and peripheral chemoreceptors
- Cerebral vasodilation increasing cerebral blood flow and intracranial pressure
- Stimulation of the sympathetic nervous system resulting in tachycardia, peripheral vasoconstriction and sweating
- Peripheral vasodilation by direct effect on vessels
- Central depression at very high levels of pCO_2

Importance of Cerebral Effects

The cerebral effects of hypercapnia are usually the most important.

These effects are:

- increased cerebral blood flow,
- increased intracranial pressure, &
- potent stimulation of ventilation.

This can result in dyspnoea, disorientation, acute confusion, headache, mental obtundation or even focal neurologic signs. Patients with marked elevations of arterial pCO_2 may be comatose but several factors contribute to this:

- Anaesthetic effects of very high arterial pCO_2 (eg > 100mmHg)
- Arterial hypoxaemia
- Increased intracranial pressure

As a practical clinical example, the rise in intracranial pressure due to hypercapnia may be particularly marked in patients with intracranial pathology (eg tumours, head injury) as the usual compensatory mechanism of CSF translocation may be readily exhausted. Any associated hypoxaemia will contribute to an adverse outcome.

Effects on Cardiovascular System

The effects on the cardiovascular system are a balance between the direct and indirect effects.

Typically, the patient is warm, flushed, sweaty, tachycardic and has a bouncing pulse.

The clinical picture may be modified by effects of hypoxaemia, other illnesses and the patient's medication. Arrhythmias may be present particularly if significant hypoxaemia is present or sympathomimetics have been used.

Acutely the acidosis will cause a right shift of the oxygen dissociation curve. If the acidosis persists, a decrease in red cell 2,3 DPG occurs which shifts the curve back to the left.

An arterial pCO_2 in excess of about 90 mmHg is not compatible with life in patients breathing room air.

Why?

This is because of the obligatorily associated severe hypoxaemia. The alveolar gas equation predicts an alveolar pO_2 of 37mmHg (and the arterial pOsub>2 would be lower than this) when the pCO_2 is 90mmHg:

$$p_AO_2 = [0.21 \times (760 - 47)] - \frac{90}{0.8} = 37mmHg$$

Higher values of $paCO_2$ have been recorded in patients breathing an increased inspired oxygen concentration which prevents the hypoxaemia. Values up to about 260mmHg have been recorded with inadvertent administration of high inspired pCO_2 but this is Guinness Book of Records stuff! High pCO_2 levels also have an anaesthetic effect.

Hypercapnia -vs- Respiratory acidosis?

Note that 'hypercapnia' and 'respiratory acidosis' are not synonymous as, for example, a patient with a severe metabolic acidosis and a concomitant respiratory acidosis could have an arterial pCO_2 less than 40mmHg.
However, most of the discussion of 'metabolic effects' on this page is more correctly the 'metabolic effects of hypercapnia' rather than respiratory acidosis per se. Despite this, even in the mixed disorder just mentioned, the effects of an elevated arterial pCO_2 are linear, so compared to the situation of a severe metabolic acidosis alone, the metabolic effects of the higher pCO_2 of the mixed acid-base disorder (ie with the concomitant respiratory acidosis) are mostly still relatively correct.

4.5: Compensation

The compensatory response is a rise in the bicarbonate level

This rise has an immediate component (due to a resetting of the physicochemical equilibrium point) which raises the bicarbonate slightly.

Next is a slower component where a further rise in plasma bicarbonate due to enhanced renal retention of bicarbonate. The additional effect on plasma bicarbonate of the renal retention is what converts an "acute" respiratory acidsosis into a "chronic" respiratory acidosis.

As can be seen by inspection of the Henderson-Hasselbalch equation (below), an increased [HCO_3^-] will counteract the effect (on the pH) of an increased pCO_2 because it returns the value of the $\frac{[HCO_3^-]}{0.03pCO_2}$ ratio towards normal.

$$pH = pKa + \log \frac{[HCO_3^-]}{0.03pCO_2}$$

Buffering in Acute Respiratory Acidosis

The compensatory response to an acute respiratory acidosis is limited to buffering.

By the law of mass action, the increased arterial pCO_2 causes a shift to the right in the following reaction:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

In the blood, this reaction occurs rapidly inside red blood cells because of the presence of carbonic anhydrase. The hydrogen ion produced is buffered by intracellular proteins and by phosphates. Consequently, in the red cell, the buffering is mostly by haemoglobin. This buffering by removal of hydrogen ion, pulls the reaction to the right resulting in an increased bicarbonate production. The bicarbonate exchanges for chloride ion across the erythrocyte membrane and the plasma bicarbonate level rises. In an acute acidosis, there is insufficient time for the kidneys to respond to the increased arterial pCO_2 so this is the only cause of the increased plasma bicarbonate in this early phase. The increase in bicarbonate only partially returns the extracellular pH towards normal.

Empirically, the [HCO_3^-] rises by 1 mmol/l for every 10mmHg increase in pCO_2 above its reference value of 40mmHg. For example, if arterial pCO_2 has risen acutely from 40mmHg to 60mmHg (due to decreased alveolar ventilaton) then this acute rise of 2 tens (i.e. 60-40=20mmHg rise) results in a rise of plasma bicarbonate by 2 from its reference value of 24mmol/l up to 26 mmol/l. Consequently, we would predict that if this acute respiratory acidosis was the only base disorder present, then plasma bicarbonate would be 26mmol/l.

Though very important for *carriage* of carbon dioxide in the blood, the bicarbonate system is not itself responsible for any buffering of a respiratory acid-base disorder. This is because a system cannot buffer itself. If HCO_3^-were to react with H^+produced from the dissociation of H_2CO_3 this would just produce H_2CO_3 again - reversing the reaction is not 'buffering'.

Ninety-nine percent of the buffering of an acute respiratory acidosis occurs intracellularly. Proteins (especially haemoglobin in red cells) and phosphates are the most important buffers involved. These take up the H^+ produced from the dissociation of H_2CO_3. This intracellular buffering results in a further increase in intracellular [HCO_3^-] because it pulls the CO_2 hydration reaction to the right. The HCO_3^- that leaves the cell causes the rise in extracellular HCO_3^-. The amount of buffering is limited by the concentration of protein as that is low relative to the amount of carbon dioxide requiring buffering.

In summary: Compensation for an acute respiratory acidosis is by intracellular buffering and plasma bicarbonate rises slightly as a result of this buffering. The buffering is predominantly due to intracellular proteins; the bicarbonate system does not contribute to this buffering.

Chronic Respiratory Acidosis: Renal Bicarbonate Retention

With continuation of the acidosis, the kidneys respond by retaining bicarbonate.

If the respiratory acidosis persists then the plasma bicarbonate rises to an even higher level because of renal retention of bicarbonate.

Thus in a chronic respiratory acidosis there are TWO factors present which elevate the plasma bicarbonate:-

- Firstly: The acute physicochemical change and consequent buffering esp by intracellular protein. (Immediate onset - as occurs with an acute respiratory acidosis.)
- Secondly: The renal retention of bicarbonate as renal function is altered by the elevated arterial pCO_2 and additional bicarbonate is added to the blood passing through the kidney. (Slow onset)

Studies have shown that an average 4 mmol/l increase in $[HCO_3^-]$ occurs for every 10mmHg increase in pCO_2 from the reference value of 40mmHg. For example, if arterial pCO_2 has risen from 40mmHg to 60mmHg (due to decreased alveolar ventilaton) and remained elevated for several days, then this chronic rise of "2 tens" (i.e. 60-40=20mmHg rise = 2 rises of 10mmHg) results in a rise of plasma bicarbonate by 8 from its reference value of 24mmol/l up to 32 mmol/l. Consequently, we would predict that if this chronic respiratory acidosis was the only base disorder present, then plasma bicarbonate would be 32mmol/l.

The renal response in underway by 6 to 12 hours with a maximal effect reached by 3 to 4 days. This maximal effect is not sufficient to return plasma pH to normal, but because of the additional renal contribution, the pH is returned towards normal much more than occurs in an acute respiratory acidosis.

The response occurs because increased arterial pCO_2 increases intracellular pCO_2 in proximal tubular cells and this causes increased H^+ secretion from the PCT cells into the tubular lumen. This results in:

- increased HCO_3^- production which crosses the basolateral membrane and enters the circulation (so plasma $[HCO_3^-]$ increases.)
- increased Na^+ reabsorption in exchange for H^+ and less in exchange for Cl^- (so plasma $[Cl^-]$ falls)
- increased 'NH_3' production to 'buffer' the H^+ in the tubular lumen (so urinary excretion of NH_4Cl increases)

'Maximal compensation' versus 'full compensation'?

The increase in plasma $[HCO_3^-]$ results in an increase in amount of bicarbonate filtered in the kidney and this amount increases as plasma bicarbonate continues to increase. Eventually a new steady state is reached which is referred to as **maximal compensation**.

This level of compensation has long been believed to be less than that required to return the plasma pH to normal. That is the actual compensation ('maximal compensation') is less than 'full compensation'. If the pH was found to actually be within the normal range, the interpretation of this was that there was a co-existing metabolic alkalosis (e.g. due to use of diuretics or corticosteroids) or there had been transient hyperventilation from the stress of arterial puncture.

A recent study[1] examined the actual maximal response in a group of patients with stable chronic hypercapnic respiratory failure without a clinical condition or medications those could cause a metabolic alkalosis. The majority of these patients had pH values in the normal range as the compensation was greater than that predicted by the classic 4 for 10 rule. They found that bicarbonate increased by 5.1 mmols/l for every 10mmHg pCO_2 rise.

Consequently, a diagnosis of mild metabolic alkalosis should not be made in patients with stable chronic respiratory acidosis with pH values in the normal range unless there is other evidence (e.g. use of thiazide or loop diuretics, or corticosteroids) consistent with the diagnosis.

In summary, the compensation for hypercapnia is:

- Acute: Buffering only and predominantly intracellular (99%)
- Chronic: Renal retention of bicarbonate (in addition to buffering)

Summary notes about the compensation terms

Maximal compensation refers to the actual maximal amount of compensation that is typically seen in a patient with a simple acid-base disorder.

Full compensation refers to the amount of compensation that would correct the pH all the way back to within the normal range.

The general rule for all acid-base disorders is that the body's compensatory response is almost never sufficient to return the plasma pH to normal. If the pH is normal then it suggests that a second, compensating acid-base disorder is present. Contrary to this 'classic' teaching, a recent paper[1] suggests that in many patients with chronic stable hypercapnia, compensation may be sufficient to return pH to within the normal range.

Differing time courses of compensation and correction

The situation may be complicated because of the differing time courses of compensation & correction. Consider a couple of typical situations which sometimes cause confusion in interpretation:

Scenario 1

Correction of a chronic respiratory acidosis can occur more rapidly than correction of the renal compensation so it is possible that the blood gases in an individual patient may appear to show 'full compensation' if the alveolar ventilation has increased and before the kidneys have had time to adjust. The stimulation of being in the Emergency Room may result in such a situation and the snapshot provided by a single set of gases may reveal such a situation. (Remember this when the junior doctor alights upon such a set of results and says, "But I thought you said that compensation never 'fully' returns the pH to normal but this is what has happened here?")

Scenario 2

If a patient with chronic respiratory acidosis is intubated and ventilated, the arterial pCO_2 can be rapidly corrected (by adjusting the ventilator parameters). This can occur quite rapidly, but the elevated bicarbonate takes longer longer than this to fall. The situation can be more complicated because some such patients have additional factors which inhibit the ready excretion of the elevated bicarbonate, as occurs in 'post-hypercapnic metabolic alkalosis'.)

References

1. Martinu T, Menzies D, and Dial S. *Re-evaluation of acid-base prediction rules in patients with chronic respiratory acidosis.* Can Respir J 2003 Sep; 10(6) 311-5. PubMed [*See also the accompanying editorial*]

4.6: Correction

Restoration of Adequate Alveolar Ventilation

The pCO_2 rapidly returns to normal with restoration of adequate alveolar ventilation

Treatment usually needs to be directed to correction of the primary cause if this is possible. In severe cases, intubation and mechanical ventilation will be necessary to restore alveolar ventilation.

The patient can deteriorate following intubation and ventilation which results in a rapid fall in pCO_2 especially if the respiratory acidosis has been present for some time. This became apparent when mechanical ventilation was instituted in the chronically hypercapnic patients during the polio epidemic in Copenhagen in about 1950. Rapid return of pCO_2 towards normal was often accompanied by severe hypotension. The sympathetic stimulation due to prolonged hypercapnia resulted in patients who were relatively vasoconstricted and volume depleted. 'Post hypercapnic alkalosis' (see below) may also contribute to the pathophysiology due to decreased myocardial contractility. The net result of such rapid correction of arterial pCO_2 was hypotension. These patients required significant fluid loading. (Incidentally, this epidemic and the experience in ventilating large numbers of patients resulted in the birth of Respiratory Units which gradually evolved into the Intensive Care Unit of today. See Pontoppidan H et al. Respiratory Intensive Care. Anesthesiology. 1977; 47: 96-116 for more details)

In some other situations, it is preferable not to return arterial pCO_2 to 40 mmHg with mechanical ventilation eg in patients with chronic CO_2 retention from severe chronic obstructive airways disease. In some asthmatics presenting with severe bronchospasm (but not respiratory arrest), the problems associated with ventilation in this situation may suggest that administration of high oxygen concentrations to prevent hypoxaemia and tolerance of significant hypercapnia (permissive hypercapnia) is a beneficial strategy. The idea is to adjust ventilation to allow adequate oxygenation using lower inspiratory pressures and so decrease the risk of barotrauma.

What is post hypercapnic alkalosis?

If a chronically elevated arterial pCO_2 is returned to normal relatively quickly (as can happen if the patient is intubated and ventilated), then the patient is in the situation of having an elevated bicarbonate (due renal compensation) without there being the physiological need for it anymore. The elevated bicarbonate is typically slow to fall as return to normal requires renal excretion of the excess bicarbonate. The kidney normally has a large capacity to excrete bicarbonate but several factors, particularly chloride depletion, impairs this. Consequently, the bicarbonate level can remain persistently elevated; this state is referred to as post-hypercapnic alkalosis.

(See Case History 18 in Section 9.6)

The general factors causing maintenance of high bicarbonate levels in this situation are the same as those involved in maintenance of a metabolic alkalosis. These factors are chloride depletion, potassium depletion, ECF volume depletion and reduction of GFR. (See Section 7.3 for discussion).

This situation occurs almost exclusively in ICU patients with chronic hypercapnia who are acutely ventilated back towards a normal arterial pCO_2. **Chloride depletion** occurring during the hypercapnia is probably the most important factor involved in the maintenance of the high bicarbonate levels. These complex patients may also have other disorders which can themselves cause a metabolic alkalosis. In particular, the use of diuretics and loss of acidic gastric secretions (by nasogastric drainage) can be important factors in causing chloride depletion. Even with use of of H2-blockers (such as ranitidine), high nasogastric drainage can still result in significant chloride losses. These patients are often avidly retaining sodium in the kidneys and in the presence of low chloride levels, this is associated with high levels of bicarbonate reabsorption. In general, bicarbonate levels in this situation are in the 30 to 45 mmol/l range. Correction of fluid and chloride depletion leads to a fall in plasma bicarbonate levels.

References

1. Banga A and Khilnani GC. Post-hypercapnic alkalosis is associated with ventilator dependence and increased ICU stay. COPD. 2009; 6: 437-440. Pubmed

4.7: Assessment

The arterial pCO_2 value is used to quantify the magnitude of the alteration in alveolar ventilation (assuming CO2 production is constant and inspired pCO_2 is negligible). The arterial pCO_2 alone is not satisfactory for assessing the magnitude of a respiratory acidosis in some cases. In particular, coexisting metabolic acid-base disorders cause compensatory changes in pCO_2 and these must be accounted for.

The best available quantitative index of the magnitude of a respiratory acidosis is the difference between the 'actual' pCO_2 and the 'expected' pCO_2

Definition of Terms

- Actual pCO_2 - the measured value obtained from arterial blood gas analysis.
- Expected pCO_2 - the value of pCO_2 that we calculate would be present taking into account the presence of any metabolic acid-base disorder. If there is no metabolic acid-base disorder then a pCO_2 of 40 mmHg is taken as the reference point - ie we would use 40mmHg as the expected pCO_2

The reason we have to allow for a metabolic acid-base disorder is that the pCO_2 value changes from 40mmHg due solely to the body's compensatory ventilatory response to a metabolic acidosis or alkalosis so just using a value of 40mmHg as normal would be wrong and lead us to incorrect conclusions.

With an acute metabolic acidosis, the body responds by increasing alveolar ventilation. This response is compensatory because hyperventilation results in a decrease in arterial pCO_2 which tends to return the arterial pH towards 7.4 *partially* correcting the acute deviation of plasma pH from normal. The value of pCO_2 at maximal compensation can be predicted using a simple bedside 'rule of thumb' and this calculated value is the 'expected' pCO_2 which we use to compare with the 'actual'(measured) pCO_2 value.

If a metabolic disorder is present, we can calculate (using a simple formula) a new reference value of pCO_2 (the expected pCO_2) that we would expect that would be present with typical levels of respiratory compensation. We use this calculated 'expected value' to compare with the actual measured value.

You will now note as a consequence of this approach something that you might think to be rather odd: that is, it is possible for a patient to have a significant respiratory acidosis and yet be hypocapnic! This seems counter-intuitive if you wrongly considered that the terms 'respiratory acidosis' and 'hypercapnia' to be synonomous.

Example 4.7.1

Consider a patient with diabetic ketoacidosis who has a bicarbonate level of 8 mmol/l - clearly a severe metabolic acidosis - and a measured arterial pCO_2 of 40mmHg.

Using the formula in Section 5.5, we calculate (and so predict) that **if** the metabolic acidosis was the only acid-base disorder present, **then**:

Patient's expected CO_2= $(1.5 \times 8) + 8 = 20 mmHg$

But the 'actual' arterial pCO_2 is 40mmHg then, as this is much higher than the expected value, we would decide that our original assumption that this was the only acid-base disorder present was wrong. In this example, a co-existing respiratory acidosis was present. The pH in this patient with a mixed acidosis would be much lower than it would be if only the metabolic acidosis was present.

As an exercise, use the Henderson-Hasselbalch equation to calculate the pH for both values of pCO_2). If we just accepted a pCO_2 of 40mmHg as 'normal' then we would have missed this significant second acid-base disorder. Of course, the term 'respiratory acidosis' is not just words to explain a number - there must be some problem present which would explain the relative hypoventilation in this patient. For respiratory disorders one tends to think of the lung first, but such disorders are frequently caused by an abnormality at another parts of the respiratory control pathway (eg muscle weakness, coma, airway obstruction)

A final point: There is a widespread use of the term 'respiratory alkalosis' to refer to the compensatory hyperventilation that occurs with a metabolic acidosis but this term is quite wrong in this situation. The terms 'acidosis' & 'alkalosis' refer to primary abnormal processes (by definition) and should never be used to refer to compensatory processes. (Refer to Section 3.1 for definitions & discussion).

4.8: Prevention

Some causes are not amenable to preventive measures. Monitoring of at-risk patients with capnography is appropriate in some situations (eg in an Intensive Care Unit, intraoperatively and in the Recovery Room) and will allow earlier detection of a problem.

The end-tidal pCO_2 is typically lower than the arterial pCO_2 and the difference between these values is an index of the magnitude of the alveolar dead space. So if the end-tidal pCO_2 is elevated then the arterial pCO_2 is usually even more elevated.

First Key Fact: Watch for inadequate alveolar ventilation

Inadequate alveolar ventilation is the underlying problem in nearly all patients so any patient who could have impaired ventilation is at risk of developing respiratory acidosis. So recognise these at-risk situations.

Second Key Fact: Give oxygen to avoid hypoxaemia

Inadequate ventilation will also necessarily affect arterial oxygenation so steps to avoid, recognise and/or treat arterial hypoxaemia are very important. The simple measure of providing supplemental oxygen by face mask to patients can often correct or prevent hypoxaemia.

Some particular medical situations where prevention can be utilised are:

- Better airway care and attention to safe positioning of cerebrally obtunded patients (ie prevent airway obstruction).
- Increased care in the use of drugs (such as CNS sedatives or opiate drugs) which can depress ventilation
- Increased attention to the care of patients at risk of aspiration (eg unconscious patients)
- Ensuring adequate reversal of neuromuscular relaxants

CHAPTER OVERVIEW

5: Metabolic Acidosis

5.1: Definition

A metabolic acidosis is an abnormal primary process or condition leading to an increase in fixed acids in the blood.

This causes the arterial plasma bicarbonate to fall to a level lower than expected. The fall in plasma bicarbonate is due to titration of HCO_3^- by H^+.

Secondary or compensatory processes which cause a fall in plasma bicarbonate should not be confused with primary processes. A fall in bicarbonate occurring in response to a chronic respiratory alkalosis should be referred to as a compensatory response and never as a secondary metabolic acidosis.

This distinction between a primary process and a secondary one has been discussed previously in section 3.1.2 when discussing terminology of acid-base disorders.

It is of course possible for a patient to have a mixed acid-base disorder with both a metabolic acidosis and a respiratory alkalosis. An example would be an adult presenting following a salicylate overdose. In this situation, direct stimulation of the respiratory centre occurs resulting in a respiratory alkalosis as well as the salicylate-related metabolic acidosis.

5.2: Causes

Classification by Patho-physiological Mechanism

A decrease in plasma bicarbonate can be caused by two mechanisms:

1. A gain of strong acid
2. A loss of base

All causes of a metabolic acidosis must work by these mechanisms. The gain of strong acid may be endogenous (eg ketoacids from lipid metabolism) or exogenous (NH4Cl infusion). Bicarbonate loss may occur via the bowel (diarrhoea, small bowel fistulas) or via the kidneys (carbonic anhydrase inhibitors, renal tubular acidosis).

Classification by Anion Gap

An alternative to the above, is to classify the causes of metabolic acidosis into two groups depending on whether the anion gap is elevated or normal. These two groups are referred to as:

1. 'high anion gap metabolic acidosis'
2. 'normal anion gap metabolic acidosis'

The term *'hyperchloraemic metabolic acidosis'* is also often used for the *'normal anion gap' group but the terms are not really synonomous* (as discussed in section 8.4). This is the *most clinically useful* way to classify metabolic acidosis and it is used extensively when assessing metabolic acidosis. The further sub-divisions within this classification are outlined in the table below.

Causes of Metabolic Acidosis (classified by Anion Gap)

A: High Anion-Gap Acidosis

1. Ketoacidosis

- Diabetic ketoacidosis
- Alcoholic ketoacidosis
- Starvation ketoacidosis

2. Lactic Acidosis

- Type A Lactic acidosis (Impaired perfusion)
- Type B Lactic acidosis (Impaired carbohydrate metabolism)

3. Renal Failure

- Uraemic acidosis
- Acidosis with acute renal failure

4. Toxins

- Ethylene glycol
- Methanol
- Salicylates

B : Normal Anion-Gap Acidosis (or Hyperchloraemic acidosis)

1. Renal Causes

- Renal tubular acidosis
- Carbonic anhydrase inhibitors

2. GIT Causes

- Severe diarrhoea
- Uretero-enterostomy or Obstructed ileal conduit
- Drainage of pancreatic or biliary secretions
- Small bowel fistula

3. Other Causes

- Recovery from ketoacidosis
- Addition of HCl, NH_4Cl

5.3: Maintenance

The disorder is maintained as long as the primary cause persists.

Additionally, in many cases the acid-base disturbance tends to increase in severity while the problem causing it persists though this is not absolute.

For example with diabetic ketoacidosis, the pH will remain low as long as the problem (relative or absolute insulin deficiency) persists and the levels of plasma keto-anions continue to rise. However, these increased plasma levels of keto-anions exceed the renal threshold and are excreted in the urine. This will limit the rate of rise as long as this additional mechanism of excreting the acid anions persists. This renal excretion also means that once treatment commences, there is now a deficiency of keto-anions to be metabolised to regenerate bicarbonate and consequently there is can be a significant delay in the return of the plasma pH to normal.

5.4: Metabolic Effects

Cardiorespiratory Effects

A metabolic acidosis can cause significant physiological effects, particularly affecting the respiratory and cardiovascular systems.

Major Effects of a Metabolic Acidosis

Respiratory Effects

- Hyperventilation (Kussmaul respirations) - this is the compensatory response
- Shift of oxyhaemoglobin dissociation curve (ODC) to the right
- Decreased 2,3 DPG levels in red cells (shifting the ODC back to the left)

Cardiovascular Effects

- Depression of myocardial contractility
- Sympathetic overactivity (incl tachycardia, vasoconstriction,decreased arrhythmia threshold)
- Resistance to the effects of catecholamines
- Peripheral arteriolar vasodilatation
- Venoconstriction of peripheral veins
- Vasoconstriction of pulmonary arteries
- Effects of hyperkalaemia on heart

Other Effects

- Increased bone resorption (chronic acidosis only)
- Shift of K^+ out of cells causing hyperkalaemia

Some Effects have Opposing Actions

The cardiac stimulatory effects of sympathetic activity and release of catecholamines usually counteract the direct myocardial depression while plasma pH remains above 7.2. At systemic pH values less than this, the direct depression of contractility usually predominates.

The direct vasodilatation is offset by the indirect sympathetically mediated vasoconstriction and cardiac stimulation during a mild acidosis. The venoconstriction shifts blood centrally and this causes pulmonary congestion. Pulmonary artery pressure usually rises during acidosis.

The shift of the oxygen dissociation curve to the right due to the acidosis occurs rapidly. After 6 hours of acidosis, the red cell levels of 2,3 DPG have declined enough to shift the oxygen dissociation curve (ODC) back to normal.

Acidosis is commonly said to cause hyperkalaemia by a shift of potassium out of cells. The effect on potassium levels is extremely variable and indirect effects due to the type of acidosis present are much more important. For example hyperkalaemia is due to renal failure in uraemic acidosis rather than the acidosis. Significant potassium loss due to osmotic diuresis occurs during diabetic ketoacidosis and the potassium level at presentation is variable (though total body potassium stores are invariably depleted). Treatment with fluid and insulin can cause a prompt and marked fall in plasma potassium. Hypokalaemia may then be a problem.

5.5: Compensation

Hyperventilation

Compensation for a metabolic acidosis is hyperventilation to decrease the arterial pCO_2.

This hyperventilation was first described by Kussmaul in patients with diabetic ketoacidosis in 1874. The metabolic acidosis is detected by both the peripheral and central chemoreceptors and the respiratory center is stimulated. The initial stimulation of the central chemoreceptors is due to small increases in brain ISF [H^+]. The subsequent increase in ventilation causes a fall in arterial pCO_2 which inhibits the ventilatory response.

Maximal compensation takes 12 to 24 hours

The chemoreceptor inhibition acts to limit and delay the full ventilatory response until bicarbonate shifts have stabilised across the blood brain barrier. The increase in ventilation usually starts within minutes and is usually well advanced at 2 hours of onset but maximal compensation may take 12 to 24 hours to develop. This is maximal compensation rather than full compensation as it does not return the extracellular pH to normal.

In situations where a metabolic acidosis develops rapidly and is short-lived there is usually little time for much compensatory ventilatory response to occur. An example is the acute and sometimes severe lactic acidosis due to a prolonged generalised convulsion: this corrects due to rapid hepatic uptake and metabolism of the lactate following cessation of convulsive muscular activity, and hyperventilation due to the acidosis does not occur.

The expected pCO_2 at maximal compensation can be calculated from a simple formula

The arterial pCO_2 at maximal compensation has been measured in many patients with a metabolic acidosis. A consistent relationship between bicarbonate level and pCO_2 has been found. It can be estimated from the following equation:

$$\text{Expected} pCO_2 = 1.5(\text{Actual}[HCO_3^-]) + 8mmHg$$

(Units: mmols/l for [HCO_3^-], and mmHg for pCO_2).

The limiting value of compensation is the lowest level to which the pCO_2 can fall - this is typically 8 to 10mmHg, though lower values are occasionally seen.

An Example

If the measured HCO_3 is 12 mmols/l, then the expected pCO_2 (at maximal compensation) would be: $(1.5 \times 12) + 8 = 18 + 8 = 26mmHg$. If the actual pCO_2 was within +/- 2 mmHg of this (and 12 to 24 hours have passed from onset) then the respiratory compensation has reached it maximal value (and there would be no evidence of a primary respiratory acid-base disorder).

If the actual pCO_2 was say 40 mmHg in this situation, this is markedly different from the expected value of 26 mmHg and indicates the presence of quite a marked second primary acid-base disorder: a respiratory acidosis. A typical clinical situation may be a diabetic patient with ketoacidosis and severe pneumonia where the respiratory disease has resulted in the respiratory acid-base disorder. Note that in this situation, a severe respiratory acidosis has been diagnosed despite the presence of a pCO_2 at the value (40 mmHg) typically considered normal!

Maintain hyperventilation in ventilated patients

If a patient with a severe metabolic acidosis requires intubation and controlled ventilation in hospital, the acidosis can markedly worsen unless the hyperventilation is maintained. The ventilation should be set to mimic the compensatory hyperventilation to keep the pCO_2 low. If ventilation is set to some standard value and the pCO_2 allowed to rise towards 40mmHg, then this represents the imposition of an acute respiratory acidosis and pH can fall rapidly!

Carbon dioxide crosses cell membranes readily so intracellular pH falls rapidly also, resulting in depression of myocardial contractility, arrhythmias and a rise in intracranial pressure. The patient may deteriorate soon after intubation and ventilation and the medical staff usually don't appreciate how they have contributed to this outcome.

Beware when initiating ventilation in a patient with a significant acidosis: the situation described above is not widely appreciated and the outcome could be fatal. Set the ventilator settings so that the arterial pCO_2 remains low. Use the "expected pCO_2" formula

as a guide to a suitable target level.

