Case 1
Acute Aspirin Overdose: Relationship to the Blood Buffering System

1.

2. These questions can be answered by using the Henderson-Hasselbalch equation:
   a. 
   \[
   pH = pK_a + \log \left( \frac{[\text{salicylate}]}{[\text{salicylic acid}]} \right)
   \]

   \[
   2.0 = 2.97 + \left( \log \left( \frac{[\text{salicylate}]}{[\text{salicylic acid}]} \right) \right)
   \]

   \[
   \frac{0.11}{1} = \frac{[\text{salicylate}]}{[\text{salicylic acid}]} \]

   At pH = 2, the percentage of salicylate (unprotonated) is 9.9% (0.11/1.11) and the percentage of salicylic acid (protonated) is 90.1% (1/1.11).

   b. 
   \[
   pH = pK_a + \left( \log \left( \frac{[\text{salicylate}]}{[\text{salicylic acid}]} \right) \right)
   \]

   \[
   8.55 = 3.0 + \left( \log \left( \frac{[\text{salicylate}]}{[\text{salicylic acid}]} \right) \right)
   \]

   \[
   \frac{1}{[\text{salicylic acid}]} = \frac{[\text{salicylate}]}{[\text{salicylic acid}]} \]
At pH = 8.5, virtually 100% of the salicylate is in the unprotonated form. The gastric lavage increases the solubility of the drug because at this pH, the salicylate is unprotonated and negatively charged. At the pH of the stomach, pH = 2, about 90% of the salicylic acid is in the protonated, or uncharged, form. This form is more lipid-soluble and will be able to pass through the membranes of the cells lining the stomach, facilitating its absorption into the bloodstream (an undesirable result). On the other hand, charged species are among the most polar, and as such, they dissolve in water very well and in lipids, not well at all. Negatively charged species can form ion-dipole interactions with water and are generally more polar (and water soluble) than neutral species, so the gastric lavage increases the solubility of the drug by converting the neutral salicylic acid to the negatively charged salicylate. This facilitates the removal of the aspirin from the stomach. At the same time, the decreased lipid solubility of the charged salicylate results in decreased absorption from the stomach into the bloodstream.

3. a. The patient’s $P_{O_2}$ pressure increases between two hours and ten hours, and the $PCO_2$ decreases in the same time period, indicating the excessive oxygen intake and excessive CO$_2$ exhalation that would be expected in a hyperventilating patient. (An additional note: In addition to causing hyperventilation, salicylates act as uncouplers of electron transport and oxidative phosphorylation; this also explains the patient’s abnormal blood gas values.) Salicylates are clearly the stimulus for this hyperventilation, as their concentration increases from 57 mg/dL to 117 mg/dL from two hours to ten hours after aspirin ingestion. The patient’s laboratory values show a low $PCO_2$ value (26 mm Hg two hours after aspirin ingestion and 19 mm Hg after 10 hours of aspirin ingestion) and a high $P_{O_2}$ value (113 mm Hg two hours after aspirin ingestion and 143 mm Hg after 10 hours of aspirin ingestion), indicating that oxygen is being taken in and carbon dioxide is being exhaled at a greater rate than normal as expected during hyperventilation (normal values for $PCO_2$ are 35-45 mm Hg and for $P_{O_2}$ the normal value is 75-100 mm Hg).

b. The carbonic acid/bicarbonate buffering system relies on these three equilibria:

$$\begin{align*}
HCO_3^-_{(aq)} + H^+_{(aq)} &\rightleftharpoons H_2CO_3_{(aq)} \quad \text{(Eqn 1)} \\
H_2CO_3_{(aq)} &\rightleftharpoons H_2O(l) + CO_2_{(aq)} \quad \text{(Eqn 2)} \\
CO_2_{(aq)} &\rightleftharpoons CO_2(g) \quad \text{(Eqn 3)}
\end{align*}$$

The patient experiences salicylate-induced hyperventilation, which means that carbon dioxide is being rapidly removed from the lungs. The removal of CO$_2(g)$ shifts the equilibrium of the third equation above to the right, which means that carbon dioxide moves out of the bloodstream and into the lungs. This causes CO$_2_{(aq)}$ to be depleted, so the equilibrium of the second equation also
shifts to the right. This depletes the carbonic acid, so the equilibrium of the first equation also shifts right to produce more carbonic acid. The result is that hydrogen ions are depleted and the blood becomes more basic. This is verified by looking at the laboratory values, which show that the patient’s blood pH after 10 hours of aspirin ingestion is 7.55 (normal is 7.35-7.45). The shift of the first equation to the right causes bicarbonate ions to be depleted. This is why the bicarbonate concentration in the patient is lower than normal (as discussed below).

c. The shift of the first equation to the right depletes both hydrogen ions and bicarbonate ions, as discussed above. If the shift is too dramatic, bicarbonate ions will be depleted and the ability of the carbonic acid/bicarbonate buffering system will be compromised. Both conjugate base and weak acid forms of a buffer are needed to “mop up” protons and hydroxide ions, respectively. A bicarbonate drip replaced the bicarbonate ions that were being depleted until the salicylates could be removed from the patient’s system and thus remove the stimulus for hyperventilation.

