Renal physiology: acid–base balance

Andrew D McTavish

Manu-Priya Sharma

Abstract

Acid–base balance is a fundamental part of human homeostasis. The human body has evolved a system which allows exquisite control, involving multi-organ systems, over the pH of the intracellular and extracellular fluid. The Henderson–Hasselbalch equation relates pH to the dissociation constant, pK_a, and relative concentrations of dissociated and undissociated acid. One of the clinical applications of this equation is in the use of local anaesthetic agents, applying knowledge of pH and pK_a to select the most appropriate drug. In order to exert such fine control over pH, buffer systems exist that rapidly permit correction of any deviance outside the normal range. The principal buffer system is the bicarbonate buffer system, mediated through carbonic anhydrase. The renal system exerts control over the ultimate fate of bicarbonate and hydrogen ions through a series of chemical reactions, culminating in the excretion of excess acid or base. Abnormalities in acid–base balance can have profound consequences and it is therefore vital to understand the basis of the abnormality in order to effectively treat the condition.

Keywords Acid–base balance; acidosis; alkalosis; buffers; physiology

Royal College of Anaesthetists CPD Matrix: 1A01, 1A02, 2A03, 2A07, 2C04

Learning objectives

After reading this article, you should be able to:

- reproduce the definitions of an acid and a base and should be able to quote the normal values for hydrogen ion concentration
- summarize the Henderson–Hasselbalch equation and its relevance to acid–base homeostasis and the use of local anaesthetic agents
- explain the main buffer systems in the body and the role of carbonic anhydrase
- summarize the absorption and excretion routes for hydrogen and bicarbonate ions
- select appropriate drugs to manipulate acid–base balance in clinical situations

The human body is dependent on a tightly controlled internal environment – homeostasis. Extracellular and intracellular pH plays a particularly significant role in maintaining body homeostasis. The body has developed the ability to rapidly correct deviation from the normal pH range of 7.35–7.45. The primary systems involved in the control of acid–base balance are the buffer system, the respiratory system and the renal system. The respiratory system and its control of acid–base balance is beyond the scope of this article but the role of buffer systems and the renal compensatory mechanisms for control of acid–base balance will be discussed in detail. Acid–base balance, or the understanding of the processes which govern the relative 'acidity' of the body, is an essential topic but one that many people find unnerving. At its simplest, it is the study of how acids and bases interact and are produced, conserved and excreted by the body. The maintenance of a constant internal environment is vital to many of the body's most basic functions; some of the most important include enzymatic processes, energy production and membrane excitability.

***Andrew D McTavish** BSc MBChB FRCA is a Senior Clinical Fellow at the North West and North Wales Paediatric Transport Service, UK. Conflicts of interest: none declared.*

***Manu-Priya Sharma** BSc MBBS MRCS MSc FRCA is a Consultant Anaesthetist at Manchester Royal Infirmary, Manchester, UK. Conflicts of interest: none declared.*

Enzymatic processes

All enzymes have an optimal pH and the ability of an enzyme to catalyse a reaction rapidly deteriorates as the pH deviates from the optimum. Furthermore, an alteration in pH can denature enzymatic proteins, rendering them useless.

Energy production

Within the mitochondrion, hydrogen ions are moved across the inner membrane to produce energy – this produces a pH gradient inside the mitochondrion which, when considered alongside the electrical gradient, is known as the electrochemical proton gradient and this underpins the ability of the mitochondrion to produce energy for the cell.

Membrane excitability

Membrane excitability, generally speaking, rises as pH rises and conversely falls as pH falls. Neuronal tissue voltage-gated ion channels and receptors are known to show strong pH dependence and any variance in physiological pH can cause a potentially life-threatening alteration in neuronal cell excitability.

Definitions: acids, acidosis, alkalosis and buffers

There are several definitions of what constitutes an acid, beginning with Lavoisier in the eighteenth century, who believed that acids were substances which existed in high oxidation states. Throughout the nineteenth century, further work was done which gradually introduced the 'hydrogen theory', and in the early twentieth century, Brönsted and Lowry stated that acids are substances which donate a hydrogen ion and bases are substances which accept a hydrogen ion. Brönsted and Lowry's definition remains in common use and in the human acid–base system, hydrogen ions are the relevant ion so it is reasonable to accept this definition.

In human physiology, an acidosis is defined as 'a process in which arterial pH is less than 7.35 or hydrogen ion concentration

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is greater than 45 nmol/l'. An alkalosis is defined as 'a process in which arterial pH is greater than 7.45 or hydrogen ion concentration is less than 35 nmol/l'. A buffer is defined as 'any substance which can reversibly bind hydrogen ions', ie: Buffer + H^+ $\leftrightharpoons$ HBuffer. While reviewing these definitions, it is worth noting that the lower limit of hydrogen ion concentration is 35 nmol/l and the upper limit is 45 nmol/l, meaning that the normal value of 40 nmol/l fluctuates by an exceptionally low value of only 5 nmol/l.