5.6: Correction

Treatment Principles

The most important approach to managing a metabolic acidosis is to treat the underlying disorder. Then with supportive management, the body will correct the acid-base disorder. Accurate analysis & diagnosis is essential to ensure the correct treatment is used. Fortunately, in most cases this is not particularly difficult in principle. Remember though that a patient with a severe metabolic acidosis may be very seriously ill and even with optimal management the patient may not survive.

The ECLS Approach to Management of Metabolic Acidosis

1. **Emergency**: Emergency management of immediately life-threatening conditions always has the highest priority. For example, intubation and ventilation for airway or ventilatory control; cardiopulmonary resuscitation; severe hyperkalaemia
2. **Cause**: Treat the underlying disorder as the primary therapeutic goal. Consequently, accurate diagnosis of the cause of the metabolic acidosis is very important. In some cases (e.g. methanol toxicity) there may be a substantial delay become the diagnosis can be confirmed so management must be based on suggestive evidence otherwise it will be too late.
3. **Losses** Replace losses (e.g. of fluids and electrolytes) where appropriate. Other supportive care (oxygen administration) is useful. In most cases, IV sodium bicarbonate is NOT necessary, NOT helpful, and may even be harmful so is not generally recommended.
4. **Specifics** There are often specific problems or complications associated with specific causes or specific cases which require specific management. For example: Ethanol blocking treatment with methanol ingestion; rhabdomyolysis requires management for preventing acute renal failure; haemodialysis can remove some toxins.

Some examples of specific treatments for underlying disorders:

- Fluid, insulin and electrolyte replacement is necessary for diabetic ketoacidosis
- Administration of bicarbonate and/or dialysis may be required for acidosis associated with renal failure
- Restoration of an adequate intravascular volume and peripheral perfusion is necessary in lactic acidosis.

The detailed treatment of the various specific disorders is not considered here, but the important message is that the treatment of each underlying disorder differs so an accurate diagnosis is essential for selection of correct treatment. Treatment of the underlying disorder will result in correction of the metabolic acidosis (ie the bicarbonate level will return to normal).

Repair of the Bicarbonate Deficit

Correction involves repair of the bicarbonate deficit in the body.

So where does this bicarbonate come from? There are three usual sources:

1. Kidney: Renal generation of new bicarbonate
This usually occurs as a consequence of an increase in ammonium excretion.

2. Liver: Hepatic metabolism of acid anions to produce bicarbonate
The normal liver has a large capacity to metabolise many organic acid anions (eg lactate, ketoanions) with the result that bicarbonate is regenerated in the liver. In severe ketoacidosis there is often a large loss of ketoanions due to the hyperglycaemia induced osmotic diuresis. This leaves a shortfall of ketoanions to be used to regenerate bicarbonate as a consequence of their metabolism in the kidney.

3. Exogenous Administration of sodium bicarbonate
This is the time honoured method to 'speed up' the return of bicarbonate levels to normal. Indeed, this may be useful in mineral acidosis (hyperchloraemic metabolic acidosis) where there are no endogenous acid anions which can be metabolised by the liver. However, in most other cases of metabolic acidosis this administration is either not helpful or may be disadvantageous.

Sodium bicarbonate solutions should NOT be given on a routine basis no matter what the arterial pH is.

Following the above stricture in clinical practice may be very difficult. A severe lactic acidosis may be associated with a very high risk of death no matter how careful the management. If the patient dies there are often those who will criticise. Development of (institutional) evidence-based protocols or guidelines can be useful to aid in selection of agreed treatments.

Administration of sodium bicarbonate may be useful in treatment of *severe* hyperkalaemia. Such hyperkalaemia may be immediately life-threatening. Calcium gluconate will be more rapidly protective against serious arrhythmias.

It should be noted that correction of a metabolic acidosis does not necessarily involve *renal* excretion of acid or *renal*regeneration of bicarbonate because of the role of hepatic metabolism of some anions. For example, in lactic acidosis and ketoacidosis, treatment results in significant correction because of predominantly hepatic metabolism of the acid anions to regenerate bicarbonate. If acid anions have been lost in the urine, then renal regeneration of bicarbonate is very important for correction of the acid-base disorder.

In a severe ketoacidosis, there is a large loss of ketoanions in the urine. When the disorder is treated (fluids & insulin) there is a relative deficiency of acid anions which can be metabolised in the liver with regeneration of bicarbonate. Consequently, it is common to find that treatment results in a rapid correction (few hours) of the hyperglycaemia and the hypovolaemia but the acidosis may take over 24 hours to return to normal. This is because 'new' bicarbonate has to be regenerated by the kidneys and this takes longer to correct the bicarbonate deficit. There has been a past tendency to speed up the process by administration of intravenous NaHCO3 solution but this is not necessary and has not been shown to have any advantage.

The liver has several important roles in acid-base metabolism and its importance is generally understated in texts. Metabolism of other bicarbonate precursors (eg citrate from blood transfusion, acetate from 'Plasmalyte 148' solution) also occurs in the liver. The liver is the major site for the synthesis of plasma proteins and this is very significant for acid-base physiology (see also Section 10.6).

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Note

'Plasmalyte 148' is an IV fluid that is available in some countries. It is used as an ECF replacement fluid. It is similar to Hartmann's solution in that it contains a bicarbonate precursor (acetate in Plasmalyte; lactate in Hartmann's). Differences from Hartmann's are that Plasmalyte has a [Na^+] of 140mmol/l and contains Mg^{2+} instead of Ca^{2+}.

5.7: Assessment

Main Aspects of Assessment

The three aspects of assessment of this acid-base disorder are:

- First: Recognise its presence
- Second: Diagnose the cause
- Finally: Measure the severity

5.7.1 Investigations

A metabolic acidosis is often strongly suspected because of the clinical presentation of the patient (eg diabetes, renal failure, severe diarrhoea). Three clues from a typical hospital automated biochemical profile are:

- Low bicarbonate (or low total CO_2)
- High chloride
- High anion gap

What is total CO_2?

This is often reported as part of the laboratory's automated biochemical profile on a venous blood sample. It represents the total concentration of all the species in the sample which can be converted to carbon dioxide gas. This is:

$$\text{Total } CO_2 = [HCO_3^-] + [H_2CO_3] + [\text{carbamino } CO_2] + [\text{dissolved } CO_2]$$

Apart from bicarbonate, all the other species are present in only small concentrations. The usefulness of the 'total CO_2' is as an estimate of the arterial bicarbonate & which can be obtained without collecting an arterial sample. The value will usually be several mmols/liter higher than the actual arterial value due to the inclusion of carbamino & dissolved CO2 and because of the higher CO_2 content of venous blood.

Arterial blood gases are important for diagnosis but should always be interpreted in conjunction with the clinical details.

In addition to arterial blood gases, some other investigations useful for indicating a metabolic acidosis and for differentiating between the various major causes are:

- Urine tests for glucose and ketones
- Electrolytes (incl chloride, anion gap, bicarbonate)
- Plasma glucose
- Urea and creatinine
- Lactate

Use of Ancillary Indices

There are several indices (which can be calculated from pathology results) which may be useful in assessing a metabolic acidosis:

- Anion gap
- Delta ratio
- Urinary anion gap
- Osmolar gap

The anion gap is useful in a couple of ways:

- **Alerting Role:** An elevated anion gap (esp if AG > 20 mmol/l) will alert the clinician to the presence of a high anion gap metabolic acidosis. This can be extremely useful in sorting out complicated mixed disorders.
- **Classification Role:** It is used to divide metabolic acidosis into two major subgroups. The next step then is to consider either the 4 major categories of high anion gap acidosis (ketoacidosis, lactic acidosis, uraemic acidosis, acidosis due toxins) or the 2 major categories of normal anion gap acidosis (renal group, GIT group). History and a few pertinent investigations will usually distinguish the cause.

The delta ratio can be useful particularly in the difficult situation of a metabolic acidosis due to two processes where one elevates the anion gap and the other does not. An example is the hyperchloraemic normal anion gap acidosis which may develop in patients who have diabetic ketoacidosis (high anion gap). The ratio gives an indication of the relative contribution of the two processes. Unfortunately, its interpretation is limited somewhat by the wide error margin in this derived variable.

The urinary anion gap and the osmolar gap may be useful in certain patients with acidosis.

5.8: Prevention

Prevention of the primary disease or better management may be an option in some cases.

A particular example would be the prevention of episodes of diabetic ketoacidosis in insulin-dependent diabetic patients. Most adult ICUs are familiar with some usually teenage or young adult patients who are admitted multiple times with acute DKA due to poor compliance with insulin administration. Some of these problems may respond to better diabetic education and counselling.

Better security of drugs may prevent accidental ingestion (eg of salicylates) by young children.

Summary of important aspects of Chapter 5 : Metabolic Acidosis

- Metabolic acidosis is an abnormal primary process causing an increase in fixed acids in the blood. Buffering causes the plasma bicarbonate to fall to a level lower than expected and tends to cause an acidaemia.
- The decrease in bicarbonate level occurs either because of a gain of fixed acid or a loss of base.
- A more clinically useful classification is to divide metabolic acidosis into 2 groups: High anion gap acidosis and Normal anion gap acidosis.
- Important metabolic effects include hyperventilation, sympathetic stimulation, decreased arrhythmia threshold, direct myocardial depression, peripheral arteriolar vasodilatation, peripheral venoconstriction and pulmonary vasoconstriction.
- The peripheral chemoreceptors sense the acidaemia and stimulate the respiratory centre. The resulting hyperventilation causes a compensatory decrease in arterial pCO2 which partly returns the arterial pH towards normal. Such compensation rarely if ever returns the pH to normal.
- The most important aspect of management involves correction of the primary disorder if possible. Different causes of acidosis have some different specific management principles.
- The anion gap & the delta ratio may be useful aids in assessment of metabolic acidosis.

CHAPTER OVERVIEW

6: Respiratory Alkalosis

6.1: Definition

A respiratory alkalosis is a primary acid-base disorder in which arterial pCO_2 falls to a level lower than expected.

If there was no compensation and no other acid-base disorder present, then this must necessarily lead to an increase in arterial pH.

If there is no metabolic acid-base disorder present, then the actual measured arterial pCO_2 is compared against the standard reference value of 40mmHg.

If there is a co-existing metabolic acidosis, then the expected pCO_2 used for comparison is not 40mmHg but a calculated value which adjusts for the amount of change in arterial pCO_2 which occurs due to respiratory compensation. (The formula used is discussed in Section 9.3). This decrease in pCO_2 that occurs as compensation for a metabolic acidosis is not a respiratory alkalosis as it is not a primary process. For this reason, hypocapnia is not synonymous with respiratory alkalosis.

Processes & Interpretation

Key fact: A respiratory alkalosis is ALWAYS due to increased *alveolar* ventilation

Now, consider the following, which are also correct:

- A primary increase in total (or minute) ventilation does NOT always result in a respiratory alkalosis, and:
- Increased alveolar ventilation will NOT always result in a respiratory alkalosis

This may seem a bit confused but consider the following:

Firstly, note the difference between an increased minute ventilation and an increased alveolar ventilation.

Minute (or total) ventilation is the product of respiratory rate and tidal volume. Alveolar ventilation can be defined as the product of respiratory rate and (tidal volume minus physiological dead space volume). If, for example, a person has a large increase in dead space then minute ventilation can be much increased but alveolar ventilation could remain unchanged. It is only the alveolar ventilation that results in excretion of carbon dioxide. Any increased ventilation of dead space is 'wasted ventilation'.

The clinical relevance is that some patients may be clinically hyperventilating or have obvious respiratory distress but yet their arterial pCO_2 will not be decreased.

Secondly, hypocapnia does not necessarily mean a respiratory alkalosis.

The two possible situations are:

- hypocapnia (or increased alveolar ventilation) occurring as a primary process -this is a respiratory alkalosis, or:
- hypocapnia occurring as a compensatory response to a metabolic acidosis -this compensatory response is secondary so is not a respiratory alkalosis.

The practical point: If you look at a set of blood gas results and find a low arterial pCO_2 (hypocapnia): this indicates increased alveolar ventilation but this may be a compensatory response to a metabolic acidosis and hypocapnia from this cause is not a primary process, and so by definition is not a respiratory alkalosis.

This may sound a bit of a technical quibble but there are adverse effects of the alternative practice. For example, if all compensatory responses were considered an acidosis or an alkalosis then all acid-base disorders would tend to occur in pairs (such as a 'metabolic acidosis' and a 'respiratory alkalosis'). It would also mean that clinically significant diagnoses may be missed in patients with some mixed acid-base disorders. For example, a patient with both a metabolic acidosis and a respiratory acidosis could be interpreted as a having a metabolic acidosis alone & the respiratory problem would be missed and lead to quite inappropriate treatment (eg large doses of sodium bicarbonate).

6.2: Causes

Hyperventilation is the mechanism in ALL cases

Hyperventilation (ie increased alveolar ventilation) is the mechanism responsible for the lowered arterial pCO_2 in ALL cases of respiratory alkalosis.

This low arterial pCO_2 will be sensed by the central and peripheral chemoreceptors and the hyperventilation will be inhibited unless the patient's ventilation is controlled.

Causes of Respiratory Alkalosis

1. Central Causes (direct action via respiratory centre)

- Head Injury
- Stroke
- Anxiety-hyperventilation syndrome (psychogenic)
- Other 'supra-tentorial' causes (pain, fear, stress, voluntary)
- Various drugs (eg analeptics, propanidid, salicylate intoxication)
- Various endogenous compounds (eg progesterone during pregnancy, cytokines during sepsis, toxins in patients with chronic liver disease)

2. Hypoxaemia (act via peripheral chemoreceptors)

- Respiratory stimulation via peripheral chemoreceptors

3. Pulmonary Causes (act via intrapulmonary receptors)

- Pulmonary Embolism
- Pneumonia
- Asthma
- Pulmonary oedema (all types)

4. Iatrogenic (act directly on ventilation)

- Excessive controlled ventilation

Can a decreased CO_2 production cause respiratory alkalosis?

Hyperventilation is the mechanism in all of the situations in the above list & indeed in all cases.

Theoretically, a decreased carbon dioxide production could result in respiratory alkalosis if alveolar ventilation remained fixed. But this would not occur in a normal person because any drop in arterial pCO_2 would reflexly cause a decreased ventilation (via chemoreceptor inhibitory input into the respiratory centre).

About the only situation where maybe a decrease in CO_2 production could be the mechanism of respiratory alkalosis would be in an intubated patient on fixed ventilation during Anaesthesia or in Intensive Care Unit and where the CO_2 production was low due to hypothermia and decreased metabolic rate. However, even in such a circumstance, this mechanism is usually referred to as 'excessive controlled ventilation' (which it is relative to the amount of CO_2 production). So the answer to the question posed must be no.

Miscellaneous Notes on Causes

- Hyperventilation due to respiratory centre stimulation is a feature of salicylate toxicity, especially in adults, and results in a mixed disorder (metabolic acidosis and respiratory alkalosis).
- Propanidid was once used as an anaesthetic induction agent - it caused prominent hyperventilation.
- A respiratory alkalosis is the commonest acid-base disorder found in patients with chronic liver disease.
- Hyperventilation syndrome related to anxiety can cause alkalosis severe enough to cause carpopedal spasm.
- A mild fairly well compensated respiratory alkalosis is the usual finding in pregnancy.
- Any condition which decreases pulmonary compliance causes a sensation of dyspnoea. Respiratory alkalosis is commonly found in patients with asthma, pneumonia & pulmonary embolism.

6.3: Maintenance

The alkalosis persists as long as the initiating disorder is acting

The alkalosis persists as long as the initiating disorder persists unless some other disorder or complication causing impairment of the hyperventilation intervenes. For example, a hyperventilating head injury patient may develop acute neurogenic pulmonary oedema and this complication would tend to cause the arterial pCO_2 to rise.

This is different to the situation with a metabolic alkalosis where maintenance of the disorder requires an abnormality to maintain it as well as the problem which initiated it.

Only one respiratory acid-base disorder can be present at one time.

A patient cannot have both a respiratory alkalosis and a respiratory acidosis. There may of course be multiple factors acting to alter an individual's alveolar ventilation but each of these various factors are not considered separate respiratory acid-base disorders. Essentially this is because a person cannot be both hyperventilating and hypoventilating at the same time.

Using the above hyperventilating head injured patient example: This patient has a neurogenic cause for hyperventilation and if the arterial pCO_2 is lowered, then she is said to have a respiratory alkalosis. If neurogenic pulmonary oedema develops subsequently and decreases alveolar ventilation to normal and returns arterial pCO_2 to 40mmHg (assuming no metabolic acid-base disorders are present), then she now has no respiratory acid-base disorder.

More than one metabolic acid-base disorder can be present at the one time

The above respiratory situation is different to that occurring with a metabolic disorder. A patient can have a lactic acidosis and then develop a metabolic alkalosis (eg due to vomiting) and end up with a HCO_3^- level & pH which are normal. This is possible if the acidosis and the alkalosis exactly balance each other. This patient is then said to have both a metabolic acidosis AND a metabolic alkalosis. It is therapeutically useful to know this rather then to say there is no acid-base disorder present.

6.4: Metabolic Effects

Note

The distinction between hypocapnia & respiratory alkalosis has been made in Section 6.1. The metabolic effects mentioned here are those of hypocapnia rather than respiratory alkalosis per se.

Effects of Hypocapnia

1. Neurological effects

- Increased neuromuscular irritability (eg paraesthesias such as circumoral tingling & numbness; carpopedal spasm)
- Decreased intracranial pressure (secondary to cerebral vasoconstriction)
- Increased cerebral excitability associated with the combination of hypocapnia & use of enflurane
- Inhibition of respiratory drive via the central & peripheral chemoreceptors

2. Cardiovascular effects

- Cerebral vasoconstriction (causing decreased cerebral blood flow) [short-term only as adaptation occurs within 4 to 6 hours]
- Cardiac arrhythmias
- Decreased myocardial contractility

3. Other effects

- Shift of the haemoglobin oxygen dissociation curve to the left (impairing peripheral oxygen unloading)
- Slight fall in plasma [K^+]

NOTES

- Most of these effects decrease with time. A chronic hypocapnia is associated with few symptoms because of the compensation that occurs.
- The underlying cause will also have effects other than hyperventilation & these may dominate the clinical picture - for example, the adverse effects of hypoxaemia

The reduction in cerebral blood flow is marked.

Cerebral blood flow (CBF) decreases quite markedly with hypocapnia: a decrease of 4% per mmHg reduction in pCO_2. For example, an acute drop in pCO_2 from 40 down to 25mmHg will decrease CBF by about 60%. In awake subjects, this can cause light-headedness and even confusion. Patients with sickle cell anaemia may be very adversely affected by the decrease in cerebral blood flow (eg development of cerebral thrombosis).

Hypocapnia causes neuromuscular irritability

The patient may complain of paraesthesias (incl circumoral numbness & tingling). Tetany may also occur and may manifest as carpopedal spasm. This is a well known problem in patients with anxiety-hyperventilation syndrome and the symptoms can be relieved by rebreathing into a paper bag (with precautions to avoid hypoxaemia of course).

Particular Effects of Hypocapnia in Anaesthetised Patients

- Decreased cerebral blood flow (CBF) [This effect may be beneficial]
- Depression of myocardial contractility
- Cardiac arrhythmias
- Cerebral excitability may occur in association with high levels of enflurane
- Shift of the oxygen dissociation curve to the left (impairing oxygen unloading peripherally)
- Fall in plasma potassium (usually slight only)
- Obligatory hypoventilation at end of the operation (This is exacerbated by residual drug effects as well)

It has been argued that these adverse effects of hypocapnia are significant enough that the Anaesthetist should aim to maintain normocapnia throughout the duration of anaesthesia in most cases. There are some situations where intraoperative hyperventilation and hypocapnia is specifically useful eg to acutely reduce increased intracranial pressure (ICP) in neuroanaesthesia. In this situation, a therapeutic respiratory alkalosis is useful. These effects are short-lived (hours rather then days) as bicarbonate equilibration occurs across the blood-brain barrier and CBF and ICP returns to normal. This is now a dangerous situation as any increase in pCO_2 towards normal will cause a rise in CBF. Hyperventilation to reduce ICP is useful because of its rapid onset but as the effect only lasts for 4 to 6 hours. The main role of acute therapeutic hypocapnia is to provide acute reduction in ICP so that surgical treatment of intracerebral mass lesions can be facilitated.

One argument for routine intraoperative use of hypocapnia is to use the induced cerebral vasoconstriction to counteract the cerebral vasodilator effects of volatile anaesthetic agents. A particular disadvantage of this is the hypoventilation at the end of the operation which delays recovery from general anaesthesia.

The clinical picture is often dominated by the signs and symptoms of the underlying disorder

6.5: Compensation

The compensatory response is a fall in bicarbonate level

As can be seen by inspection of the Henderson-Hasselbalch equation (below), a decreased [HCO3 -] will counteract the effect of a decreased pCO2 on the pH. Mathematically, it returns the value of the $\frac{[HCO_3^-]}{0.03pCO_2}$ ratio towards normal.

$$\boldsymbol{pH = pKa + \log \frac{[HCO_3^-]}{0.03pCO_2}} \tag{6.5.1}$$

Key points regarding compensation in respiratory alkalosis:

- Physicochemical effect: Initially there is an immediate physicochemical change which lowers the bicarbonate slightly.
- Role of Kidney: The effector organ for compensation is the kidney.
- Slow Response: The renal response has a slow onset and the maximal response takes 2 to 3 days to be achieved.
- Outcome: The drop in bicarbonate results in the extracellular pH returning only *partially* towards its normal value.

Compensation in an ACUTE Respiratory Alkalosis

- **Mechanism:** Changes in the physicochemical equilibrium occur due to the lowered pCO_2 and this results in a slight decrease in HCO_3^-. There is insufficient time for the kidneys to respond so this is the only change in an acute respiratory alkalosis. The buffering is predominantly by protein and occurs intracellularly; this alters the equilibrium position of the bicarbonate system.
- **Magnitude:** There is a drop in HCO_3^- by 2 mmol/l for every 10mmHg decrease in pCO_2 from the reference value of 40mmHg.
- **Limit:** The lower limit of 'compensation' for this process is 18mmol/l - so bicarbonate levels below that in an acute respiratory alkalosis indicate a co-existing metabolic acidosis. (Alternatively, there may be some renal compensation if the alkalosis has been present longer than realised.)

Compensation in a CHRONIC Respiratory Alkalosis

- **Mechanism:** Renal loss of bicarbonate causes a further fall in plasma bicarbonate (in addition to the acute drop due to the physicochemical effect and protein buffering).
- **Magnitude:** Studies have shown an average 5 mmol/l decrease in $[HCO_3^-]$ per 10mmHg decrease in pCO_2 from the reference value of 40mmHg. This maximal response takes 2 to 3 days to reach.
- **Limit:** The limit of compensation is a $[HCO_3^-]$ of 12 to 15 mmol/l.

6.6: Correction

Hypoxaemia is an important cause of respiratory stimulation and consequent respiratory alkalosis.

The decrease in arterial pCO_2 inhibits the rise in ventilation. The hypocapnic inhibition of ventilation (acting via the central chemoreceptors) may leave the patient with an impaired state of tissue oxygen delivery. Adaptation occurs over a few days and the central chemoreceptor inhibition is lessened and ventilation increases.

The number one priority is correction of any co-existing hypoxaemia

Correction of hypoxaemia is the most urgent concern and is many times more important than correction of the respiratory alkalosis. Administration of oxygen in sufficient concentrations and sufficient amounts is essential. Attention to other aspects necessary to improve oxygen delivery and minimise tissue oxygen consumption is important.

As regards the alkalosis: In most cases correction of the underlying disorder will resolve the problem.

In some cases this is easy (eg adjustment of ventilator settings, rebreathing via a paper bag with psychogenic hyperventilation) but in some cases it is a slow process.

6.7: Assessment

The severity of a respiratory alkalosis is determined by the difference between the actual pCO_2 and the expected pCO_2

The actual pCO_2 is the measured value from the blood gas results.

If no metabolic acid-base disorder is present, a pCO_2 of 40 mmHg is taken as the reference point (ie the expected pCO_2).

If a metabolic disorder is present, respiratory compensation will produce a new reference value of pCO_2 for comparison. The expected pCO_2 can be estimated using the formula in Section 5.5 (for metabolic acidosis) or Section 7.5 (for metabolic alkalosis).

6.8: Prevention

Hyperventilation of the anaesthetised patient is common and preventable. Monitoring by capnography allows early recognition and correction. In major operations, serial arterial gases for assessment of oxygenation and ventilation is appropriate especially as the size of the endtidal-arterial pCO_2 gradient can be determined and this is useful for determining ventilation settings between blood-gas analyses.

Summary of important aspects of Chapter Six: Respiratory Alkalosis

- Respiratory alkalosis is a primary acid-base disorder in which the pCO_2 falls to a level lower than expected.
- All cases are due to increased alveolar ventilation
- The compensatory response is renal loss of bicarbonate which causes a fall in plasma bicarbonate
- The fall in bicarbonate can be predicted from a simple formula
- Metabolic effects include decreased cerebral blood flow, decrease in myocardial contractility and a shift of the oxygen dissociation curve to the left
- Hyperventilation is used to acutely decrease intracranial pressure as the onset is rapid. The effect on CBF is time-limited as equilibration of bicarbonate across the blood-brain barrier occurs over 4 to 6 hours and CBF and ICP return towards normal.

CHAPTER OVERVIEW

7: Metabolic Alkalosis

7.1: Definition

A Primary Process

A metabolic alkalosis is a primary acid-base disorder which causes the plasma bicarbonate to rise to a level higher than expected. The severity of a metabolic alkalosis is determined by the difference between the actual [HCO_3^-]and the expected [HCO_3^-].

Not a Compensatory Process

Secondary or compensatory processes which cause an elevation in plasma bicarbonate should not be confused with the primary processes. An elevation in bicarbonate occurring in response to a chronic respiratory acidosis should be referred to as a 'compensatory response' and never as a secondary metabolic alkalosis.

You should be aware that many articles (esp in the surgical literature) will refer to a 'compensated metabolic alkalosis' as a 'metabolic alkalosis with a (secondary) respiratory acidosis'. This is wrong as the hypoventilation is a compensatory process and does not indicate any primary respiratory problem. Another implication of the incorrect terminology is that acid-base disorders always occur in pairs and this is ridiculous and of no help in patient management.

The terminology of acid-base disorders is covered in Section 3.1.

7.2: Causes

The kidney rapidly excretes bicarbonate if the plasma level is elevated

Whenever the plasma bicarbonate rises above 24mmols/l, bicarbonate is excreted by the kidney. This response is reasonably prompt and effective so a metabolic alkalosis will be rapidly corrected. If you infuse say 100mls of 8.4% sodium bicarbonate into a healthy person with normal renal function, the rise in plasma bicarbonate is brief because of prompt bicarbonaturia. This is one way to alkalinise the urine. An infusion of alkali causes only a brief metabolic alkalosis due to this rapid renal excretion.

This ability of the kidney to rapidly excrete bicarbonate if its level is high is in complete contrast to its powerful ability to reabsorb all of the filtered load if plasma [HCO_3^-] is low or normal. A useful analogy here is to filling a bucket. No water is lost until the bucket is full, but after that, all extra water is lost. This is sometimes called a waterfall effect.

How can a metabolic alkalosis ever persist?

The persistence of a metabolic alkalosis requires an **additional process** which acts to impair renal bicarbonate excretion. In our analogy, this would be something that increased the height of walls of the bucket. This means that two issues must be considered when analysing a metabolic alkalosis:

- **Initiation**: What process is initiating the disorder?
- **Maintenance**: What process is maintaining the disorder?

When discussing the 'cause' of a metabolic alkalosis, note this term is used in several ways. For example it may be used to describe the initiating process, or the process maintaining the disorder or it can be used to refer to the combination of both processes, so be mindful of this when reading the rest of this section as otherwise you may become a little confused.

The Initiating Process

Normally, plasma bicarbonate is kept at a steady level of about 24 mmols/l by two renal processes:

- Tubular reabsorption of nearly all of the large daily filtered load of bicarbonate
- Excretion of the net daily production of the fixed acid (which results in regeneration of the titrated plasma bicarbonate)

Causes of a metabolic alkalosis can be classified into several groups as outlined in the table.

'Causes' : Classification of Initiating Processes for Metabolic Alkalosis
Gain of alkali in the ECF
• from an exogenous source (eg IV $NaHCO_3$ infusion, citrate in transfused blood) • from an endogenous source (eg metabolism of ketoanions to produce bicarbonate)
Loss of H+ from ECF
• via kidneys (eg use of diuretics) • via gut (eg vomiting, NG suction)

Excessive intravenous administration of alkali alone will cause a metabolic alkalosis which is only short-lived because of rapid renal excretion of bicarbonate (as mentioned previously).

Hepatic metabolism of citrate, lactate, acetate or certain other organic acid anions to bicarbonate can cause a brief metabolic alkalosis. This may occur after a massive blood transfusion because of the metabolism of the administered citrate. The kidneys excrete the bicarbonate and the urine will be relatively alkaline.

Processes responsible for Maintenance of the Alkalosis

This is discussed in section 7.3.

'Causes' of clinically significant chronic metabolic alkalosis are usefully divided into 2 major groupings based on the major factor involved in the maintenance of the disorder:

- The chloride depletion group
- The potassium depletion group

Maintenance of the alkalosis requires a process which greatly impairs the kidney's ability to excrete bicarbonate and prevent the return of the elevated plasma level to normal. Chloride deficiency leads to a situation where the kidney reabsorbs more bicarbonate anion than usual because there is not sufficient chloride anion present. Reabsorption of an anion is necessary to maintain electroneutrality as Na^+ & K^+ are reabsorbed so the deficiency of chloride leads to a re-setting upwards of the maintained plasma bicarbonate level. Chloride and bicarbonate are the only anions present in appreciable quantities in extracellular fluid so a deficiency of one must lead to an increase in the other because of the strict requirement for macroscopic electroneutrality.

