Impact of acetazolamide use in severe exacerbation of chronic obstructive pulmonary disease requiring invasive mechanical ventilation

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ORIGINAL ARTICLE

ABSTRACT

Purpose: To analyse the impact of acetazolamide (ACET) use in severe acute decompensation of chronic obstructive pulmonary disease requiring mechanical ventilation and intensive care unit (ICU) admission.

Patients and Methods: Retrospective pair-wise, case-control study with 1:1 matching. Patients were defined as cases when they had received acetazolamide (500 mg per day) and as controls when they did not receive it. Patients were matched according to age, severity on admission (pH, PaO$_2$/FiO$_2$ ratio) and SAPSII score. Our primary endpoint was the effect of ACET (500 mg per day) on the duration of mechanical ventilation. Our secondary endpoints were the effect of ACET on arterial blood gas parameters, ICU length of stay (LOS) and ICU mortality.

Results: Seventy-two patients were included and equally distributed between the two studied groups. There were 66 males (92%). The mean age ($\pm$ SD) was 69.7 $\pm$ 7.4 years ranging from 53 to 81 years. There were no differences between baseline characteristics of the two groups. Concomitant drugs used were also not significantly different between two groups. Mean duration of mechanical ventilation was not significantly different between ACET(+) and ACET(-) patients (10.6 $\pm$ 7.8 days and 9.6 $\pm$ 7.6 days, respectively; $P = 0.61$). Cases had a significantly decreased serum bicarbonate, arterial blood pH, and PaCO$_2$ levels. We did not found any significant difference between the two studied groups in terms of ICU LOS. ICU mortality was also comparable between ACET(+) and ACET(-) groups (38% and 52%, respectively; $P = 0.23$).

Conclusion: Although our study some limitations, it suggests that the use of insufficient acetazolamide dosage (500 mg/d) ACET (500 mg per day) has no significant effect on the duration of mechanical ventilation in critically ill COPD patients requiring invasive mechanical ventilation. Our results should be confirmed or infirmed by further studies.

Key Words: Acute decompensation, acetazolamide, chronic obstructive pulmonary disease, outcome, weaning

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the fourth commonest cause of death worldwide, posing a large socioeconomic burden.$^{[1-3]}$ Patients with COPD have about three acute exacerbations of their disease per year, many of which result in unscheduled visits to a physician or emergency department and to hospitalization.$^{[4]}$ Severe exacerbation of COPD may require intensive care admission and invasive mechanical ventilation particularly when non-invasive positive pressure ventilation (NIPPV) fails to improve gas exchanges and respiratory mechanic.$^{[5]}$ However, weaning from mechanical ventilation can be particularly difficult and prolonged in COPD patients with severe pre-existing airflow limitation.$^{[6]}$ Moreover, metabolic alkalosis occurs
frequently in this group of patients who frequently receive therapies for cardiac and respiratory failures (steroids, diuretics, etc.). This disorder may depress central respiratory drive leading to hypoventilation and thus, hampers the weaning process. Futhermore, metabolic alkalosis can decrease cardiac output and/or disturb oxyhemoglobin dissociation. As a consequence, weaning failure become more probable with this specific condition and its correction increases both minute ventilation and partial pressure of oxygen (PaO₂).

Acetazolamide (ACET), a carbonic anhydrase inhibitor, is used to reverse metabolic alkalosis after proper fluid loading and potassium supplementation. In fact, it decreases proximal tubular HCO₃⁻ reabsorption through carbonic anhydrase (CA) inhibition in the luminal borders of renal proximal tubule cells. This leads to reversal of metabolic alkalosis and may facilitate weaning from mechanical ventilation. In fact, it was reported that a single 500-mg daily dose of ACET reverses metabolic alkalosis over 72 hours as effectively as multiple doses of 250 mg in intubated patients with COPD or asthma. However, although it was confirmed that the use of ACET improves arterial blood gas and respiratory parameters in COPD patients, its effectiveness remains unknown during weaning from ventilation and there is a paucity of literature to support the use of ACET for this purpose in mechanically ventilated COPD patients. For these reasons we conducted this study in order to evaluate the effect of ACET (500 mg per day) on the ventilator weaning process in critically ill COPD patients. The primary end-point was the effect of ACET administration on the duration of mechanical ventilation. The secondary endpoints were changes in arterial blood gas parameters, ICU mortality, and length of ICU stay.

