Case 35

Metabolic Acidosis: Diarrhea

Melanie Peterson’s wedding to the man of her dreams was perfect in every respect. However, while on her honeymoon in Mexico, Melanie had severe “traveler’s diarrhea.” Despite attempts to control the diarrhea with over-the-counter medications, she continued to have 8–10 watery stools daily. She became progressively weaker, and on the third day, she was taken to the local emergency department. On physical examination, Melanie’s eyes were sunken, her mucous membranes were dry, and her jugular veins were flat. She was pale, and her skin was cool and clammy. Her blood pressure was 90/60 when she was supine (lying) and 60/40 when she was upright. Her pulse rate was elevated at 120/min when she was supine. Her respirations were deep and rapid (24 breaths/min). Table 4-13 shows the results of laboratory tests that were performed.

<table>
<thead>
<tr>
<th>Table 4-13</th>
<th>Melanie’s Laboratory Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial blood</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.25 (normal, 7.4)</td>
</tr>
<tr>
<td>$P_{CO_2}$</td>
<td>24 mm Hg (normal, 40 mm Hg)</td>
</tr>
<tr>
<td>Venous blood</td>
<td></td>
</tr>
<tr>
<td>Na⁺</td>
<td>132 mEq/L (normal, 140 mEq/L)</td>
</tr>
<tr>
<td>K⁺</td>
<td>2.3 mEq/L (normal, 4.5 mEq/L)</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>111 mEq/L (normal, 105 mEq/L)</td>
</tr>
</tbody>
</table>

Melanie was admitted to the hospital, where she was treated with strong antidiarrheal medications and an infusion of NaCl and KHCO₃. Within 24 hours, she felt well enough to be released from the hospital and enjoy the rest of her honeymoon.

**QUESTIONS**

1. What acid–base disorder did Melanie have?
2. How did diarrhea cause this acid–base disorder?
3. What explanation can you offer for the increased depth and frequency of Melanie’s breathing?
4. What is the value for Melanie’s anion gap? Is it increased, decreased, or normal? What is the significance of the anion gap in this case?
5. Why was Melanie’s blood pressure lower than normal?
6. Why was her pulse rate so high while she was supine? Why was her skin cool and clammy? If her pulse rate had been measured while she was upright, would it have been higher, lower, or the same as when she was supine?
7. How would you expect Melanie’s renin-angiotensin II-aldosterone system to be affected?
8. Why was Melanie’s blood $K^+$ concentration so low?
9. What was the rationale for treating Melanie with an infusion of NaCl and KHCO₃?
ANSWERS AND EXPLANATIONS

1. To correctly analyze the acid-base disorder, we need to know the values for arterial pH, $P_{\text{CO}_2}$, and $HCO_3^-$. The values for pH and $P_{\text{CO}_2}$ are given, and the $HCO_3^-$ concentration can be calculated with the Henderson-Hasselbalch equation (see Case 29).

\[
pH = 6.1 + \log \frac{HCO_3^-}{P_{\text{CO}_2} \times 0.03}
\]

\[
7.25 = 6.1 + \log \frac{HCO_3^-}{24 \text{ mm Hg} \times 0.03}
\]

\[
1.15 = \log \frac{HCO_3^-}{0.72}
\]

Taking the antilog of both sides:

\[
14.13 = \frac{HCO_3^-}{0.72}
\]

\[
HCO_3^- = 10.2 \text{ mEq/L} \quad \text{(normal, 24 mEq/L)}
\]

The arterial blood values (acidic pH of 7.25, decreased $HCO_3^-$ concentration of 10.2 mEq/L, and decreased $P_{\text{CO}_2}$ of 24 mm Hg) are consistent with metabolic acidosis. Recall that the initiating event in metabolic acidosis is a decrease in $HCO_3^-$ concentration; this decrease can be caused either by a gain of fixed acid (fixed acid is buffered by extracellular $HCO_3^-$, leading to a decreased $HCO_3^-$ concentration) or by loss of $HCO_3^-$ from the body. Melanie's $P_{\text{CO}_2}$ was decreased because peripheral chemoreceptors sensed the acidemia (decreased blood pH) and directed an increase in breathing rate (hyperventilation). Hyperventilation drove off extra CO$_2$ and led to the decrease in arterial $P_{\text{CO}_2}$.

2. Melanie's metabolic acidosis was caused by the severe diarrhea. You may recall that several gastrointestinal secretions, including salivary and pancreatic secretions, have a very high $HCO_3^-$ content. If the transit rate through the gastrointestinal tract is increased (e.g., in diarrhea), there is excessive loss of this $HCO_3^-$-rich fluid. Loss of $HCO_3^-$ leads to decreased $HCO_3^-$ concentration in the blood (metabolic acidosis).

3. Melanie was breathing deeply and rapidly (hyperventilating) because of the respiratory compensation for metabolic acidosis. As explained earlier, the acidemia (secondary to loss of $HCO_3^-$) stimulated peripheral chemoreceptors, which directed an increase in breathing rate.

4. The anion gap was discussed in Case 34. Briefly, the anion gap represents unmeasured anions in serum or plasma. Unmeasured anions include albumin, phosphate, citrate, sulfate, and lactate. The average normal value for the serum anion gap is 12 mEq/L.

The anion gap is calculated whenever a metabolic acidosis is present to aid in diagnosing the cause of the disorder. In metabolic acidosis, the $HCO_3^-$ concentration is always decreased. To maintain electroneutrality, this "lost" $HCO_3^-$ must be replaced by another anion. If $HCO_3^-$ is replaced by an unmeasured anion (e.g., lactate, ketoanions, phosphate), the anion gap is increased. If $HCO_3^-$ is replaced by a measured anion (e.g., Cl$^-$), the anion gap is normal.