4. a. The ratio of bicarbonate to carbonic acid in the patient’s blood:

\[
pH = pK_a + \left( \log \frac{[\text{bicarbonate}]}{[\text{carbonic acid}]} \right)
\]

\[
7.55 = 6.4 + \left( \log \frac{[\text{bicarbonate}]}{[\text{carbonic acid}]} \right)
\]

\[
\frac{14}{1} = \frac{[\text{bicarbonate}]}{[\text{carbonic acid}]}
\]

The ratio of bicarbonate to carbonic acid in normal blood:

\[
pH = pK_a + \left( \log \frac{[\text{bicarbonate}]}{[\text{carbonic acid}]} \right)
\]

\[
7.4 = 6.4 + \left( \log \frac{[\text{bicarbonate}]}{[\text{carbonic acid}]} \right)
\]

\[
\frac{10}{1} = \frac{[\text{bicarbonate}]}{[\text{carbonic acid}]}
\]

**What makes an effective buffer?**

a. The concentration of the conjugate base to weak acid should range from 0.1/1 to 10/1 to ensure that there is some of each species, weak acid and conjugate base, present. Ratios lying outside of this range have an abundance of either the conjugate base or the weak acid alone. In order to
serve as an effective buffer (ie, absorb both added \( \text{H}^+ \) and \( \text{OH}^- \)), both a conjugate base and a weak acid must be present. In our patient, the ratio of conjugate base to weak acid does not lie within the effective buffering range. The bicarbonate concentration (conjugate base) is too high relative to the carbonic acid (weak acid) concentration; thus the relative amount of weak acid is insufficient.

b. It is not just the ratio of conjugate base to weak acid that is important—it’s the absolute concentration of each that is also important. We are given the concentration of \( \text{HCO}_3^- \) and can calculate the concentration of \( \text{H}_2\text{CO}_3 \) using the Henderson-Hasselbalch equation:

\[
pH = pK_a + \log \frac{[\text{bicarbonate}]}{[\text{carbonic acid}]} \\
7.55 = 6.4 + \log \frac{21 \times 10^{-3}}{[\text{carbonic acid}]} \\
[\text{H}_2\text{CO}_3] = 1.49 \text{ mM}
\]

The carbonic acid concentration in our patient is 1.49 mM. We can infer that in a normal patient, the carbonic acid concentration is 2.2-2.6 mM, since there is a 10:1 ratio between bicarbonate and carbonic acid. Thus both the carbonic acid and bicarbonate concentrations are lower than normal in our patient. If the concentration of buffering species is low, then the ability of the buffer to work effectively is compromised. The greater the concentration of weak acid and conjugate base, the greater the ability of the buffer to absorb added amounts of strong acid and strong base, ie, the greater the buffer capacity. Buffers with higher buffering capacities (ie, higher concentrations) can absorb greater amounts of added acid or added base and can therefore buffer more effectively.

5. As the salicylate is removed, the stimulus for salicylate-induced hyperventilation will decrease as a result. At time = 60 hours, the salicylate concentrations have not fallen to zero, but the concentrations are much decreased. In the basic blood, \( \text{OH}^- \) reacts with the \( \text{H}^+ \) to form water. This depletes the \( \text{H}^+ \) so that the first equation (shown in Question 3b) shifts left to produce more hydrogen ions. This in turn depletes \( \text{H}_2\text{CO}_3 \), so the second equation shifts left. This depletes \( \text{CO}_2\text{(aq)} \), which shifts the third equation to the left. This results in shallow breathing. The shallow breathing results in a greater concentration of \( \text{CO}_2\text{(aq)} \) in the blood which can ultimately produce more hydrogen ions, which will bring the blood pH back to normal.

6. Yes, phosphate (\( \text{H}_2\text{PO}_4^-/\text{HPO}_4^{2-}, pK_a = 7.2 \)), and proteins like hemoglobin which can bind protons can also serve as buffers. Organic acids and proteins also have a buffering role. However, unlike the bicarbonate/carbon dioxide buffer system, these buffering systems are not linked to respiration.