**PATIENTS AND METHODS**

We performed a retrospective, pair-wise, case-control study with 1:1 matching. Our study was performed during a 5-year period (2006-2011) in the intensive care unit of the Habib Bourguiba University Hospital (Sfax-Tunisia).

Patients were eligible if they were admitted to the ICU because of acute exacerbation of COPD, diagnosed on the basis of clinical history, physical examination, and chest radiograph, and had an acute respiratory failure requiring mechanical ventilation within the first 24 h of admission. COPD exacerbation is defined clinically by the presence of at least 2 of the following signs and symptoms: Change in baseline dyspnea, cough, and sputum quantity or purulence.

In our study, patients were defined as cases when they received ACET and as controls when they did not receive this therapy. In our ICU, ACET is prescribed when mixed metabolic alkalosis (serum bicarbonate >26 mmol/l and pH ≥ 7.42) is observed in patients who were ready to start weaning from mechanical ventilation, without evidence of hypovolemia. Since weaning process was considered, patients received orally 250 mg of ACET twice a day (Diamox, Sanofi-Aventis, Paris, France). ACET administration was daily monitored according to arterial blood gases. This medication was discontinued when complete reversal of metabolic alkalosis was obtained or when non-compensated acidosis occurred. In our study, patients were first kept under sedation and assisted controlled ventilation. When FiO₂ was lower than 0.5 and PEEP was lower than 5 cmH₂O, sedation was stopped and patients were kept under partial pressure support mode as soon as possible. Patients who were awake with a vigorous cough underwent a spontaneous breathing trial. After extubation, non-invasive positive pressure ventilation (NIPPV) was considered only in patients developing hypercapnic respiratory failure and respiratory depressant drugs were avoided. Enteral feeding was introduced within the first 48 hours in all patients through an oral gastric tube.

Patients were matched according to age, severity factors at admission (pH, PaO₂/FiO₂ ratio, and SAPSII score on ICU admission. We compared the ICU mortality, the duration of mechanical ventilation and intensive care unit length of stay (LOS) between the two groups. Moreover, we assessed the variations in serum bicarbonates and arterial blood gas under this therapy in the cases group.

For all included patients, demographic, clinical and radiological data on admission and during ICU stay were retrospectively reviewed and the following data were collected: Age, sex, heart rate, respiratory rate before mechanical ventilation, blood pressure, use of inotropic drugs, fluid intake, and daily urinary output. We also recorded arterial blood gas (ABG) findings and biological parameters both on ICU admission and during ICU stay. Arterial blood gases were withdrawn daily at 8.00 am. In patients requiring NIPPV, ABG were performed 1 h after. The severity of illness was evaluated by the Simplified Acute Physiology Score (SAPS II) calculated within the first 24 h of admission. The causes of COPD exacerbation was also defined in each patient. Microbiological and clinical infections were recorded as well as the antibiotics administered. During the ICU stay, all complications were recorded: Nosocomial infections, thrombocytopenia, and gastrointestinal bleeding. Because of the retrospective character of our study, other complications related to ACET (dysthyroidism, blood dyscrasias, gout attacks, and encephalopathy) were not recorded as they were rarely available in the medical charts. For each patient, the number of organ failure was calculated. All therapeutics strategies (bronchodilators, antibiotics, diuretics, modalities of ventilation) were also compared between two groups (ACET group vs ACET-free group).
Statistics
Comparison of baseline characteristics of the two matched groups was performed by the Chi-square test or Fischer’s exact test as appropriate. Continuous variables were expressed as means ± SD and the subgroups were compared by Student t test or Mann-Whitney test as appropriate. Risk factors were evaluated in univariate analysis for compared data. A P value less than 0.05 was considered as statistically significant.

