MICHAEL L. G. GARDNER

MEDICAL ACID–BASE BALANCE

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BAILLIÈRE TINDALL · LONDON

A BAILLIÈRE TINDALL book published by
Cassell Ltd,
35 Red Lion Square, London WC1R 4SG
and at Sydney, Auckland, Toronto, Johannesburg
an affiliate of
Macmillan Publishing Co. Inc.
New York

First published 1978

ISBN 0 7020 0687 4

Printed in Great Britain
at the Aberdeen University Press

British Library Cataloguing in Publication Data

Gardner, Michael L G
Medical acid–base balance.
I. Acid–base equilibrium
I. Title
612'.01522 QP90.7
ISBN 0–7020–0687–4

Preface

Acid–base balance is a large subject in its own right and its understanding requires an integrated and interdisciplinary approach to the several systems involved in acid–base homeostasis. Before a working knowledge of clinical and practical aspects can be acquired it is essential that the basic principles of biochemistry, physical chemistry and physiology, and the interactions between the various organs and systems, be mastered. This is the objective of *Medical Acid–Base Balance*.

In spite of the existing literature and although the subject is acknowledged to be of enormous and obvious relevance to patient care in many areas of contemporary medicine, it is one which the majority of medical students and many clinicians find both difficult and unattractive. Some existing texts treat the subject as a pure science and present it in almost mathematical form with little or no reference to human patients and their ills. At the other extreme, some clinically oriented books over-simplify, or even neglect totally, the fundamental physicochemical and physiological background. This book aims to come between these two extreme attitudes and to spell out in detail the basic principles of acid–base balance and, where appropriate, to illustrate their relevance with reference to clinical examples. It does not purport to teach clinical medicine or therapeutics, and it does not give advanced accounts of the physiology and pathology of pulmonary and renal function. Few current texts discuss adequately the principles underlying modern methods of the measurement of 'blood gases' and the assessment of acid–base status, and so these too are covered here in some detail.

Both S.I. and metric units have been adopted throughout the text, since the transition to S.I. units has not been uniformly completed and since much of the existing literature uses metric units. Any change of units' systems poses major communication problems and at a time of transition it is particularly important that users be familiar with both systems.

Areas of controversy such as the relative merits of actual bicarbonate, standard bicarbonate and base excess values, etc., have been aired with, it is hoped, as little prejudice as possible. Again, severe problems of communication arise if users are not familiar with the several different conventions favoured in various centres and used in the existing literature.

Medical Acid–Base Balance is intended primarily as an introductory text for preclinical and clinical students. However, it is also hoped that it will be useful to those clinicians who require to learn or re-learn the fundamental principles of acid–base balance. The content is based largely on a course which has been taught to preclinical students over a number of years, and I have been greatly helped by the

constructive comments made by many students who have also highlighted the areas which they have found to be of particular difficulty.

I am most grateful to many friends and colleagues who have given me valuable encouragement, advice and criticisms, both general and specific. In particular I wish to thank Dr I. B. R. Bowman, Professor G. S. Boyd, Professor R. B. Fisher, Sister Jeannie Fisher, Dr M. George, Dr R. Hume, Dr Anne T. Lambie, Dr G. J. R. McHardy, Dr Anne G. Morton and Dr I. A. Nimmo. However, responsibility for any errors and omissions remains my own.

In addition, I wish to thank the following for permission to reproduce their published material: Churchill Livingstone; Professor H. W. Davenport; Dr D. C. Flenley; Instrumentation Laboratory (U.K.) Ltd.; *The Lancet*; Dr R. W. Logan; *The New England Journal of Medicine*; Radiometer A/S; Professor W. B. Schwartz; University of Chicago Press; Yale University Press.

March 1978 MICHAEL L. G. GARDNER

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Introduction

Acid–base balance is a fascinating and important aspect of modern medicine. Few subjects can claim to be more interdisciplinary or to combine more closely the pre-clinical sciences with clinical medicine. The basic sciences of physiology and biochemistry merge to explain the normal functioning of the organs and systems concerned in acid–base homeostasis: in some clinical situations this normal functioning either has failed or is at risk and therefore medicine, surgery and therapeutics are all concerned in its maintenance and restoration. Although the subject has a long history, there are still many problems on which our current knowledge is incomplete and on which the way is open for further research.