The anion gap is calculated as the difference between the concentration of measured cations (Na$^+$) and measured anions (Cl$^-$ and $HCO_3^-$). Melanie's anion gap was:

\[
\text{Anion gap} = [\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-])
\]

\[
= 132 \text{ mEq/L} - (111 \text{ mEq/L} + 10.2 \text{ mEq/L})
\]

\[
= 10.8 \text{ mEq/L}
\]
Melanie’s calculated anion gap was normal. Thus, she had metabolic acidosis with a normal anion gap, whose significance is explained as follows. In her metabolic acidosis, the decrease in HCO₃⁻ concentration was offset by an increase in Cl⁻ concentration, not by an increase in unmeasured anions. One measured anion (HCO₃⁻) was replaced by another measured anion (Cl⁻), and the anion gap was unchanged from normal. (Indeed, the Cl⁻ concentration in Melanie’s blood of 111 mEq/L is higher than the normal value of 105 mEq/L.) Thus, the complete (and rather impressive) name of her acid-base disorder is hyperchloremic metabolic acidosis with a normal anion gap.

Finally, how did the Cl⁻ concentration in Melanie’s blood become elevated? We discussed the fact that an HCO₃⁻–rich solution was lost from the gastrointestinal tract in diarrheal fluid. Thus, relatively speaking, Cl⁻ was “left behind” in the body in a smaller volume (i.e., Cl⁻ became concentrated).

5. Melanie’s blood pressure was decreased because she lost large volumes of an extracellular-type fluid in diarrhea. Loss of extracellular fluid (ECF) caused a decrease in blood volume and interstitial fluid volume (i.e., ECF volume contraction). The loss of interstitial fluid was evident in her sunken eyes and dry mucous membranes. The loss of blood volume was evident in her decreased blood pressure and flat jugular veins. (When blood volume decreases, venous return decreases, leading to decreased cardiac output and arterial pressure.)

6. Melanie’s pulse rate was elevated secondary to the response of the carotid sinus baroreceptors to decreased arterial pressure. When the baroreceptors detected a decrease in arterial pressure, they initiated reflexes that increased sympathetic outflow to the heart and blood vessels to increase arterial pressure toward normal. Among these sympathetic responses is an increase in heart rate (through β₁ receptors in the sinoatrial node). Another sympathetic response is activation of α₁ receptors on arterioles, which leads to vasoconstriction in several vascular beds, including renal, splanchnic, and skin. Constriction of cutaneous blood vessels made Melanie’s skin pale and clammy.

When Melanie was upright, her blood pressure was even lower than when she was supine (orthostatic hypotension). The reason for her orthostatic hypotension was ECF volume contraction. When she was upright, venous blood pooled in her lower extremities, further compromising her venous return and further decreasing her cardiac output and arterial pressure. Thus, if her pulse rate had been measured in the upright position, it would have been even higher than when she was supine (because the baroreceptors would have been more strongly stimulated by the lower blood pressure).

7. You should have predicted that Melanie’s renin-angiotensin II-aldosterone system was activated by the decreased arterial pressure. Decreased arterial pressure (through decreased renal perfusion pressure) stimulates renin secretion and results in increased production of angiotensin II and aldosterone.

8. Recall from the earlier discussions of K⁺ homeostasis (Cases 31 and 34) that two potential mechanisms can lead to decreased blood K⁺ concentration. These mechanisms are a shift of K⁺ from extracellular to intracellular fluid and increased loss of K⁺ from the body. Melanie’s hypokalemia had two likely causes, both related to K⁺ loss from the body. (1) Significant amounts of K⁺ were lost in diarrheal fluid secondary to flow-dependent K⁺ secretion in the colon. (The colonic secretory mechanism is similar to the K⁺ secretory mechanism in the renal principal cells.) When the flow rate through the colon increases (diarrhea), the amount of K⁺ secreted into the lumen of the gastrointestinal tract increases. (2) The renin-angiotensin II-aldosterone system was activated by ECF volume contraction, as discussed earlier. One of the major actions of aldosterone is to increase K⁺ secretion by the renal principal cells. Thus, the combined effects of increased colonic and renal K⁺ secretion led to gastrointestinal and renal K⁺ losses, producing hypokalemia.

Did a K⁺ shift into cells contribute to Melanie’s hypokalemia? The major factors that cause a K⁺ shift into cells are insulin, β-adrenergic agonists, and alkalosis (see Table 4–11 in Case 34).
None appears to play a role here. It is interesting that Melanie's acidosis might have caused a K+ shift out of her cells, which would have produced hyperkalemia. Clearly, she did not have hyperkalemia; therefore, if this K+ shift mechanism was present, it was overridden by the large K+ losses in the stool and urine.

9. The rationale behind giving Melanie an infusion of NaCl and KHCO₃ was to replace the substances she lost by the gastrointestinal tract and kidney (water, Na⁺, Cl⁻, K⁺, and HCO₃⁻). It was particularly critical to replace ECF volume with an infusion of NaCl. ECF volume contraction had activated the renin-angiotensin II-aldosterone system, which led to urinary K⁺ loss and compounded the hypokalemia caused by the original gastrointestinal K⁺ loss.

Key topics
- Anion gap
- Baroreceptor reflex
- Diarrhea
- Extracellular fluid (ECF) volume contraction
- Hyperchloremic metabolic acidosis
- Hyperventilation
- Hypokalemia
- K⁺ secretion (renal)
- K⁺ shifts
- Metabolic acidosis
- Metabolic acidosis with normal anion gap
- Orthostatic hypotension
- Pancreatic secretions
- Principal cells
- Renin-angiotensin II-aldosterone system
- Saliva