Chloride Depletion

The commonest causes in clinical practice are those causing chloride depletion

Administration of chloride is necessary to correct these disorders. The four major sub-groups of metabolic alkalosis are listed in the table below. The two commonest causes of chronic metabolic alkalosis are loss of gastric juice and diuretic therapy. The gastric secretion of H^+ results in generation of new bicarbonate which is returned to the blood.

Loss of gastric acid (vomiting, NG drainage) and diuretic use account for 90% of clinical cases of metabolic alkalosis

Gastric alkalosis is most marked with vomiting due to pyloric stenosis or obstruction because the vomitus is acidic gastric juice only. Vomiting in other conditions may involve a mixture of acid gastric loss and alkaline duodenal contents and the acid-base situation that results is more variable. Histamine H2-blockers also decrease gastric H^+ losses despite continued vomiting or nasogastric drainage and alkalosis will not occur if the fluid lost is not particularly acidic - indeed loss of alkaline small intestinal contents can even result in an acidosis if gastric acid secretion is suppressed.

Diuretics such as frusemide and thiazides interfere with reabsorption of chloride and sodium in the renal tubules.Urinary losses of chloride exceed those of bicarbonate. The patients on diuretics who develop an alkalosis are those who are also volume depleted (increasing aldosterone levels) and have a low dietary chloride intake ('salt restricted' diet). Hypokalaemia is common in these patients. If dietary chloride intake is adequate then an alkaosis is unlikely to develop. This is the main reason why every patient taking diuretics such as thiazides or lasix does not develop a metabolic alkalosis. The effect of diuretic use on urinary chloride levels depends on the relationship of the time of urine collection to diuretic effect: it is high while the diuretic is acting, but drops to low levels afterwards.

Villous adenomas typically excrete bicarbonate and can cause a hyperchloraemic metabolic acidosis. Sometimes they excrete chloride predominantly and the result is then a metabolic alkalosis.

Chloride diarrhoea is a rare congenital condition due to an intestinal transport defect, where the chronic faecal chloride loss can (if associated with volume depletion and K^+ loss as maintenance factors) result in a metabolic alkalosis.

Potassium Depletion

Potassium depletion occurs with situations of mineralocorticoid excess. Bicarbonate reabsorption in both the proximal and distal tubules is increased in the presence of potassium depletion. Potassium depletion decreases aldosterone release by the adrenal cortex.

A Common Hybrid Classification of 'Causes' of Metabolic Alkalosis

A: Addition of Base to ECF

- Milk-alkali syndrome
- Excessive $NaHCO_3$ intake
- Recovery phase from organic acidosis (excess regeneration of HCO_3^-)
- Massive blood transfusion (due metabolism of citrate)

B: Chloride Depletion

- Loss of acidic gastric juice
- Diuretics
- Post-hypercapnia
- Excess faecal loss (eg villous adenoma)

C: Potassium Depletion

- Primary hyperaldosteronism
- Cushing's syndrome
- Secondary hyperaldosteronism
- Some drugs (eg carbenoxolone)
- Kaliuretic diuretics
- Excessive licorice intake (glycyrrhizic acid)
- Bartter's syndrome [1]
- Severe potassium depletion

D: Other Disorders

- Laxative abuse [2,3,4]
- Severe hypoalbuminaemia [5]

Primary Hyperaldosteronism

This condition is one cause of 'saline-resistant' metabolic alkalosis. The increased aldosterone levels lead to increased distal tubular Na^+ reabsorption and increased K^+ & H^+ losses. The increased H^+ loss is matched by increased amounts of renal HCO_3^- leaving in the renal vein. The net result is metabolic alkalosis with hypochloraemia and hypokalaemia, often with an expanded ECF volume.

Cushing's Syndrome

The excess corticosteroids have some mineralocorticoid effects and because of this can produce a metabolic alkalosis. The alkalosis is most severe with the syndrome of ectopic ACTH production.

Severe K^+ depletion

Cases have been reported of patients with metabolic alkalosis and severe hypokalaemia ($[K^+] < 2$ mmol/l) due to severe total body potassium depletion. Investigation has not shown increased mineralocorticoid activity. The aetiology in these patients is not understood but correction of the alkalosis requires correction of the potassium deficit. These patients do not respond to saline loading unless K^+ replacement is sufficient to correct the deficit. Urinary chloride losses are high (>20mmol/l).

Bartter's syndrome

This is a syndrome of increased renin and aldosterone levels due to hyperplasia of the juxtaglomerular apparatus [1,6]. It is inherited as an autosomal recessive disorder. The increased aldosterone levels usually result in a metabolic alkalosis. The condition is usually found in children. Patients who present with hypokalaemic alkalosis of uncertain cause are often suspected of having this condition but other causes which may be denied by the patient should be considered eg surreptitious vomiting and/or use of diuretics for weight loss or psychological problems. These situations have been termed 'pseudo-Bartter's syndrome'. Rare genetic disorders such as Gitelmann's syndrome should also be considered.

Excessive intake of glycyrrhizin

Glycyrrhizin is precent in licorice root. It has a sweet taste with a licorine tang and is used in some countries (eg particularly Japan) as a food additive or in traditional medicines. It inhibits the conversion of cortisol to cortisone by inhibiting the enzyme 11-betahydroxysteroid dehydrogenase. The resulting high cortisol levels have a mineralocorticoid effect (pseudohyperaldosteronism) causing Na+ retention and excessive urinary K+ loss. Excessive intake may result in hypertension, oedema, hypokalaemia and metabolic alkalosis. [7]

Usefulness of Urinary Chloride Measurements

Metabolic alkalosis may be divided into two general groups based on the measured urinary chloride level.

In most cases the cause is obvious (eg vomiting, diuretic use) but if not then measurement of a spot urinary chloride can be useful.

Two things to be aware of when interpreting the result:

- Recent diuretic use can acutely elevate the urinary chloride level but as the diuretic effect passes the urinary chloride level will fall to low levels. So seek information on the timing of diuretic use when assessing the result. (This variability in urine chloride levels has been used as an indicator of surreptious diuretic use).
- A 'spot' urine chloride may be misleading if bladder urine contains a mixture of urine from during and after diuretic effect.

A high urinary chloride in association with hypokalaemia suggests mineralocorticoid excess

(provided that recent thiazide use has been excluded).

If the clinical information is not sufficient to make a diagnosis the term 'idiopathic metabolic alkalosis' is sometimes used. The urinary chloride/creatinine ratio may occasionally be useful as it is elevated if there is an extra-renal cause of alkalosis.

Metabolic Alkalosis Based on Urinary Chloride

Urine Cl^-< 10 mmol/l

- Often associated with volume depletion (increased proximal tubular reabsorption of HCO_3^-)
- Respond to saline infusion (replaces chloride and volume)
- Common causes: previous thiazide diuretic therapy, vomiting (90% of cases)

Urine Cl^- > 20 mmol/l

- Often associated with volume expansion and hypokalaemia
- Resistant to therapy with saline infusion
- Cause: Excess aldosterone, severe K+ deficiency
- Other causes: diuretic therapy (current), Bartter's syndrome

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7.3: Maintenance

Maintenance factors

Without a second mechanism acting to maintain it, the alkalosis would be only transitory.

Why?? This is because the kidney normally has a large capacity to excrete bicarbonate and return the plasma level to normal.

This rise in urinary bicarbonate loss occurs relatively promptly (ie onset within an hour) but excretion takes 24 hours to peak unless some abnormal condition is causing renal retention of bicarbonate. The factors involved in maintenance of the disorder are very important not only because they are necessary to develop a persisting (ie chronic) alkalosis but also because they can maintain the alkalosis even after the primary process generating it has resolved!

The alkalosis can persist after the initiating process has resolved ONLY IF there are additional factors maintaining it.

What are these abnormal 'maintenance factors'?

The four factors that cause maintenance of the alkalosis (by increasing bicarbonate reabsorption in the tubules or decreasing bicarbonate filtration at the glomerulus) are:

- Chloride depletion
- Reduced glomerular filtration rate (GFR)
- Potassium depletion
- ECF volume depletion

Chloride depletion is the most common factor

Volume depletion and potassium depletion may coexist in some disorders (eg vomiting). Severe potassium depletion alone can cause a metabolic alkalosis but this is typically only of mild to moderate degree. The mechanism seems to be related to an intracellular shift of H^+ ('intracellular acidosis') in exchange for K^+. The alkalosis is generated predominantly due to non-renal mechanisms. Renal mechanisms are frequently involved in causing the potassium depletion (eg in syndromes of mineralocorticoid excess).

Volume depletion has long been implicated in maintenance of an alkalosis. The idea is that hypovolaemia is associated with increased fluid and sodium reabsorption in the proximal tubule and bicarbonate is reabsorbed in preference to chloride; the alkalosis thus being maintained. The role of volume depletion has probably been over-emphasised: the co-existing chloride depletion is the most important factor responsible for persistence of the alkalosis. Correction of the volume deficit without correction of the chloride deficit will not result in correction of the alkalosis. These deficits are often corrected together with a saline infusion.

Diuretics can cause excess renal loss of fixed acid anions and result in alkalosis. Their use can also cause depletion of chloride, water (hypovolaemia) and potassium. These factors together maintain the alkalosis. For an alkalosis to develop in patients on diuretic therapy, there generally has to some decrease in chloride intake as well (eg if the patient is on a 'salt restricted' diet). A continued normal oral chloride intake (usually as NaCl) prevents patients on diuretics from getting an alkalosis.

7.4: Metabolic Effects

Adverse effects of alkalosis

The effects of the *alkalosis* are often difficult to distinguish from the effects of *associated problems* such as hypovolaemia, potassium and chloride depletion.This makes it more difficult to characterise the effects of the alkalosis itself.

Adverse Effects of Alkalosis

- decreased myocardial contractility
- arrhythmias
- decreased cerebral blood flow
- confusion
- mental obtundation
- neuromuscular excitability
- impaired peripheral oxygen unloading (due shift of oxygen dissociation curve to left).

The disorder is associated with significantly increased morbidity and mortality especially in critically ill patients. The compensatory rise in arterial pCO_2 will tend to counteract some of these effects (eg the effect on cerebral blood flow)

Risk of Hypoxaemia

Hypoxaemia may occur and oxygen delivery to the tissues may be reduced. Factors involved in impaired arterial oxygen content are:

- Hypoventilation (due respiratory response to metabolic alkalosis)
- Pulmonary microatelectasis (consequent to hypoventilation)
- Increased ventilation-perfusion mismatch (as alkalosis inhibits hypoxic pulmonary vasoconstriction)

Peripheral oxygen unloading may be impaired because of the alkalotic shift of the haemoglobin oxygen dissociation curve to the left. The body's major compensatory response to impaired tissue oxygen delivery is to increase cardiac output but this ability is impaired if hypovolaemia and decreased myocardial contractility are present.

Give oxygen!

The need for administration of supplemental oxygen to patients with metabolic alkalosis is a neglected part of therapy.

7.5: Compensation

The compensatory response is hypoventilation

It was believed that the peripheral chemoreceptors alone acted as the initial sensor responding to the rise in blood pH but further animal studies have indicated that metabolic acid-base disorders do cause a slow change in brain ISF [H^+] and this change allegedly could be sufficient for account for the change in ventilation that occurs. This view is not accepted by all - see discussion in Section 2.3)

The hypoventilation causes a compensatory rise in arterial pCO_2 but the magnitude of the response has generally been found to be quite *variable*. More recent studies have almost invariably shown that hypoventilation does reliably occur in metabolic alkalosis.

Why is hypoventilation not always found?

This has been attributed to various problems with some of the older studies which did not account for the presence of conflicting factors, particularly those causing hyperventilation:

- **Hyperventilation due to pain** - in response to the stress of a painful arterial puncture. This could lower the measured pCO_2 during the procedure.
- **Hyperventilation due to pulmonary congestion.** Some patients with metabolic alkalosis due to diuretic use have subclinical pulmonary congestion sufficient to stimulate intrapulmonary receptors and cause tachypnoea and give a sensation of dyspnoea. This slight hyperventilation is sufficient to negate the rise in arterial pCO_2.
- **Hyperventilation due to hypoxaemia.** An associated hypoxaemia will stimulate the peripheral chemoreceptors and cause hyperventilation if the arterial pO_2 is below 50 to 55mmHg. This may not have been considered in early studies.

This common association of metabolic alkalosis with factors causing hyperventilation probably accounts for most of the past findings of variability of the change in arterial pCO_2. In effect, this is saying that many of these patients had a co-existent respiratory alkalosis.

The arterial pCO_2 can be quite high in severe cases

It was also widely believed that the maximum value of arterial pCO_2 due to compensatory hypoventilation was 55 to 60mmHg. There is no doubt that this is wrong.

Arterial pCO_2 can rise higher than this and values up to 86mmHg have been reported in severe cases of metabolic alkalosis!

If hypoventilation is sufficient to cause hypoxaemia, this also may stimulate respiration via the peripheral chemoreceptors. As mentioned above, associated hypoxaemia is probably responsible for variability in the measured arterial pCO_2 in patients who also have a sufficiently low arterial pO_2. Patients who present with hypoxaemia and hypercapnia may be diagnosed with respiratory failure if the association with metabolic alkalosis is not appreciated. It is usually best in these patients to administer oxygen and to avoid intubation and ventilation.

A couple of cautions for severe cases:

- For patients that you do not intubate and ventilate: If significant hypoxaemia was present, its relief can remove the hypoxic respiratory drive with resultant hypoventilation and a rise in arterial pCO2. This reveals the appropriate (in acid-base terms) physiological response but can cause concern.
- For patients that you you intubate and ventilate: It is easy to render ventilated patients hypocapnic and this respiratory alkalosis can greatly worse the alkalemia. Convulsions have occurred in such patients.

The expected pCO_2 due to appropriate hypoventilation in simple metabolic alkalosis can be estimated from the following formula:

$$\text{Expected } \boldsymbol{pCO_2 = 0.7[HCO_3^-] + 20mmHg} \text{ (range: } \boldsymbol{\pm 5}\text{)}$$

Note the wide variation allowed (ie a 10 mmHg range) because of the conflicting factors that affect ventilation (discussed above). This formula is used to determine if a coexistent respiratory acid-base disorder is present. For example, if pCO_2 is much lower than expected, a respiratory alkalosis is also present.

7.6: Correction

Principles

The main principles are:

- Correct the primary cause of the disorder
- Correct those factors which maintain the disorder (esp ***chloride administration*** in the common Cl^- deficient cases)

Repletion of chloride, potassium and ECF volume will promote renal bicarbonate excretion and return plasma bicarbonate to normal.

Must Give Chloride

Chloride administration[1] is essential for correction of chloride-depletion metabolic alkalosis and the alkalosis can be corrected with chloride even if volume depletion persists. Because of electroneutrality requirements it is not possible to give chloride alone, so 'giving chloride' is equivalent to 'giving saline' in most cases. (One exception to this is giving a dilute HCl infusion -see below)

Volume administration will not correct the alkalosis unless the administered fluid contains chloride. This is not difficult though as all available ECF replacement fluids contain chloride so administering these IV fluids to correct the volume deficiency must necessarily replenish chloride.

Maintenance IV fluids (eg 5% dextrose) are poor at replenishing IV volume and contain little or no chloride; they are not useful for this correction and should not be used.

Mineralocorticoid excess causes renal potassium wasting. This can maintain a metabolic alkalosis even in the absence of chloride depletion.

Rarely, it may be advantageous to institute treatments (eg HCl infusion; acetazolamide) that can return the bicarbonate level to normal more quickly.

Rarely, it may be advantageous to institute treatments (hydrochloric acid infusion, or acetazolamide) that can return the bicarbonate level to normal more quickly. These are not routine components of management, and should not deflect attention from correcting the primary cause and from correcting a chloride deficiency, but may be useful for occasional patients with 'resistant' metabolic alkalosis managed in an Intensive Care Unit.

Proton pump inhibitors (eg omeprezole) have been successfully used to decrease gastric acid loss and prevent or ameliorate metabolic alkalosis [2,3,4]

Hydrochloric Acid Infusion

An infusion of hydrochloric acid [5] can be given via a central line [6,7,8]. The correct placement of the line very important. It is confirmed by the ability to easily withdraw blood AND by x-ray confirmation of the tip position. Continued vigilance of the tip position is required; extravasation of acid from a central line has caused death[9].

The infusion will selectively correct the chloride deficiency and the infusion can be titrated to an end-point of a specific bicarbonate level of pH level. The H^+ will consume HCO_3^- provided the excess CO_2 can be ventilated off.

Studies have shown that improvement in gas exchange occurs with a fall in arterial pCO_2 and an increase in arterial pO2. These changes were originally considered to be due to the increase in ventilation that occurs (and the subsequent decrease in pulmonary microatelectasis) but the paO2 will increase even in patients maintained on constant ventilation[7,10]. The probable cause is an improvement in ventilation-perfusion matching. Alkalosis impairs the efficiency of hypoxic pulmonary vasoconstriction so its correction could acutely result in improvements in the lung's V/Q matching and an increase in arterial pO2.

The correction of alkalosis will also result in a right shift in the oxygen dissociation curve which will improve peripheral oxygen unloading.

A HCl infusion is a dramatic way of administering chloride but published reports [7,11,12] attest to its safety and successful use. An increase in arterial pO_2 and a decrease in pCO_2 generally occurs and may assist with weaning from mechaical ventilation. The administration of chloride in a small volume [12] may be useful in patients who are at risk of volume overload.

(Further details about hydrochloric acid infusions)

Use of Acetazolamide

Acetazolamide is a carbonic anhydrase inhibitor which has also been used to speed the rapidity of correction of alkalosis [13]. It is usually more readily available than sterile hydrochloric acid solutions and is a more acceptable therapeutic option. It causes renal bicarbonate loss to increase and plasma bicarbonate levels fall. Only one or two doses probably should be used. Some problems with acetazolamide are:

- Renal losses of water, Na^+ and K^+ increase (so appropriate adjustments in IV fluids and K^+ supplementation are necessary)
- It interferes with CO_2 transport
- It is slower acting and more difficult to titrate to a given bicarbonate level

Other sources of HCl have been used (eg lysine HCl, ammonium chloride). Hepatic metabolism of the ammonium generates hydrogen ions.

These ancillary measures may prove useful in a small number of patients but are not generally recommended.

Treatment Outline -Metabolic Alkalosis

1. Correct cause if possible (eg correct pyloric obstruction, cease diuretics)
2. Correct the deficiency which is impairing renal bicarbonate excretion (ie give chloride, water and K^+)
3. Expand ECF Volume with N/saline (and KCl if K^+ deficiency)
4. Rarely ancillary measures such as:
    - HCl infusion
    - Acetazolamide (one or two doses only)
    - Oral lysine hydrochloride
5. Supportive measures (eg give O_2 in view of hypoventilation; appropriate monitoring and observation)
6. Avoid hyperventilation as this worsens the alkalaemia

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7.7: Assessment

The pattern of high values of [HCO_3^-] and pCO_2 occurring together suggests either a metabolic alkalosis or a respiratory acidosis (or both). If pCO_2 is over 60mmHg, the metabolic alkalosis is either very severe or there is a mixed disorder with a respiratory acidosis.

Metabolic alkalosis is suspected if one of the known causes of the disorder is present especially vomiting, nasogastric suction, pyloric obstruction, excess mineralocorticoid syndromes or diuretic use.

The delta ratio can be a useful adjunct in detecting the presence of a second acid-base disorder in patients with a metabolic acidosis. In patients who have a metabolic acidosis and a chronic metabolic alkalosis the delta ratio has a value greater then 2. Such a high value can also occur in patients with a pre-existing chronic respiratory acidosis because the bicarbonate is also elevated in that disorder as well. Because of potential errors, the delta ratio should be assessed cautiously.

Practical Hints for Bedside Diagnosis of Metabolic Alkalosis

Most cases are easy to diagnose on history and then can be confirmed on arterial blood gases. In patients with mixed acid-base disorders, the structured approach to assessment (discussed in Chapter 9), will usually result in a correct diagnosis.
The most common causes (90% of cases) are:

- Vomiting (or NG tube drainage)
- Diuretic use

Other causes should be mostly obvious (eg post-hypercapnoeic alkalosis in ICU, post-massive transfusion).
If you're still stuck for a diagnosis:

- Spot urine chloride is useful here: low levels suggest Cl^- depletion and need for replacement; high levels suggest adrenocortical excess and need for K^+ replacement
- Consider surreptitious diuretic use in females as there is a certain group who abuse diuretics for 'weight loss'. (Urine Cl^- may be high or low depending on timing of last diuretic dose)
- If nothing more obvious is apparent, don't forget about adrenocortical excess syndromes which are rare but do occur.
- Don't let diagnostic quibbles delay replacement of K^+ if needed as low [K^+] can be life-threatening (& may be worsened by treatment!)

7.8: Prevention

There are 2 aspects of prevention for a metabolic alkalosis:

- Prevention of the primary or initiating process, ***and/or***
- Prevention of the factors that are involved in maintaining the alkalosis.

Patients with nasogastric drainage and pyloric obstruction should receive adequate fluid replacement using a chloride containing fluid. Patients receiving thiazide diuretics likewise need to have adequate chloride intake.

Proton pump inhibitors can be used to greatly decrease gastric acid loss [1,2,3] despite continuing nasogastric drainage.

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Important Points - Chapter 7 : Metabolic Alkalosis

- Metabolic alkalosis is an abnormal primary process causing a decrease in fixed acids in the blood. Buffering results in an increase in plasma bicarbonate level.
- An acute metabolic alkalosis will NOT persist long as the normal kidney rapidly increases bicarbonate excretion from the body
- A metabolic alkalosis requires BOTH an **initiating process** and a **maintaining process**. Without an abnormal process maintaining it, the alkalosis will rapidly correct as the kidney pours out HCO_3^- in the urine.
- The maintaining process causing persistence of the elevated plasma bicarbonate level works by impairing renal bicarbonate excretion. The four factors which are involved in maintaining the disorder are:
  - chloride depletion
  - reduced GFR
  - potassium depletion
  - ECF volume depletion
- The initiating cause in most cases is loss of gastric acid (eg **vomiting**) *or* **diuretic** use. Chloride depletion is the abnormality that impairs renal bicarbonate excretion.
- All these patients (>90% of clinical cases) require chloride replacement (usually as saline solution) before they can be corrected
- Rare causes include various adrenocortical excess syndromes.
- Hypokalaemia is the most common associated electrolyte abnormality and can be life-threatening itself
- Metabolic alkalosis is **classified** into 2 major groups:
  - those causes associated with chloride depletion (urinary chloride > 10 mmol/l), and
  - those causes not associated with chloride depletion (urinary chloride > 20mmol/l)
- Urinary chloride levels are particularly useful in differentiating the cause in those cases where vomiting or thiazide diuretic use are uncertain.
- The compensatory response is hypoventilation but there is variation in the degree of this. Oxygen therapy should be used in most hospital patients.
- Remember: Correction usually requires ***replacement of chloride*** usually in association with fluid and potassium. In rare severe cases, hydrochloric acid infusion or use of acetazolamide may be used but there are risks

CHAPTER OVERVIEW

8: Major Types of Metabolic Acidosis

8.1: Lactic Acidosis

Daily Production of Lactate

Each day the body has an excess production of about 1500 mmols of lactate (about 20 mmols/kg/day) which enters the blood stream and is subsequently metabolised mostly in the liver. This internal cycling with production by the tissues and transport to and metabolism by the liver and kidney is known as the Cori cycle. This normal process does not represent any net fixed acid production which requires excretion from the body.

All tissues can produce lactate under anaerobic conditions but tissues with active glycolysis produce excess lactate from glucose under normal conditions and this lactate tends to spill over into the blood. Lactate is produced from pyruvate in a reaction catalysed by lactate dehydrogenase:

$$\text{Pyruvate} + \text{NADH} + \boldsymbol{H}^+ \Leftrightarrow \text{Lactate} + \text{NAD}^+$$

This reaction is so rapid that pyruvate and lactate can be considered to be always in an equilibrium situation. Normally the ratio of lactate to pyruvate in the cell is 10 to 1. The ratio [NADH]/[NAD^+] by the Law of Mass Action determines the balance between lactate and pyruvate. This ratio is also used to denote the redox state within the cytoplasm. Lactic acid has a pK value of about 4 so it is fully dissociated into lactate and H^+ at body pH. In the extracellular fluid, the H^+titrates bicarbonate on a one for one basis.

Tissue Production & Metabolism

Lactate is released from cells into the ISF and blood.

Tissues Producing Excess Lactate

At rest, the tissues which normally produce excess lactate are:

- skin - 25% of production
- red cells - 20%
- brain - 20%
- muscle - 25%
- gut - 10%

During heavy exercise, the skeletal muscles contribute most of the much increased circulating lactate.[4,5]
During pregnancy, the placenta is an important producer of lactate which passes into both the maternal and the foetal circulations.

Lactate is metabolised predominantly in the liver (60%) and kidney (30%)[6]. Half is converted to glucose (gluconeogenesis) and half is further metabolised to CO_2 and water in the citric acid cycle. The result is no net production of H^+ (or of the lactate anion) for excretion from the body. Other tissues can use lactate as a substrate and oxidise it to CO_2 and water but it is only the liver and kidney that have the enzymes that can convert lactate to glucose.

Note

- The balance between release into the bloodstream and hepatorenal uptake maintains plasma lactate at about one mmol/l.
- The renal threshold for lactate is about 5 to 6 mmols/l so at normal plasma levels, no lactate is excreted into the urine.
- The small amount of lactate that is filtered (180mmol/day) is fully reabsorbed.

Mechanisms involved in Lactic Acidosis

Lactic acidosis can occur due to:

- excessive tissue lactate production
- impaired hepatic metabolism of lactate

In most clinical cases it is probable that both processes are contributing to the development of the acidosis. The liver has a large capacity to metabolise lactate so increased peripheral production alone is unlikely to lead to other than transient acidosis. The situation is analogous to a respiratory acidosis where increased CO_2 production alone is rarely responsible because of the efficient ventilatory regulation of pCO_2. Impaired ventilation (impaired excretion of CO_2) is almost invariably present and responsible for a respiratory acidosis.

In situations where lactic acidosis is clearly due to excessive production alone (such as severe exercise or convulsions), the acidosis usually resolves (due to hepatic metabolism) within about an hour once the precipitating disorder is no longer present. In severe exercise, lactate levels can rise to very high levels eg up to 30 mmol/l. Respiratory compensation for the acidosis may not be significant because of the short time involved. However, there are other causes of hyperventilation present and arterial pCO_2 is typically reduced providing partial compensation. For example, exercise results in markedly increased ventilation and the cause of this is largely unknown. The arterial pCO_2 usually falls with exercise and this is not considered to be due to the lactic acidosis as it occurs even in less severe exercise where there is little excess lactate produced.

A continuing lactic acidosis means that there is continuing production of lactate that exceeds the liver's capacity to metabolise it. This may be due to clearly very excessive production (eg convulsions) with a normal liver at one extreme, or to increased production in associated with greatly impaired hepatic capacity to metabolise it (eg due to cirrhosis, sepsis, hypoperfusion due hypovolaemia or hypotension, hypothermia, or some combinations of adverse factors) at the other extreme.

Definitions

Definitions differ concerning the blood level at which a lactic acidosis is regarded as 'significant'. For our purposes:

Hyperlactaemia: a level from 2 mmols/l to 5 mmol/l.

Severe Lactic Acidosis: when levels are greater than 5 mmols/l

As levels rise above 5mmols/l, the associated mortality rate can become very high. A serious lactic acidosis can be present without much noticeable elevation of the anion gap. This is because the lactate levels associated with high mortality (say 6 to 10 mmols/l) may not cause much change in a derived variable (the anion gap) which has a 95% reference range of +/-5mmols/l.

The brief and often very high lactate levels that occur with severe exercise or generalised convulsions (eg up to 30 mmol/l) are associated with an extremely low mortality rate. Indeed the mortality rate in these causes is usually extremely low. A lactate level of 15 mmols/l in an elderly ill septic patient in an Intensive Care Unit would be associated with a very high risk of death.

The absolute lactate level (alone) is not a good predictor of outcome unless the cause of the high level is also considered.

Lactate can be converted to glucose in the liver and kidney. This part of the Cori cycle is an example of gluconeogenesis.

Anaerobic glycolysis produces lactate and equivalent amounts of H^+ from ATP hydrolysis. If both these reactions are combined, then there is effectively a net production of equal amounts of lactate and H^+ but the low pKa of lactic acid dissociation means that lactic acid (the undissociated form) is present only in miniscule amounts.

Causes of Lactic Acidosis

Lactic acidosis is commonly classified into either Type A or Type B (Cohen & Woods, 1976) with the main differentiating point being the adequacy of tissue oxygen delivery. In both types, the fundamental problem is the inability of the mitochondria to deal with the amount of pyruvate with which they are presented.

Type A lactic acidosis refers to circumstances where the clinical assessment is that tissue oxygen delivery is inadequate. This is the most common clinical situation. The inadequate oxygen supply slows mitochondrial metabolism and pyruvate is converted to lactate (and NADH to NAD^+) The conversion of NADH to NAD^+ is important as it regenerates NAD^+ needed for glycolysis to continue. This situation is known as anaerobic metabolism and results in a small net ATP production: two moles of ATP per mole of glucose. The mitochondrial reactions are presumed to be intact but unable to function because of inadequate oxygen If hypoxaemia is the only factor present, it needs to be severe (eg paO_2 < 35mmHg) to precipitate lactic acidosis because of the protection afforded by the body's compensatory mechanisms which increase tissue blood flow. Similarly anaemia needs to be severe (eg [Hb] <5G%) if present alone because tissue blood flow is increased in compensation.

Reduced perfusion is the most important factor in causing impaired oxygen delivery in type A lactic acidosis.