These values are often unworkably small so the pH scale is used to make the numbers more manageable and relevant to clinical work. In chemistry, the prefix 'p' is used to denote that the value is a negative logarithm, so it becomes clear that:

$$\mathrm{pH} = -\log_{10}[\mathrm{H}^+]$$

If the normal hydrogen ion concentration is taken to be 40 nmol/l, converting into moles/l makes the equation:

$$\mathrm{pH} = -\log_{10}40^{-9}$$

Thus the calculated physiological pH, for a hydrogen ion concentration of 40 nmol/l is pH 7.3979.

Henderson–Hasselbalch equation

This equation is a method of deriving the pH from the known concentrations of dissociated and undissociated acid and base and the dissociation constant, pK_a. The original equation was derived in 1908 by Lawrence Henderson and was added to in 1916 by Karl Hasselbalch, who introduced the logarithmic function.

Dissociation constant and pK_a

The dissociation constant allows us to quantify how chemically 'strong' or 'weak' an acid is when it is in solution. If we take an acid, HA, and place it into solution, the acid will dissociate to a greater or lesser degree, ie: HA $\leftrightharpoons$ H^+ + A^- where H^+ is a dissociated hydrogen ion and A^- is a dissociated base. The dissociation constant, pK_a, is obtained by dividing the dissociated proportion (H^+ and A^-) by the undissociated proportion (HA), ie:

$$K_a = \frac{[H^+][A^-]}{HA}$$

The prefix 'p' denotes a negative logarithm, so pK_a is the negative logarithm of K_a. The use of the logarithmic function of K_a makes calculations easier to manipulate. The lower the pK_a value, the stronger the acid, where 'strong' signifies an acid which dissociates completely or almost completely when it is placed in solution. Values less than −2 generally indicate a strong acid. Additionally, the pK_a is the pH value at which there is a 50:50 ratio of dissociated:undissociated proportions. If the pH of an acid is 4 and the pK_a is also 4 then the proportion of H^+ is equal to the proportion of undissociated acid, HA. The further distant the pK_a from the pH, the wider the disparity between the proportions of dissociated and undissociated acid or base. This is particularly applicable to local anaesthetic pharmacology.

Henderson and Hasselbalch worked further on the concept of pK_a and pH and derived the equation:

$$\mathrm{pH} = \mathrm{p}K_a + \log_{10}\frac{\text{base}}{\text{undissociated acid}}$$

In biological systems, this equation is used to estimate pH if the concentrations of bicarbonate and the PCO_2 are known.

Local anaesthetic agents and pK_a

Local anaesthetic agents are poorly soluble weak **bases**, all with a pK_a value above 7.4. Therefore these drugs exist predominantly in the dissociated (or ionized) state at physiological pH (7.35–7.45). The pK_a value is a method of quantifying the relative proportions of dissociated to undissociated (or ionized to unionized) acid molecules. Local anaesthetics are all weak bases and the subscript 'b' may be used to denote a base, ie: pK_b. However, the terms pK_a and pK_b are often used interchangeably and we will use the term pK_a in this article.

Local anaesthetic drugs diffuse from the site of injection to the nerve cell. They diffuse across the membrane in the undissociated form. Only the smaller, undissociated proportion of the drug can cross cell membranes. Once inside the cell membrane, they dissociate and bind to the sodium channels within the cell, blocking them in the open form and thus preventing transmission of nerve impulses.

A drug's pK_a value indicates the speed of onset of the drug and is related to the amount of undissociated drug which is available to cross the cell membrane. For example if lidocaine, with a pK_a value of 7.9 is injected subcutaneously into an environment where the pH is 7.4, 25% of the drug will exist in the undissociated form. Bupivacaine has a pK_a value of 8.1 and at pH 7.4, 15% of the drug exists in the undissociated form.

A drug has a fixed value for its pK_a but the pH within tissues can fluctuate, commonly as a result of infection. Therefore if lidocaine is injected into infected tissue where the pH may be as low as 7.1, only 16% of the drug exists in the undissociated form.

Buffer systems

A buffer is defined as 'any substance which can reversibly bind hydrogen ions'. Any physiological buffer system should have a pK_a relatively close to the desired physiological pH of 7.40, giving the buffer maximal chemical ability to absorb changes in the blood pH. There are four major buffer systems within the body.

- proteins
- haemoglobin (pK_a 6.8)
- phosphate (pK_a 7.2)
- bicarbonate/carbonic acid (pK_a 6.1).

Proteins

As a heterogeneous group, it is difficult to assign a pK_a value to body proteins. Proteins have free carboxylate groups ($-COO^-$) and free amino groups ($-{NH_3}^+$) and these groups are able to absorb hydrogen (H^+) and hydroxyl (OH^-) ions (Figure 1).

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