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BRIEF REPORT

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Effectiveness of acetazolamide for reversal of metabolic alkalosis in weaning COPD patients from mechanical ventilation

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Abstract *Purpose:* To evaluate the effects of a single daily dose of acetazolamide (ACET) on metabolic alkalosis and respiratory parameters in weaning chronic obstructive pulmonary disease (COPD) patients from invasive mechanical ventilation. *Design:* Case–control study. *Setting:* An 18-bed intensive care unit (ICU) in a university hospital. *Patients:* Twenty-six intubated COPD patients with mixed metabolic alkalosis (serum bicarbonate >26 mmol/l and arterial pH ≥7.38) were compared with a historical control group ($n = 26$) matched for serum bicarbonate, arterial pH, age, and severity of illness at admission to ICU. ACET administration (500 mg intravenously) was monitored daily according to arterial blood gas analysis from readiness to wean until extubation. *Results:* ACET was administered 4 (1–11) days throughout the weaning period. Patients with ACET treatment significantly decreased their serum bicarbonate ($p = 0.01$ versus baseline) and arterial blood pH ($p < 0.0001$), increased their PaO_2/FiO_2 ratio ($p = 0.04$), but did not change their $PaCO_2$ ($p = 0.71$). Compared with matched controls, administration of ACET did not improve arterial blood gas and respiratory parameters except PaO_2/FiO_2 ratio ($p = 0.03$). ACET patients and their matched controls had similar duration of weaning. Extubation success rate was not significantly different between groups, and causes of reintubation were comparable. *Conclusions:* ACET used at the dosage of 500 mg per day reduces metabolic alkalosis but has no benefit in terms of improving $PaCO_2$ or respiratory parameters in weaning COPD patients from mechanical ventilation.

Keywords Acetazolamide · Chronic obstructive pulmonary disease · Mechanical ventilation · Weaning · Metabolic alkalosis

Introduction

Metabolic alkalosis, resulting from loss of noncarbonic acid or increase in alkali, commonly develops in patients with chronic respiratory acidosis who are receiving therapy for cardiac and respiratory failure, inducing mixed or "complex" metabolic alkalosis [1, 2]. Metabolic alkalosis may depress cardiac output and/or central respiratory drive, and involves alterations in oxyhemoglobin dissociation, causing weaning failure, especially in patients with chronic obstructive pulmonary disease (COPD) [3, 4].

Acetazolamide (ACET), a carbonic anhydrase inhibitor, is used to reverse metabolic alkalosis when fluid and potassium replacements are insufficient to correct blood alkalinity. It has been established that a single daily 500 mg dose of ACET reverses metabolic alkalosis for 72 h in intubated patients with COPD or asthma as

effectively as multiple doses of 250 mg [5]. Reversal of metabolic alkalosis might facilitate weaning from mechanical ventilation [6]. Although ACET has been proposed for improving arterial blood gas and respiratory parameters in COPD patients, its effectiveness remains unknown during weaning from ventilation.

The aim of our study was to evaluate the effects of ACET on metabolic alkalosis and respiratory parameters in weaning COPD patients from invasive mechanical ventilation. Our primary outcome was to assess variations in serum bicarbonate and arterial blood gas between readiness to wean and extubation. Our secondary endpoint was to appraise changes in respiratory parameters induced by ACET treatment throughout the weaning period.

Methods

Study design

We conducted a case–control study over a 1-year period in a university teaching hospital. Adult COPD patients intubated for acute respiratory failure and with mixed metabolic alkalosis (serum bicarbonate >26 mmol/l and pH ≥7.38) for the period of weaning were recruited between November 2006 and October 2007 to receive ACET. The local Ethics Committee approved the study, and informed consent was obtained from all participants or next of kin. Weaning period was defined as the time between readiness to wean and extubation. Criteria for assessing readiness to wean are shown in the Electronic Supplementary Material. Case patients were compared with a historical control group matched in 1:1 proportion with each case for the variables of metabolic alkalosis at readiness to wean, age, and severity of illness at intensive care unit (ICU) admission. Data on the matching and details on weaning process standardization are included in the Electronic Supplementary Material.

ACET administration

At inclusion, patients received intravenously a single dose (500 mg) of ACET (Diamox®, Sanofi-Aventis, Paris, France). Then, ACET administration (500 mg IV per day) was monitored according to arterial blood gases performed each day at 7.00 am on pressure support ventilation or volume-assisted ventilation (Evita 4®, Dräger Medical France, Antony, France). ACET was discontinued when complete reversal of metabolic alkalosis was obtained (serum bicarbonate ≤26 mmol/l) or when noncompensated acidosis (arterial pH <7.38) occurred. ACET administration was withdrawn after extubation.

Statistical analysis

Details are shown in the Electronic Supplementary Material. All statistical analyses were performed using StatView 4.5 Software (Abacus Concepts Inc., Berkeley, CA, USA).