Anaemia or hypoxaemia alone is not sufficient unless severe or associated with reduced perfusion.

Type B lactic acidosis refers to situations in which there is no clinical evidence of reduction in tissue oxygen delivery. Carbohydrate metabolism is disordered for some reason and excess lactic acid is formed. Research using more sophisticated methods to assess tissue perfusion have now shown that occult tissue hypoperfusion is present in many cases of Type B acidosis.

An **ischaemic bowel** can produce large amounts of lactate. Mesenteric ischaemia can cause a severe lactic acidosis even if perfusion in the rest of the body is adequate. This situation can easily be overlooked especially in those cases where abdominal clinical signs are minimal.

Phenformin is a biguanide oral hypoglycaemic agent which was associated with a severe form of Type B lactic acidosis. The incidence was highest among diabetics with renal insufficiency where blood levels are highest. The mechanism of action is not fully established but the drug probably interferes with mitochondrial function. High levels of phenformin significantly depress myocardial contractility. The decrease in cardiac output undoubtably contributes a major component of tissue hypoperfusion to many cases.

Other factors predisposing to development of lactic acidosis are sepsis, liver failure and some malignancies.

Patients with cirrhosis often have a much reduced ability to take up and metabolise lactate. Despite this, patients with chronic hepatic disease alone do not commonly develop lactic acidosis unless other factors such as sepsis, shock, bleeding or ethanol abuse are also present. So, the development of lactic acidosis in patients with cirrhosis suggests severe liver damage and the presence of other factors. In this setting, death rates are high.

Any factor which stimulates glycolysis (eg catecholamine administration, cocaine) will lead to an increased lactate production. Lactic acidosis occurs in up to 10% of patients presenting with diabetic ketoacidosis. This may be due to poor peripheral perfusion or phenformin administration but may occur without the presence of these factors.

Classification of Some Causes of Lactic Acidosis (Cohen & Woods, 1976)

Type A Lactic Acidosis : Clinical Evidence of Inadequate Tissue Oxygen Delivery

- Anaerobic muscular activity (eg sprinting[7], generalised convulsions)
- Tissue hypoperfusion (eg shock -septic, cardiogenic or hypovolaemic; hypotension; cardiac arrest; acute heart failure; regional hypoperfusion esp mesenteric ischaemia; malaria[8,9])
- Reduced tissue oxygen delivery or utilisation (eg hypoxaemia, carbon monoxide poisoning, severe anaemia)

Type B Lactic Acidosis: No Clinical Evidence of Inadequate Tissue Oxygen Delivery

- **type B1** : Associated with underlying diseases (eg ketoacidosis, leukaemia, lymphoma, AIDS)
- **type B2**: Assoc with drugs & toxins (eg phenformin, cyanide, beta-agonists, methanol, nitroprusside infusion, ethanol intoxication in chronic alcoholics, anti-retroviral drugs)
- **type B3**: Assoc with inborn errors of metabolism (eg congenital forms of lactic acidosis with various enzyme defects eg pyruvate dehydrogenase deficiency)

Note

This list does not include all causes of lactic acidosis

Diagnosis

The condition is often suspected on the history and examination (eg shock, heart failure) and is easily confirmed and quantified by measuring the blood lactate level. A particular problem is the diagnosis of the condition when present as part of a mixed acid-base disorder. It may be associated with other causes of a high anion gap acidosis (eg ketoacidosis, uraemic acidosis) and not be suspected. Coexistent lactic acidosis and metabolic alkalosis may result in minimally altered plasma bicarbonate level. A high anion gap may be a clue in this later situation but the anion gap is not invariably elevated out of the reference range.

Why do clinicians have difficulty diagnosing lactic acidosis?

The main reason is that traditionally a lactate level was an uncommon investigation and the diagnosis of lactic acidosis was by exclusion in patients with a high anion gap metabolic acidosis and some evidence of impaired perfusion. Other factors were a low index of clinical suspicion and a tendency to not appreciate the significance of an elevated lactate result.

The basic investigations needed to supplement the history, examination and electrolyte results in differentiating the causes of a high anion gap acidosis are:

- blood glucose level
- urinary ketones
- urea & creatinine
- urine output
- blood lactate level
- calculation of osmolar gap

Management

The principles of management of patients with lactic acidosis are:

- Diagnose and correct the underlying condition (if possible)
- Restore adequate tissue oxygen delivery (esp restore adequate perfusion)
- Avoid sodium bicarbonate (except possibly for treatment of associated severe hyperkalaemia)

When the circulation is restored, the liver can metabolise the circulating lactate. If lactic acidosis is severe and the cause cannot be corrected, the mortality can be quite high.

What is the role of IV bicarbonate?

Quite large doses of bicarbonate (eg 1,000 to 3,000 mmols/day!) have traditionally been administered to severe cases but the success rate is low. Interestingly, metabolic alkalosis induced by administration of sodium bicarbonate can lead to a substantial increase in the production of lactate. This may be because the intracellular acidosis strongly inhibits phosphofructokinase which is the rate-limiting enzyme in glycolysis. This suggests that bicarbonate therapy could result in induction of alkalosis intracellularly which could release this inhibition and increase pyruvate and lactate production (& thus a vicious cycle). No wonder massive doses of bicarbonate seem necessary and why the outcome is so poor.

[See also: Use of Bicarbonate in Metabolic Acidosis]

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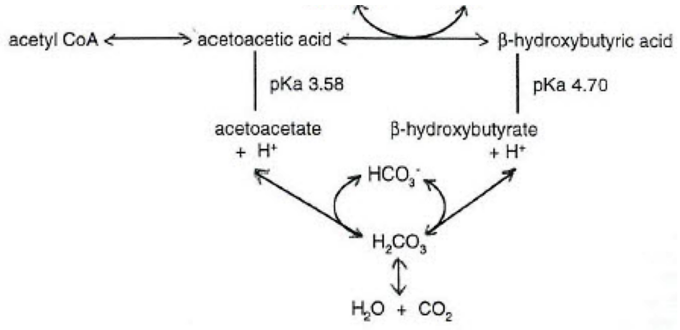
8.2: Ketoacidosis

What is ketoacidosis?

Ketoacidosis is a high anion gap metabolic acidosis due to an excessive blood concentration of ketone bodies (keto-anions). Ketone bodies (acetoacetate, beta-hydroxybutyrate, acetone) are released into the blood from the liver when hepatic lipid metabolism has changed to a state of increased ketogenesis. A relative or absolute insulin deficiency is present in all cases. The major reactions starting from the production of acetoacetate from hepatic acetyl CoA are outlined in the box.

Reactions in Ketoacidosis



Note:

- There is one H^+ produced for each acid anion produced
- Buffering results in the loss of one HCO_3 for each H^+ buffered

Therefore one predicts that:
Increase in Anion Gap = Decrease in [HCO_3^-]

The major ketone bodies are acetoacetate and beta-hydroxybutyrate and the ratio between these two acid anions depends on the prevailing redox state (eg as assessed by the NADH/NAD^+ ratio).

A mixed acid-base disorder may be present (eg lactic acidosis from peripheral circulatory failure, or metabolic alkalosis from vomiting). An associated lactic acidosis may mask the presence of the ketoacidosis. This occurs because the lactic acidosis decreases the acetoacetate : beta-hydroxybutyrate ratio (ie more beta-hydroxybutyrate produced) because NAD^+ is produced in the production of lactate. The common test used to detect ketones (eg Acetest) depends on the reaction of acetoacetate (and to a lesser extent acetone) with the nitroprusside reagent. A decreased acetoacetate level may lead to a weak or absent test reaction despite high total levels of total ketoanions (acetoacetate and beta-hydroxybutyrate combined) because the beta-hydroxybutyrate is not detected.

Outline of Interaction between Lactic Acidosis and Ketoacidosis

diagram to be added

Note

Increased lactate cause increased beta-OHB and decreased AcAc by Law of Mass Action

The three major types of ketosis are:

- Starvation ketosis
- Alcoholic ketoacidosis
- Diabetic ketoacidosis

Starvation Ketosis

When hepatic glycogen stores are exhausted (e.g. after 12-24 hours of total fasting), the liver produces ketones to provide an energy substrate for peripheral tissues. Ketoacidosis can appear after an overnight fast but it typically requires 3 to 14 days of starvation to reach maximal severity. Typical ketoanion levels are only 1 to 2 mmol/l and this will not much alter the anion gap. The acidosis even with quite prolonged fasting is only ever of mild to moderate severity with ketoanion levels up to a maximum of 3 to 5 mmol/l and plasma pH down to 7.3. This is probably due to the insulin level, which though lower, is still enough to keep the FFA levels less than 1mM. This limits substrate delivery to the liver restraining hepatic ketogenesis. Ketone bodies also stimulate some insulin release from the islets. The anion gap will usually not be much elevated.

Alcoholic Ketoacidosis

Typical Presentation

This typical situation leading to alcoholic ketoacidosis is a chronic alcoholic who has a binge, then stops drinking and has little or no oral food intake. Food intake may be limited because of vomiting. The two key factors are the combination of ethanol and fasting. Presentation is typically a couple of days after the drinking binge has ceased.

Pathophysiology

The poor oral intake results in decreased glycogen stores, a decrease in insulin levels and an increase in glucagon levels. Hepatic metabolism of ethanol to acetaldehyde and then to acetate both involve NAD^+ as a cofactor. The NADH/NAD^+ratio rises and this:

- inhibits gluconeogenesis
- favours the production of beta-hydroxybutyrate over acetoacetate

The insulin deficiency results in increased mobilisation of free fatty acids from adipose tissue. The decreased insulin/glucagon ration results in a switch in hepatic metabolism favouring increased beta-oxidation of fatty acids. This results in an increased production of acetylCoA which forms acetoacetate (a keto-acid). (The pathophysiology of the insulin deficiency and the switch in hepatic metabolism is discussed in more detail in DKA section below.)

Other points to note:

- Volume depletion is common and this can result in increased levels of counter-regulatory hormones (eg glucagon)
- Levels of FFA can be high (eg up to 3.5mM) providing plenty of substrate for the altered hepatic lipid metabolism to produce plenty of ketoanions
- GIT symptoms are common (eg nausea, vomiting, abdominal pain, haematemesis, melaena)
- Acidaemia may be severe (eg pH down to 7.0)
- Plasma glucose may be depressed or normal or even elevated
- Magnesium deficiency is not uncommon
- Patients are usually not diabetic

Management

This syndrome is rapidly reversed by administration of glucose and insulin.

This diagnosis is often overlooked. A strong suspicion should be raised in any ill chronic alcoholic with a sweet ketone breath who presents to a hospital Emergency Department. Such patients are often dishevelled, and can be noisy and generally uncooperative.

A mixed acid-base disorder may be present: high anion gap due to ketoacidosis, metabolic alkalosis due to vomiting and a respiratory alkalosis.

8.2.4 Diabetic Ketoacidosis: (DKA)

Pathophysiology

An absolute or relative lack of insulin leads to diabetic metabolic decompensation with hyperglycaemia and ketoacidosis. A precipitating factor (eg infection, stress) which causes an excess of stress hormones (which antagonise the actions of insulin) may be present.

Situations leading to DKA

The most common situations in patients presenting with DKA are:

- Infection as precipitant (30% of cases)
- Treatment non-compliance (20%)
- New diagnosis of diabetes (25%)
- No known precipitating event (25%)

Since the discovery and therapeutic use of insulin, the mortality from DKA has dropped dramatically from 100% to perhaps 2 to 5% in Western countries today. (Lebovitz, 1995)

An outline of the pathophysiology is presented below. The pathogenesis requires two events:

- Increased mobilisation of free fatty acids (FFA) from adipose tissue to the liver
- A switch of hepatic lipid metabolism to ketogenesis

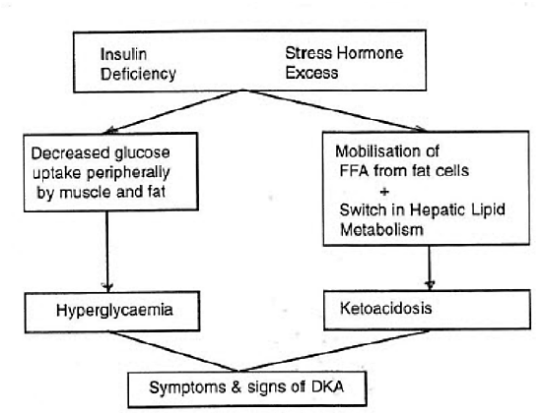
FFA mobilisation is initiated by the effect of absolute or relative insulin deficiency on fat cells. FFA levels can be quite high (eg 2.5 to 3.5 mM). This provides the liver with plenty of substrate. These FFA levels are much less then ketone levels and contribute only a small amount to the metabolic acidosis.

The major switch in hepatic lipid metabolism occurs in response not just to insulin deficiency but additionally to the concomitant rise in levels of the stress hormones (glucagon, corticosteroids, catecholamines, growth hormone). The role of glucagon is the most clearly established. The hepatic effects of a fall in the insulin:glucagon ratio are:

- Increased glycogenolysis
- Increased gluconeogenesis
- Increased ketogenesis

The net effect is an increase in the hepatic output of both ketone bodies and glucose.

Initial Events in Pathophysiology of Diabetic Ketoacidosis (INCOMPLETE)



Why does the major switch in hepatic metabolism occur?

The inhibition of the enzyme acetyl CoA carboxylase is probably the key step. This enzyme is inhibited by increased FFA levels, decreased insulin levels and particularly by the rise in glucagon. All three of these factors are present in DKA. The effect is to decrease the production and level of **malonyl CoA**. This compound has a central role in the regulation of hepatic fatty acid metabolism as is mediates the reciprocal relationship between fatty acid synthesis and oxidation. It is the first committed intermediate in fatty acid metabolism. Malonyl CoA inhibits fatty acid oxidation by inhibiting carnitine acyltransferase I.

A fall in malonyl CoA levels removes this inhibition resulting in excessive fatty acid oxidation with excessive production of acetyl CoA and excess acetoacetate.

Hyperglycaemia & Ketoacidosis cause most symptoms

Two basic mechanisms underlie the pathophysiology of DKA: hyperglycaemia and ketoacidosis. The above discussion shows how both these problems follow from relative insulin deficiency coupled with stress hormone excess. The problem however is not just of hepatic over-production of glucose and ketones but also of peripheral underutilisation of both glucose and ketones.

Acetoacetic acid (pKa 3.58) and beta-hydroxybutyric acid (pKa 4.70) dissociate producing H^+ which is buffered by HCO_3^- in the blood. For each anion produced there is a loss of one bicarbonate. The increase in the anion gap (representing the increase in the unmeasured acid anions) should approximately equal the decrease in the $[HCO_3^-]$. A pure high anion gap metabolic acidosis results.

Development of hyperchloraemic acidosis

In some cases, a hyperchloraemic metabolic acidosis develops: this is most common during the treatment phase. Why does this occur? Acetoacetate and beta-hydroxybutyrate are moderately strong acids and even at the lowest urinary pH are significantly ionised. They are excreted with a cation (usually Na^+ or K^+) to maintain electroneutrality. The net effect is the loss of potential bicarbonate equal to the level of urinary ketone body loss. The HCO_3^- is replaced in the blood by Cl^- derived from renal reabsorption, gut absorption or (particularly) IV saline administered during treatment. The effect is to cause a rise in plasma $[Cl^-]$ and the anion gap returns towards normal despite the persistence of the metabolic acidosis. At presentation, both types of acidosis may be present and the elevation in the anion gap will be less than expected for the degree of depression in the bicarbonate level (resulting in Delta ratio < 0.8).

A predominant hyperchloraemic acidosis (defined as a DKA patient with a delta ratio < 0.4) is present in about 10% of patients on arrival at hospital and in about 70% after 8 hours of treatment. Patients who are more severely dehydrated retain more keto-anions and have a lower incidence of hyperchloraemic acidosis.

Administration of large volumes of normal saline in resuscitation of patients with acute DKA promotes continued diuresis (and continued loss of ketone bodies with Na^+ as the cation) and provides plenty of chloride to replace the lost ketoanions. This hyperchloraemic acidosis is slower to resolve because the keto-anions needed for regeneration of bicarbonate have been lost. Patients who have been able to maintain fluid intake during development of their illness are more likely to have a hyperchloraemic acidosis component present on admission.

Other acid base disorders may be present

It should not just be assumed that the patient only has a diabetic ketoacidosis. Possible complicating acid-base disorders are:

- Lactic acidosis due to hypoperfusion and anaerobic muscle metabolism
- Metabolic alkalosis secondary to excessive vomiting
- Respiratory acidosis due to pneumonia or mental obtundation
- Respiratory alkalosis with sepsis
- Renal tubular acidosis (type 4)

Renal tubular acidosis (type 4) is present in some diabetic patients and the associated urinary acidification defect can cause a hyperchloraemic normal anion gap acidosis. This syndrome (known as *hyporeninemic hypoaldosteronism*) occurs in some elderly diabetics who have pre-existing moderate renal insufficiency but is not a common problem in acute DKA.

Summary of Events in Pathophysiology of DKA

- First: A precipitating event occurs which results in insulin deficiency (absolute or relative) and usually an excess of stress hormones (particularly glucagon)
- Hyperglycaemia occurs due to decreased glucose uptake in fat and muscle cells (due to insulin deficiency)
- Lipolysis in fat cells now occurs promoted by the insulin deficiency releasing FFA into the blood
- Elevated FFA levels provide substrate to the liver
- A switch in hepatic lipid metabolism occurs due to the insulin deficiency and the glucagon excess, so the excess FFA is metabolised resulting in excess production of acetyl CoA.
- The excess hepatic acetyl CoA is converted to acetoacetate (a keto-acid) which is released into the blood
- Ketoacidosis and hyperglycaemia both occur due to the lack of insulin and the increase in glucagon and most of the clinical effects follow from these two factors
- Other acid-base and electrolyte disorders may develop as a consequence and complicate the clinical condition

Management of DKA

An outline of management is presented: this should be tailored to individual circumstances. Management of DKA has passed through 3 stages in the last 100 years:

- Stage 1: Preinsulin era (Feature: mortality of 100%)
- Stage 2: High dose insulin regime (Feature: mortality down to 10% but metabolic complications due to the treatment)
- Stage 3 (the present): Low dose insulin regime (Feature: low mortality)

Mortality with the low dose insulin regime is down to about 2 to 5% overall. In older patients with DKA precipitated by a major medical illness (eg acute pancreatitis, myocardial infarction, septicaemia), the mortality rate is still high due to the severity of the precipitating problem.

Overall aims of treatment

- Replace fluid and electrolyte losses
- Restore normal carbohydrate and lipid metabolism
- Treat the underlying cause
- Manage specific complications

Management can be considered in terms of emergency and routine components.

Emergency Management

A: Airway

- Protect by intubation with a cuffed tube if patient is significantly obtunded.
- Consider placing a nasogastric tube in all patients.

B: Breathing

- Oxygen by mask initially in all patients
- Intubation may be necessary for airway protection or ventilation (eg if aspiration, coma, pneumonia, pulmonary oedema, acute pancreatitis and ARDS) but this is not common.

Special Danger in Ventilated Patients

Maintain compensatory hyperventilation in intubated patients
Patients with metabolic acidosis (eg severe DKA) have marked hyperventilation (ie respiratory compensation, Kussmaul respirations) and typically low arterial pCO_2 levels. If intubated and ventilated, ventilatory parameters (tidal volume and rate) need to be set to continue a high minute ventilation. If this is not done and pCO_2 is inappropriately high, a severe acidaemia and consequent severe cardiovascular collapse may occur
This is a particular problem in all situations where a patient with a compensated metabolic acidosis is intubated and ventilated. The rule of thumb is to aim for a pCO_2 level of 1.5 times the bicarbonate level plus eight as this mimics the normal response by the body. As bicarbonate levels recover, adjust ventilation downwards.

C: Circulation

- If shock is present, this requires urgent colloid infusion to restore intravascular volume and tissue perfusion
- Arrhythmias require urgent clinical management dependent on the type and the clinical situation (eg hyperkalaemia, myocardial infarction)
- The typical patient who presents with poor peripheral perfusion but normotension can be adequately managed initially with ECF replacement fluids (eg Hartmann's solution or Normal saline)

Other Specific Emergency Treatment

Cerebral oedema is a dangerous complication that occurs in about 1% of children and adolescents with DKA.

Onset of headache and deteriorating level of consciousness typically occurs between 2 and 24 hours after onset of treatment. Onset of symptoms is often sudden. Mortality is about 70% in this group.

Recommended treatment is immediate IV mannitol in a dose of 0.5 to 2.0 g/kg body weight. Dexamethasone or hyperventilation have no proven benefit. (Lebovitz, 1995)

DKA : Routine Management

1. General

- Oxygen by mask
- Urinary catheter
- Consider low dose calcium heparin to decrease risk of arterial thrombosis
- Investigate for underlying illness (history, examination, cultures of blood, urine or sputum, chest xray, ECG etc)

2. Fluids

Immediate aim is to restore intravascular volume to improve tissue perfusion.

Replacement solutions (eg Normal saline or Hartmann's solution) are appropriate for initial management. Subsequently fluids need to be adjusted to provide free water to replenish intracellular fluid and to provide glucose. Maintenance fluids such as dextrose-saline or oral fluid intake are appropriate at this later stage depending on the individual circumstances but such solutions should not be used initially.

Colloids are necessary only in shocked patients. Colloids are expensive and have a low but significant risk of reactions. Albumin solutions are not required.

3. Potassium

Serum level is commonly normal or high (due to the acidosis) at presentation despite the presence of a large total body potassium deficit (due to renal losses). The best approach is to commence therapy with fluid and insulin and monitor the serum $[K^+]$.

Potassium replacement can be commenced when the [K^+] falls below 5 mmols/l. Infuse at 10 to 30 mmol/hr dependent on [K^+]. Rates greater than 20 mmols/hr are reserved for severe hypokalaemia and require at least hourly [K^+] monitoring. Never commence a potassium infusion without checking the level.

4. Insulin

Fluid resuscitation is necessary to deliver insulin to its sites of action in liver, muscle and adipose tissue. Rehydration itself will cause a fall in blood glucose level.

A typical regime would be to give a stat dose initially (say 10-20U IV) and commence the patient on a continuous insulin infusion at 5 to 10 U/hr decreasing to 1-3 U/hr to maintain blood glucose at 5 to 10 mmols/l. A paediatric regime would be: insulin at 0.1U/kg IV loading dose then infusion at 0.1U/kg/hr.

The blood glucose always falls on this regime and control of blood glucose is almost never a problem. Insulin reverses the peripheral mobilisation of FFA and alters hepatic metabolism to switch off ketone body production. These effects are maximal at insulin levels of 100 micromoles/l and this level is achieved with the low dose regime. The average rate of fall of plasma glucose at this insulin level is about 4.5 mmol/l/hr. There is no advantage in giving more insulin once the ceiling level is reached. This absence of additional effectiveness with very high insulin levels has been referred to in the past as *insulin resistance*

5. Phosphate

Though a total body deficiency is always present, it has not been possible to show that acute phosphate administration makes any difference to outcome. However the occasional patient develops extremely low phosphate levels and phosphate administration is undoubtably necessary in these patients and must be given. Phosphate level on presentation is typically high so phosphate administration should be delayed.

By twelve hours after commencement of treatment, the majority (90%) of patients are hypophosphataemic. Ampoules of phosphate available in my hospital contain about 15 mmoles of phosphate and 20 mmoles of potassium and one ampoule can be diluted in the IV fluids and infused over an hour.

6. Bicarbonate

Sodium bicarbonate in DKA has arguably a minor role is in urgent management of serious arrhythmias due to hyperkalaemia in DKA. However, glucose-insulin is the preferred treatment in this patient group.

None of the studies done in DKA have shown any benefit of bicarbonate treatment. Potential problems are sodium overload, CSF acidosis, intracellular acidosis, exacerbation of hypokalaemia, rebound alkalosis and impaired tissue oxygen delivery (shift of oxyhaemoglobin dissociation curve). After treatment of DKA starts, the slowest biochemical parameter to recover is usually the serum bicarbonate - this is especially so when substantial amounts of ketones have been lost in the urine. New bicarbonate is generated when the condition is reversed and the ketones are metabolised. Bicarbonate administration is not necessary.

7. Monitoring

Management in an Intensive Care Unit is recommended.

Monitoring should include observations of airway, breathing, circulation and level of consciousness, serial blood gases and electrolytes, urinary ketones and urine output. Serum lactate is occasionally useful. A *Biochemistry Flowchart* of results is strongly recommended.

Cerebral oedema presents 2 to 12 hours after start of treatment

Cerebral oedema is the commonest single cause of mortality, particularly in children. It typically develops after treatment has commenced. A headache or decreasing level of consciousness are the usual initial sign. Onset may be sudden. Treat urgently with IV mannitol. Intubation for airway protection may be required. Maintain hyperventilation in ventilated patients.

8. Treat the Underlying Cause

The commonest precipitants in young diabetics are inadequate insulin (eg first presentation of diabetes, omission of doses) and infection. Often no specific cause can be found. In older diabetics, DKA may be precipitated by a major medical illness (esp infection). Antibiotics or surgical management are necessary in some cases. Patient education to prevent further episodes is very important.

8.3: Acidosis and Renal Failure

Mechanisms

Metabolic acidosis occurs with both acute and chronic renal failure and with other types of renal damage. The anion gap may be normal or may be elevated.

A generalization that can be made is:

- If the renal damage affects both glomeruli and tubules, the acidosis is a high-anion gap acidosis. It is due to failure of adequate excretion of various acid anions due to the greatly reduced number of functioning nephrons.
- If the renal damage predominantly affects the tubules with minimal glomerular damage, a different type of acidosis may occur. This is called Renal Tubular Acidosis (RTA) and this is a normal anion gap or hyperchloraemic type of acidosis. The GFR may be normal or only minimally affected.

Uraemic Acidosis

The acidosis occurring in uraemic patients [1] is due to failure of excretion of acid anions (particularly phosphate and sulphate) because of the decreased number of nephrons. There is a major decrease in the number of tubule cells which can produce ammonia and this contributes to uraemic acidosis.

Serious acidosis does not occur until the GFR has decreased to about 20 mls/min. This corresponds to a creatinine level of about 0.30-0.35 mmols/l.

The plasma bicarbonate in renal failure with acidosis is typically between 12 & 20 mmols/l. Intracellular buffering and bone buffering are important in limiting the fall in bicarbonate. This bone buffering will cause loss of bone mineral (osteomalacia).

Most other forms of metabolic acidosis are of relatively short duration as the patient is either treated with resolution of the disorder or the patient dies. Uraemic acidosis is a major exception as these patients survive with significant acidosis for many years. This long duration is the reason why loss of bone mineral (and bone buffering) is significant in uraemic acidosis but is not a feature of other causes of metabolic acidosis.

Acidosis due to Acute Renal Failure

Retention of metabolic acids occurs with acute renal failure.

The clinical details in these patients are often complex and the actual severity of acidosis is variable. Some other complicating factors are catabolism (increased metabolic acid production), vomiting, diarrhoea, lactic acidosis due to poor perfusion, bicarbonate therapy and dialysis.

Hyperkalaemia is often present and is often the factor determining the need for acute dialysis.

References

1. Kraut JA and Kurtz I. *Metabolic acidosis of CKD: diagnosis, clinical characteristics, and treatment.* Am J Kidney Dis 2005 Jun; 45(6) 978-93. PubMed

8.4: Hyperchloraemic Metabolic Acidosis

Is this the same as normal anion gap acidosis?

In hyperchloraemic acidosis, the anion-gap is normal (in most cases). The anion that replaces the titrated bicarbonate is chloride and because this is accounted for in the anion gap formula, the anion gap is normal.

There are **TWO problems** in the definition of this type of metabolic acidosis which can cause confusion. Consider the following:

What is the difference between a "hyperchloraemic acidosis" and a "normal anion gap acidosis"?

These terms are used here as though they were synonymous. This is mostly true, *but* if hyponatraemia is present the plasma [Cl^-] may be normal despite the presence of a normal anion gap acidosis. This could be considered a '*relative hyperchloraemia*'. However, you should be aware that in some cases of normal anion-gap acidosis, there will not be a hyperchloraemia if there is a significant hyponatraemia.

In a disorder that typically causes a high anion gap disorder there may sometimes be a normal anion gap!

The anion gap may still be within the reference range in lactic acidosis. Now this can be misleading to you when you are trying to diagnose the disorder. Once you note the presence of an anion gap within the reference range in a patient with a metabolic acidosis you naturally tend to concentrate on looking for a renal or GIT cause.

Now how could this happen?

1. One possibility is the increase in anions may be too low to push the anion gap out of the reference range.

In lactic acidosis, the clinical disorder can be severe but the lactate may not be grossly high (eg lactate of 6mmol/l) and the change in the anion gap may still leave it in the reference range. So the causes of high anion gap acidosis should be considered in patients with hyperchloraemic acidosis if the cause of the acidosis is otherwise not apparent. Administration of IV saline solution may replace lost acid anion with chloride so that treatment may result in the acidosis converting to a hyperchloraemic type.

2. Another possibility is intracellular movement of acid anions in exchange for chloride

In lactic acidosis, the movement of lactate intracellularly in exchange for chloride occurs via an antiport. It has been found that when lactic acidosis occurs in association with grand mal seizures then as many as 30% of this group of patients may present with a hyperchloraemic component to their acidosis. This is an interesting situation because the lactic acidosis is due solely to muscular over-production, occurs rapidly & can be severe BUT it also resolves rapidly. This should therefore be a pure lactic acidosis initially without any respiratory compensation or evidence of other acid-base problem. So if we find a hyperchloraemic component this clearly suggests that the lactate is being taken up by some cells in exchange for chloride. This movement of the acid anion intracellularly is one mechanism responsible for a hyperchloraemic component in some types of high anion gap acidosis.