An understanding of both the theoretical and practical aspects of acid–base balance is vital to patient care in many branches of contemporary medicine. While the physicochemical theory of buffers and equilibria may appear to some clinicians and medical students to be an uninteresting and even irrelevant realm of pure science, there is no doubt that a firm grasp of basic principles really does provide essential background for diagnosis, interpretation and treatment of many respiratory and metabolic disturbances encountered in both medical and surgical practice.

For example, the diagnosis and particularly the assessment of severity of many respiratory conditions, even in the out-patient clinic, relies on measurements of the 'blood gases', that is determination of P_{O_2} and P_{CO_2} values. The same is true for the management of patients on artificial ventilators (where the P_{CO_2} values achieved in the arterial blood are regulated solely by the medical and nursing staff) and for the control of ventilation during anaesthesia especially during major procedures such as those involving cardiopulmonary surgery. Since the kidney is fundamentally involved in the regulation of the electrolyte concentrations in the body fluids and the reabsorption and excretion of acids and bases it is obvious that an understanding of these processes is required by all who undertake the treatment of renal disease. Many other metabolic disorders involve disturbances of acid–base balance: simple examples include the excess metabolic production of non-volatile acids (e.g. keto-acids in diabetic ketoacidosis) and the direct loss of the base bicarbonate in some forms of renal failure. Other important but less obvious examples include the lactic acidosis sometimes associated with shock or with side-effects of certain drugs or caused by cardiac arrest and the excess H^+ ion excretion caused by hyperaldosteronism.

Investigations of acid–base status also often play an important part in the diagnosis of paediatric conditions and in some cases here speed and accuracy of measurement and interpretation are particularly vital. The advent in recent years of intensive care (critical care) units has also demanded more attention to the monitoring and management of acid–base and electrolyte status. Particularly in these units and in operating

theatres correct and rapid assessment of acid–balance considerations saves patients' lives. In some centres physiotherapists refer to blood gas measurements on ventilated patients, especially infants, as a guide to the degree of chest treatment which is necessary or which can be tolerated and also as an index of the efficacy of treatment.

Hence no clinician, especially in hospital practice, should be without an intimate understanding of the principles and practice of acid–base balance: indeed in many intensive care areas the nursing staff also are expected to be familiar with the basic principles and practice of the subject.

In some units the various physical and chemical measurements are made by technical and laboratory staff; however in others the clinician personally makes the measurement on the spot. In any case it is the clinician's responsibility to provide a suitable and valid sample (generally blood, sometimes CSF), then to interpret the numerical results as correctly as possible, and to initiate the appropriate therapeutic action and any further monitoring that may be subsequently required. Thus both practical and theoretical knowledge are absolutely essential.

It will be clear both from this book and from personal clinical experience that many topics in acid–base and electrolyte balance are incompletely understood. There is therefore a continuing need for first-class clinical and experimental research, and for this an interdisciplinary attitude embodying the principles of physiology, biochemistry and medicine is demanded.

2

The Need for Acid–Base Regulation

pH dependence of metabolism

The normal functioning of metabolism requires that the compositions of the environments and contents of cells be kept constant, or at least within certain limits. Thus the pH of extra- and intracellular fluids must be kept fairly constant. It is not possible to point to any single reason for this; the activities of virtually all the thousands of enzymes within cells are to some extent pH-dependent. However, the pH-dependence of the activity of most enzymes is much less dramatic than the pH-dependence of the overall normal functioning of the body and other factors must be involved. Also the ionic states of all substrates which have acidic or basic chemical groups are determined by the pH. Membrane transport processes are markedly pH-dependent: therefore the composition of intracellular fluids and of the contents of subcellular organelles, and hence the metabolic activities of cells, can be affected to an important extent by pH change.

