Water, strong ions, and weak ions
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Key points
The law of electrical neutrality states that, in any aqueous solution in equilibrium, the sum of the positive charges always equals the sum of the negative charges.

An acid or base is defined as strong if it is fully dissociated at the pH of interest.

Strong ion difference (SID) is the amount by which the strong positive ions (cations) are in excess of the strong negative ions (anions).

Weak acids and bases are only partially dissociated in the range of body pH.

Acid–base balance can be characterized quantitatively in terms of three independent variables: $P_{CO_2}$, [SID], and total weak acid.

The definitions of acid and base to include reactions that do not involve hydrogen ions.

Lewis base. This concept usefully extends the definitions of acid and base to include reactions that do not involve hydrogen ions.

Strong electrolytes are always completely dissociated into ions when dissolved in water.

The effects of strong and weak electrolytes on acid–base physiology.

The complex calculations involved in this approach were not possible in the precomputer era but are easily done today. He wrote of this approach having ‘revolutionized our ability to understand, predict and control what happens to hydrogen ions in living systems’.

Definitions
‘Acid’ and ‘alkali’ are derived from Latin (acidus = sour) and Arabic (al qaliy = ashes of plant). Acids possess a sour taste in solution and alkalis reverse their action in solution.

The Arrhenius theory of acids and bases was based on their dissociation into ions. Thus, acids are defined as producers of hydrogen ions and all bases produce hydroxyl ions. Lowry and Bronsted gave this theory a more general basis. They defined an acid as a molecule or ion that can lose or donate a proton (a hydrogen ion is a single free proton released from a hydrogen atom) and a base as a molecule or ion that can accept a proton. Lewis further extended this concept. He defined an acid as any substance that accepts electrons and a base as any substance able to donate electrons. Since a Lowry–Bronsted base donates electrons to a hydrogen ion, a Lowry–Bronsted base is also a Lewis base. This concept usefully extends the definitions of acid and base to include reactions that do not involve hydrogen ions.

Stewart defined a solution as neutral if the concentration of hydrogen ions was equal to the concentration of hydroxyl ions, acidic if the concentration of hydrogen ions was greater than the concentration of hydroxyl ions and basic if the concentration of hydroxyl ions was greater than hydrogen ions. According to his approach, an acid is a substance that increases the [H+] of a solution and a base is a substance that decreases it, relative to the hydroxyl ion concentration. Electrolytes are substances that dissociate into ions when dissolved in water. Stewart classified these into strong and weak. Strong electrolytes are always completely dissociated in solution and the resulting ions are called strong ions. Weak electrolytes are substances that only partly dissociate into ions when dissolved in water and yield weak ions. The effects of strong and weak electrolytes on acid–base balance are very different.
dissociation in solution): strong ions (complete dissociation), e.g. Na\(^+\), K\(^+\), Mg\(^2+\), Ca\(^2+\), SO\(_4^{2-}\), Cl\(^-\), and weak ions (incomplete dissociation), e.g. protein, phosphate, HCO\(_3^-\).

**Stewart's concept of acid–base: the 'modern' approach**

According to this view, the acid–base state in different parts of the body depends on: (i) water; (ii) strong ions; (iii) weak ions; and (iv) solutions containing CO\(_2\) as indicated by the P\(_{CO_2}\) of the solution. To understand this concept we have to keep the following principles in mind:

1. The law of electroneutrality: this states that in aqueous solutions in any compartment the sum of all the positive ions must equal the sum of all the negatively charged ions.
2. The law of mass action: this law dictates the dissociation equilibrium of incompletely dissociated substances.
3. The law of conservation of mass: the amount of a substance in any compartment remains constant unless it is added, removed, generated or destroyed. The total concentration is the sum of the concentration of dissociated and undissociated forms.

**Law of electrical neutrality**

In any aqueous solution in equilibrium, the sum of the positive charges always equals that of the negative charges. For instance, in a solution of NaCl

\[
[Na^+] + [H^+] = [Cl^-] + [OH^-]
\]

This concept can be expressed graphically, using two columns: one each for positive and negative charges, keeping them equal in height. Gamble developed figures now called 'Gamblegrams' to help express the composition of complex solutions such as plasma (Fig. 1).

