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Acid-Base and Electrolyte Teaching Case

Evaluation and Treatment of Respiratory Alkalosis

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Respiratory alkalosis is the most frequent acid-base disturbance encountered in clinical practice. This is particularly true in critically ill patients, for whom the degree of hypocapnia directly correlates with adverse outcomes. Although this acid-base disturbance often is considered benign, evidence suggests that the alkalemia of primary hypocapnia can cause clinically significant decreases in tissue oxygen delivery. Mild respiratory alkalosis often serves as a marker of an underlying disease and may not require therapeutic intervention. In contrast, severe respiratory alkalosis should be approached with a sense of urgency and be aggressively corrected.
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INDEX WORDS: Respiratory alkalosis; hyperventilation; alkalemia; hypocapnia.

Note from Feature Editor Jeffrey A. Kraut, MD: This article is part of a series of invited case discussions highlighting the diagnosis and treatment of acid-base and electrolyte disorders. Advisory Board member Horacio Adrogué, MD, served as the Consulting Editor for this case.

INTRODUCTION

Respiratory alkalosis is a common acid-base disturbance. Although often considered benign by many clinicians, it can be associated with a significant increase in mortality. Therefore, recognition of its presence, elucidation of its cause, and initiation of therapy is important to ensure a good clinical outcome.

The level of arterial carbon dioxide tension ($Paco_2$) normally is maintained at 35-45 mm Hg (at sea level). The terms hypocapnia and hypercapnia refer to decreases and increases less than and more than the normal value, respectively, and can be primary or secondary. Primary hypocapnia refers to a reduction in carbon dioxide tension with subsequent alkalization of body fluids and is synonymous with respiratory alkalosis.

$Paco_2$ is $<$35 mm Hg in patients with a simple respiratory alkalosis. In patients with a primary metabolic alkalosis, an element of respiratory alkalosis may still be present when $Paco_2$ is normal or increased, but still lower than the value considered appropriate as a compensatory response. Respiratory alkalosis should be distinguished from secondary hypocapnia, the latter condition being a compensatory response to metabolic acidosis. In this setting, if the decrease in $Paco_2$ is greater than expected, coexisting respiratory alkalosis may be present.

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CASE REPORT

Clinical History and Initial Laboratory Data

A 34-year-old man with recently diagnosed HIV (human immunodeficiency virus) infection presents with increasing shortness of breath. He was initiated on highly active retroviral therapy, and daily trimethoprim-sulfamethoxazole and weekly azithromycin were prescribed for antibiotic prophylaxis. Two weeks prior to admission, trimethoprim-sulfamethoxazole was replaced with daily dapsone secondary to development of a rash. Over the last 5 days, he noted the gradual onset of dyspnea on exertion that has progressively increased in severity. Physical examination shows blood pressure of 110/70 mm Hg, pulse rate of 104 beats/min, and respiratory rate of 22 breaths/min. His lips are a dark grayish-brown. The lungs are clear to auscultation. Laboratory examination shows the following values: serum sodium, 138 mEq/L (138 mmol/L); potassium, 4.2 mEq/L (4.2 mmol/L); chloride, 108 mEq/L (108 mmol/L); bicarbonate, 18 mEq/L (18 mmol/L); creatinine, 0.8 mg/dL (70.7 μmol/L); and estimated glomerular filtration rate, 135 mL/min/1.73 m^2 (2.25 mL/s/1.73 m^2), calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation. The blood sample is brown.

Additional Investigations

Pulse oximetry on room air is 88%. An arterial blood gas on room air shows pH of 7.47, $Paco_2$ of 28 mm Hg, Pao_2 of 110 mm Hg, and calculated oxygen saturation $>$95%. Methemoglobin concentration is 28% of total hemoglobin level, which was 13.4 g/dL (134 g/L).

Diagnosis

Respiratory alkalosis secondary to dapsone-induced methemoglobinemia.

Clinical Follow-up

The patient was treated with methylene blue (2 mg/kg given intravenously over 5 minutes), and 30 minutes later, pulse oximetry increased to 98% and methemoglobin level decreased to 6.4%.

Table 1. Arterial Blood Gas Measurements and Calculated Values of Gas Exchange in 4 Climbers at a High Elevation

Variable	Group Mean
pH	7.53
Pa_{O_2} (mm Hg)	24.6
Pa_{CO_2} (mm Hg)	13.3
HCO_3 (mEq/L)	10.8
Lactate (mg/dL)	19.8
Sa_{O_2} (%)	54
Hb (g/dL)	19.3

Note: Measurements obtained from 4 climbers at 8,400 m during descent from the summit of Mt Everest. At the summit of Mt Everest, alveolar ventilation is increased approximately 5-fold. Conversion factors for units: lactate in mg/dL to mmol/L, ×0.111; Hb in g/dL to g/L, ×10. No conversion necessary for bicarbonate in mEq/L and mmol/L.