While any one metabolic process may be affected only to a small extent by a change in pH, the whole overall pattern of metabolism can be drastically changed by pH variation. For example, lactate production from glucose by isolated rat diaphragm muscle falls at pH 7·1 to 63% of the rate at pH 7·4. Also the contractile force of heart muscle varies considerably as the extracellular pH is changed. Furthermore, since the acid or base form of every buffer is ionized (by definition), and the relative amount of the ionized species is intimately related to pH, it follows that the amount of counter-ion required is pH-dependent. Hence there is a close association between electrolyte balance and acid–base balance.

The need for regulation of acid–base balance can best be judged by the practical consequences of a disturbance from normal blood pH (7·40). The consequences of a blood pH as low as 6·8 are so severe as to be almost certainly lethal. In practice, the blood pH in a healthy individual is normally maintained between 7·35 and 7·45 by the physiological mechanisms involving lungs and kidneys and by the physicochemical action of buffers which are discussed in the following chapters. While this range of 'normal' pH values may seem very narrow it is worth bearing in mind that the pH scale is a logarithmic scale and that these values correspond to a range of H^+ ion concentration of 45–35 nmole/litre*; i.e. a 25% change in $[H^+]$ is quite acceptable, and in this sense the body regulates hydrogen-ion concentrations far less precisely than, for example, plasma sodium-ion concentration. A logarithmic scale which relates pH and $[H^+]$ values is given in Appendix II (p. 94).

* A nmole, or nanomole, abbreviated to nmol is 10^{-9} moles. One mole is one gram molecule. See also Appendix II.

Extremes of pH

It is not possible to state a definite extreme range of pH values encountered in disease, although pH values of as low as 6·8 ($[H^+]$ = 158 nmol/litre) and as high as 7·8 ($[H^+]$ = 16 nmol/litre) have been observed for brief periods in patients who have survived. However it is emphasized that these are particularly extreme abnormal values and that far smaller deviations from pH 7·40 should cause concern.

Metabolic production of acids

Under normal physiological circumstances the body produces a substantial quantity of acid since many end-products of metabolism are acids. Thus a normal sedentary individual produces carbon dioxide (which becomes hydrated to carbonic acid especially rapidly since the enzyme carbonic anhydrase is present in erythrocytes) equivalent to about 13 000–15 000 nmol (mEq) of hydrogen ions per day, i.e. the same amount of H^+ ions as are present in 13–15 litres of 1 M HCl. Clearly, if this were allowed to accumulate then the effect on blood, tissue fluid and intracellular fluid pH would be dramatic and lethal. However since carbon dioxide is volatile it can be excreted via the lungs and it is normally possible to excrete it as fast as it is produced; hence no accumulation should occur. In addition a much smaller quantity of non-volatile acids, the so-called 'fixed acids', is produced metabolically.

On a normal diet the main non-volatile acid which has to be excreted is sulphuric acid formed during the oxidation of sulphur-containing amino acids (i.e. methionine, cystine and cysteine) from proteins. A smaller amount of phosphoric acids is also excreted; these arise mainly from oxidation of nucleic acids, phospholipids and phosphoproteins such as casein and egg albumin. A small contribution is made by non-metabolizable organic acids of dietary origin (or at least whose rate of metabolism is slower than their rate of production or intake).

The amount of non-volatile acid produced and excreted by a normal individual thus depends largely on the dietary intake, especially of protein; it is generally of the order of 50–100 mmol (mEq) H^+ per day. Clearly this is a trivial amount compared with the amount of the volatile component (CO_2) which has to be excreted by the lungs each day. However the addition of non-volatile acids to the blood poses an additional problem which has to be considered since they cause depletion of the plasma base, bicarbonate, as follows:

Consider the equilibrium:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$
$$\longleftarrow H^+$$

By the law of mass action the addition of H^+ will displace the equilibrium towards the left. Therefore the HCO_3^- concentration decreases and more CO_2 is formed. This can also be seen in another way by taking a specific example such as the addition to blood of sulphuric acid which is a very strong acid (i.e. virtually fully ionized):

$$H_2SO_4 \rightarrow 2H^+ + SO_4.$$

Then we have:

$$H_2SO_4 + 2HCO_3^- \rightarrow 2CO_2 \uparrow + SO_4^{2-} + 2H_2O$$

In practice the CO_2 concentration normally hardly increases since the respiratory centre controls respiration and causes hyperventilation, thus venting off CO_2 (see below) to keep the P_{CO_2} in arterial blood fairly constant, close to 40 mmHg (5·3 kPa). However the loss of HCO_3^- (converted into CO_2 which is then exhaled) is a potentially

serious event, since this base is one of the most important buffers in the body. The buffering capacity of each buffer obviously depends on, among other factors, the concentration or total amount of that buffer present. Hence loss of buffer is undesirable.