RESULTS

Baseline characteristics
During the period of the study, 131 patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) were admitted in our ICU. ACET was used only in 36 patients (27%). These cases were 1:1 matched to control patients.

There were 66 males (92%) and 6 females (8%). The mean age (± SD) was 69.7 ± 6.4 years ranging from 53 to 81 years. Recent spirometric findings were available only for five patients. For the remaining patients, the diagnosis of acute exacerbation of COPD was considered based on clinical history, physical examination, and arterial blood gas findings. Baseline characteristics of all included patients are summarized in Table 1. None of our patients had received diuretics prior to ICU admission. During ICU stay, all patients (100%) required invasive mechanical ventilation. NIPPV was required for 10 patients (13%) after extubation because of hypercapnic respiratory failure (seven patients in the ACET (+) group and three patients in the ACET(-) group; P = 0.17).

The comparison between the two groups showed that they had the same epidemiological, clinical and biological findings on ICU admission. The comparison of arterial blood gas parameters showed that patients in the ACET(+) group had significantly higher PaCO₂ and bicarbonate levels whereas no significant difference was found in terms of pH or PaO₂/FiO₂ ratio on ICU admission [Table 2]. The frequency of patients receiving long-term aminophylline or inhaled steroids was significantly higher in the ACET(+) group [Table 3].

Impact of the use of acetazolamide on the duration of mechanical ventilation
In our study, the comparison ACET and ACET-free groups showed that the use of acetazolamide was not associated with a significant reduction in the duration of mechanical ventilation (10.6 ± 7.8 vs 9.6 ± 7.6 days; P = 0.61) [Figure 1].

Impact of the use of acetazolamide on arterial blood gas parameters, ICU LOS, and ICU mortality
The use of ACET significantly decreased serum bicarbonate, arterial blood pH and PaCO₂ [Figure 2], but did not affect PaO₂/FiO₂ ratio (P > 0.05) [Figure 3]. Moreover, ICU mortality was not significantly
different between ACET(+) and ACET(−) patients (14/36 (38%) and 19/36 (52%), respectively; \( P = 0.23 \)). ICU LOS was also comparable between these two groups (11.6 ± 8.1 days and 9.9 ± 7.9 days, respectively; \( P = 0.36 \)).

There was no difference in terms of complications observed during ICU stay between ACET(+) and ACET(−) groups [Table 3].

**DISCUSSION**

Severe exacerbation of COPD may require intensive care admission and initiation of invasive mechanical ventilation may be necessary, particularly if NIPPV is not effective to improve gas exchanges and respiratory mechanics.[5,13-15] However, weaning from mechanical ventilation can be particularly difficult and prolonged in COPD patients with severe pre-existing airflow limitation.[7] Metabolic alkalosis occurs frequently in the critically ill, particularly in COPD patients leading to alveolar hypoventilation which may cause several difficulties in the weaning process.[7] As a
Moreover, metabolic alkalosis, and may decrease cardiac output and disturb oxyhemoglobin dissociation, causing weaning failure.[8,16] Thus, the correction of this acid-base disorder both increases minute ventilation and partial pressure of oxygen (PaO₂), and may shorten the duration of the ventilator weaning process.[8] Acetazolamide (ACET) is one of the most common drugs used to treat metabolic alkalosis when administered after appropriate fluid loading and potassium supplementation. It decreases proximal tubular bicarbonate absorption through carbonic anhydrase (CA) inhibition in renal proximal tubule cells.[8] In addition, ACET can improve cardiac function and gas exchange by stimulating diuresis. However, in the current study like in other,[9] the systemic ACET therapy significantly decreased serum bicarbonate, arterial blood pH and PaCO₂, but did not affect PaO₂/FiO₂ ratio (P > 0.05), the duration of mechanical ventilation and the length of ICU stay.