Results

Characteristics of the patients

Characteristics of the 26 included patients and their 26 matched controls are detailed in the Electronic Supplementary Material. Briefly, ACET patients and their controls were similar in terms of descriptive and demographic characteristics, modality of ventilator support used for weaning, treatment with drugs interfering with acid–base balance, and arterial blood gas and biological data at intubation and at readiness to wean.

Effects of ACET on arterial blood gas and respiratory parameters

ACET was administered for median duration of 4 (1–11) days. Patients with ACET treatment decreased their serum bicarbonate ($p = 0.01$ versus baseline) and arterial blood pH ($p < 0.0001$), increased their PaO_2/FiO_2 ratio ($p = 0.04$), but did not significantly change their $PaCO_2$ ($p = 0.71$) during weaning procedure (Fig. 1). However, variations in arterial blood gas did not differ significantly between ACET and control patients except for PaO_2/FiO_2 ratio [$\Delta PaO_2/FiO_2 = 18$ (−80 to 155) mmHg with ACET versus −5 (−237 to 108) mmHg without ACET, $p = 0.03$, Fig. 1]. ACET treatment did not significantly change respiratory frequency and tidal volume or minute ventilation on mechanical ventilation, and variations in respiratory parameters were not significantly different between ACET and control patients (Fig. 2). The effects of ACET on the pure metabolic and the respiratory acidotic components of mixed metabolic alkalosis are detailed in the Electronic Supplementary Material.

Weaning from mechanical ventilation

ACET patients and their matched controls were similar in terms of duration of weaning, number of failed spontaneous breathing trials before extubation, and use of noninvasive ventilation after extubation, while causes of reintubation were comparable (Table 1). No tracheotomies were performed. No significant side-effects imputed to ACET were reported, in particular no severe hypokalemia.