Conservation of bicarbonate

Therefore the kidney in a healthy individual on a normal diet has two important tasks in the conservation of bicarbonate: (1) *all* the filtered HCO_3^- must be reabsorbed (normal urine does not contain any HCO_3^-: this would be a waste of an important buffer) and (2) any HCO_3^- lost through addition of non-volatile acids to the blood as explained above must be resynthesized or regenerated within the renal tubule cells. The processes of H^+ excretion into the urine and of reabsorption of filtered HCO_3^- and also of regeneration of lost plasma HCO_3^- by the kidneys are all closely related and are discussed in detail in Chapter 6.

Accumulation of excess acid

The problem of pH regulation is clearly even more crucial in severe exercise and in pathological conditions where, for example, more acid end-products of metabolism may be produced faster than they can be oxidized to the volatile acid CO_2. Normally lactic acid is oxidized to CO_2 and H_2O at approximately the same rate as that at which it is formed. If, however, its oxidation is impaired and/or its production is increased then lactic acid may accumulate in blood, especially during tissue hypoxia, e.g. owing to circulatory or respiratory failure. Lactic acid is quite a strong acid with a pK value of about 3·7 and so it will deplete the plasma bicarbonate. In starvation or in diabetic keto-acidosis the relatively strong acids acetoacetic acid (pK 3·6) and β-hydroxybutyric acid (pK 4·4) are formed faster than they can be oxidized and so deplete the HCO_3^-, the so-called 'alkali-reserve'. Furthermore when these acids are excreted they, being strong acids and therefore mainly ionized, must be accompanied by cations. Excess loss of Na^+ and K^+ ions into the urine would obviously be undesirable, and therefore a mechanism is required to minimize or 'spare' the loss of these cations during excretion of strong acids.

Accumulation of bases

While the normal end-products of metabolism tend to be acids, bases can accumulate in the body under certain circumstances, such as the ingestion of large quantities of anti-acid preparations or of fruits containing citrate as salts. Citrate is metabolized to form a volatile acid (CO_2) which is easily excreted plus a non-volatile or 'fixed' base (HCO_3^-) which has to be disposed of together with a counter-cation via the kidneys. Normally the kidneys can cope, but if renal function is impaired this can create a disturbance of acid–base balance.

The excessive excretion of H^+ ions such as in hyperaldosteronism or hypokalaemia (see Chapter 6) is equivalent, in its effect on acid–base balance, to retention of excess base. This is also discussed further in Chapter 8.

Defences against variation in acid–base status

Thus in the face of a continual production of acids the body has to minimize the pH changes in the body fluids. Furthermore, even in a healthy individual, the amount of acid produced varies from time to time and so the mechanisms have to be capable of

'recognizing' the requirements for correct regulation and of adapting the regulatory systems accordingly.

In general, the defence mechanisms can be divided into two distinct categories. (1) The chemical buffers which by their physicochemical nature minimize the effect which addition of acids or bases would have on the H^+ ion concentration of the body fluids. These are dealt with in detail in Chapter 3. (2) The physiological mechanisms which, largely through the functioning of the respiratory system and the kidneys, regulate the composition of the body fluids. Thus the lungs can excrete CO_2, an acid, and the kidneys can excrete H^+ ions and can reabsorb and regenerate bicarbonate, the base, as required. These mechanisms are discussed in detail in Chapters 5, 6 and 7.

