

Acetazolamide for selected cases of sleep apnea-related hypercapnia

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INTRODUCTION

Chronic hypercapnic respiratory failure (CHRF) most often results from obstructive loading (i.e., obstructive lung disease), restrictive loading (e.g. obesity, kyphoscoliosis, or fibrotic lung disease) or reduced neuromuscular capacity (e.g., amyotrophic lateral sclerosis). Obstructive sleep apnea (OSA) is a common cause of CHRF. These patients often have edema (e.g., due to cor pulmonale or left heart failure) that is treated with loop diuretics. Opiates, sedatives, and oxygen may also attenuate alveolar ventilation.^{1,2} Acetazolamide, used for prophylaxis and treatment of mountain sickness has not been well-investigated for treatment of CHRF.³ We report three cases of patients with obstructive sleep apnea (OSA) and severe chronic hypercapnic respiratory failure (CHRF) in whom treatment with acetazolamide was associated with remarkable reversal of hypercapnia.

CASE REPORTS

CASE 1

A 58 year-old man with a past medical history of severe COPD, obstructive sleep apnea (OSA) treated with nocturnal bi-level positive pressure ventilation (BiPAP), a body mass index (BMI) of 26 kg/m², and opiate and benzodiazepine dependence, with three hospital admissions over the preceding 3 months for acute-on-chronic hypercapnic respiratory failure (HRF), presented with dyspnea. He denied cough, fever, chest pain, or chills but reported tremulousness. His initial venous blood gas (pH/PCO₂/PO₂, 7.35/105/56) showed chronic hypercapnia and metabolic alkalosis (Table 1). Chest radiography was unremarkable, and no acute illness was identified.

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His home medications were continued, and he remained drowsy and comfortable, with arterial pH ranging from 7.30 to 7.38 (measured both during spontaneous and BiPAP-assisted breathing), and PCO₂ ranging from 97 to 115 mmHg. The Palliative Care suggested comfort measures only, which the patient rejected. On his fifth hospital day, he refused reductions of opiates/benzodiazepines but accepted the risks of acetazolamide. After a single 500-mg dose of acetazolamide, his next venous blood gas showed a pH of 7.38 and a PCO₂ of 64 mmHg. After discontinuation of furosemide and volume expansion, on day 3 of acetazolamide therapy, his venous blood gas showed a pH of 7.31 and a PCO₂ of 56 mmHg. On the day of discharge (after 4 days of acetazolamide), his pH was 7.32, PCO₂ was 53 mmHg, and PO₂ was 51 mmHg on room air. He was discharged on his prior medications, including furosemide 20 mg twice weekly and acetazolamide 250 mg twice weekly. Methadone was to be reduced by 2 mg each week and alprazolam was to be decreased over the following 4 months. Over the ensuing months, his PCO₂ rose to 78–96 mmHg with a pH of 7.28–7.32, but he did not require readmission to the hospital.

CASE 2

A 56 year old woman with metastatic breast cancer, right malignant effusion, obesity (51.8 kg/m²), OSA and CHRF presented with dyspnea on exertion and room air hypoxemia that corrected with 3 L/min oxygen via nasal cannula (NC). Medications included gabapentin 900 mg twice daily, oxycodone-acetaminophen every 4 hours as needed, and lorazepam 0.5 mg three times daily for anxiety or nausea. No blood gas was performed, but the serum bicarbonate was 32 mEq/L, and she was alert with an unremarkable physical examination. Diagnostic thoracentesis revealed an exudate with malignant cells. On the third hospital day, she developed lethargy and somnolence with a respiratory rate of 16–20 breaths/min. Arterial blood gas analysis on 5 L/min oxygen via nasal cannula

Table 1. Selected Blood Gases in the 3 Months Prior to Introduction of Acetazolamide on 3/11/23

Date	Arterial (a) or Venous (v)	FiO ₂	Ventilation BiPAP, Spontaneous	pH	PCO ₂	PO ₂
12/20/22	a	40%	BiPAP 20/5	7.46	87	61
12/23/22	a	2 L	spontaneous	7.36	64	59
1/6/23*	v	2 L	spontaneous	7.37	52	37
2/21/23	v	3 L	spontaneous	7.43	75	38
3/6/23	v	3 L	spontaneous	7.35	101	14
3/6/23	a	40%	BiPAP 12/6	7.30	115	67
3/7/23	v	28%	BiPAP 18/6	7.38	97	23
3/11/23	v	2 L	spontaneous	7.35	64	50
3/13/23	a	Room air	spontaneous	7.31	56	59
3/14/23	a	Room air	spontaneous	7.32	53	51

*Admission included several days of endotracheal intubation/positive pressure ventilation.

