Sheets Physiology

Number: 8

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Correction:

Introduction

In this sheet, we discuss acid-base balance in our body and the role of kidneys in its establishment. Arrangement of topics is different from that of the lecture, to assure consistency of sections and avoid repetitions.

Acids, Bases and pH*; a review*

What is pH?

pH is a measure of the acidity or basicity of fluids. pH is calculated as follows:

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

What is buffer?

Buffers resist changes in pH. When adding a small amount of strong acid to a buffer system, the strong acid is turned into a weak acid, resulting in smaller change in pH. Similarly, adding a small amount of strong base to a buffer system results with a weak base production, with a small elevation of the pH of the solution.

Buffers are systems of weak acid and its conjugate base, or weak base and its conjugate acid. Such systems resist changes in pH around a range of pH values, which resides around the pK of the system. But what is pK?

What is pK?

pK is the pH of the solution when the concentration of the acid and the concentration the base of the buffer system are the same. In other words, the

pH of the system is the same as the pK when each of the components (base and acid) constitutes 50% of the total concentration of the buffer system.

What is the Henderson-Hasselbalch equation?

In the topic of body buffers, we care about this equation since it is useful for estimating the pH of a buffer solution.

This is the equation:

$$pH = pk + log \frac{[base]}{[acid]}$$

The concept of pK can be clearer when applying it in the Henderson-Hasselbalch equation:

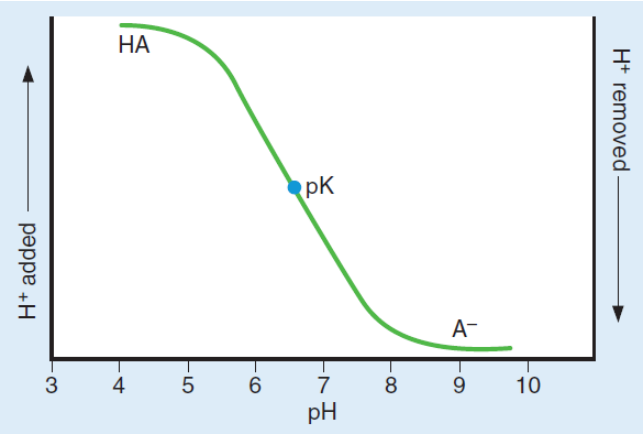
$$pH = pk + log \frac{[base]}{[acid]}$$

When [base] = [acid]:

$$pH_1 = pk + log 1$$
$$pH_1 = pk + 0$$
$$pH_1 = pk$$

Buffers Power

This figure is the titrastion curve of a buffer. According to this curve, adding acids and bases around the pK results with minimal change in pH. This means that the buffer resists the change in pH (horizontal axis) when adding an acid (left axis) or a base (right axis). This property is most obvious at pH values ±1 to pK. Beyond these limits, the buffering power rapidly diminishes.



Acids and Bases in The Body

The body produces acids. These acids can be volatile or nonvolatile. Carbonic acid, the sole volatile acid in our body, is produced at rate of 10 mol/L. Because it is volatile, this big amount is being dealt with by the lungs, by excreting 300 L/day of CO_2.

However, what we care about in nephrology is nonvolatile acids, which cannot be directly excreted by lungs. Such acids include:

- Phosphoric acid: produced in metabolism of phosphoproteins, phospholipids, nucleic acids.
- Sulfuric acid: produced in metabolism of cysteine and thiamine
- Lactic acid; and others

1 mol/Kg/day of H + are added to the extracellular fluid per day (80 mEq for an 80-kg person), and that is done by the production of nonvolatile acids. Since the volume of the extracellular fluid is 14 liters, its pH would be exceedingly lowered by this added amount of protons; it would even be incompatible with life (pH of >6.8 to <8 is the range that is compatible with life).