Requirement for regulation of carbon dioxide concentration

The concentration of carbon dioxide, expressed as the partial pressure (P_{CO_2}), in the blood and other body fluids must be regulated also in its own right and not only as a means of regulating the pH. Quite apart from effects which could be due to change in pH, changes in P_{CO_2} can have serious effects on the body. In particular the cardiovascular and central nervous systems are at risk. For example, accumulation of carbon dioxide (respiratory acidosis, hypercapnia) causes important changes in blood flow such as an increase in cerebral circulation and peripheral vasodilation, but there is vasoconstriction in the pulmonary vascular system. In addition there is depression of the central nervous system. The respiratory system therefore is well adapted to minimize severe changes in P_{CO_2} under normal circumstances and the mechanisms are discussed in Chapter 5.

3

Physiological Buffers

Definitions of buffers, acids and bases

A *buffer solution* is one which resists or minimizes change of pH when acid or base is added. Thus the buffers in the body fluids act as a physicochemical defence against pH change; other mechanisms such as the physiological control mechanisms of the kidneys and lungs also operate to minimize changes in pH and also to restore the composition of the body fluids to normal following a disturbance. These physiological mechanisms will be considered in subsequent chapters.

A buffer always consists of a mixture of a weak acid (or base) and its conjugate base (or acid) respectively. Such a mixture is said to constitute a conjugate pair. These terms can be defined according to Brönsted and Lowry as follows.

An *acid* is a proton donor, that is anything which dissociates into one or more protons, i.e. a hydrogen ion, plus a conjugate base.

e.g. $\underset{\text{acid}}{HA} \rightleftharpoons \underset{\text{proton}}{H^+} + \underset{\text{conjugate base}}{A^-}$

example: carbonic acid $H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$

Conversely a *base* is a proton acceptor, i.e. anything which can combine with a proton to form a conjugate acid.

e.g. $\underset{\text{base}}{B} + H^+ \rightleftharpoons \underset{\text{conjugate acid}}{BH^+}$

or $\underset{\text{base}}{BH} + H^+ \rightleftharpoons \underset{\text{conjugate acid}}{BH_2^+}$

example: ammonia $NH_3 + H^+ \rightleftharpoons NH_4^+$

bicarbonate $HCO_3^- + H^+ \rightleftharpoons H_2CO_3$

Other definitions of acids and bases have been proposed but those of Brönsted and Lowry are adequate for all medical purposes.

Note that some biological substances (e.g. phosphates and amino acids, see below) can behave as both bases and acids, i.e. they can both accept and donate protons respectively. Such substances are described as being amphiprotic or amphoteric.

e.g. $\underset{\text{acid}}{H_2PO_4^-} \rightleftharpoons H^+ + HPO_4^{2-}$

$\underset{\text{base}}{H_2PO_4^-} + H^+ \rightleftharpoons H_3PO_4$

In aqueous solution hydrogen ions, i.e. protons, can themselves be hydrated to form hydroxonium (or hydronium) ions, H_3O^+:

$$H^+ + H_2O \rightleftharpoons H_3O^+$$

Therefore the ionization of an acid in aqueous solution is more correctly written as:

$$\underset{\text{acid}}{HA} + H_2O \rightleftharpoons \underset{\text{base}}{A^-} + \underset{\text{hydroxonium ion}}{H_3O^+}$$

Nevertheless it is convenient to consider the more simple dissociation equilibria and to ignore the hydroxonium ion for practical purposes.

It can thus be seen that water behaves as an amphoteric molecule since it can both donate and accept protons:

$$\underset{\text{acid}}{H_2O} \rightleftharpoons H^+ + OH^-$$

and

$$\underset{\text{base}}{H_2O} + H^+ \rightleftharpoons H_3O^+$$

Equilibrium and dissociation constants and pK values

The equilibrium position of any reaction is described quantitatively by an equilibrium constant, K. This is defined as follows:

For the equilibrium $A + B \rightleftharpoons C + D$

$$K = \frac{[C] \,.\, [D]}{[A] \,.\, [B]}$$

and for the equilibrium $A + B \rightleftharpoons C$

$$K = \frac{[C]}{[A] \,.\, [B]}$$

Therefore for the dissociation of dihydrogen phosphate:

$$H_2PO_4^- \rightleftharpoons H^+ + HPO_4^{2-}$$

the equilibrium constant is

$$K = \frac{[H^+] \,.\, [HPO_4^{2-}]}{[H_2PO_4^-]}$$

which has a value of $1{\cdot}6 \times 10^{-7}$ mole $\cdot$ litre^{-1}.

