Review Article

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Post-Hypercapnic Alkalosis: A Brief Review

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Metabolic alkalosis is a common acid-base imbalance frequently observed in intensive care unit (ICU) patients and is associated with increased mortality. Post-hypercarbia alkalosis (PHA) is a type of metabolic alkalosis caused by sustained high serum bicarbonate levels following a rapid resolution of hypoventilation in patients with chronic hypercapnia due to prolonged respiratory disturbance. Common causes of chronic hypercapnia include chronic obstructive pulmonary disease (COPD), central nervous system disorders, neuromuscular disorders, and narcotic abuse. Rapid correction of hypercapnia through hyperventilation leads to a swift normalization of pCO_2, which lacks renal compensation, consequently causing an increase in plasma HCO_3^- levels and severe metabolic alkalosis. Most of PHA occurs in the ICU setting requiring mechanical ventilation and can progress severe alkalemia due to secondary mineralocorticoid excess from volume depletion or decreased HCO_3^- excretion from decreased glomerular filtration rate and increased proximal tubular reabsorption. PHA is associated with increased ICU stay, ventilator dependency, and mortality. Acetazolamide, a carbonic anhydrase inhibitor, has been utilized for managing PHA by inducing alkaline diuresis and reducing tubular reabsorption of bicarbonate. While acetazolamide effectively improves alkalemia, its impact on hard outcomes may be limited by factors such as patient complexity, co-administered medications, and underlying conditions contributing to alkalosis.

Key Words: Metabolic alkalosis, Hypercapnia, Hyperventilation, Chronic obstructive pulmonary disease, Carbonic anhydrase

INTRODUCTION

Metabolic alkalosis is a prevalent acid-base imbalance frequently observed in patients admitted to intensive care unit (ICU). Severe alkalosis is related with clinical manifestations such as hypoventilation, neurological symptoms, and diminished systemic oxygenation[1]. In an observational investigation involving 409 patients, those presenting alkalemia with pH levels greater than 7.48 were identified to have a 27.9% mortality rate. Within the group, patients with a pH greater than 7.60 exhibited a significantly increased mortality rate of 48.5%[2].

In ICU patients, contraction of the extracellular fluid (ECF) due to vomiting, nasogastric suctioning or diuretic treatment can cause chloride-responsive metabolic alkalosis[3]. Besides metabolic alkalosis caused by volume depletion, post-hypercapnic alkalosis (PHA), a form of compensated metabolic alkalosis caused by chronic hypercapnia due to respiratory insufficiency, is relatively common in specific clinical situations. This review aims to offer a comprehensive overview of PHA by examining a case presentation and discussing the pathophysiology, epidemiology, and management, with a focus on the effects of acetazolamide treatment.

Case Presentation

An 84-year-old male presented to the emergency depart-

ment with a complaint of decreased consciousness that occurred 1 hour prior to his visit. He was hospitalized 4 years ago for an event of generalized tonic-clonic seizure and was also diagnosed with chronic obstructive pulmonary disease (COPD), hypertension, dilated cardiomyopathy, atrial fibrillation and was prescribed azilsartan 40 mg, amlodipine 5 mg, apixaban 2.5 mg twice daily, valproate 300 mg twice daily, levetiracetam 1,000 mg twice daily, doxofylline 400 mg twice daily, and a beclomethasone/formoterol inhaler 100/6 μg. The patient recently experienced a loss of appetite and poor adherence to his prescribed medications, including anti-epileptic drugs. A point-of-care test revealed a positive result for the COVID-19 PCR. The physical examination showed a blood pressure of 120/92 mmHg, pulse rate of 68 beats/min, respiratory rate of 19 breaths/min, temperature of 36.6°C, and a Glasgow coma scale (GCS) score of E3V4M5. Skin turgor was mildly reduced. Arterial blood gas analysis (ABGA) at admission demonstrated a pH of 7.37, pCO_2 of 51.8 mmHg, pO_2 of 52.2 mmHg, and HCO_3^- of 30.0 mmol/L. Biochemistry results included Na at 137 mmol/L, K at 5.2 mmol/L, Cl at 101 mmol/L, BUN/creatinine (Cr) at 18.0/0.87 mg/dL, N-terminal pro-B-type natriuretic peptide at 536.0 pg/mL, and C-reactive protein at 0.57 mg/dL.