Note that this range of pH values means that $[H^+]$ extracellularly is normally 40 nM (pH of 7.4); and it is livable to have a minimum and maximum $[H^+]$ of 10 nM and 160 nM, respectively (ph of 8, ph of 6.8). This means that our body is more able to withstand added acids than to bear up with added bases.

Buffers in The Body

Acid-base balance defense lines in the body are of three levels:

- First line: Buffers, works momentarily (discussed in this section)

- Second line: Lungs, works in minutes to hours (not discussed)
- Third line: Kidneys, works in hours to days (discussed in the next section)

Buffers work instantaneously; that is, they bind the added protons fast. But by doing so, the protons are not removed from the body.

As mentioned in the review, buffers resist changes in pH. Adding a small amount of strong acid to a buffer system turns it into weak acid with minimal pH change. The same concept applies to added bases.

$\underline{HCl} + NaHCO_3 = NaCl + \underline{H_2CO_3}$ Strong acid: HCl; Weak acid: H_2CO_3
$\underline{HCl} + Na_2HPO_4 = NaCl + Na\underline{H_2PO_4}$ Strong acid: HCl; Weak acid: $H_2PO_4^-$
$\underline{NaOH} + H_2CO_3 = Na\underline{HCO_3} + H_2O$ Strong base: NaOH; Weak base: HCO_3^-
$\underline{NaOH} + Na_2HPO_4 = Na_2\underline{HPO_4} + H_2O$ Strong base: NaOH; Weak base: HPO_4^{-2}

Body Buffers Systems

In the body, many buffer systems work together to resist the changes in pH. These include:

- Phosphate: important renal tubular buffer
- Bicarbonate: important ECF buffer
- Proteins: important intracellular buffers. These are the most abundant buffers yet not the most effective
- Ammonia (not important in blood): important renal tubular buffer

But, how to know which buffer system is the main contributor in the different body compartments? (See next)

Which Buffer System is the "Strongest"?*; 3 criteria*

To decide the main buffer system functioning in the various body parts, we go into three criteria:

1. Absolute concentration:
   The higher the concentration of the buffer system components the more effective the buffer is. With low concentrations of the buffers, only a small amount of acid or base added to the solution changes the pH considerably. The arterial concentration of bicarbonate is 24 mmol/L, which is 24 times the concentration of phosphates (1 mmol/L).

   00:00 – 10:00

2. pK of the buffer system:
   As mentioned in the review, The pH of the system is the same as the pK when each of the components ($HCO3^-$ and CO2, for example) constitutes 50% of the total concentration of the buffer system.

Buffering capacity and titration curve

- for bicarbonate buffer system:

$$H_2O + CO_2 = H_2CO_3 \text{ (carbonic anhydrase)}$$
$$H_2CO_3 = H^+ + HCO_3^-$$

Let us apply the Henderson–Hasselbalch equation for this buffer system in the arterial blood:

$$pH_{blood} = pk_{bicarbonate} + log \frac{[HCO3-]}{[CO2]}$$

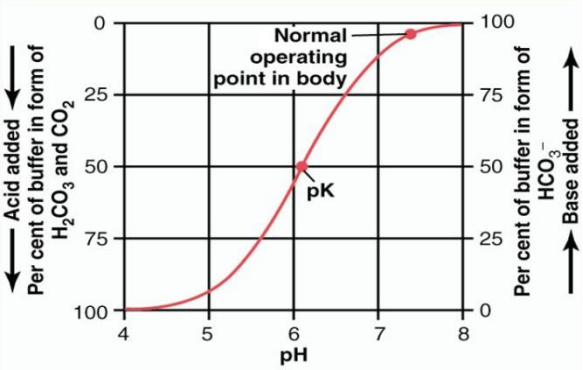
We know that pK for bicarbonate is 6.1, and $[HCO_3^-]$ in arterial blood is 24 mmol/L. for CO_2, P_{CO2} in the arteries is 40 mmHg (45 mmHg in veins). To use it in the equation, we must calculate it in the units mmol/L, by multiplying the mmHg by 0.03:

$$40 \text{ mmHg} * 0.03 = 1.2 \text{ mmol/L}$$

To continue on the equation:

$$pH_{blood} = 6.1 + log \frac{24}{1.2}$$
$$pH_{blood} = 6.1 + log\ 20$$
$$= 7.4$$

As we discussed in the review, and according to the titration curve, the buffering property is most obvious at pH values ±1 to pK. Beyond these limits, the buffering power rapidly diminishes.