showed a pH of 7.25, PCO₂ of 99 mmHg, and PO₂ of 100 mmHg (serum bicarbonate 39 mEq/L). Opiates, benzodiazepines, and inspired oxygen were reduced, and acetazolamide 500 mg was administered intravenously daily for 2 days, resulting in a venous blood gas of pH 7.32, PCO₂ 60 mmHg, and PO₂ 46 mmHg (serum bicarbonate 30 mEq/L). She was transferred for inpatient rehabilitation on acetazolamide 250 mg three times weekly. Three days later, a venous blood gas was pH 7.28, PCO₂ 62 mmHg, and PO₂ 60 mmHg on room air (serum bicarbonate 28 mEq/L). Just prior to discharge, her room air ABG was 7.42/52/52, and 1 month after discharge, while receiving acetazolamide 250 mg daily and furosemide 40 mg twice weekly, her serum bicarbonate was 25 mEq/L.

CASE 3

A 66 year old woman with obesity/OSA (BMI 53 kg/m²), CHRF requiring 5 L/min home oxygen, and peripheral edema presented with worsening pedal/leg edema and dyspnea. Her home medications included furosemide 20 mg daily. She was mildly dyspneic with respiratory rates of 21–28/min, and the initial blood gas on BiPAP (16/8 cm H₂O, FiO₂ 60%) was 7.19/106/62 (serum bicarbonate 36 mEq/L). Reducing the oxygen concentration to 50% on the same day resulted in a blood gas of 7.25/85/62, and further reduction to 8 L/min via nasal cannula resulted in 7.28/82/47. Over the next

3 days, she received no furosemide and acetazolamide 500 mg, 500 mg, and 250 mg, with blood gases obtained on the day following each dose: 7.30/49/67, 7.39/49/51, and 7.32/61/65. A regimen of furosemide 20 mg twice weekly and acetazolamide 125 mg twice weekly maintained the serum bicarbonate in the 24–31 mEq/L range over the following 2 months.

DISCUSSION

These cases suggest that acetazolamide may be useful in carefully selected cases of acute-on-chronic hypercapnia. These patients were somnolent and lethargic, with respiratory rates <30/min, suggesting that acute hypercapnia was not precipitated by mechanical overloading but rather by iatrogenic factors, including furosemide, hyperoxia, narcotics, or combinations thereof.

The pathogenesis of hypercapnia in OSA is not completely understood. Pioneering work by Goldring suggests that:

Acute hypercapnia during periodic breathing occurs due to either reduction in the magnitude of inter-event ventilation and/or reduction in inter-event ventilatory duration relative to the duration of the preceding event. The transition between acute hypercapnia during sleep and chronic sustained hypercapnia during wakefulness may be determined by an

interaction between respiratory control and renal handling of HCO_3^- .⁴ These respiratory-renal interactions create a cumulative effect over subsequent periods of sleep that eventually results in a self-perpetuating state of chronic hypercapnia.⁵

Adding furosemide to this model would be expected to accentuate inter-event bicarbonate retention, thereby contributing to hypercapnia in patients with OSA. It is plausible that acetazolamide may attenuate chronic hypercapnia while addressing iatrogenic factors. Respiratory depressants including opiates, benzodiazepines/tranquilizers, and administered oxygen – known to promote acute-on-chronic hypercapnia in 20–40% of patients with hypercapnia – almost certainly contributed to both acute and chronic hypercapnia in our patients.^{1,2}

Use of acetazolamide in these patients carries risks.⁶ There are small studies of patients with obstructive lung disease suggesting safety and reduced hypercapnia, but the quality of the evidence remains low, and the impact on PCO_2 has been modest (3 mmHg).^{7–9} Even fewer data exist examining the impact of acetazolamide in patients with OSA. One study showed a modest decrease in PCO_2 (from 43 to 36 mmHg) in 9 patients with mild obesity hypoventilation treated with acetazolamide 250 mg.¹⁰ We found no studies of severe OSA-related CHRF treated with acetazolamide.

In conclusion, these cases demonstrate that acetazolamide can be a useful tool, in conjunction with other measures, to safely reverse chronic hypercapnia in monitored settings. The optimal use of acetazolamide, both acutely and chronically, remains to be determined. It might be considered, at least, to attenuate furosemide-induced contraction alkalosis that might contribute to CO_2 escalation, as described by Goldring above. These examples of patients with extreme hypercapnia are not uncommon in emergency rooms and critical care units. Until appropriate prospective clinical studies are conducted, clinicians might consider a trial of acetazolamide (e.g., to offset furosemide) in selected patients with OSA-related CHRF. Further prospective studies are required to systematically identify which, if any, patients benefit from this therapy.

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