3. The situation may also be due to the wide normal range of the anion gap.

This could result in a situation where the anion gap is only elevated slightly or still within the normal range due to the combination of small errors in the measurement of the component electrolytes.

Causes of Hyperchloraemic Acidosis

Some of the causes are listed in the Table in Section 5.2 and some of these are discussed below. Renal tubular acidosis is discussed in the next section.

A review of these causes shows that the predominant mechanism is **loss of base** (bicarbonate or bicarbonate precursors) and this may occur by either GIT or renal mechanisms. A gain of acid can occur with certain infusions but this situation can be diagnosed easily on history.

In general then the diagnosis of a normal anion gap acidosis is just to look for evidence of one of only two mechanisms:

- GIT loss of base
- Renal loss of base

A key question is to distinguish GIT causes from renal causes. In most cases, this will be obvious from the history. In some cases though some factors may be involved or there may be some doubt as to which cause is the most significant.

GIT Bicarbonate Loss

Secretions into the large and small bowel are mostly alkaline with a bicarbonate level higher than that in plasma. Excessive loss of these fluids can result in a normal anion gap metabolic acidosis.

Some typical at risk clinical situations are:

- severe diarrhoea
- villous adenoma
- external drainage of pancreatic or biliary secretions (eg fistulas)
- chronic laxative abuse
- administration of acidifying salts

Severe diarrhoea

This can cause either a metabolic acidosis or a metabolic alkalosis. Development of a significant acid-base disturbance requires a significant increase in stool water loss above its normal value of 100 to 200 mls/day. The more fluid and anions lost, the more marked the problem.

Hyperchloraemic metabolic acidosis tends to be associated with acute infective diarrhoea. This is the classical finding in patients with cholera. The problem is an excessive loss of bicarbonate in the diarrhoeal fluid. Diarrhoeas which are caused by predominantly *colonic* pathology may cause a metabolic alkalosis: this includes chronic diarrhoeas due to ulcerative colitis, colonic Crohn's disease and chronic laxative abuse.

The acid-base situation with severe diarrhoea can be complicated by other factors (see Table below) and it may not be possible to completely sort out all the factors in the acid-base disturbance in an individual case.

Multiple Factors which affect Acid-Base balance in patients with Severe Diarrhoea

Situation	Comment
Acute infective diarrhoea (small bowel origin)	Normal anion gap(hyperchloraemic) metabolic acidosis due loss of bicarbonate
Chronic colonic diarrhoea	May be metabolic alkalosis due predominant loss of Cl^-
Hypovolaemia causing prerenal renal failure	High anion gap acidosis due to renal retention of phosphate &sulphate.
Hypovolaemia causing peripheral circulatory failure	Type A lactic acidosis
Hypovolaemia causing an increase in plasma protein concentration (increased unmeasured anion)	Increased anion gap
Vomiting	Metabolic alkalosis due loss of gastric HCl
Abdominal pain	Hyperventilation (respiratory alkalosis)

Villous adenoma

This can cause hypokalaemia. Acid-base disorders may also occur: this is:

- a hyperchloraemic acidosis if bicarbonate is the principal anion lost, *or:*
- a metabolic alkalosis if chloride is the predominant anion lost.

If hypovolaemia occurs, this may cause a metabolic acidosis. Plasma bicarbonate levels of less than 10 mmol/l have been recorded.

Drainage of pancreatic or biliary secretions

Loss of these secretions can cause a hyperchloraemic acidosis due to the high bicarbonate levels in these secretions. The frequency and severity depend on the daily volume of secretions lost. Low output fistulae don't cause a problem. Pharmacological treatments (eg somatostatin) which decrease the volume lost by high output fistulae are effective at preventing the acidosis.

Losses via a nasogastric tube

In patients with a small bowel obstruction, these losses can be predominantly of bile and pancreatic secretions and cause an acidosis (rather than an alkalosis as is usual with severe vomiting). Patients on proton pump inhibitors or H2-blockers may also be

more likely to lose predominantly alkaline secretions.

Urinary Diversions

Implantation of the ureters into the sigmoid colon or a vesicocolic fistula can result in a hyperchloraemic acidosis due to absorption of Cl^- in exchange for HCO_3^- across the bowel mucosa. Absorption of urinary NH_4^+ in the sigmoid colon may also contribute to the development of acidosis as metabolism of the ammonium in the liver results in production of H^+. Some of these patients develop renal failure related to infection, stones or urinary obstruction. This can result in uraemic acidosis or renal tubular acidosis as well.

Acidosis is much less of a problem with an ileal conduit (acidosis incidence 2 to 20%) than it was with the older procedure of ureterosigmoidostomy (incidence 30-80%). (Incidence data from Cruz, 1997) This is because the continuous external drainage from the ileal conduit usually results in a short dwell time in the conduit with minimal time for Cl^--HCO_3^- exchange.

The presence of urinary diversion operations will usually be obvious from the history.

Other Causes

Recovery Phase of Diabetic Ketoacidosis

Hyperchloraemic metabolic acidosis commonly develops during therapy of diabetic ketoacidosis. The mechanisms involved have been discussed in Section 8.2. The mechanism is effectively renal loss of base even though it is not bicarbonate which is lost in the urine. The actual loss is of ketoacids (keto-anions) and water. When therapy commences, the ketoacids are metabolised in the liver resulting in the production of equal amounts of bicarbonate. If excessive ketoacids have been lost in the urine and fluid therapy is initially with normal saline, there is a deficiency of bicarbonate precursors and a surfeit of chloride to replace bicarbonate. Correction of the acidosis will now involve renal excretion of chloride and its replacement with bicarbonate. This is a slower process than metabolism of ketoacids to regenerate bicarbonate. The net result then is that full correction of the acidosis is much slower when a hyperchloraemic acidosis develops.

Chronic Administration of Carbonic Anhydrase Inhibitors

Normally 85% of filtered bicarbonate is reabsorbed in the proximal tubule and the remaining 15% is reabsorbed in the rest of the tubule. In patients receiving acetazolamide (or other carbonic anhydrase inhibitors), proximal reabsorption of bicarbonate is decreased and distal delivery is increased. The distal tubule has only a limited capacity to reabsorb bicarbonate and when exceeded bicarbonate appears in the urine. This results in a hyperchloraemic metabolic acidosis. This can be considered as essentially a form of proximal renal tubular acidosis (see section 8.5) but is usually not classified as such.

Oral Ingestion of Acidifying Salts

Oral administration of $CaCl_2$ or NH_4Cl is equivalent to giving an acid load. Both of these salts are used in acid loading tests for the diagnosis of renal tubular acidosis. $CaCl_2$ reacts with bicarbonate in the small bowel resulting in the production of insoluble $CaCO_3$ and H^+.The hepatic metabolism of NH_4^+ to urea results in an equivalent production of H^+.

8.5: Renal Tubular Acidosis

Definition

Renal Tubular Acidosis (RTA) is a syndrome due to either a defect in proximal tubule bicarbonate reabsorption, or a defect in distal tubule hydrogen ion secretion, or both. This results in a hyperchloraemic metabolic acidosis with normal to moderately decreased GFR. Anion gap is normal. A typical situation where RTA would be suspected is if urine pH is greater than 7.0 despite the presence of a metabolic acidosis.

In contrast, the acidosis that occurs with acute, chronic, or acute on chronic renal failure is a high anion gap metabolic acidosis.

As a general overview to help understand why renal disease can give different types of acidosis consider the following: Acidosis due to renal disease is considered in 2 categories depending on whether the predominant site of renal damage is in the *glomeruli* or in the *tubules*.

Renal tubular acidosis is a form of hyperchloraemic metabolic acidosis which occurs when the renal damage primarily affects tubular function without much effect on glomerular function. The result is a decrease in H^+ excretion which is greater than can be explained by any change in GFR. In contrast, if glomerular function (ie GFR) is significantly depressed (hence 'renal failure'), the retention of fixed acids results in a high anion gap acidosis.

Acidosis and Location of Renal Damage

- Predominantly tubular damage ---> Normal anion gap acidosis (Renal tubular acidosis - RTA)
  - Distal (or type 1) RTA
  - Proximal (or type 2) RTA
  - Type 4 RTA
- Predominantly glomerular damage ---> High anion gap acidosis
  - Acidosis of acute renal failure
  - Uraemic acidosis

Three main clinical categories or 'types' of renal tubular acidosis (RTA) are now recognised but the number of possible causes is large. The mechanism causing the defect in ability to acidify the urine and excrete acid is different in the three types. [1,2]

Distal (Type 1) Renal Tubular Acidosis

This is also referred to as classic RTA or distal RTA. The problem here is an inability to maximally acidify the urine. Typically urine pH remains > 5.5 despite severe acidaemia ($[HCO_3^-]$ < 15 mmol/l). Some patients with less severe acidosis require acid loading tests (eg with NH_4Cl) to assist in the diagnosis. If the acid load drops the plasma $[HCO_3^-]$ but the urine pH remains > 5.5, this establishes the diagnosis.

There are many different causes but the majority of cases can be placed into one of several groups:

General Classification of Causes

- Hereditary (genetic) [3,4]
- Autoimminue diseases (eg Sjogren's syndrome, SLE, thyroiditis)
- Disorders which cause nephrocalcinosis (eg primary hyperparathyroidism, vitamin D intoxication)
- Drugs or toxins (eg amphotericin B, toluene inhalation)
- Miscellaneous - other renal disorders (eg obstructive uropathy)

The basic problem is reduced H^+ secretion in the distal nephron but there are several possible mechanisms (see table below).

Pathophysiological Mechanisms in Reduced H^+ Secretion in Distal Tubule

- **"Weak pump"** - Inability for H^+ pump to pump against a high H^+ gradient
- **"Leaky membrane"** - Back-diffusion of H^+ [eg This occurs in RTA due amphotericin B]
- **"Low pump capacity"** - Insufficient distal H^+ pumping capacity due to tubular damage.

Typical findings are an inappropriately high urine pH (usually > 5.5), low acid secretion and urinary bicarbonate excretion despite severe acidosis. Renal sodium wasting is common and results in depletion of ECF volume and secondary hyperaldosteronism with increased loss of K^+ in the urine. The diagnosis of type 1 RTA is suggested by finding a hyperchloraemic acidosis in association with an alkaline urine particularly if there is evidence of renal stone formation.

Treatment with $NaHCO_3$ corrects the Na^+ deficit, restores the extracellular fluid volume and results in correction of the hypokalaemia. Typical alkali requirements are in the range of 1 to 4 mmol/kg/day. K^+ supplements are only rarely required. Sodium and potassium citrate solutions can be useful particularly if hypokalaemia is present. Citrate will bind Ca^{++} in the urine and this assists in preventing renal stones.

Diagnosis of Distal Renal Tubular Acidosis

Hyperchloraemic metabolic acidosis associated with a urine pH > 5.5 despite plasma [HCO_3^-] < 15 mmol/l

Suppportive findings: hypokalaemia, neprocalcinosis, presence of a disorder known to be associated with RTA (see list in text)

Note

If [HCO_3^-] > 15 mmol/l, then acid loading tests are required to establish the diagnosis.

Proximal (Type 2) Renal Tubular Acidosis

Pathophysiology

Type 2 RTA is also called proximal RTA because the main problem is greatly impaired reabsorption of bicarbonate in the proximal tubule.

At normal plasma [HCO_3^-], more than 15% of the filtered HCO_3^- load is excreted in the urine. When acidosis is severe and HCO_3^- levels are low (eg <17 mmols/l), the urine may become bicarbonate free. Symptoms are precipitated by an increase in plasma [HCO_3^-]. The defective proximal tubule cannot reabsorb the increased filtered load and the distal delivery of bicarbonate is greatly increased. The H^+ secretion in the distal tubule is now overwhelmed by attempting to reabsorb bicarbonate and the net acid excretion decreases. This results in urinary loss of HCO_3^- resulting in systemic acidosis with inappropriately high urine pH. The bicarbonate is replaced in the circulation by Cl^-.

The increased distal Na^+ delivery results in hyperaldosteronism with consequent renal K^+ wasting. The hypokalaemia may be severe in some cases but as hypokalaemia inhibits adrenal aldosterone secretion, this often limits the severity of the hypokalaemia.

Hypercalciuria does not occur and this type of RTA is not associated with renal stones. During the NH_4Cl loading test, urine pH will drop below 5.5.

Note that the acidosis in proximal RTA is usually not as severe as in distal RTA and the plasma [HCO_3^-] is typically greater than 15 mmol/l.

Causes

There are many causes but most are associated with multiple proximal tubular defects eg affecting reabsorption of glucose, phosphate and amino acids. Some cases are hereditary.[5] Other causes include vitamin D deficiency, cystinosis, lead nephropathy, amyloidosis and medullary cystic disease.

Treatment

Treatment is directed towards the underlying disorder if possible. Alkali therapy ($NaHCO_3$) and supplemental K^+ is not always necessary. If alkali therapy is required, the dose is usually large (up to 10 mmols/kg/day) because of the increased urine bicarbonate wasting associated with normal plasma levels. K^+ loss is much increased in treated patients and supplementation is required. Some patients respond to thiazide diuretics which cause slight volume contraction and this results in increased proximal bicarbonate reabsorption so less bicarbonate is needed.

Type 3 Renal Tubular Acidosis

This term is no longer used. Type 3 RTA is now considered a subtype of Type 1 where there is a proximal bicarbonate leak in addition to a distal acidification defect.

Type 4 Renal Tubular Acidosis

A number of different conditions have been associated with this type but most patients have renal failure associated with disorders affecting the renal interstitium and tubules. In contrast to uraemic acidosis, the GFR is greater than 20 mls/min.

Useful differentiating point: Hyperkalaemia occurs in type 4 RTA (but NOT in the other types)

The underlying defect is impairment of cation-exchange in the distal tubule with reduced secretion of both H^+ and K^+. This is a similar finding to what occurs with aldosterone deficiency and type 4 RTA can occur with Addison's disease or following bilateral adrenalectomy. Acidosis is not common with aldosterone deficiency *alone* but requires some degree of associated renal damage (nephron loss) esp affecting the distal tubule. The H^+ pump in the tubules is not abnormal so patients with this disorder are able to decrease urine pH to < 5.5 in response to the acidosis.

The table below provides a useful summary of some of the key points in differentiating the types of renal tubular acidosis.

Comparison of Major Types of RTA

	Type 1	Type 2	Type 4
Hyperchloraemic acidosis	Yes	Yes	Yes
Minimum Urine pH	>5.5	<5.5 (but usually >5.5 before the acidosis becomes established)	<5.5
Plasma potassium	Low-normal	Low-normal	High
Renal stones	Yes	No	No
Defect	Reduced H^+ excretion in distal tubule	Impaired HCO_3^- reabsorption in proximal tubule	Impaired cation exchange in distal tubule

Incomplete forms of RTA also occur. The arterial pH is normal in these patients and acidosis develops only when an acid load is present.

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8.6: Metabolic Acidosis due to Drugs and Toxins

Several drugs and toxins have been implicated as direct or indirect causes of a high-anion gap metabolic acidosis (HAGMA). A consideration of these drugs needs to be included in an differential diagnosis of a HAGMA. The three most common ones to consider are methanol, ethylene glycol and salicylates. Other toxins which can cause acidosis are isopropyl alcohol and butoxyethanol. Toluene also causes an acidosis and the anion gap may be normal or elevated.

The acidosis caused by these toxins may sometimes present as a normal anion-gap hyperchloraemic acidosis so don't exclude the diagnosis in such a circumstance.

Co-ingestion of ethanol delays the metabolism of the more toxic methanol and ethylene glycol but can also delays the diagnosis. In this situation the osmolar gap will be even more elevated than can be explained by the measured ethanol level alone.

[See also Section 11.3: Acid-Base Disorders due to Drugs & Toxins.]

Methanol Poisoning

Presentation & Diagnosis

Ingestion of methanol can occur accidentally, or deliberately if used as an ethanol substitute.

Methanol itself is non-toxic. Onset of symptoms is delayed until the toxic metabolites are produced by the liver. Because the hepatic metabolism is slow, there is usually a considerable **latent period** (12-48 hours) before any toxic effects develop. Patients presenting early with a history of methanol ingestion have few symptoms due to the methanol (other than mild CNS depression), but may have symptoms due to other drugs or toxins (e.g. ethanol). Additionally co-ingestion of ethanol also contributes to the latent period by delaying metabolism of methanol.

Patients presenting late are often deeply comatose and bradycardic with depressed respirations. Survivors have a high incidence of irreversible blindness. Abdominal pain is a common symptom and may be due to acute pancreatitis.

Diagnosis may be delayed if the history is not available (e.g. obtunded patient) or because of the significant delay between ingestion and symptoms. Early diagnosis is important because prompt and effective treatment can decrease mortality and decrease the incidence of blindness. A useful screening test is determination of the osmolar gap. If the osmolar gap is greater than 10, it indicates the presence of appreciable quantities of low molecular weight substances such as methanol. This can alert you to the diagnosis before the acidosis (due to metabolites) develops. As the methanol is metabolised, the osmolar gap returns toward normal and the anion gap increases. A patient presenting late after a significant ingestion may have a normal osmolar gap and a high anion gap acidosis. The osmolar gap is more likely to be elevated in methanol ingestion than with ethylene glycol ingestions because of the lower molecular weight of methanol. Osmolar gaps of >100 have been reported.

The ideal way to assess and monitor response to treatment is to measure methanol blood levels. This test is NOT readily available at short notice in laboratories because of infrequent need and because the test is labour intensive. Specimens often are transferred to a larger hospital where batch testing may only be done every week or two. Treatment should NOT be delayed because of delays in obtaining a blood methanol level. Methanol levels >20mg/dl are associated with severe toxicity.

The most serious toxic manifestations are:

- metabolic acidosis
- visual impairment which can be permanent blindness
- CNS depression ('intoxication') up to coma
- death

In patients with severe acidosis (indicating high formic acid levels), the mortality rate may be 50% or more.

Pathophysiology

Methanol is slowly converted to formaldehyde (by alcohol dehydrogenase), then rapidly to formic acid (by formaldehyde dehydrogenase) in the liver. Formic acid is then slowly metabolised (by 10-formyl tetrahydrofolate dehydrogenase). This particular combination of slow, fast, then slow reactions accounts for the delay in onset of toxic effects (latency), and the prolonged effect (accumulation of formic acid).

As little as 10 mls of pure methanol can cause permanent visual disturbance, 30mls can be fatal, but 100mls is the median lethal dose in an adult. (See ref)

Methanol is not directly toxic, but formic acid is both directly toxic (e.g. direct optic nerve toxicity) and inhibits mitochondrial cytochrome oxidase (causing a form of histotoxic hypoxia). The acidosis is due to both formic acid, and acidic metabolites (such as lactate) from the mitochondrial dysfunction. The worsening of the acidosis due to these other acids results in lower dissociation of formic acid and more diffusion of this undissociated formic acid across cell membranes to produce more intracellular effects. As methanol is converted to its metabolites, the osmolar gap falls (due less low MW uncharged methanol) and the anion gap rises (due increased charged formate anion).

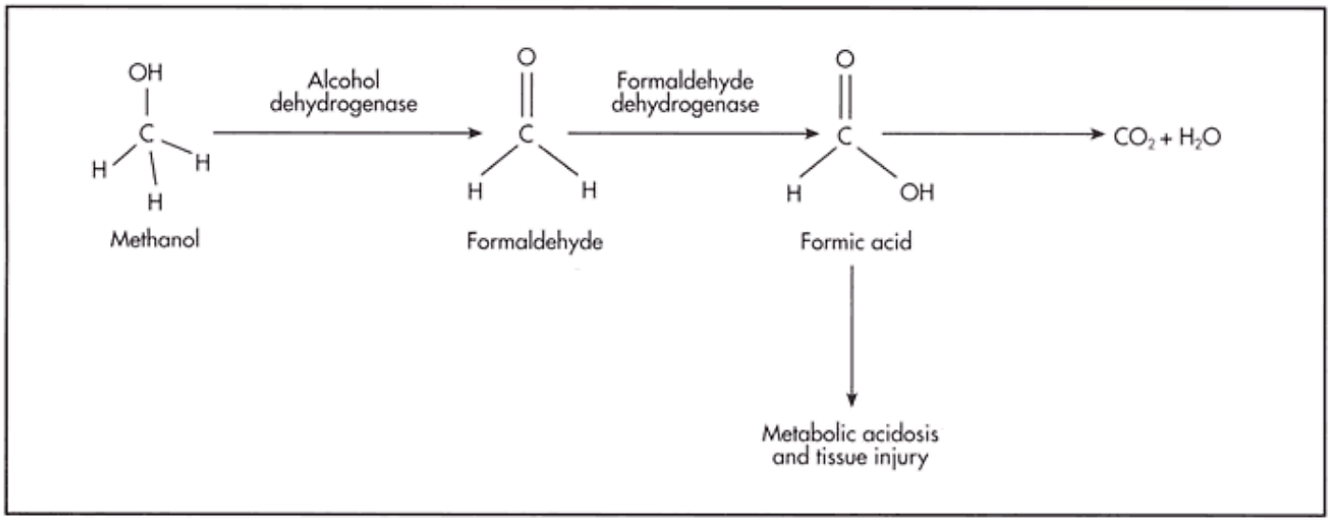

Figure 8.6.1: *Metabolism of Methanol*

Some patients ingest ethanol as well as methanol and this (fortuitously) is protective as it further delays the metabolism and limits the peak levels of the toxic metabolites. Such co-ingestion of ethanol can cause diagnostic problems. Clinicians are typically alerted to the possibility of ingestion of methanol (or ethylene glycol) by the combination of an acidosis and CNS symptoms (eg intoxication). Ethanol can mislead the clinician because its further delays the onset of the acidosis, 'explains' the presence of intoxication and also explains the presence of an osmolar gap. (See here for more details).

'Methylated spirits' is freely available in Australia from hardware stores. In addition to its high ethanol content (say 95%) this product contains other chemicals to discourage human ingestion. These additives may be toxic (e.g. methanol) or have a very disagreeable taste (e.g. pyridine). Methylated spirits in Australia and New Zealand no longer contains methanol, but the situation may be different in other countries.

Acid-Base Disorders in Methanol Toxicity

- Initially no acid-base disorder ('latent period') while methanol is metabolised to formic acid
- Later, typically develop a high anion gap metabolic acidosis (due to formic acid and histotoxic hypoxia)
- May also develop a respiratory acidosis secondary to CNS depression (with depression of respiratory centre and/or airway obstruction)
- May occasionally present with normal anion gap acidosis with a smaller ingestion
- If patient is an alcoholic, there may other acid-base disorders present as well (eg alcoholic ketoacidosis, starvation ketoacidosis, lactic acidosis, respiratory acidosis due aspiration, respiratory alkalosis due chronic liver disease.)
- Consequently, sorting out the acid-base diagnosis in an individual can be complicated and delayed, and because of the potentially serious adverse outcome treatment often needs to commence before the definitive diagnosis of methanol toxicity has been made
- Acidosis in a patient with an elevated osmolar gap should raise clinical suspicion of methanol ingestion and lead to prompt management. The contribution of ethanol to such osmolar gap can be quickly assessed by a (readily available) blood alcohol level.

Treatment

This is a general guide only presented in the context of understanding acid-base disorders, and is not meant to be a practical guide to the treatment of any individual patient.

Treatment must be individualised to individual patient circumstances. The best outcome is obtained with patients who present early, particularly during the latent period, and when clinical suspicion leads to prompt appropriate management by experienced clinicians. For details see the AACT Practice Guidelines for the Treatment of Methanol Toxicity.

Principles of Treatment of Methanol Poisoning

1. Emergency Management

Resuscitation: Airway, Breathing, Circulation. Obtunded patients require intubation for airway protection and ventilation. Emergency care should commence pre-hospital.

2 . Methanol Removal from body

Haemodialysis is the most effective technique; it also removes ethanol so ethanol infusion rate must be increased during periods of dialysis

3 . Blocking of Metabolism

This involves competitive inhibition of alcohol dehydrogenase (ADH). The aim is to delay the production of the toxic metabolites (and limit their peak concentrations). The delay also increases urinary methanol excretion. Two agents are currently in use:

- **Ethanol**: "Ethanol blocking" treatment is the traditional treatment but has the disadvantage of causing intoxication (CNS depression). It is also irritant and should be given via a central line.
- **Fomepizole** (aka 4-methylpyrazole): This is currently approved for this use in some countries (eg USA and Canada as 'Antizol'). Its advantages are effectiveness, ease of administration and absence of intoxication. Its use may obviate the need for haemodialysis in patients without visual impairment or severe acidosis.

4. Intensive supportive care and monitoring

Management in an Intensive Care Unit is recommended; Intubation & mechanical ventilation may be indicated if there is inadequate airway protection (eg CNS depression) or inadequate ventilation; Monitoring includes methanol levels (if available), osmolar gap, anion gap, serum creatinine, and ethanol level (if used).
If intubated, hyperventilation should be maintained to mimic the body's compensatory response

Fomepizole Use

Fomepizole is preferred to ethanol if it is available. The drug is an orphan drug in some countries. It is not currently (2014) available in Australia. In 2012 an application was made to include fomepizole in the WHO list of essential drugs. IV ethanol can be used instead but may even that may not be readily available in sufficient amounts in Australian hospitals.

A typical course of fomepizole would be:

- Initial 15mg/kg IV bolus (over 30 minutes)
- 10mg/kg IV bolus at 12 hourly intervals for 4 doses
- Increase to 15mg/kg IV after 48 hours
- Continue until methanol levels are low (eg <20mg/dl)

Fomepizole has an affinity for alcohol dehydrogenase which is 8,000 times higher than that of methanol. Its use can result in methanol levels remaining almost constant. This effectively blocks production of the toxic metabolites and methanol is slowly excreted in urine. Haemodialysis can remove methanol from the body more rapidly. Fomepizole is an extremely effective antidote to methanol poisoning if started soon after the ingestion. Fomepizole induces its own metabolism so its dose needs to be increased after 48 hrs.

Ethanol therapy requires a blood level of 100-150 mg/dl to be effective and to maintain this level regular monitoring of blood ethanol level and adjustment of infusion rate is required. The patient is significantly intoxicated by this therapeutic ethanol level. Fomepizole does not cause any intoxication.

Australian perspective: Methanol poisoning is now rare within Australia. Methanol produced in Australia is present in some model and racing car fuels, and may be present in toxic amounts in home-distilled alcohol beverages, but the current risk is ingestion of adulterated alcoholic drinks by locals on holiday in Bali.

[Example Acid-base Case: Child with ingestion of Windscreen washer fluid]

Ethylene Glycol Poisoning

Ethylene glycol is a colorless sweet tasting solvent which is used in antifreeze solutions. It is nontoxic itself but is converted to toxic metabolites in the liver:

- **Glycolic acid** (->glycolate anion) is the major contributor to the often severe high anion gap acidosis that develops
- **Oxalic acid** (->oxalate anion) is one of the final metabolic products which is excreted in the urine. Precipitation of calcium oxalate crystals in the kidney causes renal failure if a sufficient dose has been ingested.

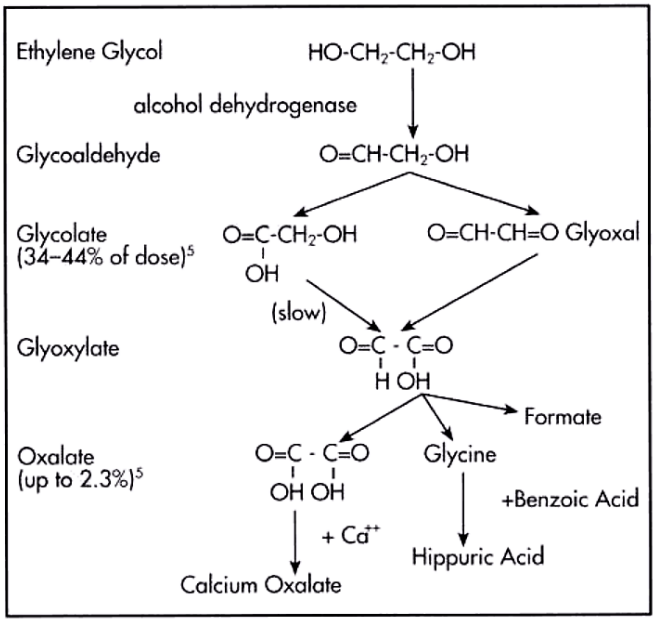

Figure 8.6.2: *Metabolism of Ethylene Glycol*

If untreated, ingestion of only 30 to 60 mls may be sufficient to cause permanent organ damage or death. The osmolar gap may be raised (to > 10) early in the course but this is variable.

The detection of calcium oxalate crystals in the urine is often stated to be a useful guide but this is wrong. Certainly. these crystals have a characteristic appearance (lsee figure below) and a urinanalysis will easily detect them. The problem is that oxalate crystals in urine are generally very common (80% of specimens) and their presence alone means nothing for a diagnosis of ethylene glycol ingestion. Oddly, cases of ethylene glycol ingestion have also been reported without oxalate crystals in the urine. There is also no point in differentiating between the monohydrate and the dihydrate crystals.