The patient was treated for an acute exacerbation of COPD and congestive heart failure using 30 mg of methylprednisolone and intravenous furosemide. On the second day of hospitalization, the patient's mental status declined from confusion to drowsiness, with a GCS score of E3V3M4. ABGA at this time revealed pH 7.40, $PaCO_2$ 60 mmHg, PaO_2 101 mmHg, and HCO_3^- 37.1 mmol/L. The EEG displayed periodic spike waveforms.

On the third day of hospitalization, the patient's level of consciousness further decreased to stupor, and hypoxia worsened. Consequently, tracheal intubation and mechanical ventilation therapy were performed. The ABGA was pH 7.40, pCO_2 60 mmHg, pO_2 47 mmHg, and HCO_3^- 37.2 mmol/L. Six hours after initiating mechanical ventilation, the ABGA showed pH 7.44, pCO_2 51 mmHg, pO_2 101 mmHg, and HCO_3^- 34.6 mmol/L. Following 48 hours of continuous ventilation therapy, the ABGA indicated pH 7.60, pCO_2 28 mmHg, pO_2 105 mmHg, and HCO_3^- 27.5 mmol/L, suggesting the presence of respiratory and metabolic alkalosis. Serum biochemistry results included Na at 144 mmol/L, K at 4.7 mmol/L, Cl at 101 mmol/L, BUN/creatinine (Cr) at 26.0/0.65 mg/dL.

In the present case, the patient was referred to a nephrologist on tenth day of hospitalization, seven days after developing metabolic alkalemia. The patient's ABGA results were pH 7.55, pCO_2 28 mmHg, pO_2 123 mmHg, and HCO_3^- 24.5 mmol/L. After being diagnosed with PHA, the patient's pCO_2 was brought back toward normal range by allowing hypercapnia, and the furosemide dose was adjusted to maintain a euvolemic status. The day following PHA treatment, the ABGA results were pH 7.46, pCO_2 38 mmHg, pO_2 83 mmHg, and HCO_3^- 27.0 mmol/L.

On hospital day 13, the patient developed new-onset aspiration pneumonia and hypercapnia, which were managed by administering antibiotics and methylprednisolone at a dosage of 0.5 mg/kg/day. On day 14, the ABGA results indicated pH 7.41, pCO_2 60 mmHg, pO_2 104 mmHg, and HCO_3^- 38.0 mmol/L, with an electrolyte panel showing Na^+ 143 mmol/L, K^+ 3.5 mmol/L, Cl- 105 mmol/L, and a urine Cl level of 45 mmol/L. These findings suggested concomitant alkalosis that might occurred by secondary mineralocorticoid excess by administration of methylprednisolone and furosemide. Consequently, spironolactone was administered at a dose of 12.5 mg twice daily. The alkalosis subsequently corrected; however, the patient died due to the progression of pneumonia at hospital day 19.

Case Summary

The diagnosis of the presented case is PHA due to rapid correction of respiratory acidosis. PHA is an acid-base disturbance that occurs in patients with chronic hypercapnic respiratory failure when rapid hyperventilation (e.g., mechanical ventilation, non-invasive ventilation), results in a rapid correction of $PaCO_2$ that is not accompanied by sufficient reversal of renal HCO_3^- reabsorption, resulting in metabolic alkalosis. PHA frequently occurs in acute, intensive care settings, often accompanying rapid hyperventilation therapy. The complexity of patient's condition can lead to misidentification of other causative factors for metabolic alkalosis, resulting in delayed accurate diagnosis and appropriate management. The presented case illustrated a patient with multiple comorbidities such as epilepsy, COPD, and heart failure, experienced a prolonged mechanical ven-

tilation therapy due to the delayed identification of PHA resulting from hyperventilation.