**Dissociation of water**

Let us consider the water molecule. Water is formed by strong covalent bonding between H and O and dissociates only very slightly. The reaction: H\(_2\)O \rightleftharpoons H\(^+\) + OH\(^-\) is therefore far to the left. At equilibrium, if we apply the law of mass action: K = [H\(^+\)] [OH\(^-\)], the concentration of water [H\(_2\)O] is altered very minutely by dissociation; therefore, K \times [H\(_2\)O] can be taken as a constant known as K\(_w\) (the ion product of water). Therefore, [H\(^+\)] [OH\(^-\)] = K\(_w\).

To ensure electrical neutrality, [H\(^+\)] = [OH\(^-\)] and both [H\(^+\)] and [OH\(^-\)] = \(\sqrt{K_w}\). At 25°C pure water has a K\(_w\) of 1.008 \times 10\(^{-14}\) mol\(^2\) l\(^{-1}\) and thus we can approximately state: [H\(^+\)] = [OH\(^-\)] = 10\(^{-7}\) Eq litre\(^{-1}\). As activity increases with temperature, at 37°C in solutions in the body, K\(_w\) = 4.4 \times 10\(^{-14}\) mol\(^2\) l\(^{-1}\). Thus both [H\(^+\)] and [OH\(^-\)] are increased.

Pure water is always acid–base neutral, i.e. [H\(^+\)] = [OH\(^-\)] but, as described above, its hydrogen ion concentration varies considerably with temperature from pH 7.5 at 0°C to pH 6.1 at 100°C. The neutral pH (i.e. 7) occurs at 25°C and at body temperature the neutral pH is 6.8.

Water has a large dielectric constant. This means that molecules containing strong ionic bonds dissociate to some extent in water. Its own dissociation constant is small (~10\(^{-16}\) mEq litre\(^{-1}\)), i.e. it dissociates to a very small extent. Thus the concentration of hydrogen ions in body fluids is much lower than in water. The extent of dissociation of water depends on temperature, concentration, ionic strength, and the presence of specific substances. Water has a concentration of 55.3 M at 37°C, which is around 400 times the concentration of any other substance in the body fluids (Fig. 2). However, it is vital to realize that because water dissociates so little, the concentrations of hydrogen ions in body fluids are very small. Hydrogen ion concentrations are measured in NANO moles (nmol, 10\(^{-9}\) mol) whereas important ions such as sodium are present in concentrations nearly a million times greater (nmol, 10\(^{-3}\) mol) (Fig. 2). Figure 3 shows Gamblegrams for some important body fluids.
Let us now explore the concept of strong ions. An acid or base is defined as strong if it exists in a fully dissociated state at the pH of interest. Consider the strong acid HX: the reaction $\text{HX} \rightarrow \text{H}^+ + \text{X}^-$. Similar conditions would apply for the strong base BOH and the reaction $\text{BOH} \rightarrow \text{B}^+ + \text{OH}^-$. When a known amount of HX or BOH is added to a solution, the increase in $\text{X}^-$ and $\text{B}^+$ is equal to the amounts added.

Strong ions are derived from compounds that dissociate completely in water. A strong ion is one that is always present in a fully dissociated state. The predominant strong cations in blood are $\text{Na}^+$, $\text{K}^+$, $\text{Ca}^{2+}$, and $\text{Mg}^{2+}$, and $\text{Cl}^-$ and $\text{SO}_4^{2-}$. These relate to the substances we think of as powerful acids and bases, such as sulfuric acid or sodium hydroxide. In a pure salt solution, $\text{NaCl}$ exists as equal amounts of $\text{Na}^+$ and $\text{Cl}^-$. Thus, the $[\text{H}^+]$ and pH of the solution will remain unchanged upon addition of sodium chloride. Following the law of electrical neutrality: $[\text{Na}^+] + [\text{Cl}^-] = [\text{H}^+] - [\text{OH}^-] = 0$.