According to the following table of pK values, we can notice that pK of phosphate buffer system is the closest to the blood pH. Ammonium buffer system, however, has a power range residing in the useless pH values in blood. So, in terms of pK, phosphate system is better than bicarbonate system, whereas, in terms of concentration, bicarbonate system is better.

Buffer	pK
Bicarbonate	6.1
Phosphate	6.8
Ammonium	9.2

3. Renewal of the buffer components:
   The body ability to renew the buffer is the most important point in evaluating the strength of buffer systems. For phosphate system, we cannot renew it; we actually ingest its components. But for bicarbonate, the body can make *new* HCO_3^- (as we will see later).

Conclusions

ECF: After analyzing the three criteria, we conclude that bicarbonate buffer system is the main ECF buffer.

Intracellularly: concentration of phosphate ions is very high intracellularly (point 1), the pH in the cell is 7 (pK of phosphate buffer is the closest; point 2). Consequently, phosphate buffer system is the main buffer intracellularly.

10:00 – 20:00

Intratubular: pH in the proximal tubules is 6.5 (pK of phosphate buffer is the closest, point 2). Additionally, water gets reabsorbed here, so phosphate ions concentration increases (point 1). According to that, phosphate system is the main buffer in the intratubular space.

Kidneys and Acid-Base Balance

As we discussed earlier, 80 mmol of H+ are added to ECF daily. This amount of protons should be excreted somehow. In this section we will discuss how our bodies excrete them, and renew its buffering ability.

<u>80 mmol Excreted Directly in Urine?</u>

Can we just excrete these protons directly in urine?

In the distal tubules and collecting ducts occur the last modifications on urine material. Some cells there (*a-Intercalated cells*) actively secrete H^+ into the tubular lumen against a 900-fold concentration gradient.

Accordingly, these cells make the pH of tubular fluid in the collecting ducts more acidic than the pH of the cells in 3 points (pH in tubules = pH intracellularly - 3):

$$pH_{intracellular} = 7;\ [H^+]_{intracellular} = 10^{-7}\ mol/L$$

$$[H^+]_{tubular} = [H^+]_{intracellular} * 900 = a\ little\ less\ than\ 0.1\ mmol/L$$

$$So,\ minimum\ pH_{tubular} = 4.5$$

Notice that the excreted free H^+ for 1 liter of urine (daily output) is less than 0.1 mmol/L. But we have already said we want to excrete 80 mmol of H^+ per day. This means that 79.9 mmol of H^+ would accumulate each day!

So, as we see, we cannot simply excrete 80 mmol of H^+ per day in urine, because the active transport of protons is limited (900-fold).

So, what to do with these 80 mmol of H^+?

Well, if we add 80 mmol of HCO_3^- per day, they will bind the protons, producing carbonic acid, which gets split into water and CO_2, which can be excreted by the lungs.

Being volatile made bicarbonate crucial for this mission, and made its levels extremely important to be maintained. In this section, we discuss the kidneys role in the reabsorption of filtered HCO_3^- and the generation of new HCO_3^- (HCO_3^- gain).

Absorption of Bicarbonate Ions

Bicarbonate ions are so precious that we do not just want all the filtered molecules to be reabsorbed, but we also want the kidneys to generate new molecules (+80 mmol/day), as we discussed earlier. (So, HCO_3^- has a negative clearance.)