Pathophysiology of PHA

Chronic hypercapnia due to respiratory insufficiency can be caused by various conditions, including COPD, central nervous system disorders, neuromuscular disorders, and narcotic abuse. When chronic hypercapnia and respiratory acidemia develops, patients undergo a renal compensation as bicarbonate reabsorption resulting in an increase in plasma HCO_{3-} and amelioration of the acidemia[4]. The retention of plasma sodium bicarbonate ($NaHCO_3$) increases effective arterial blood volume, leading to enhanced sodium chloride (NaCl) excretion. In this context, euvolemia is sustained by high total ECF $NaHCO_3$ and low total ECF NaCl.

Swift correction of hypercapnia subsequently results in primary metabolic alkalosis due to elevated plasma HCO_{3-} levels and normal pCO_2. The kidneys then attempt to rectify the alkalosis by excreting HCO_{3-}, accompanied by the excretion of sodium and potassium, the relative proportions of which are determined by aldosterone levels. If the patient has a low NaCl intake, which is common in this situation, bicarbonate excretion will cease, leading to a persistent metabolic alkalosis maintained by volume contraction and hypokalemia. Raising the total ECF NaCl can enhance effective arterial blood volume, rectifying metabolic alkalosis. It is crucial to consider that these patients often use diuretics, which can exacerbate volume depletion and play a role in the creation and persistence of metabolic alkalosis[1,5].

Epidemiology of PHA

COPD is known to be a common cause of chronic hypercapnia. In a study conducted by Dreher et al. that examined the prevalence of chronic hypercapnia among 231 patients diagnosed with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 3 or 4 COPD, the researchers discovered that 25% of the patients had $PaCO_2$ levels exceeding 45 mmHg, while 9% exhibited hypercapnia with levels exceeding 50 mmHg[6].

There is limited evidence regarding the frequency of PHA following hyperventilation therapy. In a study conducted by Banga et al., of 84 patients experiencing acute exacerbation of COPD with CO_2 retention, 17 patients (20%) exhibited alkalemia as confirmed by ABGA with a pH of 7.45 or higher, 72 hours after receiving mechanical ventilator therapy. The group of patients with PHA experienced longer days of ICU stay and ventilator dependency[7].

Diagnosis and Management of PHA

PHA is a potential complication from hyperventilation therapy in patients with underlying chronic hypercapnic respiratory failure. This condition can result from various underlying disorders, such as COPD, neuromuscular disorders, central nervous system depression, or chronic narcotic abuse. Patients with chronic hypercapnia, characterized by a pCO_2 greater than normal value of 40 mmHg, often maintain a normal blood pH of approximately 7.40 due to renal compensation. However, when an additional acute respiratory failure event, such as an acute infection, occurs, the pCO_2 may further increase, leading to additional acute respiratory acidosis. In these clinical situations, the correction of hypoventilation through mechanical or non-invasive ventilation can result in uncompensated metabolic alkalosis. This occurs due to the persistence of the underlying pathophysiology associated with hypercapnic metabolic alkalosis, which leads to severe alkalemia with a pH greater than 7.50-7.60. This results from the coexistence of mixed metabolic alkalosis and respiratory acidosis[8]. The primary goal in treating metabolic alkalosis is to address the underlying condition. Upon diagnosing post-hypercapnic alkalosis (PHA), the presence of various co-existing conditions can complicate the correction of metabolic alkalosis. ECF deficits induced by diuretics or gastrointestinal loss, the use of steroids with mineralocorticoid effects, and electrolyte imbalances such as potassium and magnesium also can contribute to alkalosis, potentially delaying the diagnosis of PHA and impeding effective treatment[3,9].