Abbreviations: Hb, hemoglobin; HCO_3, bicarbonate; Sa_{O_2}, arterial saturation.

Based on data from Grocott et al.[2]

DISCUSSION

Respiratory alkalosis develops when alveolar ventilation is increased relative to carbon dioxide production. Under most circumstances, carbon dioxide production is relatively stable, such that hypocapnia usually is the result of increased carbon dioxide elimination. Decreased carbon dioxide production can be the underlying mechanism when the basal metabolic rate is severely decreased, as in a patient with severe hypothyroidism or hypothermia. However, even in these circumstances, alveolar ventilation needs to be fixed (intubation with fixed ventilation) because the decrease in Pa_{CO_2} would reflexively decrease ventilation due to inhibitory chemoreceptor input to the respiratory center.

Increased ventilatory drive can be the result of input from a variety of anatomic sites, resulting in pulmonary hyperventilation and primary hypocapnia. Stimulatory input often originates in the lung, carotid, and aortic chemoreceptors; brainstem chemoreceptors; and other centers of the brain. In the setting of liver disease and sepsis, the response to carbon dioxide of the brain stem chemoreceptors is augmented. Pharmacologic agents, volition, and anxiety, among other influences, also may facilitate this response.

A key stimulus to pulmonary ventilation is hypoxemia. A healthy individual ascending to high altitude is illustrative of this effect. As altitude increases, barometric pressure decreases progressively, accompanied by a progressive decrease in P_{O_2}. Maintenance of arterial oxygen content in this setting is achieved primarily by an involuntary increase in ventilation.[1,2] Arterial hypoxemia stimulates peripheral chemoreceptors primarily in the carotid and aortic bodies, causing an increase in the depth and rate of breathing. The reduction in alveolar P_{O_2} and therefore Pa_{O_2} stimulates increased ventilation, thus causing respiratory alkalosis. At sea level, a decrease in Pa_{CO_2} normally would exert an inhibitory effect on respiration, causing Pa_{CO_2} and pH to return to normal levels. However, at altitude with hypoxia-driven hyperventilation, this inhibitory effect is overridden by central medullary chemoreceptors such that high levels of ventilation are maintained. The persistent increase in ventilation is partly dependent on the exit of bicarbonate from the cerebrospinal fluid, with subsequent lowering of pH, which in turn stimulates ventilation. Ventilation also is driven by sensitization of the carotid body to hypoxia during prolonged exposure to high altitude (Table 1).

In patients with cardiopulmonary disease, increased ventilation can be the result of input from nociceptive receptors (irritants), stretch receptors (pulmonary expansion and collapse), and juxtacapillary (J) receptors (capillary congestion; Box 1). Tissue hypoperfusion stimulates alveolar ventilation as a result of oxygen deprivation. In the setting of severe circulatory failure, arterial hypocapnia and alkalemia may coexist with venous and tissue hypercapnia and

Box 1. Causes of Hypocapnia

- Reduced oxygen-carrying capacity of the blood
  - ◇ Altitude
  - ◇ Ventilation/perfusion ($\dot{V}/Q$) mismatch
  - ◇ Right-to-left shunting
  - ◇ Hypotension
  - ◇ Anemia
  - ◇ Hemoglobinopathy
- Drugs
  - ◇ Salicyate
  - ◇ Quetiapine
  - ◇ Xanthines
- Central nervous system disease
  - ◇ Voluntary hyperventilation
  - ◇ Anxiety hyperventilation
  - ◇ Infection (meningitis, encephalitis)
  - ◇ Tumor
- Pulmonary
  - ◇ Interstitial lung disease
  - ◇ Embolism
  - ◇ Pneumonia
  - ◇ Edema
- Extrapulmonary carbon dioxide removal
  - ◇ Acetate hemodialysis
  - ◇ Heart-lung machine
  - ◇ Extracorporeal membrane oxygenation
- Miscellaneous
  - ◇ Pregnancy
  - ◇ Progesterone
  - ◇ Sepsis
  - ◇ Hepatic failure
- Decreased carbon dioxide production[a]
  - ◇ Myxedema
  - ◇ Hypothermia

[a]Ventilation usually is fixed (ventilator) in this setting; myxedema coma also can be associated with respiratory acidosis.