Filtered Load

$$Filtered\ Load_{HCO3-} = GFR * P_{conc}$$

$$Filtered\ Load_{HCO3-} = 180 * 24$$

$$Filtered\ Load_{HCO3-} = 4320\ mmol/day$$

Although charged, HCO_3^- is a small molecule that is freely filtered. 4320 mmol/day of HCO_3^- get filtered, and *all* of these 4320 mmol/day should get reabsorbed.

Reabsorption

85% of reabsorption occurs in the proximal tubules, and 15% occurs elsewhere.

CO_2 either diffuses into the tubular cells from the interstitium or the filtrate, or is formed by metabolism in the tubular epithelial cells. (CO_2 diffuses freely.)

CO_2, under the influence of the enzyme carbonic anhydrase, combines with H2O to form H_2CO_3, which dissociates into HCO_3^- and H^+. H^+ is secreted from the cell into the tubular lumen by Na^+/H^+ counter-transporter, which uses the energy released by transporting Na^+ downhill to secrete H^+ uphill (secondary active transport). Here, no ATP is directly used; ATP is rather used by Na^+ carriers at the basolateral border.

At the same time, the formed HCO_3^- moves downhill across the basolateral membrane and is reabsorbed by the peritubular capillaries. (HCO_3^- is charged, and cannot freely diffuse through the cell membrane; it needs a carrier.)

The secreted H^+ binds HCO_3^- ions in the tubular lumen. The resultant carbonic acid is split into water and CO_2, by the enzyme carbonic anhydrase. The resultant CO_2 gets into the cells and the cycle goes on. So, the 4320 mmol can be reabsorbed by a single proton.

The net result is that for each H^+ secreted, an HCO_3^- enters the blood. There is neither net secretion of protons nor net gain of HCO_3^-; what has been filtered gets reabsorbed. (Net gain is when reabsorbed is > filtered.)

Drugs that inhibit carbonic anhydrase (some diuretic) decrease H^+ secretion and HCO_3^- reabsorption, thereby increasing the risk of acidosis.

20:00 – 30:00

HCO_3^- Gain

As we said previously, 80 mmol of nonvolatile acids are produced per day. Therefore, HCO_3^- gain should be 80 mmol per day. Now, for each H^+ ion

lost, HCO_3^- gain is achieved. In other words, net secretion of H^+ results with net gain of HCO_3^-. Any H^+ secretion lowers pH of tubular fluid.

At the proximal tubules, H^+ is exchanged with Na^+ via carriers (secondary countertransport), as we mentioned before. The concentration of Na^+ inside the cells is 14 mM, whereas it is 140 extracellularly (Na^+ moves downhill). For H^+, pH in cells is 7. Secondary countertransport achieves a maximum $[H^+]$ difference of 5 or 6 across the membrane. Thus, pH in proximal tubules fluid is 6.5 (you can calculate this). Notice that secondary countertransport achieves a 5-fold difference in $[H^+]$, which is so much less than the 900-fold difference achieved by active transport at the collecting ducts, which pumps H^+ only and uses ATP directly.

In conclusion, we discovered that the secretion of 80 mmol of free protons is not achievable, because of the limited carriers' capacity. However, Having 80 mmol of any form of buffers (phosphates, for example) in the tubular fluid enables H^+ trapping. Wherefore, 80 mmol of H^+ get secreted in urine in conjugated form:

$$H^+ + Na_2HPO_4 = Na2H_2PO4$$

But, do we have 80 mmol of buffers in tubular fluid? This is discussed in the next lecture.

The more important step in acid-base balance in the kidney is the absorption of bicarbonate ions, which is responsible for the reabsorption of 4320 mmol per day of bicarbonate ions. HCO_3^- gain, on the other hand, is responsible for the formation of new 80 mmol of bicarbonate ions per day, to fight added acids. As a result, 4400 mmol of bicarbonate ions are carried in the renal veins every day.

30:00 – 40:00

Our lives begin to end the day we become silent about things that matter.