Carbonic anhydrase inhibitor is a class of medications that impede bicarbonate reabsorption in the proximal tubule by inhibiting the activity of the enzyme carbonic anhydrase. Acetazolamide has been used in the management of metabolic alkalosis, by inducing alkaline diuresis

Table 1. A summary of studies on acetazolamide treatment in patients with respiratory failure and metabolic alkalosis

Author (year)	Study design	Target group	Intervention	Study participants	Major outcomes	Results
Faisy et al. (2016)[11]	Randomized, double blind, placebo controlled, multicenter trial	Patients with COPD requires IMV less than 24 h with MA, defined as a pH ≥7.35 and HCO_3^- >26 mmol/L	ACET 500 or 1,000 mg (in case with furosemide) twice daily or placebo	ACET group, N=187 Placebo group, N=193	Duration of IMV Duration of ICU stay ICU Mortality Change of HCO_3^-	Median 136.5 vs 163 h, difference -16.0 h (95% CI, -36.5, 4.0) Median 10 vs 10 d Difference -2.1 d (95% CI, -6.1, 1.9) 11.7% vs 13.4% (p-value, 0.61) Median -0.3 vs 0.3 meq/L Difference -0.8 meq/L (95% CI, -1.2, -0.5)
Rialp et al. (2017)[12]	Randomized, double blind, placebo controlled, multicenter trial	Patients with COPD or OHS on IMV during less than 72 h with MA, defined as a pH > 7.35 and HCO_3^- >28 mmol/L	ACET 500 mg once daily or placebo when 7 AM HCO_3^- >26 mmol/L	ACET group, N=24 Placebo group N=23	Duration of IMV Duration of ICU stay Hospital mortality HCO_3^- at day 3	Median 4.9 vs 7.2 d (p-value, 0.30) Median 8.5 vs 11 d (p-value, 0.19) 16% vs 9% (p-value, 0.41) Median 30 vs 34 meq/L (p-value <0.001)
Gulsvik et al. (2013)[13]	Randomized, double blind, placebo-controlled trial	Patients with respiratory failure by pulmonary disease (PaO_2 ≤8 kPa and/or $PaCO_2$ ≥ 7 kPa) with BE of 8 meq/L	ACET 250 mg three times daily or placebo for 5 days	ACET group, N=35 Placebo group, N=35	Change of pO_2 Change of pCO_2 Change of pH Change of HCO_3^-	Mean 1.41 vs 0.81 kPa, difference 0.55 kPa (95% CI, -0.03, 1.06) Mean -0.29 vs -0.45 kPa, difference 0.19 kPa (95%CI, -0.25, 0.64) Mean -0.087 vs -0.084, difference -0.084 (95% CI, -0.102, -0.067) Mean -8.62 vs -2.16 meq/L, difference -6.31 meq/L (95% CI, -7.77, -4.86)
Vos et al. (1994)[14]	Randomized, double blind, placebo-controlled trial	Patients with COPD and hypoxemia of pO_2 ≤8.5 kPa	ACET 250 mg twice daily or placebo for 2 days with O_2 therapy via nasal cannula	ACET group, N=17 Placebo group, N=18	Change of pO_2 Change of pCO_2 Change of pH Change of HCO_3^-	Mean 1.9 vs 0.4 kPa (p-value <0.05) Mean -0.5 vs 0.3 kPa (p-value <0.05) Mean -0.07 vs -0.01 (p-value <0.05) Mean -6.7 vs 0.3 meq/L (p-value <0.05)

COPD, chronic obstructive pulmonary disease; IMV, invasive mechanical ventilation; MA, metabolic alkalosis; ACET, acetazolamide; BE, base excess.

by reducing tubular reabsorption of bicarbonate and inhibiting distal tubule secretion of hydrogen ions. After hours of acetazolamide administration, urinary bicarbonate loss occurs, leading to a decrease in serum bicarbonate levels. This reduction is typically a 4-6 mM decrease within 24 hours, accompanied by a fall in arterial pH of approximately 0.05-0.1 units. If there were no mechanical limitation to the increase of lung ventilation, the pCO_2 would decrease by approximately 5-6 mmHg due to the respiratory response[10].