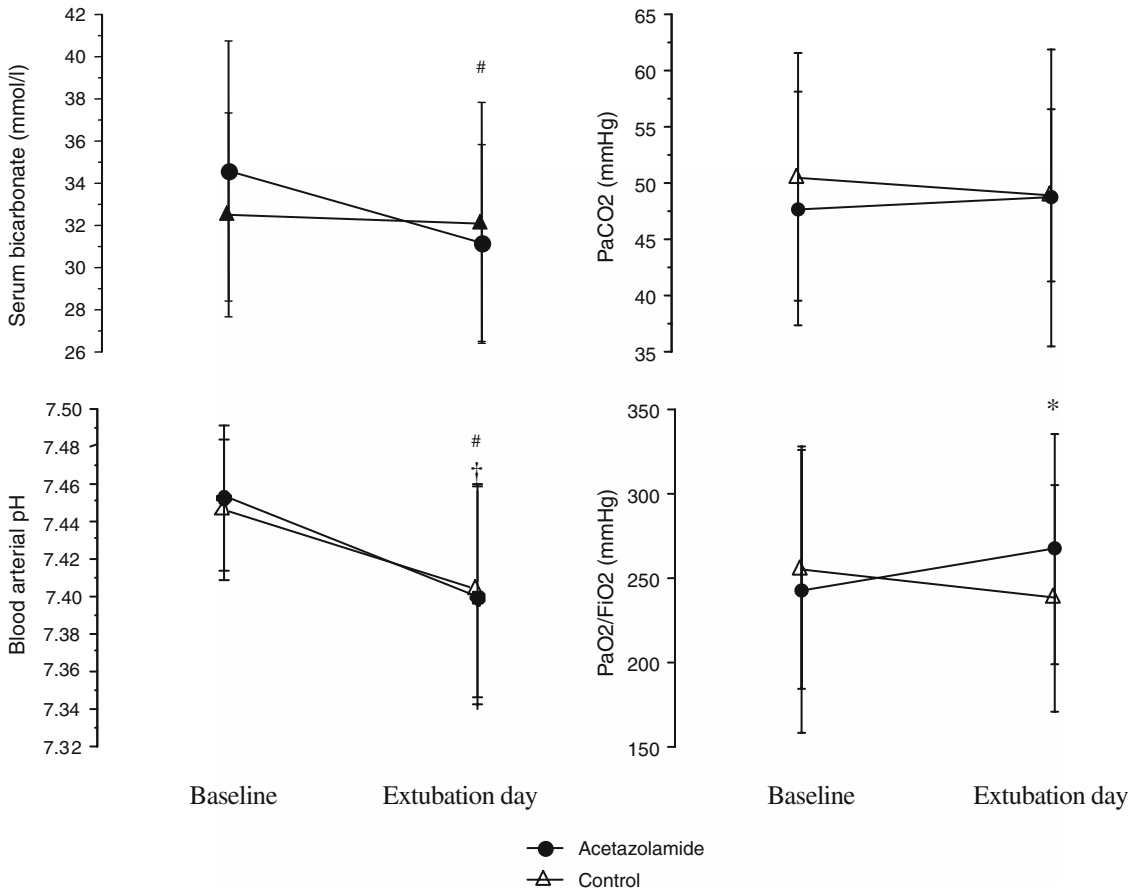

Fig. 1 Effects of acetazolamide (ACET) on arterial blood gas in COPD patients with metabolic alkalosis during weaning from mechanical ventilation. Arterial blood gases (ABL 725®; Radiometer Copenhagen, Copenhagen, Denmark) were performed at 7.00 a.m. on pressure support ventilation or volume-assisted ventilation. Baseline corresponded to the day of study inclusion. For ACET baseline versus ACET extubation day: $^{*}p < 0.05$, $^{\#}p < 0.01$; for control baseline versus control extubation day: $^{\dagger}p < 0.001$

Patient outcome

ACET patients and their matched controls did not differ significantly in terms of length of mechanical ventilation, ICU stay or ICU mortality (details are shown in the Electronic Supplementary Material).

Discussion

ACET could be useful for improving minute ventilation in patients with significant reduction of respiratory drive during weaning from mechanical ventilation, since failure of weaning depends on the balance between the ventilatory request and the ventilatory reserve of the patient. During weaning, restoration of a typical COPD respiratory drive pattern with spontaneous hyperventilation and the widespread use of drugs interfering with acid–base balance, such as furosemide, may alter the effectiveness of ACET for improving minute ventilation. The absence of fall in central respiratory drive could explain the lack of effectiveness of ACET in our COPD patients. An important limitation of the present study is the absence of measurement of mouth occlusion (P.01) pressure, which would provide information on the drive to breathe and muscle function. However, the use of noninvasive P.01 in mechanically ventilated COPD is limited by several factors, especially the increase in functional residual capacity and the active expiration [7, 8]. In our study, the changes in arterial pH were comparable in patients treated with ACET and their controls, whereas serum bicarbonate level was only reduced with ACET treatment, suggesting a similar respiratory pattern in the two groups.

It has been shown that ACET at the dosage of 500 mg per day reduces $PaCO_2$ without changes in minute ventilation in stable hypercapnic COPD patients [9]. Differences between stable and mechanically ventilated COPD may explain our conflicting results. Indeed, a complex interaction occurs between the components of mixed metabolic

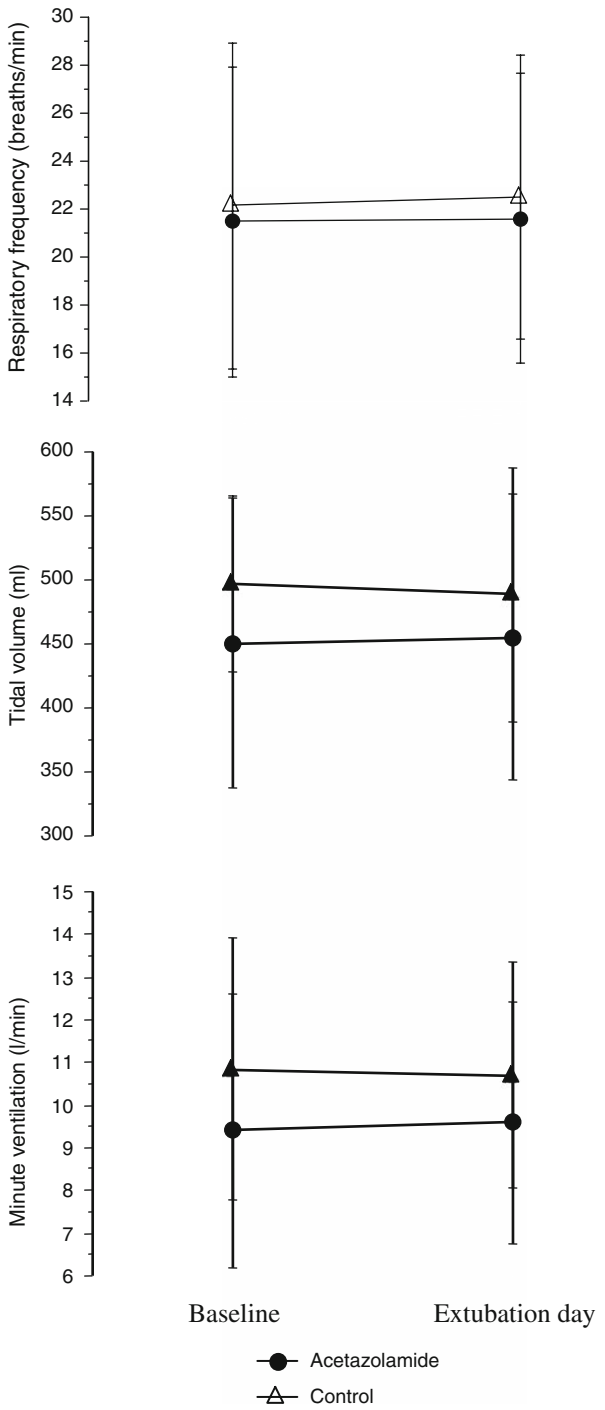

Fig. 2 Effects of acetazolamide (ACET) on respiratory parameters in COPD patients with metabolic alkalosis during weaning from mechanical ventilation. Respiratory parameters were collected at 7.00 a.m. on mechanical ventilation. Baseline corresponded to the day of study inclusion. No difference was statistically significant