Addition of the strong acid HCl increases $[\text{Cl}^-]$ more than $[\text{Na}^+]$, thus $[\text{H}^+]$ increases to make up the difference and the solution becomes acidic. $[\text{OH}^-]$ must decrease because the dissociation equilibrium of water is constant and electrical neutrality has to be maintained. On the other hand, addition of a strong alkali NaOH increases $[\text{Na}^+]$ more than $[\text{Cl}^-]$ and $[\text{OH}^-]$ increases. By the law of mass action, and according to the dissociation constant of water, $[\text{H}^+]$ decreases so that $[\text{H}^+] \times [\text{OH}^-]$ is constant.

**Strong ions difference**

SID (Fig. 4) indicates the amount by which the strong positive ions (cations) are in excess of the strong negative ions (anions). It is an indication of ‘unmeasured’ ions in the solution: $\text{SID} = [\text{Na}^+] + [\text{K}^+] + [\text{Mg}^{2+}] + [\text{Ca}^{2+}] - ([\text{SO}_4^{2-}] + [\text{Cl}^-])$. However, the simplification: $\text{SID} = [\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-]$ is generally sufficient, as these are the dominant ions.
Within the cells: SID = [K+] + [Mg2+] as the concentration of other anions is very low and [Na+] ≈ [Cl−].

SID as calculated above may be termed ‘inorganic’. However, in diseases, organic strong ions such as lactate may make an additional contribution to the SID. The SID for human fluids can then be calculated as: SID = [Na+] + [K+] + [Mg2+] + [Ca2+] – ([lactate−] + [Cl−]). This is known as the apparent SID or SIDa, as it does not take into account the role of weak acids (buffers).

Fige et al. developed a formula for effective SID (SIDe), which allowed the contribution of weak acids to be taken into account. The strong ion gap (SIG) is the difference between apparent and effective SID and measures the contribution to SID of unmeasured anions such as sulphate, ketoacids, pyruvate, acetate, and gluconate. This is sometimes termed the ‘anion gap’.

Weak ions

Weak acids and bases are only partially dissociated in the range of body pH. For a weak acid: HA ⇔ H+ + A−. At equilibrium, the flux in one direction is equal to that in the other, and the balance may be affected by the other ions present. For a strong ion in solution, the ionized form X− is unchanged whatever happens, but for weak ions, only the total amount of A (Atot or HA + A−) is constant. The ratio [A−]/[HA] depends on the equilibrium constant Ka. As [H+] increases, [A−] decreases and [HA] increases in equal amounts. Following the law of mass action: [H+] = Ka[HA]/[A−] or pH = pKa + log([A−]/[HA]) (Henderson–Hasselbach equation). pKa can be defined as the pH at which the concentration of a conjugate base equals that of the acid, the ‘midpoint’ of the dissociation of the substance. pKa allows calculation of the degree of dissociation at any pH.

The constraints of electrical neutrality imply that in a solution containing both strong ions and weak ions, if something happens to change the [H+] then the extent of the change will be less than it would have been if strong ions alone had been present. This brings us to the phenomenon of buffering. A buffer is a substance which can bind or release H+ in solution, and can maintain an almost constant pH, despite addition of considerable amounts of acid or base. The Henderson–Hasselbach equation is used to describe the pH changes due to the addition of H+ or OH− to any buffer system.

Principal buffers in body fluids are as follows:

(i) Blood: H2CO3 ⇔ H+ + HCO3−; HProt ⇔ H+ + Prot−;
HHb ⇔ H+ + Hb−
(ii) Intersitial fluid: H2CO3 ⇔ H+ + HCO3−
(iii) Intracellular fluid: HProt ⇔ H+ + Prot−
(iv) Kidneys: H2CO3 ⇔ H+ + HCO3−; NH3 + H+ ⇔ NH4;
HPO4 2− + H+ ⇔ H2PO4−

Fige quantified the contribution of weak acids to SID as:

(i) Bicarbonate [HCO3−] = 1000 × 2.46 × 10−11 × PCO2/10−47

Table 1 Clinical situations illustrating the interaction of SIG with weak acids

<table>
<thead>
<tr>
<th>Metabolic change</th>
<th>SIG</th>
<th>Condition</th>
<th>Clinical scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperalbuminaemia</td>
<td>↓</td>
<td>Acidosis</td>
<td>ECF loss, cholera</td>
</tr>
<tr>
<td>Hypoalbuminaemia</td>
<td>↑</td>
<td>Alkalosis</td>
<td>Critically ill patients</td>
</tr>
<tr>
<td>Hyperphosphataemia</td>
<td></td>
<td>Acidosis</td>
<td>Renal failure</td>
</tr>
</tbody>
</table>

(ii) Plasma protein, mainly albumin [Alb−] = [Alb] × (0.123 × pH − 0.631)
(iii) Phosphate [HPO4 2−] = [Phos] × (0.309 × pH − 0.469)
(iv) SIDeff = [HCO3−] + [Alb−] + [HPO4 2−]

Weak acids cause a slight increase in the hydrogen ion concentration of the plasma. Therefore, a decrease in weak acids will cause alkalosis, and an increase produces acidosis. Also note that an increase in SID produces an increase in dissociated proteins and an increase in Pco2 reduces dissociated protein.

Clinical situations illustrating the interaction of SIG with weak acids are listed in Table 1.

Solutions containing carbon dioxide

We are already familiar with the CO₂–bicarbonate system. This is an ‘open’ system capable of varying the total CO₂ content within wide limits. CO₂ is present in the body in metabolic substrates, in bone and as HCO3− in tissues. The ‘fixed’ stores cannot be accessed but about 500 mmol is readily available. In the basal state, a healthy adult produces at least 10 000 mmol of CO₂ in 24 h. It is highly diffusible and completely equilibrates across membranes. Pco2 is controlled by rapid changes in ventilation. Thus, CO₂ is the most mobile component and the CO₂–bicarbonate system a very powerful plasma buffer system.

The reaction involved is: H2CO3 ⇔ H+ + HCO3−. Most buffers are not free to leave the tissues and [A tot] is almost constant in any particular compartment. However, CO₂ is freely diffusible and [CO₂tot] (i.e. [H2CO3] + [HCO3−]) can vary considerably. CO₂ dissolves in water producing H2CO3, HCO3− and CO3 2−. The concentrations of the dissolved CO₂ and H2CO3 are directly proportional to the Pco2, but the concentrations of HCO3− and CO3 2−, H+, OH− are also affected by changes in SID.

Summary

Stewart’s work has simplified our understanding of the mechanisms of conditions such as dilutional acidosis, concentational alkalosis, hyperchloraemic acidosis, hypochloraemic alkalosis, and hyperalbuminaemic alkalosis (Fig. 5). Using basic physicochemical laws, such as the law of mass action, law of conservation of mass, and the law of electrical neutrality, we can explain the acid–base systems of the body. Acid–base balance can be understood quantitatively in terms of three independent variables:

Pco2, [SID] and total weak acid, i.e. [A tot] (usually protein and phosphates) and their regulation by the lungs, kidneys, gut, and
liver. The dependent variables: \([\text{HCO}_3^-]\), \([\text{HA}]\), \([\text{A}^-]\), \([\text{CO}_3^{2-}]\), \([\text{OH}^-]\), and \([\text{H}^+]\) or pH can be calculated from these.

The pH and other dependent variables for any body fluid are determined by the independent variables in that particular fluid since hydrogen ions are affected by the other, more abundant, strong ions. Body fluids interact through membranes. Most membranes are impermeable to proteins under normal physiologic conditions so \([\text{A}_{tot}]\) interactions are significant only when disease damages membranes.

Changes in respiration and circulation match the tissue production of carbon dioxide and control \(P_{\text{CO}_2}\). These are responsible for the acute alterations in acid–base disorders. Movement of \(\text{H}^+\) between solutions cannot affect the \(\text{H}^+\), only changes in the strong ions can. Strong ions move freely in body fluids, across membranes. The kidneys and gut regulate their levels and thus are the major determinants of SID in chronic acid–base disorders.

**Further reading**


*Please see multiple choice questions 25–29*