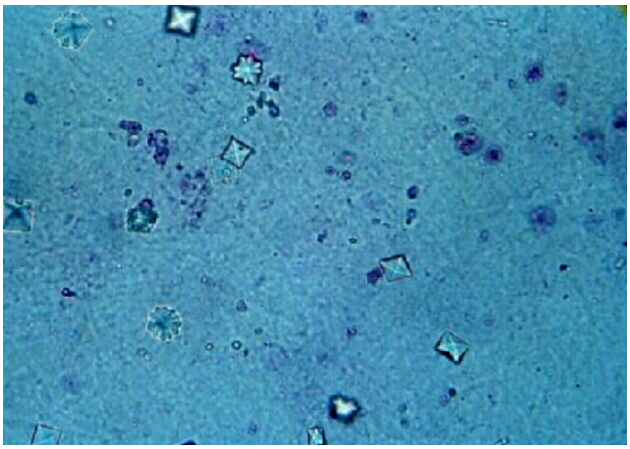

Figure 8.6.3: *Calcium dihydrate crystals in urine - the ones with the 'folded envelope' appearance*

Toxicity is usually considered as occurring in 3 stages: intoxication, cardiorespiratory changes and renal toxicity (see below)

Stages of Ethylene Glycol Toxicity

Stage 1: Intoxication

Up to 12 hours post-ingestion

- An ethanol-like intoxicated state (without an appropriate odour on the breath) progressing to CNS depression
- Fits and coma may occur
- A high anion gap metabolic acidosis develops
- Nausea, vomiting, arrhythmias and tetany (due to hypocalcaemia) may occur

Stage 2: Cardiorespiratory Changes

From 12 to 24 hours post-ingestion.

- Tachycardia, tachypnoea. Shock may occur in major ingestions

Stage 3: Renal Toxicity

At 24-72 hrs post-ingestion

Acute anuric renal failure may occur due to precipitation of calcium oxalate crystals in the renal tubules.

Principles of Treatment of Ethylene Glycol Poisoning

1. Emergency Management

R esuscitation: Airway, Breathing, Circulation. Obtunded patients require intubation for airway protection and ventilation.

2. Ethylene Glycol Removal from body

- Haemodialysis is the most effective technique; it also removes ethanol so ethanol infusion rate must be increased during periods of dialysis
- Avoid lavage - Lavage is effective only if used within the first hour after ingestion and patients do not present within this interval.
- Avoid activated charcoal - This is NOT effective

3. Blocking of Metabolism

- **Ethanol**: "Ethanol blocking" treatment is the traditional treatment but has the disadvantage of causing intoxication (CNS depression). It is also irritant and should be given via a central line.
- **Fomepizole** ('Antizol'): This is currently approved for this use in some countries (eg USA and Canada). Its advantages are effectiveness, ease of administration and absence of intoxication. Its use may obviate the need for haemodialysis in patients without severe acidosis.

4. Intensive supportive care & monitoring

Management in Intensive Care Unit is recommended; Intubation & mechanical ventilation may be indicated if there is inadequate airway protection (eg CNS depression) or inadequate ventilation.

If intubated, hyperventilation must be maintained to mimic the body's compensatory response

Salicylate Toxicity

Salicylate overdose causes a high anion gap metabolic acidosis in both children and adults. Adults commonly develop a mixed acid-base disorder as a respiratory alkalosis due to direct respiratory centre stimulation occurs as well. This second disorder is uncommon in children.

Acid-Base Disorders in Salicylate Toxicity

Adults: Metabolic acidosis AND Respiratory alkalosis

Children: Metabolic acidosis

If fasting=>starvation ketosis may develop

Regarding pharmacokinetics of salicylate:

- Absorption: Salicylates are readily absorbed in the unionised form from the small intestine
- Metabolism: The major route of biotransformation is conjugation with glycine in the liver
- Excretion: The amount of drug excreted unchanged in the urine is small but can be markedly increased if urine is alkaline

Large overdoses of aspirin can cause a large tablet mass or bezoar in the stomach. This delays absorption and plasma salicylate levels continue to rise over 20 hours or more. For this reason, serial salicylate levels should be measured until the peak has been reached. Repeated oral doses of activated charcoal are indicated in this situation.

High levels of salicylate are toxic because the drug uncouples oxidative phosphorylation as well as inhibiting some enzymes in the cell.

Salicylates directly stimulate the respiratory center to cause hyperventilation (respiratory alkalosis) which is dose-dependent. This stimulation is much more pronounced in adults than in children.

Metabolic acidosis is the most serious acid-base disorder and is due to increased production of endogenous acids rather than the salicylate itself. Plasma salicylate levels rarely exceed a maximum of about 5 mmol/l and the decrement in the [HCO3] is significantly higher than this in these severe cases.

Acidosis is much more pronounced in infants as compared to adults, which is the reverse of the situation with the hyperventilation. In adults, respiratory alkalosis usually predominates. The particular organic acid anions involved in the acidosis of salicylate intoxication have not been identified.

Ketoacidosis may also occur in children who are ill and fasted (ie starvation ketosis).

The combination of metabolic acidosis and respiratory alkalosis can be a difficult situation to diagnose from the blood gases. The problem relates to whether the hyperventilation is primary (ie respiratory alkalosis) or is compensatory for the metabolic acidosis.

Simple urinary alkalinisation with administration of sodium bicarbonate is used to increase urine pH to between 7.5 and 8.5. Hypokalaemia is a risk and potassium should be given at the same time. Hypokalaemia also interferes with the kidney's ability to alkalinise the urine. One recommended regime for an adult is to administer one litre of 1.26% sodium bicarbonate solution (containing 20-40mmols of K^+) IV over a 3 hour period

Clinical Presentation

The presentation in severe overdose is a comatose patient with marked hyperventilation and possibly convulsions. Small children usually have a fever. In adults, the diagnosis of overdose or over-ingestion is usually easily made from the history.

Clinicians should have a high index of suspicion in children with a metabolic acidosis particularly if ketoacidosis, lactic acidosis and renal failure have been excluded.

Another clue is that salicylates greatly increase urinary uric acid excretion and plasma urate level is usually very low. If suspicious of overdose it is better to measure salicylate level urgently.

Urine can be screened with a ferric chloride test for salicylates.

Principles of Treatment of Salicylate Toxicity

1. Emergency Management

Resuscitation: Airway, Breathing, Circulation. Obtunded patients require intubation for airway protection and ventilation.

2. Salicylate Removal from body

- **Alkaline diuresis**: Urinary excretion is very significantly increased by alkalisation of the urine. This may be easily achieved by giving IV sodium bicarbonate to raise urine pH to between 7.5 and 8.5; It is advisable to give K^+ to avoid hypokalaemia. Plasma [K^+] should be regularly monitored. ('Forced alkaline diuresis' should be avoided as it confers no advantage and can cause fluid overload.) However, **IV fluid loading** is generally important to assist in maintaining an adequate urine output.
- **Haemodialysis** is more effective and is the treatment of choice in severe poisonings. Criteria for dialysis are severe clinical features, resistant metabolic acidosis, renal failure or salicylate level >700mg/l.
- Gastic lavage is not useful unless time from ingestion is short.
- Activated charcoal - repeated doses can delay absorption; particularly indicated if tablet concretion has formed in the stomach

3. Intensive supportive care & monitoring

Management in Intensive Care Unit is recommended; Intubation & mechanical ventilation is indicated in comatose or significantly obtunded patients.
If intubated, hyperventilation must be maintained to mimic the body's compensatory response

Toluene toxicity

Inhalation of toluene (eg by 'glue-sniffing') may cause either a high anion-gap or a normal anion gap acidosis. The high anion gap is probably a consequence of its metabolism to hippuric acid.

Toluene may also cause significant renal damage especially with chronic use. A consequence of this is a toluene-induced renal tubular acidosis in some patients.

Patients with toluene toxicity may initially be suspected of having ethylene glycol toxicity especially as the presentation may be similar (eg a patient with mental obtundation, appearance of intoxication and a metabolic acidosis). These disorders have different treatments and differentiation is important. Toluene toxicity can cause very profound **hypokalaemia** and often present with muscle weakness and may develop serious arrhythmias (eg ventricular tachycardia).

Overview of Toxic Ingestions

Overview of Diagnosis of Toxic Ingestions.

As a general rule, the diagnosis of a toxic ingestion should be actively investigated in a patient with a high anion gap acidosis where a diagnosis of ketoacidosis, lactic acidosis or renal failure is not apparent. Treatment can be life-saving if diagnosis is made early.

Key Points:

- High index of suspicion (esp if patient appears intoxicated)
- Always check the osmolar gap if you have the slightest concern (If >10 then suspect ethylene glycol, methanol or ethanol)
- **Don't be put off if there is a normal anion gap or a normal osmolar gap as both these situations can occur even with life-threatening ingestions.**

Guidelines

- Always pursue a cause for a high anion gap acidosis and consider factors suggestive of toxic ingestions
- Toxic ingestions usually have predominant **neurological signs and symptoms**
- Routine measurement of a lactate level is useful in excluding this as the cause of the acidosis

Important Points in Diagnosing High Anion Gap Acidosis

Ketoacidosis	Can be excluded if normoglycaemia & urine negative for ketones
Lactic acidosis	Excluded if lactate level is normal. Suggested if shock or peripheral hypoperfusion.
Renal failure	Excluded as cause of acidosis if urea and creatinine normal or only slightly elevated. (In chronic renal failure acidosis is uncommon if creatinine is < 0.30 mmol/l)
Methanol	Suggested if visual impairment and CNS depression or intoxication. Abdominal pain is common. Check the osmolar gap. Do NOT delay therapy until blood level obtained.
Ethylene glycol	Suggested if appear intoxicated and no visual disturbance. Check the osmolar gap but it is often normal.
Salicylate	Suggested if marked hyperventilation (esp in adults) **and** mental obtundation.

8.7: Use of Bicarbonate in Metabolic Acidosis

Metabolic acidosis causes adverse metabolic effects (see Section 5.4). In particular the adverse effects on the cardiovascular system may cause serious clinical problems.

Bicarbonate is an anion and cannot be given alone. Its therapeutic use is as a solution of sodium bicarbonate. An 8.4% solution is a molar solution (ie it contains 1mmol of HCO_3^- per ml) and is the concentration clinically available in Australia. This solution is very hypertonic (osmolality is 2,000 mOsm/kg).

Why Use Alkali?

The main goal of alkali therapy is to counteract the extracellular acidaemia with the aim of reversing or avoiding the adverse clinical effects of the acidosis (esp the adverse cardiovascular effects).

Other reasons for use of bicarbonate in some cases of acidosis are:

- emergency management of hyperkalaemia
- to promote alkaline diuresis (eg to hasten salicylate excretion)

Undesirable effects of bicarbonate administration

In general, the severity of these effects are related to the amount of bicarbonate used. These undesirable effects include:

- hypernatraemia
- hyperosmolality
- volume overload
- rebound or overshoot alkalosis
- hypokalaemia
- impaired oxygen unloading due to left shift of the oxyhaemoglobin dissociation curve
- acceleration of lactate production by removal of acidotic inhibition of glycolysis
- CSF acidosis
- hypercapnia

Important points about bicarbonate

1. Ventilation must be adequate to eliminate the CO_2 produced from bicarbonate

Bicarbonate decreases H^+ by reacting with it to to produce CO_2 and water. For this reaction to continue the product (CO_2) must be removed. So bicarbonate therapy can increase extracellular pH only if ventilation is adequate to remove the CO_2. Indeed if hypercapnia occurs then as CO_2 crosses cell membranes easily, intracellular pH may decrease even further with further deterioration of cellular function.

2. Bicarbonate may cause clinical deterioration if tissue hypoxia is present

If tissue hypoxia is present, then the use of bicarbonate may be particularly disadvantageous due to increased lactate production (removal of acidotic inhibition of glycolysis) and the impairment of tissue oxygen unloading (left shift of ODC due increased pH). This means that with lactic acidosis or cardiac arrest then bicarbonate therapy may be dangerous.

3. Bicarbonate is probably not useful in most cases of high anion gap acidosis

Lactic acidosis can get worse if bicarbonate is given. Clinical studies have shown no benefit from bicarbonate in diabetic ketoacidosis. In these cases, the only indication for bicarbonate use is for the emergency management of severe hyperkalaemia.

4. The preferred management of metabolic acidosis is to correct the primary cause and to use specific treatment for any potentially dangerous complications

The organic acid anions serve as bicarbonate precursors to regenerate new bicarbonate once the primary cause is treated. In some forms of acidosis specific treatment to prevent problems is possible (eg ethanol blocking therapy in ethylene glycol poisoning.)

If hyperkalaemia is present then $[K^+]$ can be decreased by bicarbonate therapy. Also, bicarbonate therapy can cause an alkaline diuresis which hastens renal salicylate excretion.

5. Bicarbonate therapy may be useful for correction of acidaemia due to non-organic (or mineral) acidosis (ie normal anion gap acidosis)

In non-organic acidosis, there is no organic anion which can be metabolised to regenerate bicarbonate. Once the primary cause is corrected, resolution of the acidaemia occurs more rapidly if bicarbonate therapy is used. Amounts sufficient for only partial correction of the disorder should be given. The aim is to increase arterial pH to above 7.2 to minimise adverse effects of the acidaemia and to avoid the adverse effects of bicarbonate therapy. If the patient is improving without serious clinical problems then waiting (for renal bicarbonate regeneration) and watching (for clinical improvement) is a better strategy than giving bicarbonate.

CHAPTER OVERVIEW

9: Assessment of Acid-Base Disorders

9.1: Structured Approach to Assessment

The purpose of this chapter is to teach a structured method for the assessment of acid-base disorders. The three stages involved are outlined in the table below.

Structured Approach to Diagnosis of Patients with Acid-Base Disorders

First: Initial Clinical Assessment

A clinical assessment based on clinical details is an essential first step

- From the history, examination and initial investigations, make a clinical decision as to what is the most likely acid-base disorder(s).
- This is very important but be aware that in some situations, the history may be inadequate, misleading or the range of possible diagnoses large.
- Mixed disorders are often difficult: the history and examination alone are usually insufficient in sorting these out.

Second: Acid-Base Diagnosis

Perform a systematic evaluation of the blood gas and other results and make an acid-base diagnosis

The steps are outlined in Section 9.2

Finally: Clinical Diagnosis

Synthesise the information to make an overall clinical diagnosis

Attempt to produce an overall diagnosis of the patient's condition to guide therapy. Do not view the acid-base disorder in isolation. The history, examination and results often allow very early diagnosis but it is very useful to systematically check the whole picture.

The essential first step is to assess the available clinical information (history, examination, investigations) and use this to make a clinical decision as to the possible and most likely acid-base diagnosis. A knowledge of the pathophysiology of conditions which cause acid-base disorders is extremely useful in making these initial assessments.

Sometimes these initial assessments are easy but sometimes they are misleading but in all cases they provide an initial clinical hypothesis used to guide the next step. Consider the following clinical scenario as a practical example.

Example 9.1.1

Initial Clinical Assessment : An Example

History: A 23 year old woman with a history of insulin-dependent diabetes mellitus is on holidays and is not using her insulin regularly. She presents with vomiting, polyuria and feels unwell. Clinically she is tachypnoeic and looks ill. Findings on urinalysis are 4+ glucose and 2+ ketones.

Asessment: The diagnosis is obvious on this information: the patient has a significant diabetic ketoacidosis. Further investigations such as arterial blood gases and plasma biochemistry will provide:

- confirmation of the diagnosis
- assessment of severity of the acid-base disorder
- evidence of the presence of other acid-base disorders (ie a mixed disorder)

The clinical assessment provides your initial orientation as to what is most likely. Effectively, you are maximising your use of the available clinical information and setting up a hypothesis about the diagnosis which you then test. You also use your knowledge of the pathophysiology to consider what other disorders or complications may coexist or may develop.

What other acid-base disorders could be present?

If she has pneumonia, respiratory compensation could be inadequate indicating the presence of a respiratory acidosis. These patients are significantly volume depleted and impaired perfusion can lead to a lactic acidosis and prerenal azotaemia. Excessive infusion of normal saline can lead to a hyperchloraemic metabolic acidosis and this has implications for therapy and expectations for the rate of correction of the acidosis. Vomiting can lead to a metabolic alkalosis. Useful investigations to sort out these are arterial blood gases, electrolytes, anion gap, urea and creatinine, glucose and lactate. So the obvious simple diagnosis can turn out to be much more complex.

9.2: Systematic Evaluation of Acid-Base Status

The next stage of assessment is to systematically evaluate the arterial blood gas results and other results to make a complete diagnosis of the acid-base disturbance. An overview of the six sequential steps involved are outlined below and then again in detail on the opposite page.

CAUTION: An occasional problem occurs due to incorrect transcription of blood-gas results. If you are working from a hand-written copy of results then you should always consider whether there has been an error in writing the results down (eg mis-heard over the phone for example). A check of pH, pCO_2 & HCO_3^- against the Henderson-Hasselbalch equation is usually difficult without a calculator. However, a quick check of the logical consistency of the results is often possible. For example, pH must be less then 7.4 if PCO_2 is high & HCO_3^- is low. It is preferable to review the result print-out from the machine.

The Six Steps of Systematic Acid-Base Evaluation

1. pH: Assess the net deviation of pH from normal
2. Pattern: Check the pattern of bicarbonate & pCO_2 results
3. Clues: Check for additional clues in other investigations
4. Compensation: Assess the appropriateness of the compensatory response
5. Formulation: Bring the information together and make the acid base diagnosis
6. Confimation: Consider if any additional tests to check or support the diagnosis are necessary or available & revise the diagnosis if necessary

The **first step** is to look at the arterial pH. A net acidaemia means that an acidosis must be present. A net alkalaemia means that an alkalosis must be present. A normal pH gives 2 possibilities: no acid-base disorder or a mixed disorder with an alkalosis compensating for an acidosis

The **next step** is to determine whether any disorder is of the respiratory or metabolic type by reviewing the pattern and magnitude of the bicarbonate and pCO_2 results. If the disorder is a simple one (ie only one primary disorder present) then the acid-base disorder is diagnosed at this step. But the real problem is that this is not known so the evidence must always be checked for evidence of a mixed disorder. This is an important part of steps 2, 3 and 4

Systematic Approach to Blood Gas Analysis

1. pH: Check arterial pH

Principle: The net deviation in pH will indicate whether an acidosis or an alkalosis is present (but will not indicate mixed disorders)

Guidelines:

- IF an acidaemia is present THEN an acidosis must be present
- IF an alkalaemia is present THEN an alkalosis must be present
- IF pH is normal pH THEN Either (no acid-base disorder is present) ***or*** (Compensating disorders are present ie a mixed disorder with an acidosis and an alkalosis)

2. PATTERN: Look for suggestive pattern in pCO_2 & $[HCO_3^-]$

Principle: Each of the simple disorders produces predictable changes in $[HCO_3^-]$ & pCO_2.

Guidelines:

- IF Both $[HCO_3^-]$ & pCO_2 are low THEN Suggests presence of either a Metabolic Acidosis or a Respiratory Alkalosis (but a mixed disorder cannot be excluded)
- IF Both $[HCO_3^-]$ & pCO_2 are high THEN Suggests presence of either a Metabolic Alkalosis or a Respiratory Acidosis (but a mixed disorder cannot be excluded)
- IF $[HCO_3^-]$ & pCO_2 move in opposite directions THEN a mixed disorder MUST be present

Which disorder is present is dependent on which change is primary and which is compensatory, and this requires an assessment based on the history, examination & other results.

3. CLUES: Check for clues in the other biochemistry results

Principle: Certain disorders are associated with predictable changes in other biochemistry results

Examples: See separate list of 'Aids to Interpretation' below

4. COMPENSATION: Assess the Compensatory Response

Principle: The 6 Bedside Rules are used to assess the appropriateness of the compensatory response.

Guidelines:

- If the expected & actual values match => no evidence of mixed disorder
- If the expected & actual values differ => a mixed disorder is present

5. FORMULATION: Formulate the Acid-Base Diagnosis

- Consider all the evidence from the history, examination & investigations and try to formulate a complete acid-base diagnosis

6. CONFIRMATION: Check for specific biochemical evidence of particular disorders for confirmation

Principle: In some cases, further biochemical evidence can confirm the presence of particular disorders. Changes in these results may be useful in assessing the magnitude of the disorder or the response to therapy.

Examples: Lactate, urinary ketones, salicylate level, aldosterone level, various tests for renal tubular acidosis

Step 3 involves reviewing other results looking for specific evidence of particular disorders. Some of these 'clues' are outlined in the table below. In most circumstances, these clues are confirmatory of the expected diagnosis but on occasion can alert to the presence of an unanticipated second disorder. An elevated anion gap can be particularly useful. Most of these 'clues' are obtained from the biochemistry profile. An alert clinician can often correctly pick the diagnosis before the gas results are back.

Some Aids to Interpretation of Acid-Base Disorders

"Clue"	*Significance*
High anion gap	*Always* strongly suggests a metabolic acidosis.
Hyperglycaemia	If ketones also present in urine -> diabetic ketoacidosis
Hypokalaemia and/or hypochloraemia	Suggests metabolic alkalosis
Hyperchloraemia	Common with normal anion gap acidosis
Elevated creatinine and urea	Suggests uraemic acidosis or hypovolaemia (prerenal renal failure)
Elevated creatinine	Consider ketoacidosis: ketones interfere in the laboratory method (Jaffe reaction) used for creatinine measurement & give a falsely elevated result; typically urea will be normal.
Elevated glucose	Consider ketoacidosis or hyperosmolar non-ketotic syndrome
Urine dipstick tests for glucose and ketones	Glucose detected if hyperglycaemia; ketones detected if ketoacidosis

The 4th step is to assess acid-base compensation. The approach discussed here involves the use of a set of six rules. These are discussed in Section 9.3. Much of the emphasis here is to pick the presence of a second acid-base disorder.

Step 5: The stage should now be reached in that a definitive overall acid-base assessment can be made.

Step 6: Sometimes the diagnosis suggests additional tests that can be used to confirm the diagnosis or at least allow more precise diagnosis. An example would be a measurement of blood salicylate level in a child which if high can confirm a clinical suspicion of a salicylate overingestion. If a diagnosis of renal tubular acidosis is suspected then further specific tests can be done to further specify the diagnosis.

available upon request.

9.3: Bedside Rules for Assessment of Compensation

The Six Bedside Rules

The method of assessing acid-base disorders discussed here uses a set of six rules which are used primarily to assess the magnitude of the patient's compensatory response. These rules are now widely known and are soundly based experimentally. These rules are used at Step 4 of the method of Systematic Acid-Base Diagnosis outlined in Section 9.2.- (You should read section 9.1 & 9.2 before this section.) These rules are called 'bedside rules' because that can be used at the patient's bedside to assist in the assessment of the acid-base results. The rules should preferably be committed to memory - with practice this is not difficult.

A full assessment of blood-gas results must be based on a clinical knowledge of the individual patient from whom they were obtained and an understanding of the pathophysiology of the clinical conditions underlying the acid-base disorder. Do not interpret the blood-gas results as an intellectual exercise in itself. It is one part of the overall process of assessing and managing the patient.

Know the clinical details of the patient

A set of blood-gas and electrolyte results should NOT be interpreted without these initial clinical details. They cannot be understood fully without knowledge of the condition being diagnosed.

Find the cause of the acid-base disorder

Diagnosing a metabolic acidosis, for example, is by itself, often of little clinical use. What is really required is a more specific diagnosis of the cause of the metabolic acidosis (eg diabetic ketoacidosis, acute renal failure, lactic acidosis) and to initiate appropriate management. The acid-base analysis must be interpreted and managed in the context of the overall clinical picture.

The snapshot problem: Are the results 'current'?

Remember also that a set of blood gas results provides a snapshot at a particular point in time and the situation may have changed since the blood gases were collected so serial assessment of results can be important in assessment (eg of response to therapy).

Determine the major primary process then select the correct rule

The major primary process is usually suggested by the initial clinical assessment and an initial perusal of the arterial pH, pCO_2 and [HCO_3^-] results. Once this major primary process is known, then the appropriate rule is chosen to assess the appropriateness of the patient's compensatory response.

The rules assess compensation and are a guide to detecting the presence of a second primary acid-base disorder: For example in a patient with a metabolic acidosis if the measured pCO_2 level was higher than is expected for the severity and duration of the metabolic disorder, than this points to the coexistence of a respiratory acidosis. With a little practice the rules are simple to remember and are quick and easy to apply at the bedside. Rules 1 to 4 are best remembered by the description rather then memorizing the formula. These rules are outlined below

Rules for Respiratory Acid-Base Disorders

Rule 1 : The 1 for 10 Rule for Acute Respiratory Acidosis

The [HCO_3^-] will increase by 1 mmol/l for every 10 mmHg elevation in pCO_2 above 40 mmHg.

$$\text{Expected } [HCO3^-] = 24 + \frac{\text{Actual } pCO_2 - 40}{10}$$

Comment: The increase in CO_2 shifts the equilibrium between CO_2 and HCO_3^- to result in an acute increase in HCO_3^-. This is a simple physicochemical event and occurs almost immediately.

Example: A patient with an acute respiratory acidosis (pCO_2 60mmHg) has an actual [HCO_3^-]of 31mmol/l. The *expected [*HCO_3^-*]* for this acute elevation of pCO_2 is 24 + 2 = 26mmol/l. The actual measured value is higher than this indicating that a metabolic alkalosis must also be present.

Rule 2 : The 4 for 10 Rule for Chronic Respiratory Acidosis

The $[HCO_3^-]$ will increase by 4 mmol/l for every 10 mmHg elevation in pCO_2 above 40mmHg.

$$\text{Expected } [HCO_3^-] = 24 + 4 \cdot \frac{\text{Actual } pCO_2 - 40}{10}$$

Comment: With chronic acidosis, the kidneys respond by retaining HCO_3^- that is, renal compensation occurs. This takes a few days to reach its maximal value.

Example: A patient with a chronic respiratory acidosis (pCO_2 60mmHg) has an actual $[HCO_3^-]$ of 31mmol/l. The expected $[HCO_3^-]$ for this chronic elevation of pCO_2 is 24 + 8 = 32mmol/l. The actual measured value is extremely close to this so renal compensation is maximal and there is no evidence indicating a second acid-base disorder.

Rule 3 : The 2 for 10 Rule for Acute Respiratory Alkalosis

The $[HCO_3^-]$ will decrease by 2 mmol/l for every 10 mmHg decrease in pCO_2 below 40 mmHg.

$$\text{Expected } [HCO_3^-] = 24 - 2 \cdot \frac{40 - \text{Actual } pCO_2}{10}$$

Comment: In practice, this acute physicochemical change rarely results in a $[HCO_3^-]$ of less than about 18 mmol/s. (After all there is a limit to how low pCO_2 can fall as negative values are not possible!) So a $[HCO_3^-]$ of less than 18 mmol/l indicates a coexisting metabolic acidosis.

Rule 4 : The 5 for 10 Rule for a Chronic Respiratory Alkalosis

The $[HCO_3^-]$ will decrease by 5 mmol/l for every 10 mmHg decrease in pCO_2 below 40 mmHg.

$$\text{Expected } [HCO_3^-] = 24 - 5 \cdot \frac{40 - \text{Actual } pCO_2}{10} \text{ (range: } \pm 2)$$

Comments:

- It takes 2 to 3 days to reach maximal renal compensation
- The **limit of compensation** is a $[HCO_3^-]$ of about 12 to 15 mmol/l

9.3.3: Rules for Metabolic Acid-Base Disorders

Rule 5 : The One & a Half plus 8 Rule - for a Metabolic Acidosis

The expected pCO2 (in mmHg) is calculated from the following formula:

$$\text{Expected } [pCO_2] = 1.5 \times [HCO_3^-] + 8 \text{ (range: } \pm 2)$$

Comments:

- Maximal compensation may take 12-24 hours to reach
- The **limit of compensation** is a pCO_2 of about 10 mmHg
- Hypoxia can increase the amount of peripheral chemoreceptor stimulation

Example: A patient with a metabolic acidosis ($[HCO_3^-]$ 14mmol/l) has an actual pCO_2 of 30mmHg. The expected pCO_2 is $1.5 \times 14 + 8)$ which is 29mmHg. This basically matches the actual value of 30 so compensation is maximal and there is no evidence of a respiratory acid-base disorder (provided that sufficient time has passed for the compensation to have reached this maximal value). If the actual pCO_2 was 45mmHg and the expected was 29mmHg, then this difference (45-29) would indicate the presence of a respiratory acidosis and indicate its magnitude. See Section 5.5 for more details.

Rule 6 : The Point Seven plus Twenty Rule - for a Metabolic Alkalosis

The expected pCO2(in mmHg) is calculated from the following formula:

$$\text{Expected } [pCO_2] = 0.7 \cdot [HCO_3^-] + 20 \text{ (range: } \pm 5)$$

Comment: The variation in pCO_2 predicted by this equation is relatively large. (The reasons for this are discussed in section 7.5)

The combination of a low $[HCO_3^-]$ and a low pCO_2 occurs in metabolic acidosis and in respiratory alkalosis. If only one disorder is present it is usually a simple matter to sort out which is present. The factors to consider are:

- The history usually strongly suggests the disorder which is present
- The net pH change indicates the disorder if only a single primary disorder is present (eg acidaemia => acidosis)
- An elevated anion gap or elevated chloride define the 2 major groups of causes of metabolic acidosis

Remember that only primary processes are called acidosis or alkalosis. The compensatory processes are just that-- compensation. Phrases such as secondary respiratory alkalosis should not be used. (see Section 3.1)

Check Anion Gap and Delta Ratio

An elevated Anion Gap always strongly suggests a Metabolic Acidosis.

- If AG is 20-30 then high chance (67%) of metabolic acidosis
- If AG is > 30 then a metabolic acidosis is definitely present

If a metabolic acidosis is diagnosed, then the Delta Ratio should be checked

Delta Ratio Assessment Guidelines in patients with a metabolic acidosis

- < 0.4 - Hyperchloraemic normal anion gap acidosis
- 0.4 to 0.8 - Combined high AG and normal AG acidosis
- 1 - Common in DKA due to urinary ketone loss
- 1 to 2 - Typical pattern in high anion gap metabolic acidosis
- > 2 Check for either a co-existing Metabolic Alkalosis (which would elevate [HCO_3^-]) or a co-existing Chronic Respiratory Acidosis (which results in compensatory elevation of [HCO_3^-])

9.4: Assessment- The Rationale

The rules assess compensation & are therefore a guide to detecting the presence of a second primary acid-base disorder

Rules 1 to 4 deal with respiratory acid-base disorders and provide a simple way to calculate the [HCO_3^-] that would be expected in a person who has a simple respiratory acid-base disorder. That is they predict the maximal amount of compensation that would occur.