Several clinical trials have investigated the use of acetazolamide for the reversal of alkalosis in patients with prolonged PHA. While some studies have focused on comparing changes in pH and HCO_3^-, a biochemical marker related to alkalosis, others, such as the study conducted by Faisy et al. and the study by Rialp et al., have examined outcome as duration of mechanical ventilation, and mortality in larger number of patient cohorts through randomized, placebo-controlled trials[11-14].

Based on the results of the studies reviewed, 250 to 500 mg PO or IV acetazolamide would be appropriate as first-line treatment in patients with PHA. The dose of acetazolamide should be adjusted, ranging from 250 to 500 mg once or twice daily, depending on response to therapy. However, dose adjustments are required when there is renal function impairment, as the drug is eliminated by the kidneys. Pharmacokinetic studies of acetazolamide have shown that serum acetazolamide concentrations are elevated in patients with decreased renal function or dialysis[15-17]. In patients with decreased renal function, CNS toxicity or acidosis may occur due to the accumulation of acetazolamide, and aplastic anemia, agranulocytosis or anaphylaxis may occur in a non-dose-dependent manner[18-20]. In these patients, a dose of 125 mg to 250 mg of acetazolamide would be appropriate.

Table 1 provides an overview of the clinical trials conducted on PHA patients. In all studies, acetazolamide demonstrated a significant improvement in base excess. In the largest study involving 380 COPD patients received mechanical ventilation therapy, acetazolamide administration resulted in a 16-hour decrease in the duration of mechanical ventilation compared to placebo. However, the difference did not reach statistical significance (95% CI, -36.5 to 4.0 h; p=0.17). Furthermore, acetazolamide therapy did not significantly reduce the duration of hospital stay or decrease mortality[11]. Rialp et al. compared the effectiveness of ace-

tazolamide 500 mg once daily versus placebo in patients with obesity hypoventilation syndrome (OHS) and COPD undergoing invasive mechanical ventilation therapy. In the randomized controlled trial, which included a total of 47 patients, acetazolamide did not reduce the duration of ventilator therapy or ICU stay and showed no effect on mortality[12]. Two other smaller studies examined changes in blood gas analysis profiles between acetazolamide and placebo in patients with COPD and chronic respiratory failure. In both studies, the results showed that acetazolamide improved alkalemia[13,14].

Although acetazolamide effectively improves alkalemia in patients with PHA, its impact on hard outcomes, such as duration of mechanical ventilation, length of stay, and mortality, may be limited by factors like patient complexity and co-administered medications. For example, loop diuretics and corticosteroids can interfere with acetazolamide's pharmacodynamics and reduce its ability of bicarbonate excretion. When these drugs are being co-administrated, a higher dose of acetazolamide (500 to 1,000 mg twice daily) may be appropriate to achieve the therapeutic effect[21]. Furthermore, diuretics contribute to chloride-responsive metabolic alkalosis via volume depletion, and mineralocorticoids result in hypokalemia and augmented ammonium excretion and bicarbonate reabsorption in the distal tubule. In such situations, acetazolamide's effectiveness in reversing alkalosis may be diminished[3].

CONCLUSION

PHA is one of the common causes of alkalosis in the process of treating respiratory failure in patients with chronic obstructive pulmonary disease. Not only PHA due to rapid correction of compensated hypercapnia, but also diuretic-induced alkalosis or mineralocorticoid excess that commonly occurring in intensive care units can be worsen severe alkalosis.

Critically ill patients with PHA are at increased risk for delayed weaning from mechanical ventilation and mortality. Therefore, prevention, monitoring, and appropriate treatment of alkalosis are essential in acutely deteriorated patients with chronic hypercapnia due to respiratory diseases.

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