alkalosis, the activity of respiratory central drive, and reventilation in intubated COPD patients (details are provided in the Electronic Supplementary Material). A decrease in CO_2 production or an increase in dead space could also bias our observations. Nevertheless, ACET patients and their controls had comparable lung function in our study and we used standardized protocols of nutrition and mechanical ventilation in both groups. Moreover, unfavorable mechanic properties in severely flow-limited COPD patients are possible and could explain why the reversal of the depressive metabolic stimulus to the respiratory drive may not have produced an increase in minute ventilation and a reduction in $PaCO_2$. In this line, it is known that nonresponders to acetazolamide had more severe obstruction than responders in COPD patients [10]. Furthermore, the ACET-induced increase in PaO_2/FiO_2 ratio observed in our study may reflect additional diuretic effect and not necessarily ACET specifically. Therefore, many factors impact on the pharmacodynamics of ACET in weaning of COPD patients and partly explain the lack of effectiveness of ACET in our study. In this way, higher dose of ACET could restore the clinical efficacy of ACET in ICU patients. However, it is not known if the respiratory effects of ACET are dose dependent in intubated COPD patients. In addition, the potential negatives of bicarbonate wasting in response to higher ACET dosing, by raising minute ventilation, may increase work of breathing and respiratory muscle fatigue, and decrease exhalation time, enhancing intrinsic positive end-expiratory pressure and hyperinflation. Our study suggests that ACET may be of more interest to overcome the increased work of breathing after withdrawal of mechanical ventilation.

There is a paucity of literature to support only one ACET dosing strategy in mechanically ventilated COPD [5, 6, 11, 12]. ACET pharmacokinetics and pharmacodynamics remain unknown in ICU patients, since they may be influenced by various conditions that modulate acid–base balance. In addition, ACET can stimulate minute ventilation via various pathways different from the reversal of metabolic alkalosis. Indeed, at low dose (4 mg/kg), ACET preferentially inhibits carbonic anhydrase localized in respiratory muscles [13, 14], whereas at higher doses (7–12 mg/kg), ACET abolishes the activity of carbonic anhydrase in red blood cells, peripheral chemoreceptors, kidneys, peripheral muscles, and endothelial cells [14]. Further research is needed to resolve the impact of tissue compartmentalization of carbonic anhydrase on ACET pharmacodynamics and the effects of ACET on respiratory mechanics.

Conclusion

Our study shows that use of ACET at the dosage of 500 mg per day reduces metabolic alkalosis but has no benefit in terms of improving $PaCO_2$ and respiratory parameters in weaning COPD patients from mechanical ventilation. Inefficiency of ACET might be related to

Table 1 Weaning from mechanical ventilation

Variables	ACET ($n = 26$)	Control ($n = 26$)	p Value
Length of weaning (days)	4.5 (1–11)	5 (2–22)	0.11
Failed spontaneous breathing trials	3 (0–8)	4 (0–7)	0.35
Extubation success (%)	12 (46.1)	7 (26.9)	0.15
Extubation failure			
Need for noninvasive ventilation <48 h (%)	12 (46.1)	13 (50)	0.78
Reintubation <48 h (%)	5 (19.2)	9 (34.6)	0.21
Cause of reintubation			
Upper airway obstruction (%)	2 (7.6)	2 (7.6)	0.69
COPD-related encephalopathy (%)	2 (7.6)	3 (11.5)	0.50
Cardiopulmonary arrest (%)	0	1 (3.8)	0.50
Nosocomial pneumonia (%)	1 (3.8)	3 (11.5)	0.30

Criteria for extubation success/failure and for diagnosis of nosocomial pneumonia are detailed in the Electronic Supplementary Material
ACET acetazolamide, *COPD* chronic obstructive pulmonary disease

various factors modulating ACET pharmacodynamics. The clinical relevance of reversal of mixed metabolic alkalosis by ACET in mechanically ventilated COPD patients remains questionable. Our study was not powered to detect any major difference in duration of weaning or patient outcome. A large multicenter randomized trial is warranted to demonstrate the benefit of ACET in weaning of mechanically ventilated COPD patients.

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