Question: How were these rules determined?

Answer: By direct animal and human experimentation. For example, the pCO_2 of the subjects was altered and the blood gases were measured. The data from these whole-body titrations allowed the normal physiological response and its time course to be quantified.

Question: What is the principle behind the use of these rules?

Answer: The rules allow calculation of the compensatory response that would be 'expected' if the primary respiratory or metabolic acid-base disorder were the only disorder present. That is, we predict the expected compensatory response so that we can separate what is expected (ie compensation) from the unexpected (ie a co-existent second disorder).

For example, consider a patient with a primary metabolic acidosis. Using rule 5, we calculate what we expect the arterial pCO_2 will be in that person if this metabolic acidosis was the ONLY acid-base disorder present. We then compare this 'expected' pCO_2 with the actual pCO_2 (ie the measured value in the patient). If there is a significant difference between these two values, then this 'reveals' the presence of a second primary acid-base disorder (In this case, a discrepancy would reveal a co-existent respiratory acid-base disorder.)

Question: Are there limitations in this method?

Answer: Yes. Certain combinations of primary acid-base disorders cannot be revealed in this way.

In particular, if the patient has two types of primary metabolic acidosis, then this cannot be detected by this method (However, there are other ways to detect this as discussed elsewhere).

In general, the rules are useful for detecting a co-existent respiratory disorder in a patient with a metabolic disorder (or, conversely detecting a co-existent metabolic disorder in a patient with a respiratory disorder.)

Mixed acid-base disorders

A mixed acid-base disorder is present when two or more primary disorders are present simultaneously. Assessment of mixed disorders requires knowledge of the expected degree of compensation that is present with all of the simple acid-base disorders. This is the knowledge that is summmarised in the Interpretation Rules described in section 9.1. The history and examination are necessary to diagnose all acid-base disorders but are particularly useful in sorting out a mixed disorder.

A **double disorder** is present when any two primary acid-base disorders occur together, but not all combinations of disorders are possible.

The particular exclusion here is that *a mixed respiratory disorder can never occur* as carbon dioxide can never be both over- and under-excreted by the lungs at the same time!

You can however have a mixed acid base disorder with simultaneous metabolic acidosis and alkalosis. For example you could have a patient with gastric outlet obstruction who has been vomiting for several days to the extent they have become severely volume depleted with poor peripheral perfusion and pre-renal failure. Such a patient could have a severe metabolic alkalosis (from the loss of gastric acid from vomiting) and also a metabolic acidosis (eg lactic acidosis from poor perfusion & maybe an acidosis from the acute renal failure).

A **triple disorder** is present when a respiratory acid-base disorder occurs in association with a double metabolic disorder.

9.5: The Great Trans-Atlantic Acid-Base Debate

The approach to evaluation of acid-base disorders used in this on-line text is known as the Boston approach. The researchers promoting this approach are from Boston. An alternative method of evaluation promoted by Astrup and Siggaard-Anderson from Copenhagen uses the Base Excess approach. At times the differences between the two groups has stirred controversy (called the '**Great Trans-Atlantic Acid-Base Debate**' by Bunker in 1965). Many of the differences between the two groups persist and it is important to have some understanding of the issues involved. The controversy has recently been stirred again by Severinghaus (1993) who favours the Copenhagen approach.

The basic idea is that we need a way to quantify the various acid-base disorders. This tells us the severity of the acid-base disturbance and this is important clinical information. We also need to determine whether the body's compensation for the acid-base disorder is appropriate. If not, this indicates the presence of a second acid-base disorder.

Background to Copenhagen Approach

Acid-base disorders are classified as being of respiratory origin (primary change in pCO_2) or of metabolic origin (primary change in fixed acids). Some basic questions to be answered by any approach are:

- How can the magnitude of a respiratory disorder be determined?
- How can the magnitude of a metabolic disorder be determined?

Respiratory disorders are quantified by the amount of change in pCO_2 in the arterial blood. If the pCO_2 is further away from its normal value, then a larger disorder is present. This seems simple enough as CO_2 is the respiratory acid and can be easily measured.

Metabolic disorders are quantified by the amount of excess fixed acids (the metabolic acids) present in the blood. If more fixed acids are present, then a disorder of larger magnitude is present. This is clear enough *but* in a particular metabolic disorder, we may not know what are the particular fixed acids that are causing the acidosis. Indeed there may be more than one type involved.

Is it feasible to measure every possible fixed acid?

No. BUT we can estimate the total amount of excess fixed acid present indirectly.

The argument goes like this:
1. Buffering of fixed acids in the extracellular fluid is predominantly by bicarbonate.
2. One bicarbonate molecule will react with one H^+ molecule produced by one molecule of fixed acid.
3. So $[HCO_3^-]$ will decrease by one molecule for every molecule of fixed acid present.
4. The total amount of excess fixed acids should therefore be equal to the amount by which the bicarbonate concentration drops from its usual value.

Conclusion: The magnitude of the metabolic disorder (in the ECF) can be quantified indirectly by the amount of change in the $[HCO_3^-]$. This seems an improvement because now there is only one quantity to measure and also it is easy to 'measure' (Bicarbonate is not actually measured in a blood-gas machine but instead is calculated, using the Henderson-Hasselbalch equation, by substituting into this equation the measured values of pH & pCO_2).

But there are other problems:

- The implicit assumption so far that pCO_2 and HCO_3^- are independent of one another is not correct (***What this means is*** that changes in pCO_2 also will change the bicarbonate level because these 2 compounds are in chemical equilibrium. This interferes with the usefulness of changes in bicarbonate as a way to quantify the metabolic component of an acid-base disorder because respiratory disorders also alter the baseline HCO_3^-)
- The buffering by the HCO_3^- in the blood sample is not representative of the buffering by the ECF as a whole (***What this means is*** that because blood is a better buffer than ECF as a whole then doing your measurements in a blood-gas machine on blood will not give you results representative of the *whole ECF*. Blood is a better buffer then the whole ECF because of its content of the buffer haemoglobin.)
- The assumption that all buffering of metabolic acids is by HCO_3^- and not other unmeasured ECF buffers is not totally correct.
- Buffering by intracellular buffers is ignored
- The system assesses compensation as another primary disorder

The Copenhagen approach has developed several 'work-arounds' to cope with some of these problems.

As stated above, the pCO_2 and the $[HCO_3^-]$ are not independent of one another as the argument so far has tacitly assumed. An increase in pCO_2 will cause an increase in $[HCO_3^-]$. This occurs because of the Law of Mass Action in the following equation:

$$CO_2 + H_2O \Leftrightarrow H_2CO_3 \Leftrightarrow H^+ + HCO_3^- \quad (9.5.1)$$

This is a problem because a change in respiratory acid is changing the baseline used for assessment of the metabolic disorder. What we need is some way of assessing the metabolic disorder that corrects or allows for this interaction between CO_2 and HCO_3^- .

Several **pCO_2-independent indices** have been proposed as being suitable for this purpose:

- Standard bicarbonate
- Buffer Base
- Base Excess

Standard bicarbonate is the bicarbonate concentration of a sample when the pCO_2 has been adjusted (or standardised) to 40 mmHg at a temperature of 37°C. This would remove the influence of changes in pCO_2 by seeing what the $[HCO_3^-]$ would be if the respiratory component was made the same for all measurements. The term was introduced by Jorgensen & Astrup in 1957 but is conceptually the same as the idea of a 'standard pH' (at pCO_2 of 40mmHg & temperature of 37° C) introduced by Henderson much earlier.

Buffer base is a measure of the concentration of *all* the buffers present in either plasma or blood.

Base Excess (BE) is a measure of how far Buffer Base has changed from its normal value & was introduced by Astrup and Siggaard-Andersen in 1958. BE in whole blood is independent of pCO_2 in the sample when measured in the blood gas machine. BE is proposed as a measure of the magnitude of the metabolic disorder because it assesses all the extracellular buffers (in the blood sample) and is independent of pCO_2 (in vitro). Unfortunately, there are several problems with the use of BE in this way. For example:

- It is not independent of pCO_2 *in vivo* (This is because blood -which contains haemoglobin - is a better buffer than the total ECF
- It does not distinguish compensation for a respiratory disorder from the presence of a primary metabolic disorder

If BE is calculated for a haemoglobin concentration of 30 or 50 g/l instead of the actual haemoglobin, the differences between in vitro and in vivo behaviour can be mostly eliminated (See Severinghaus, 1976). This lower [Hb] is considered to be the effective [Hb] of the whole ECF (ie what the [Hb] would be if the haemoglobin was distributed throughout the whole ECF rather than just the intravascular compartment). This attempts to eliminate the error introduced by the incorrect assumption that the buffering of blood is the same as the buffering by the whole ECF.

The *Radiometer* range of blood gas machines are made in Copenhagen and are very successfully used worldwide. These machines provides a printout with the full family of 'derived' (or 'contrived', depending on your perspective) Copenhagen-type blood gas variables for those who are interested. Other brands of machine have usually followed this practice so they can survive in the competitive marketplace. This assists in the survival of the Copenhagen approach.

Background to Boston Approach

The alternative method of quantifying acid-base disorders has been developed by investigators from Boston (eg Schwartz & Relman). This Boston approach is the method used so far in this book and the six bedside rules have been outlined in section 9.3

This approach is based on actual experimental work in humans (eg whole body titrations) rather than on blood samples in a machine.

The aim has been to determine the magnitude of the compensation that occurs to graded degrees of acid-base disturbance.

These results are based on buffering and compensatory processes that affect the whole body rather than just the blood. Additionally, appropriate compensation for both acute and chronic disorders can be determined and corrected for when interpreting the blood gas results. The results are presented in a couple of different ways: as graphs with 90% confidence intervals, or as a set of calculation rules. This book uses the rules method because these can be easily committed to memory and can be easily used at the bedside when assessing patients with acid-base disorders.

This does not require the introduction of new terms like Base Excess and Buffer Base. The assessment of the magnitude of metabolic disturbances is based on a comparison of the actual (ie measured) and the expected values of [HCO_3^-]. The determination of the expected value (using clinical knowledge and the rules of section 9.3) incorporates the corrections necessary to adjust for the interaction between pCO_2 and HCO_3^-.

What Approach is 'The Best'?

Conclusion: Boston approach is better the Copenhagen approach

Within the traditional approach to acid-base analysis, the Boston 'bicarbonate method' is preferable to the Copenhagen 'base excess method' because:

- it is simpler to understand and to teach
- it is based on whole body experiments rather than on test tube results on a blood sample
- it emphasises the need for clinical assessment and interpretation rather than being driven by laboratory based derived quantities

Quote from the original critique of Schwartz and Relman in 1963

"The traditional measurements of pH, pCO_2 and plasma bicarbonate concentration continue to be the most reliable biochemical guides in the analysis of acid-base disturbances. These measurements, when considered in the light of the appropriate clinical information and a knowledge of the expected response of the intact patient to primary respiratory or metabolic disturbance, allow rational evaluation of even the most complicated acid-base disorders."

BUT is the Stewart Approach the best of all?

Despite the above, it should be noted that the quantitative approach pioneered by Stewart may be a better approach. It has great strength in aiding understanding about what is going on but unfortunately it is difficult to use clinically. It is very limited in usefulness for routine clinical application and interpretation of blood-gas results. An introduction to this alternative approach is presented in Chapter 10.

9.6: Clinical Examples

The Need for Experience: Practicing on Example Cases

The rules of the Boston approach are useful only if we know how to apply them clinically to patient care. This section provides a series of examples of their use in real patients so you can gain experience in interpretation. Many of these cases are from our own unit but some are based on published cases. These examples provide good practice in the application of the rules.

The central importance of the history and your clinical knowledge of the patient in assessment is emphasised.

In some cases, an enlarged history and serial results are provided. This should provide some experience in:

- discriminating the important data from the clinical picture
- seeing the acid-base assessment as just one component of the total patient assessment
- getting a feel for how the results change with therapy

Some of the assessments are long and perhaps repetitive but previous experience has indicated that this thinking out loud approach increases the usefulness of the examples as teaching material. Brief explanations don't seem to teach much. The index to the Case Histories is at the bottom of this page.

The Prime Directive: Importance of the Clinical Details

But first, to illustrate how the history and examination are of prime importance in correct interpretation of blood gas results, consider the following set of arterial blood gases:

Arterial Blood Gases
pH 7.21
pCO_2 70 mmHg
pO_2 75 mmHg
HCO_3^- 27 mmol/l

These identical gases were obtained from the following two patients (based on Bernards).

- **Case 1:** A healthy 37 year old man is having an elective open cholecystectomy under a N_2O/Enflurane/Pancuronium anaesthetic. He has no significant past medical history and is on no routine medication. Preoperative urea and electrolytes were all within the reference range.
- **Case 2:** A 75 year old man with a long history of severe acute chronic obstructive airways disease (COAD) is admitted to hospital with fever, confusion and significant respiratory distress. He lives alone but his neighbour says he has been unwell for a week and has deteriorated over the previous 4 days. There is a long history of heavy smoking. Biochemistry & haematology results are not yet available.

Is the assessment of the results the same even though the clinical situation is very different?

No!

The pattern (pCO_2 & HCO_3^- both elevated) suggests either a respiratory acidosis or a metabolic alkalosis but the severe acidaemia means that it is a respiratory acidosis that is present. This much is common ground to these two cases. The clinical details are necessary to decide if a simple or a mixed acid-base disorder is present.

Assessment of Case 1:

This patient is receiving a relaxant anaesthetic for an upper abdominal procedure. His ventilation is fully controlled. A perusal of the results in the light of the clinical details (respiratory acidosis in a well patient on controlled ventilation) suggests strongly that the most likely primary problem is hypoventilation in a patient with previously normal acid-base results. A marked acute respiratory acidosis is present. [In any anaesthetised patient with an acute acidosis, malignant hyperthermia, though rare, should always be considered.]

Is a metabolic disorder also present in this patient? (eg due to lactic acidosis) The [HCO_3^-] would be expected to increase by 1 mmol/l for each 10 mmHg rise in pCO2 above the nominal usual value of 40 mmHg. (Rule 1 in Section 9.3). A rise of 30mmHg

predicts a [HCO_3^-] of 27 (ie 24 + 3). The actual value matches the predicted value. There is no metabolic component present.

If the history suggested that the situation may be more complex then a check should be made for any suggestive evidence of a mixed metabolic component (coexistent metabolic acidosis and metabolic alkalosis) as well as the acute respiratory acidosis. This check would include initially anion gap, [K+], [Cl-] and glucose. In this case there is no clinical indication.

Acute respiratory acidosis due to alveolar hypoventilation is the acid-base assessment in this case. The cause for this should be found and corrected. The absence of a metabolic component and the other clinical evidence makes a diagnosis of excessive CO2 production (eg malignant hyperthermia) very unlikely.

Assessment of Case 2:

This man has severe chronic obstructive airways disease and has an elevation in his pCO_2 which has probably been present for at least 3 or 4 days. He is probably a chronic CO_2 retainer with some chronic elevation in his pCO_2. Review of previous blood gas results or bicarbonate (ie total CO_2) levels on a biochemistry profile may confirm this. In any case, the history suggests chronic respiratory acidosis.

Based on rule 2, the predicted [HCO_3^-] is 36 mmol/l [ie: $24 + \frac{70-40}{10} \times 4$]. The actual [HCO_3^-] is 9 mmol/l lower then this indicating a coexistent severe metabolic acidosis. Note that the pO_2 is not severely depressed. Patients admitted with respiratory distress are almost invariably commenced on oxygen by ambulance and hospital staff. This may be life-saving as the pO_2 in increased.

A lactic acidosis related to hypoxaemia and maybe peripheral circulatory failure is the probable cause of the metabolic acidosis. Other causes of metabolic acidosis should be considered. Infection is a potent precipitant of diabetic ketoacidosis. A finger-prick test for glucose and urine tests for glucose and ketones should be performed on arrival in the Casualty department. The anion gap will define the type of metabolic acidosis present and guide further investigation.

This patient has a severe mixed acidosis. An acute severe metabolic acidosis is superimposed on a compensated chronic respiratory acidosis. The metabolic compensation for the respiratory disorder has disguised the magnitude of the metabolic acidosis.

It is noted that the gas results in these two cases are identical, but that the interpretation and therefore management are different.

Commenting on an isolated set of blood gas results without benefit of any pertinent history can lead to serious error.

Remember that the clinician is focusing on the assessment of the patient and here our attention is predominantly on the acid-base assessment.

Clinical Cases

Index to Clinical Examples

Further examples with more extensive discussions can be found in the **Gas Archives**	
1. Postoperative Cardiac Arrest	2. A Sick Diabetic Patient
3. A weak old lady	4. A case of pneumonia
5. A motor vehicle crash	6. A COAD patient with acute abdominal pain
7. A dehydrated man with diarrhoea	8. A diabetic patient with vomiting and polyuria
9. A man with a postop cardiac arrest	10. A semi-comatose diabetic taking diuretics
11. A man with CCF & vomiting	12. A weak patient following a week of diarrhoea
13. A case with a postop morphine infusion	14. A man with an out-of-hospital cardiac arrest
15. An old man with abdominal pain and shock	16. A woman with muscle weakness and vomiting
17. An intoxicated baby	18. A lady with respiratory failure and failure to improve
19. A young man who ingested barium carbonate	20. An alcoholic with GIT bleeding and shock
21. A vague historian with weakness and diarrhoea	22. An old man with hiccoughs and confusion
23. A diabetic using phenformin	24. A man with a leaking aneurysm

25. An old lady with abdominal pain and vomiting	26. A man with a gunshot wound and a cardiac arrest
27. A man with chest trauma from a car crash	28. A lady with a rigid abdomen
29. A teenage boy with an obstructed colonic bladder	30. A child with ingestion of windscreen washer fluid
31. A man with hypokalaemic paralysis	32. To be added

CHAPTER OVERVIEW

10: Quantitative Acid-Base Analysis

10.1: The System

The 'New Paradigm'?

Recently, attention has shifted to a quantitative physicochemical approach to acid-base physiology. Many of the generally accepted concepts of hydrogen ion behaviour (as discussed above) are viewed differently and indeed are often shown to be wrong! This analysis introduced by Peter Stewart [1,2] in 1978 [3] provides a chemical insight into the complex chemical equilibrium system known as acid-base balance. The impact of the Stewart analysis has been slow in coming but there has been a recent resurgence in interest, particularly as this approach provides explanations for several areas which are otherwise difficult to understand (eg dilutional acidosis, acid-base disorders related to changes in plasma albumin concentration). [As discussed in section 1.1, the majority of this book covers the traditional acid-base aproach.]

Stewart's book now online

Peter Stewart's influential 1981 book ("How to Understand Acid-Base") [1] has long been out-or-print and it has been difficult for many people to obtain access to a copy. Recently, Stewart's widow has given the copyright on the book to Paul Elbers from Amsterdam and Paul has placed the whole book on-line at his new website http://www.AcidBase.org

The interested reader is referred to Bellomo(1999)[4] and the associated review articles in that edition of Current Opinion in Critical Care where the 'new paradigm' of Stewart's acid-base approach is considered with the enthusiasm of the true believer.

Undoubtedly the physiochemical approach will become more important in the future and this chapter provides an introduction. A bit of background is necessary first.

Terms & Concepts

This approach requires a consideration of solutions as systems. In particular:

". . . it is a general property of systems that the quantitative results of several interacting but independent mechanisms can not be explained or understood solely in terms of the action of any single one of these mechanisms." (Stewart 1983, p1444-5)[2]

A simple introduction to the concepts and the terms which are used by Stewart is necessary to understand the framework in which he discusses acid-base chemistry in the body. A biological fluid is a very complex dynamic system but useful analysis is possible by considering the chemical species involved and how they interact chemically with each other. Consider the argument developing in this way:

- There are often multiple mechanisms involved in influencing the particular concentration of any single chemical species.
- Hydrogen ion is an example of one of these species whose concentration is dependent on several interacting chemical mechanisms (equilibriums).
- Finally (and rapidly) these multiple mechanisms must come into equilibrium and the $[H^+]$ in the solution at that point in time is determined.
- An attempt to calculate the equilibrium concentration of any species must take into account all the mechanisms involved.
- This is not quite as difficult as may be supposed because certain simplifications are possible. (These will be considered later).
- Finally, a formula for the calculation of the equilibrium value of a chemical species (eg $[H^+]$) can be obtained. The equation for $[H^+]$ is complex but solution of it is easy and quick on a computer.

What we are planning to do is to decide what it is that determines $[H^+]$ (and the other chemical concentrations) in a biological solution by considering the several interacting mechanisms involved. One aim is to develop a formula for calculating $[H^+]$, but more importantly a new understanding of how acid-base physiology really works at the chemical level should be gained.

The concentrations of the various chemical species present are the variables whose values are used in the equations. From the perspective of considering a biological solution as a system of interacting chemical species, we can consider these variables as being of two types. All the variables can be classified as either dependent variables or as independent variables. This is extremely important in discussing cause and effect so first consider the meaning of these terms:

Dependent and Independent Variables

Dependent variables have values which are determined internally by the system. They are determined by the equations (chemical equilibria) which determine the system and can be altered only by changes in the values of the independent variables.

Independent variables have values which are determined by processes or conditions which are external to the system; they are imposed on the system rather than being determined by it.

Consider a simple analogy: A goldfish in a bowl which is full to the brim. The bowl-water-goldfish combination is the system in this example. The amount of oxygen in the solution is a dependent variable: its value at any time is determined by the rate of oxygen consumption of the goldfish and this is a process which is completely internal to the system. Now consider the volume of water in the bowl: this is an independent variable as its value is determined by factors external to the system within the bowl. If there were any reactions within the bowl that produced more water (eg metabolic water production by the goldfish) then it would simply overflow the edges of the full bowl. The volume would be held constant despite internal changes within the bowl. Consider further the dependent variable oxygen content in the bowl. This is not just determined by the internal process (O_2 consumption by the goldfish) but is affected by the value of various independent variables such as the volume of the bowl and the temperature of the water. More oxygen will dissolve in water at a lower temperature. The temperature of the water is determined by the environmental temperature which is independent of the goldfish in bowl system. The water temperature is another independent variable.

Why is the concept of dependent and independent variables so important?

- The reason is that the values of all the dependent variables are determined by and can be calculated from the values of the independent variables.
- And a very important particular point: In the acid-base system in body fluids, **$[H^+]$ is a dependent variable!**

The traditional analysis of acid-base makes the implicit assumption that $[H^+]$ is an independent variable and this is wrong. Hydrogen ion concentration can therefore be calculated if the values of the independent variables are known.

Preliminary Remarks about the Significance of this

Now the significance of this and why it is so different from the traditional understanding may not be immediately apparent to you. So lets consider the following:

Consider a cell where H^+ ions are being pumped out of a cell into the ISF.

Using the traditional approach we would predict that this would decrease the intracellular $[H^+]$ (and increase the pH) because there is now less H^+ in the ICF in that cell. But the Stewart approach would say this understanding was wrong. Because $[H^+]$ is a dependent variable, its concentration cannot be changed in this way; its concentration can only be changed if the value of one of the independent variables changes and all that is happening is a pumping of H^+ ions. The Stewart approach would predict that the chemical equilibria within the cell would readjust to replace any H^+ lost (by being pumped out of the cell) with the result that the intracellular $[H^+]$ would remain unchanged.

So, what really happens? Well if the pumping of H^+ out of the cell was the only change occurring than the ICF $[H^+]$ would not change and the Stewart approach would correctly predict this. The source of the replacement H^+ would be an extremely small increase in the dissociation of H_2O within the cell.

But, wait a minute, surely this cannot be so. As another example, consider what happens in the parietal cells in the stomach. After a meal, the parietal cells actively pump large amounts of H^+ into the gastric lumen. The $[H^+]$ in the parietal cells decreases and this is reflected in the gastric venous blood as an increase in pH (the 'post-prandial alkaline tide').

Doesn't this mean then that the prediction of the Stewart approach is wrong afterall? Not at all. In fact, a proper analysis of this example shows that the outcome is consistent with that predicted by the Stewart approach. One important fact that has been overlooked in our analysis so far is the requirement for electroneutrality. It is just not possible to pump much H^+ because this sets up a potential difference across the cell membrane. Now the cell can only tolerate an extremely tiny charge separation (and such a minute charge separation is sufficient to set up a transmembrane potential difference or RMP of say 100mV). The actual concentration difference that this RMP represents is too small to measure other than as a potential difference (ie membrane potential).

What is happening in the parietal cell is that both H^+ and Cl^- are being transferred out of the cell and into the gastric lumen. Electroneutrality is maintained. The vital point to notice here is the movement of Cl^- and the effect of this. As there is no potential difference set up by pumping H^+ and Cl^- together there is no electrochemical force inhibiting the movement. Consequently large amounts of Cl^- are being moved out of the cell. This causes a change in the strong ion difference (SID). Don't worry about what this means at present (it will be explained in section 10.3), just note that it is one of the independent variables in this system and thus determines the values of the dependent variables, of which $[H^+]$ is one. The correct explanation (as provided by the Stewart approach) is that yes, the $[H^+]$ in the gastric parietal cell does decrease but it is not the pumping of the H^+ which causes this, but rather the loss of Cl^- from the cell. The loss of Cl^- changes the value of one of the independent variables.

The explanations of the two approaches as to why the $[H^+]$ changes is quite different. The Stewart approach is the one that is correct in the sense of explaining the cause.

References

1. Stewart PA *How to Understand Acid-Base. New York*: Elsevier, 1981
2. Stewart PA. *Modern quantitative acid-base chemistry.* Can J Physiol Pharmacol 1983 Dec; 61(12) 1444-61. PubMed
3. Stewart PA. *Independent and dependent variables of acid-base control.* Respir Physiol 1978 Apr; 33(1) 9-26.PubMed
4. Bellomo R & Ronco C *New paradigms in acid-base physiology* Current Opinion in Critical Care 1999; 5:427

All Medline abstracts: PubMed HubMed

10.2: The Background

Some chemical background about the classifications of substances in solution is necessary before we proceed further.

In particular, the substances which affect acid-base balance in body fluids can all be classified into 3 groups based on their degree of dissociation. This allows certain generalisations & simplifications which are useful in understanding complex solutions.

Body fluids can be considered as aqueous solutions that contain:

- strong ions
- weak ions
- non-electrolytes

Strong ions in solution are always fully dissociated

They exist only in the charged form.

For example: dissolving sodium chloride in water produces a solution containing Na^+ and Cl^-. There is no NaCl present so it is strictly incorrect to speak of sodium chloride solutions as this species does not exist in the solution! An important practical consequence of this when analysing solutions is that the amount of the strong ion present is not affected by conversion back to the parent compound (as occurs with weak ions -see below) AND the dissociation equilibrium of this reaction does not need to be included in the analysis. The concentration of any individual strong ion in the solution is fixed unless it is transported out of the solution (eg by a cell membrane pump or transporter.)

Strong ions are mostly inorganic (eg Na^+, Cl^-, K^+) but some are organic (eg lactate). In general, any substance which has a dissociation constant greater then 10^{-4} Eq/l is considered as a strong electrolyte.

Weak ions are those ions produced from substances that only *partially* dissociate in solution

Ions that are classified as 'weak ions' are produced from substances which only partly dissociate when dissolved in water. For the purposes of acid-base analysis, the weak ions in body fluids as classified into 2 groups:

- Carbon dioxide and associated ions (volatile)
- Weak acids (nonvolatile) : $HA \Leftrightarrow H^+ + A^-$ HA <=> H^+ + A^-

Incomplete dissociation of the weak acids means that the solution contains the weak acid plus the products of its dissociation. A dissociation equilibrium equation can be written:

$$[H^+] \times [A^-] = K_A \times [HA] \qquad (10.2.1)$$

- where K_A is the dissociation constant for the weak acid.

Non-electrolytes are those substances in solution which never dissociate into ions

Non-electrolytes are not charged. As a consequence, non-electrolytes contribute to the osmolality of a solution but do not contribute to the charge balance in the solution.

How clearcut is the distinction between strong ions, weak ions & non-electrolytes?

The distinction is not completely clearcut of course **BUT** for practical purposes it is a sufficiently accurate & useful approximation.

Stewart uses the value of the dissociation constant (K_A) to provide a clear (but still a bit arbitrary) distinction between the three groups:

- Non-electrolyte : $K_A < 10^{-12} \frac{Eq}{l}$
- Weak electrolyte : K_A between 10^{-4} and 10^{-12} Eq/l
- Strong electrolyte : $K_A > 10^{-4} \frac{Eq}{l}$

- -

NoteS

- Strong in this section means *strongly dissociated* and does not mean a 'strong solution' (ie meaning a concentrated one).
- Those strong ions eg Ca^{2+} which are partly bound to plasma proteins don't quite fit into the system but this is not a major problem partly because their concentrations are low.

10.3: The Variables

The equation for calculating $[H^+]$ developed by Stewart contains 3 independent variables and 6 dependent ones. The nature of the independent variables will seem strange at first but the purpose of this section is to introduce them and briefly discuss what they are and why they are independent.

The Three Independent Variables

These are:

- **pCO_2** -the partial pressure of CO_2 in the solution under examination
- **SID** -this stands for the 'strong ion difference' in the solution
- **$[A_{Tot}]$** -the total concentration of weak acid in the solution.