Several hypotheses can be advanced to explain the inefficacy of acetazolamide to shorten the duration of mechanical ventilation in our study. First, this inefficacy may be related to pharmacokinetic reasons. In fact, there are several isoforms of human carbonic anhydrase, and some may be more inhibited than others by ACET, which may complicate the reversal of metabolic alkalosis.[17,18] Moreover, several covariates such SAPSII at ICU admission, serum chloride level and co-administration of furosemide or systemic steroid can interfere with ACET pharmacokinetics.[7] Thus, the effect of the same dose of ACET on the acid-base balance may vary from one patient to another. This hypothesis seems unlikely in our study as we observed a significant decrease in bicarbonate levels regarding the baseline values, 48 hours after the initiation of this therapy.

The optimal dosage of acetazolamide to be administered to alakotic COPD patients is unclear.[8,19,20] However, the dose of ACET used in the present study may be insufficient to significantly improve respiratory parameters in invasive mechanical ventilation patients (IMV) patients with COPD.[18,20] In fact, the results of a recent study[20] suggest that higher doses of acetazolamide (>1000 mg daily) are necessary to induce a substantial increase in minute ventilation and hence a decrease in PaCO₂, in alkalotic mechanically ventilated COPD patients. Additionally, this study[20] also suggests that the increase in minute ventilation following the administration of acetazolamide is obtained at the price of an increase in respiratory rate rather than tidal volume, whatever the ventilatory mode. In our study, as our primary endpoint was the effect of ACET on the duration of mechanical ventilation and our secondary endpoints were the effect of ACET on arterial blood gas parameters, ICU length of stay (LOS) and ICU mortality, respiratory parameters (respiratory frequency, tidal volume, and minute ventilation) were not analysed in this study. Moreover, it was previously established that ACET treatment with the same dose (500 mg per day) did not significantly change respiratory frequency and tidal volume or minute ventilation on mechanical ventilation.[8,20]

Third, the poor mechanic capacities in severely flow-limited COPD patients may explain why the reversal of the depressive metabolic stimulus of the respiratory drive did not induce an increase in minute ventilation and thus, did not make weaning from ventilator support easier. Finally, the ACET induces a metabolic acidosis which stimulates the respiratory neural-driving. As a consequence, a hyperventilation with polyneea can be
observed. This polypnea will significantly increase the workload of respiratory muscles and shortens the time of the respiratory cycle with its two components inspiratory and expiratory.

Our study has some limitations. The major limitation is the sample size which was not powered enough to detect a significant difference in ICU outcomes. The retrospective design of our study represents a methodological limitation. In fact, several factors such as spirometric parameters, echocardiographic examinations were usually lacking in the medical charts. Finally, modalities of mechanical ventilation and weaning process were not standardized in both groups. This may suggested by the fact that serum bicarbonate levels were significantly decreased since the second day of ACET administration whereas PaCO₂ levels remain unchanged till the fourth day. This may be related to the effect of other factors on the acid-base balance such as different ventilation modalities (tidal volume, respiratory rate, etc.) or the need of further medical therapies (diuretics, steroids, etc.). The lack of standardization of ventilation modalities incites us to interpret the evolution of oxygenation parameters (particularly the PaO₂/FiO₂ ratio) with caution. In fact, Faisy et al.[8] reported in a case–control study, in which mechanical ventilation modalities and weaning procedures were well standardized, that ACET induced a significant increase of the PaO₂/FiO₂ ratio under ACET whereas PaCO₂ levels remained unchanged. This positive effect of acetazolamide on oxygenation parameters may be related to its diuretic properties.

**CONCLUSIONS**

Although our study has several limitations, it shows that the use of insufficient acetazolamide dosage (500 mg per day) significantly decreases serum bicarbonate, arterial blood pH, and PaCO₂ in patients with COPD exacerbation requiring mechanical ventilation. However, it suggests that systemic ACET therapy in this specific condition is not helpful to reduce the duration of mechanical ventilation and to make the weaning process easier. Thus, further studies are needed to evaluate the effect of ACET on ventilator weaning process in critically ill COPD patients.

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