Since typical values of K are very small it is often convenient to use pK values. The pK for any equilibrium is defined as

$$pK = \frac{1}{\log K} = -\log K$$

in an analogous way to Sørensen's definition of

$$pH = \frac{1}{\log [H^+]} = -\log [H^+]$$

where K is the equilibrium constant for the equilibrium in question. Thus the pK value for the dissociation of dihydrogen phosphate mentioned above is 6·8.

The lower the pK value, the stronger is an acid. This reflects that the stronger an acid is, the further to the right lies the equilibrium

$$HA \rightleftharpoons H^+ + A^-$$

i.e. the greater is the degree of dissociation. Hence, the equilibrium constant (dissociation constant), K, will be larger and pK smaller. Thus acetoacetic acid (pK 3·6), which accumulates in diabetic keto-acidosis, is a stronger acid than acetic acid (pK 4·7).

The equilibrium constant (K), and hence the pK value, is constant under stated conditions of temperature, etc. Note that for substances which can dissociate or associate in several ways (i.e. the so-called polybasic, polyprotic, amphiprotic or amphoteric acids and bases) there are several pK values, one for each possible association or dissociation equilibrium.

Thus the amino acid histidine has three separate pK values, 1·8, 6·0 and 9·2. These values are associated with the α-carboxyl, imidazole and α-amino groups respectively.

1. Dissociation of the α-carboxyl group ($pK_1 = 1{\cdot}8$):

2. Association of the imidazolium side-chain group ($pK_2 = 6{\cdot}0$):

3. Association of the α-amino group ($pK_3 = 9{\cdot}2$):

The Henderson–Hasselbalch equation

From the definitions

$$\text{Acid} \rightleftharpoons H^+ + \text{base}^-$$

$$pH = -\log [H^+]$$

$$pK = -\log K$$

$$K = \frac{[H^+] \,.\, [\text{base}^-]}{[\text{acid}]}$$

one can simply derive the *Henderson equation*:

$$[H^+] = \frac{K \,.\, [\text{acid}]}{[\text{base}^-]}$$

or the more useful logarithmic version, the *Henderson–Hasselbalch equation* (see Appendix I for detailed derivation), which is:

$$pH = pK + \log \frac{[\text{base}^-]}{[\text{acid}]}$$

This equation is fundamental to the consideration of all acid–base equilibria and should preferably be memorized.

Obviously, according to the law of mass action, addition of H^+ ions to a mixture containing acid and base

$$\text{acid} \underset{\longleftarrow}{\rightleftharpoons} H^+ + \text{base}^-$$

will displace the equilibrium towards the left as written above; thus the concentration of the base component will fall, while the concentration of the acid component must rise by an exactly corresponding amount. The Henderson–Hasselbalch equation enables one to relate quantitatively the change in [base], [acid] and pH. One therefore can see that the pH of a solution depends on the *logarithm of the ratio* of base to acid concentration* and not on the ratio itself or on one or other concentration by itself.

Consider the equilibrium:

$$\text{acid} \rightleftharpoons H^+ + \text{base}^-$$

$$pH = pK + \log \frac{[\text{base}^-]}{[\text{acid}]}$$

Addition of x mmole of H^+ ions per litre will reduce [base] by an amount x, and will increase [acid] by an equal amount x, so that the pH becomes

$$pH = pK + \log \left\{ \frac{[\text{base}] - x}{[\text{acid}] + x} \right\}$$

It can be shown that the smallest change in the ratio will be produced (for a given value of x) if initially [acid] = [base]. This means that a buffer is best, i.e. it minimizes

* In turn, the hydrogen ion concentration itself depends on the ratio of base to acid concentration (not logarithm) according to the Henderson equation:

$$[H^+] = K \,.\, \frac{[\text{base}^-]}{[\text{acid}]}$$