(These 3 variables are explained further in the subsections below)

The first independent variable : pCO_2

The pCO_2 is the easiest to understand. Some facts:

- Carbon dioxide is produced by all cells in the body
- It crosses all cell membranes easily, traverses the ISF and enters the blood
- It is excreted from the body by the lungs
- The arterial pCO_2 is under sensitive and powerful feedback control via the peripheral and central chemoreceptors

These receptors respond to an increase in arterial pCO_2 by increasing ventilation and this returns arterial pCO_2 to normal. Arterial pCO_2 is frequently said to be determined by the ratio of CO_2 production to alveolar ventilation (See Section 2.3). This is quite correct but does not indicate the effect of the control system which is very effective at maintaining normal arterial pCO_2. A consideration of the equation would suggest that a doubling of CO_2 production would result in a doubling of arterial pCO_2 but this does not occur in the intact person (unless ventilation is fixed eg as in an anaesthetised ventilated patient).

Any rise in arterial pCO_2 is detected by the sensors (ie the chemoreceptors) and activates the control system resulting in increased alveolar ventilation. This returns the arterial pCO_2 towards normal. In abnormal situations, the control system is disturbed or otherwise ineffective at keeping arterial pCO_2 constant.

The gist is that the value of pCO_2 in arterial blood and all body fluids is effectively set by mechanisms other than the chemical equilibria occurring in the fluids. The value is determined and controlled by factors external to the chemical system in the body fluids. It is therefore an independent variable.

The second independent variable: SID

This abbreviation stands for Strong Ion Difference. It is defined as:

SID = (the sum of all the strong cation concentrations in the solution) minus (the sum of all the strong anion concentrations in the solution).

For example: if a solution contained Na^+, K^+ and Cl^- as the only strong ions present, then:

$$SID = [Na^+] + [K^+] - [Cl^-]$$

SID = $[Na^+]$ + $[K^+]$ - $[Cl^-]$

If these strong ions were the only charged species present, then the powerful requirement for electrical neutrality would mean that SID would be zero. Most biological fluids contain weak electrolytes (mostly weak acids). If the SID is not zero, then it means that the solution must contain other charged species ie weak electrolytes. The SID represents the net charge which must be balanced by charges on the weak acids in the solution for electrical neutrality to be maintained.

In plasma, the formula for SID is approximately:

$$SID = [Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] - [Cl^-] - [\text{Other strong anions}^-] \quad (10.3.1)$$

Why is SID considered an 'independent variable'?

The components (ie the strong ions) which are used to calculate the SID are not altered by any of the reactions in the system. None of these ions are produced or consumed. The concentrations are imposed on the solution from outside and are controlled by outside mechanisms. The kidney is the most important regulator of most of these ion concentrations.

Inorganic strong ions (eg Na^+, Cl^-) are mostly absorbed from the gut and control is mostly by variations in renal excretion due to various control systems in the body.

Organic strong ions (eg lactate, keto-anions) are produced by metabolism and may be metabolised in the tissues or excreted in the urine. However, their concentrations in most body fluids are not dependent on the reactions within the solution but are regulated by mechanisms external to the system.

The derived value **SID** is used because it is a term which arises in the equation for electrical neutrality and allows us to *lump together* all the independent concentrations in the form in which the strong ions are involved in affecting acid-base balance (ie by their overall net charge). The SID is that part of the charge on the strong ions which has to be balanced (because of the electroneutrality requirement) by the net opposite charges of the total weak ions present. Unlike the strong ions, the amount of these weak ions varies because of varying amounts of dissociation. The amount of dissociation of these weak ions varies such that the net amount of charge of them all considered together, is equal and opposite to the charge due to the strong ions. This is just a chemical fact due to the requirement for electroneutrality that is imposed on the system by physical laws.

If only the strong ions which are typically present in health are considered, the **apparent SID (SIDa)** can be calculated as:

$$SID_a = [Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] - [Cl^-] - [\text{lactate}^-] \tag{10.3.2}$$

SIDa has a normal value of 40 to 42 mEg/l.

This is a useful simplification but it is possible to go further. Only $[Na^+]$ and $[Cl^-]$ are present in high concentrations so the SID can be roughly approximated as ($[Na^+]$ - $[Cl^-]$). Now if we remember that $[Na^+]$ is tightly controlled by the body because it controls tonicity, then the major way that the ECF pH can be altered is by changes in $[Cl^-]$ relative to a constant $[Na^+]$.

The third independent variable: $[A_{Tot}]$

The abbreviation represents the total amount of non-volatile weak acid present in the system.

All the weak acids in the system are represented collectively as HA. The anion for each acid will be different but because they all behave similarly all the weak acids are represented as though they were a single acid (for which the symbol HA is used) which has a single apparent dissociation constant. This is a useful simplifying assumption which is basically an averaging process. The dissociation reaction is:

$HA \Leftrightarrow H^+ + A^-$

The law of conservation of mass means that *the total amount of A* (symbol: $[A_{Tot}]$) in the system must be constant. None of the reactions in the system produce or consume A. Conservation of A can be represented as:

$[A_{Tot}] = [HA] + [A^-]$

In plasma, the major non-volatile weak acids present are:

- Proteins ($[Pr_{Tot}] = [Pr^-] + [HPr]$)
- Phosphates ($[Pi_{Tot}] = [PO_4^{3-}] + [HPO_4^{2-}] + [H_2PO_4^-] + [H_3PO_4]$)

Albumin is the most important protein present that acts as a weak acid so the total amount of protein is approximated by the albumin concentration ([Alb]). Globulins do not contribute significantly to the total negative charge due to plasma protins. The level of albumin in body fluids is imposed upon the acid-base system and is not regulated by it. The colloid osmotic pressure & osmolality of the extravascular liver space is the primary factor which controls the rate of production of albumin. (Pietrangelo et al, 1992).

Phosphates are present in several forms but the total amount is normally fairly constant. Its level in plasma is controlled as part of the system for regulating calcium levels. Phosphates normally contribute only about 1mM of A_{Tot}. Phosphates represent only 5% of A_{Tot} at normal phosphate levels. If phosphate levels are elevated then its contribution becomes more important.

The point of all this is that the [Albumin] alone can be used as an estimate of A_{Tot} in plasma.

As an overview of these independent factors, consider the following generalisations that have been made:

- The first independent variable is pCO_2 which is controlled by a respiratory control system.
- The 2nd independent variable is SID and this can be roughly estimated as ($[Na^+]$ - $[Cl^-]$) and this is controlled by the kidney.
- The 3rd independent variable is A_{Tot} and this is estimated as [Alb] which is controlled by the liver.

10.4: The Equations

The whole purpose of Stewart's model is to discover what determines the $[H^+]$ (and thus pH) in aqueous solutions such as body fluids. Lets look at two simple systems to gain some experience in deciding what determines the $[H^+]$ in these systems.

Example 10.4.1: Pure Water

Consider first a solution of pure water and ask the question here: What determines the $[H^+]$?

Solution

We can determine a formula for this as follows:

Water dissociates into H^+ and OH- to a very small degree:

$$H_2O \rightleftharpoons H^+ + OH^-$$

The dissociation equilibrium equation for this reaction is:

$$[H^+] \times [OH^-] = K_w \times [H_2O]$$

where K_w is the **dissociation constant** for water.

The value for Kw is temperature dependent. The term $[H_2O]$ is very large (55.5M at 37°C) and the values of $[H^+]$ and $[OH^-]$ are both very small: that is water dissociates to such a very small extent that the value of $[H_2O]$ is essentially constant. The terms Kw and $[H_2O]$ can be combined into a new constant K'w.

Kw which is called the **ion product for water**. Thus:

$$K_w = [H^+] \times [OH^-]$$

Electrical neutrality must also be present in the solution. As H^+ and OH- are the only ions present:

$$[H^+] = [OH^-]$$

These 2 simultaneous equations have two unknowns so a solution for $[H^+]$ is possible:

$$[H^+] = (K_w)^{\frac{1}{2}}$$

This is the simplest system possible but illustrates the point that analysis of a system results in several equations that can be solved for $[H^+]$.

Overview of Basic Principles

The basic principles used in analyzing all systems and determining the equation for $[H^+]$ are simple:

- Electroneutrality must be conserved
- Mass must be conserved
- All dissociation equilibriums must be met

The result is a set of simultaneous equations which may be solved. No matter how complex the solution, all these 3 conditions must be met.

Example 10.4.2: A Solution of Sodium chloride

Now consider a slightly more complicated system: an aqueous solution containing only Na^+ and Cl^-. This example shows how the SID term arises. What determines the $[H^+]$ in this solution?

Solution

We can write the following equations for this system:

Water Dissociation Equilibrium:

$$K_w = [H^+] \times [OH^-]$$

Electrical Neutrality:

$$[Na^+] + [H^+] = [Cl^-] + [OH^-]$$

Solving for $[H^+]$:

$$[Na^+] - [Cl^-] = [OH^-] - [H^+]$$

$$[OH^-] = \frac{K_w}{H^+}$$

Combining these:

$$[H^+]^2 + [H^+]([Na^+] - [Cl^-]) - K_w = 0$$

Now $[Na^+] - [Cl^-] = SID$ for the solution in this example, so:

$$[H^+]^2 + (SID \cdot [H^+]) - K_w = 0$$

Solving this quadratic equation, the 2 solutions are:

$$[H^+] = \frac{-SID}{2} + \sqrt{K_w + \frac{SID^2}{4}}$$

and

$$[H^+] = \frac{-SID}{2} - \sqrt{K_w + \frac{SID^2}{4}}$$

For solutions containing Na^+ and Cl- in water, the $[H^+]$ is determined by the SID **alone** (as this is the only variable on the right hand side of the equation)! This simple example illustrates how the SID term is useful as a independent variable which arises out of the equations used to analyse the chemical systems in body fluids.

The Equation Set for Body Fluids

The preceding two examples outline the approach that can be taken with any aqueous solution. Even though body fluids are much more complex, Stewart was able to find the equations which describe the system and solve them for $[H^+]$.

Body fluids are aqueous solutions which contain strong ions (inorganic and organic) and weak ions (the volatile CO_2/HCO_3^- system and various non-volatile weak acids HA). The independent variables which determine the $[H^+]$ in all body fluids are the pCO_2, SID and $[A_{Tot}]$.

All the other variables (eg $[H^+]$, $[OH^-]$, $[HCO_3^-]$, $[A^-]$) are dependent on the values of the 3 independent variables. There are six simultaneous equations necessary to describe this system (see table below)

A full discussion and derivation of these equations is not presented here: the interested reader is referred to Peter Stewart's book "How to Understand Acid-Base" (1981)

The Six Simultaneous Equations used by Stewart
1. Water Dissociation Equilibrium
$$[H^+] \times [OH^-] = K_w$$
2. Electrical Neutrality Equation
$$[SID] + [H^+] = [HCO_3] + [A^-] + [CO_3^{2-}] + [OH^-]$$
3. Weak Acid Dissociation Equilibrium
$$[H^+] \times [A^-] = KA \times [HA]$$
4. Conservation of Mass for "A"

$$[A_{Tot}] = [HA] + [A^-]$$
$[A_{Tot}] = [HA] + [A^-]$
5. Bicarbonate Ion Formation Equilibrium
$$[H^+] \times [HCO_3^-] = KC \times pCO_2$$
6. Carbonate Ion Formation Equilibrium
$$[H^+] \times [CO_3^{2-}] = K3 \times [HCO_3^-$$

Equation 5 is the basis of the familiar Henderson-Hasselbalch equation. It is interesting to note that the traditional approach to acid-base physiology uses the Henderson-Hasselbalch equation alone and ignores all the other equations!

The three basic constraints that lead to these six equations are chemical or physical laws that must be obeyed by the system:

- Electrical neutrality must be present in the solution
- Conservation of mass must occur
- All dissociation equilibria must be satisfied simultaneously

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10.5: The Solutions

The set of six simultaneous equations derived by Stewart (see previous section) include:

- the 3 independent variables (pCO_2, SID and $[A_{Tot}]$)
- the 6 dependent variables ($[HA]$, $[A^-]$, $[HCO_3^-]$, $[CO_2^{-3}]$, $[OH^-]$, $[H^+]$)

These equations can be solved mathematically to express the value of any one of the dependent variables in terms of the 3 independent variables (and the various equilibrium constants). The values of the equilibrium constants have been experimentally determined under a range of conditions and can be obtained from various reference sources.

To focus only on the solution of the six equations for $[H^+]$, one derives a formula of the following form:

$$\boldsymbol{ax^4 + bx^3 + cx^2 + dx + e = 0} \tag{10.5.1}$$

Mathematicians call this type of equation a ***4th order polynomial*** or a quartic equation. The unknown value is x and a,b,c,d and e are constants. (The actual value of these "constants" can change - eg with change in temperature - but are a fixed value under a given set of conditions. If, for example, the temperature changes, then different values of the constants have to be used.) The actual equation for $[H^+]$ that Stewart derived is listed below.

Equation used to Solve for $[H^+]$

$$\boldsymbol{a \cdot [H^+]^4 + b \cdot [H^+]^3 + c \cdot [H^+]^2 + d \cdot [H^+] + e = 0}$$

where:

- $a = 1$
- $b = [SID] + KA$
- $c = KA \times ([SID] - [A_{Tot}]) - K_w - KC \times pCO_2$
- $d = -(KA \times (K_w + KC \times pCO_2) - K3 \times KC \times CO_2)$
- $e = -(KA \times K3 \times KC \times pCO_2)$

(see Stewart's book for values of the constants in this equation)

A daunting equation and there is a general formula for solving such quartic equations, but this is very complex. Solution is however fast and easy on an appropriately programmed computer, and can be done online, if you know the values for the constants. Some of the constants are temperature dependent, so not actually "constant". A similar type of equation can be produced for any of the 6 dependent variables. The point here is not to become involved in complicated mathematics but to show that it is possible to solve the equation and determine the hydrogen ion concentration (ie $[H^+]$) in the solution using only the values of the three independent variables and various equilibrium constants. What is not stated explicitly are the error bounds related to the calculation. These become important (i.e. they are wide) as there are so many variables and constants involved, and such indirect calculation of pH can never be as accurate as actual pH measurement.

10.6: The Implications

Stewart has essentially produced a mathematical model of the acid-base balance of body fluids.

His analysis gives new insights into what is really happening at the chemical level and this is different from the conventional approach. The conventional understanding of acid-base balance is:
***cluttered with jargon, chemically meaningless derived quantities, a misunderstanding of what is happening and an artificial use of the Henderson-Hasselbalch equation as the single equation determining acid-base balance in any body fluid* (Stewart).**

The Henderson-Hasselbalch equation is just one of the 6 equations which must always be simultaneously satisfied.

All disturbances of acid-base balance MUST result from a changes in the independent variables (& only the independent variables.

Respiratory acid-base disorders are caused by changes in the independent variable pCO_2

Metabolic acid-base disorders are caused by changes in SID and/or $[A_{Tot}]$

Changes in pCO_2 can occur quickly as ventilation can be rapidly altered. Changes in SID are due to changes in the concentrations of strong ions. The basic system for strong ions is absorption from the gut and excretion via the kidneys. These are both much slower processes than pCO_2 changes. The main contributor to $[A_{Tot}]$ in body fluids are the proteins. For the ECF, this is essentially [albumin] as discussed previously. Most plasma proteins are produced by the liver. Changes in protein concentration occur even more slowly than strong ion changes so changes in SID account for most metabolic acid-base disturbances. If plasma protein levels are normal ($[A_{Tot}]$ constant), then acid-base disturbances can be analysed in terms of changes in pCO_2 and SID.

Interactions across Membranes

The Stewart approach seeks to determine the factors that determine the acid-base state in a given body fluid compartment. The fluid compartments in the body are separated by cell membranes or by epithelial layers. In each compartment, the $[H^+]$ is determined by the values of the independent variables. An acid-base disturbance in a compartment is due to a change in one or more of the independent variables occurring in that compartment.

How do acid-base interactions occur across the membranes that separate the different compartments?

Consider the following:

- The 3 major fluid compartments in the body are the ICF, ISF and plasma.
- These compartments interact with each other across membranes (eg cell membrane, capillary membrane).
- Acid-base interactions occur across these membranes also.
- These interactions can produce changes in acid-base status only if the result of the interaction is to change the value of one or more of the independent variables.

Carbon dioxide diffuses across membranes rapidly and easily. Changes in pCO_2 can occur rapidly via ventilatory changes. This has 2 important consequences:

- $[H^+]$ in all fluid compartments can be altered rapidly, but equally.
- Changes in pCO_2 cannot be used to produce differences in $[H^+]$ in fluids on opposite sides of a membrane.

Proteins are present in significant concentrations in ICF and in plasma but the ISF level is low. Proteins such as albumin are large molecules which cannot cross membranes except in unusual circumstances. The effect of this is that $[H^+]$ changes across a membrane cannot be due to movement of protein between the fluids. The phosphate level in plasma is low and regulated by the calcium control system. Transfer of phosphates across membranes could produce acid-base changes but these movements do not contribute significantly to acid base interactions.

This leaves only SID to consider. Strong electrolytes can cross membranes but usually via specific mechanisms such as ion channels and transport pumps. Strong ions can move down or against a concentration gradient. The movement of strong ions can be varied (eg pumps can be activated, ion channels can be open or closed)

So of the 3 independent variables:

- pCO_2 : CO_2 crosses membranes very easily and cannot contribute to causing acid-base differences across a membrane
- $[A_{Tot}]$: Proteins cannot cross membranes at all and so cannot contribute to causing acid-base differences

- SID : Strong ions (the determinants of SID) can cross membrane and this transport can be varied.

Conclusion: A change in [SID] alone is the major mechanism by which acid-base *differences* occur across a membrane as the other two independent variables cannot be responsible.

Important processes involved include Na^+-H^+ exchange and K^+-H^+ exchange across the cell membrane.

The kidney is usually said to excrete acid from the body (ie if urine has a lower pH than plasma, some net amount of $H^+$is being excreted). This is not correct. The kidney certainly has a role in decreasing the $[H^+]$ of plasma but the real mechanism is different from the conventional explanation. As proteins cannot cross membranes, this decrease in plasma $[H^+]$ must be due to the kidney causing changes in SID across the renal tubules. The change in $[H^+]$ is due to differential movement of strong electrolytes (eg Na^+, Cl^-, K^+) across the tubules causing a change in the SID on each side of the membrane: it cannot be due directly to the secretion or absorption of H^+ or HCO_3^- (or adjustment in any of the other dependent variables). For example in the distal tubule. it is not the secretion of H^+ that causes the pH of the distal tubular fluid to fall but the movement of the strong ion (eg Na^+) associated with the process.

A further example of acid-base interactions across a membrane is that occurring in the stomach. Gastric juice is acidic not because of the transport of H+ into the stomach but because of the movement of Cl^- that occurs. Alternatively, if the H^+ was exchanged for a positive ion like Na^+ or K^+ then the SID would be altered by the same amount and again gastric secretions would be acidic. The factor which determines the $[H^+]$ is the change in SID due to movement of Cl^- into the gastric juice.

The intracellular pH is altered mostly by control of intracellular SID. The ion pumps regulate concentrations of the various ions and thereby indirectly control the intracellular SID and pH.

The control of $[H^+]$ in all body fluids is due to changes in the 3 independent variables.

Proteins don't normally contribute much to acid-base interactions because they cannot cross membranes. Most plasma proteins are synthetised in the liver. If protein levels fall (eg due to hepatic dysfunction or excretion as in the nephrotic syndrome) this will have predictable effects on acid-base balance. Strong ions are normally absorbed in the gut and excreted by the kidney. What is important is not the absolute concentrations of the individual strong ions, but the total amount of charge which is present on them which is not balanced by other strong ions (ie SID). The pCO_2 is under respiratory control. Changes in pCO_2 can cause rapid changes in the $[H^+]$ of all body fluids.

Changes in SID are very important in controlling transmembrane exchanges which affect the acid-base situation in adjacent fluid compartments.

Acid-Base Disorders

Respiratory acidosis and alkalosis are due to hypercapnia and hypocapnia respectively (ie the pCO_2 is the important independent variable in these disorders).

Metabolic acidosis is mostly due to a decreased SID and metabolic alkalosis is mostly due to an increase in SID.

However changes in $[A_{Tot}]$ can also cause metabolic acid-base disorders. Hypoalbuminaemia causes a metabolic alkalosis and hyperalbuminaemia causes a metabolic acidosis. An example is the contribution of low albumin levels to the alkalosis associated with cirrhosis or the nephrotic syndrome. An increase in phosphate in plasma occurs in renal failure and contributes to the metabolic acidosis of uraemia. The phosphate level is low in plasma so a drop in phosphate level in plasma cannot contribute to causing a detectable metabolic alkalosis.

Conclusion

The Stewart approach *"shows the way to a complete quantitative treatment of body fluids as physico-chemical systems, through numerical solution of the sets of simultaneous equations that describe their acid-base behaviour."* (Fencl & Leith, 1993).

This approach is slowly gaining acceptance in research papers and in modeling of the acid-base homeostasis of body fluids. It also provides an insight into the chemical processes that determine the pH of body fluids. The conclusions are often quite different to those of the traditional approach. For example, the traditional approach to metabolic acid-base disorders is concerned with bicarbonate but the Stewart approach emphasises that chloride is the most important anion when causative factors are considered.

So, should we be using this approach?

From anaesthetist.com

- **Quote**: "There is little doubt in my mind that the Stewart approach makes sense, and provides a slightly better model of how acid-base works than does the conventional approach. I believe that Stewart provides a refinement of the conventional approach. Under many, perhaps most circumstances, the 'old-fashioned' approach works fine, but we should be aware of the exceptions (gross volume dilution with fluids which have a low SID; hypoalbuminaemia in association with metabolic acidosis) and invoke the physicochemical approach in these circumstances. This new approach also helps us explain how our therapeutic interventions work.

  Much still needs to be done. We need a viable model based on physicochemical principles that can be consistently shown to be as good as or better than the older models. Ideally this model should also extend to assessment of whole blood acid-base status, and even allow us to predict whole-body pH changes in response to therapeutic interventions."

From acid-base.com

- **Quote**: "For most acid-base disturbances, and for the foreseeable future, the traditional approach to acid-base balance seems certain to prevail. For the clinician, the three variables of greatest us are the pH, pCO_2, and standard base excess (SBE). What might change this? The answer would have to be published cases where clinical management has been critically improved by using Stewart's approach. Such cases would have to be accumulated, evaluated, and approved before any major switch to his approach seems warranted."

An editorial view

- **Quote**: " . . . . it would be premature at present to propound the SID approach. Although it certainly will remain a powerful tool in acid-base research, for clinical management it is more cumbersome, possibly more expensive, and not sufficiently better than a critical assessment of the base excess, anion gap, or pH/pCO_2 maps to warrant its widespread adoption.[19] Interpretation of acid-base disorders will always remain partly an art, one that combines an intelligent synthesis of the clinical history, physical examination, and other ancillary laboratory data taken together in the context of the individual patient and the nature and temporal course of his or her disease."

CHAPTER OVERVIEW

11: Special Aspects of Acid-Base Physiology

11.1: Acid-Base Aspects of Pregnancy

Hyperventilation

The hyperventilation that occurs during pregnancy is probably due in part to progesterone stimulating the respiratory center. Lung volume changes and altered compliance may also contribute. The effect is a chronic respiratory alkalosis which is compensated by renal excretion of bicarbonate. Typical blood gases results in the third trimester are:

Typical ABGs in the Third Trimester

pH: 7.43

pCO_2: 33mmHg

$[HCO_3^-]$: 21mmHg

pO_2: 104 mmHg.

The reduction in bicarbonate results in a slightly reduced ability to buffer a metabolic acid load. The lower pCO_2 would shift the oxygen dissociation curve to the left, but the minimal change in pH and the increased 2,3 DPG levels during pregnancy mean the ODC is little altered in position.

Hyperemesis

Nausea and vomiting occur commonly in the first trimester. Rarely, this may be severe (hyperemesis gravidarum) and intractable vomiting can cause fluid loss and electrolyte disturbances. The acid-base result is typically a metabolic alkalosis but ketosis may also occur if oral intake is poor. The actual acid-base effect of vomiting depends on the actual mix of acidic gastric fluid and alkaline intestinal secretions in the vomitus. Alkalosis does not always occur with prolonged vomiting.

Maternal Ketosis

The pregnant woman is prone to develop elevated ketone levels because:

- fasting during pregnancy more rapidly results in hypoglycaemia and low insulin levels
- insulin resistance develops as pregnancy progresses (probably due to placental hormones)

Fasting ketosis develops in less than 16 hours in late pregnancy as compared to usually greater than 24 hours in the non-pregnant female. Ketones can cross the placenta and the foetus can adapt to use them as an energy source. Ketones may be important in myelination in the developing central nervous system. This mild ketosis that occurs with fasting does not seem to have any adverse effect on the mother or foetus. There is no information on which to base treatment of ketosis in labouring women.[1]

Ketoacidosis due to maternal diabetes is more serious and can have very serious adverse effects on the foetus.

Other

Diuretic use may cause a metabolic alkalosis. This results in a mixed alkalosis because the hyperventilation has already reduced the pCO_2.

References

1. Toohill J, Soong B, and Flenady V. *Interventions for ketosis during labour.* Cochrane Database Syst Rev 2008 Jul 16 CD004230. PubMed

11.2: Acid-Base Physiology in Children

Most aspects of acid-base physiology in children are the same as for adults and will not be repeated here. Some differences in neonates and infants are briefly indicated below. The most common acid-base problems in neonates are respiratory disorders due to respiratory insufficiency.

Many inherited disorders affecting intermediary metabolism can result in an accumulation of organic acids and these nearly all present during childhood. These are briefly considered below.

General Factors affecting Acid-Base Balance in Infants

Low Bicarbonate depends on Gestational Age

As compared to normal adults, the plasma [HCO_3^-] in neonates is lower due to the lower renal threshold and lower capacity to reabsorb bicarbonate. The more immature the neonate, the lower the level. Very low birth weight babies have bicarbonate levels of 12-16 mmoles/l but term babies have levels of 20-22 mmol/l.

Low Reserve to excrete an Acid Load

At birth in term infants, acid excretion is working near maximum capacity and there is little reserve to deal with acidosis. The lower bicarbonate levels in preterm babies means they have even less capacity than a term neonate to buffer an acid load. The ability to excrete an acid load improves over the first couple of months of life.

Other Factors

- Growth results in deposition of base in new bone as the calcium salts in bone are alkaline salts.
- On a weight basis, fixed acid production is higher than in adults (eg neonates and children < 12 months : fixed acid production is 2 to 3 mmol/kg/day).

Infantile Metabolic Acidosis

As mentioned previously, a large number of different inborn errors of metabolism cause a metabolic acidosis. This may be:

- organic acidosis (enzyme defect resulting in accumulation of acidic metabolic intermediates)
- lactic acidosis
- hyperchloraemic acidosis

Feeding difficulties often in association with tachypnoea are common in neonatal metabolic acidosis.

Some examples of organic acidoses in children are:

- maple syrup urine disease
- methylmalonic acidaemia
- propionic acidaemia
- isovaleric acidaemia
- glutaric aciduria.

Some of these disorders also cause a ketoacidosis.

Typical Presentation
A typical presentation of many organic acidaemias is as recurrent episodes of metabolic acidosis with coma often preceded by vomiting, mental obtundation, hypotonia or seizures.
Episodes may be precipitated by increased protein breakdown associated with surgery.

These inherited conditions, though individually uncommon, should be considered in any child with an acidosis especially if associated with coma. Neurological manifestations are common. Expert advice and investigation is required to sort out these disorders.

[The interested are referred to Ozand & Gascon (1991) for a review of organic acidaemias.]

Lactic acidosis can also result from enzyme defects and present during childhood. For example, pyruvate carboxylase deficiency, fructose-1,6-diphosphatase deficiency and pyruvate dehydrogenase deficiency. The lactic acidosis is not an isolated finding as these children have serious dysfunctions of organ systems esp affecting brain, liver and muscle.

Renal tubular acidosis may be hereditary and cause a hyperchloraemic acidosis in infants. Without treatment, growth retardation occurs in these children.

Other Acid-Base Disorders in Children

Final points:

- Insulin dependent diabetes mellitus usually presents during childhood or adolesence.
- Poisoning in children may cause an acid-base disorder and the disorder may be different from that typically seen in an adult (eg salicylate poisoning).

11.3: Acid-Base Disorders due to Drugs and Toxins

Classification by Mechanism

Drug-induced acid-base disorders:

1. Metabolic acidosis induced by large acid loads
- from exogenous sources (e.g. NH_4Cl, or toxin ingestion)
- from endogenous acid production (e.g. generation of ketoacids or lactic acids by alcohol or phenformin)
- from base loss (eg laxative abuse).

2. Renal tubular acidosis

2. Metabolic alkalosis resulting from exogenous bicarbonate loads or effective extracellular fluid contraction, potassium depletion plus hyperaldosteronism

4. Respiratory acidosis from drug-induced respiratory depression or neuromuscular impairment

5. Respiratory alkalosis from drug-induced hyperventilation

Some Drugs & Toxins which have been involved in various Acid-Base Disorders

Respiratory Acidosis

- CNS depressants
- Narcotics
- Muscle Relaxants

High Anion Gap Metabolic Acidosis

- Methanol
- Ethylene glycol (due glycolic acid)
- Salicylates
- Paraldehyde
- Phenformin & metformin (lactic acidosis)
- Sodium nitroprusside (lactic acidosis due cyanide)

Renal Tubular Acidosis

- Amphotericin B
- Acetazolamide
- Toluene
- Lithium
- Cyclamate
- Analgesics
- Carbonic Anhydrase Inhibitors (eg acetazolamide)
- Lead
- NSAIDs
- Outdated tetracycline
- Pentamidine in AIDS patients

Other causes of Hyperchloraemic Metabolic Acidosis

- Potassium-sparing diuretics
- Acidifying infusions (eg HCl, NH_4Cl, lysine-HCl & arginine-HCl infusions)
- $CaCl_2$ ingestion (loss of HCO_3^- due to precipitation of carbonate)

Respiratory Alkalosis

- Salicylates
- Propanidid

Metabolic Alkalosis

- Emetics
- Diuretics

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Glossary

Sample Word 1 | Sample Definition 1

Detailed Licensing

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