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Effects of early administration of acetazolamide on the duration of mechanical ventilation in patients with chronic obstructive pulmonary disease or obesity-hypoventilation syndrome with metabolic alkalosis. A randomized trial

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ABSTRACT

Background: Metabolic alkalosis (MA) inhibits respiratory drive and may delay weaning from mechanical ventilation (MV). MA is common in CO_2-retainer patients that need MV. Acetazolamide (ACTZ) decreases serum bicarbonate concentration and stimulates respiratory drive. This study evaluated the effects of ACTZ on the duration of MV in patients with MA and COPD or obesity hypoventilation syndrome (OHS) intubated with acute respiratory failure.

Methods: Multicenter, randomized, controlled, double-blind study, with COPD or OHS patients with MV < 72 h and initial bicarbonate >28 mmol/L and pH > 7.35. Test-treatment, ACTZ 500 mg or placebo, was daily administered if pH > 7.35 and bicarbonate >26 mmol/L. Clinical, respiratory and laboratory parameters were recorded.

Results: 47 patients (36 men) were randomized. There were no significant differences between groups in comorbidities, baseline characteristics or arterial blood gases at inclusion. The mean difference in the duration of MV between placebo and ACTZ group was 1.3 days (95%CI, −2.1–4.8; p = 0.44). Kaplan-Meier curves showed no differences in the duration of MV (Log-Rank p = 0.41). Between-group comparison of estimated marginal means (CI 95%) during MV were, respectively: $PaCO_2$ 55 (51–59) vs 48 (47–50) mm Hg, p = 0.002; bicarbonate concentration 34 (32–35) vs 29 (28–30) mmol/L, p < 0.0001; and minute volume 9.7 (8.9–10.4) vs 10.6 (9.2–12.0) L/min, p = 0.26. There were no severe adverse effects with ACTZ administration.

Conclusions: Among patients with MA and COPD or OHS, early treatment with ACTZ did not shorten significantly the duration of MV compared with placebo.

Trial registry: clinical.trials.gov; NCT01499485; URL:.www.clinicaltrials.gov

Abbreviations: ACTZ, acetazolamide; IQR, interquartile range; OHS, Obesity hypoventilation syndrome; MA, metabolic alkalosis; MV, mechanical ventilation; SD, standard deviation.

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1. Introduction

Metabolic alkalosis is a common acid-base disorder observed in critically ill patients [3,7,14,37,38] during mechanical ventilation (MV) as a consequence of vomiting, lung-protective strategies or after correction of chronic hypercapnia. This condition may be aggravated by the simultaneous use of corticosteroids and loop diuretics commonly administered to these patients [19,37].

Metabolic alkalosis attenuates respiratory central drive performance by reducing the stimulatory effects of hypercapnia [17,29] and impairs oxygenation mainly due to a shift to the left of the dissociation curve of oxyhemoglobin [4]. It may also worsen cardiac output, favour cardiac arrhythmias and metabolic disturbances or alter mental state [19]. Moreover, metabolic alkalosis may negatively influence patient outcome [22] being associated with longer dependence on the ventilator [3,37], longer ICU stay [3] and increased morbidity and mortality [1,22].

Acetazolamide, an inhibitor of the carbonic anhydrase, has proven to be safe and effective in correcting metabolic alkalosis [18,26] by promoting renal excretion of bicarbonate and inducing a decrease in plasmatic bicarbonate concentration [23,24]. It acts as a respiratory stimulant on the central respiratory drive by increasing the hypercapnic respiratory response in healthy subjects [30,32,35], patients with COPD [35,36], obesity hypoventilation syndrome (OHS) [28] or sleep apnea syndrome, either obstructive or central [5,15,16], inducing a decrease in $PaCO_2$. Acetazolamide increases PaO_2 [8,11,18,21] principally due to the restoration of the oxygen dissociation curve to the normal position.

It has been suggested a beneficial effect of acetazolamide on the duration of MV in patients with metabolic alkalosis [21,37] arguing that the stimulation exerted on the respiratory center, the increase in minute ventilation and the improvement in oxygenation could hasten withdrawal of MV. However, there are few studies evaluating the prognostic repercussion of acetazolamide treatment in invasively ventilated critically ill patients [2,7,8] and, in the only clinical trial published to date [7], inclusion criteria were irrespective of patients' acid-base status.

Patients with COPD or OHS with chronic hypercapnia that need intubation due to acute respiratory failure may experience an early decrease of $PaCO_2$ induced by MV settings while plasmatic bicarbonate concentration remains still high. In this scenario, metabolic alkalosis appears promptly after intubation and acetazolamide, if administered, should be started early in the course of MV.

Our aim was to analyse the effects of acetazolamide on the duration of MV in COPD or OHS patients with metabolic alkalosis at initiation of MV. Secondarily, we examined whether acetazolamide shortened weaning period, ICU or hospital stay or reduced hospital mortality. A drug safety evaluation was also undertaken.

2. Material and methods

This was a multicenter, randomized, placebo-controlled, phase III, double-blind study held in seven intensive care units in Spain. The study was approved by the Ethics Committee (CEIC-IB 1411/10 PI) and was conducted in accordance with the amended Declaration of Helsinki. Patients or patients' next of kin provided written informed consent. Patients were consecutively included from November 2011 to February 2014.

2.1. Patients

The study included patients older than 18 years, with COPD or OHS that required invasive MV due to acute respiratory failure for less than 72 h and showed metabolic alkalosis with pH > 7.35 with plasmatic bicarbonate >28 mmol/L, while being on invasive MV.

COPD was defined as the presence of a post-bronchodilator FEV1/FVC <0.70 or, alternatively, a clinical diagnosis of COPD was considered if a history of dyspnea, chronic cough and/or sputum production, and exposure to risk factors for the disease, was present [33]. OHS was defined as the presence of obesity (body mass index $\geq$ 30 kg/m^2) and baseline arterial hypercapnia ($PaCO_2$ > 45 mm Hg) while awake, with polysomnography that revealed sleep hypoventilation with nocturnal hypercapnia [27].

Exclusion criteria comprised surgical procedures during hospital admission, presence of psychiatric disorders, epilepsy, pregnancy, liver cirrhosis, intolerance or allergy to acetazolamide or other sulfonamide-based components, plasma creatinine values > 2.5 mg/dL or creatinine clearance <20 mL/min, intolerance to enteral nutrition, or the administration of sodium bicarbonate or acetazolamide before inclusion. Patients with an expectancy of life shorter than 6 months or with do-not-resuscitate-orders were excluded.

2.2. Randomization and allocation

Patients were allocated randomly on a 1:1 basis to receive capsules of 500 mg of acetazolamide or placebo by nasogastric tube. Randomization was based on computer-generated random numbers that were distributed in fixed blocks. Treatment and placebo capsules were prepared, packaged and blinded in a centralized hospital pharmacy and distributed to all ICUs. Investigators, patients and caregivers were unaware of the randomization list.

2.3. Study protocol

The assigned treatment was initiated at inclusion and assessed daily until extubation according to arterial blood gases performed at 07:00 a.m. If plasmatic bicarbonate concentration and pH were, respectively, greater than 26 mmol/L and 7.35, a capsule of treatment was administered. If bicarbonate level was >26 mmol/L but pH was $\leq$7.35, then minute volume had to be increased in order to achieve pH greater than 7.35, in which case treatment was administered. If bicarbonate level was $\leq$26 mmol/L, treatment was not administered on that day. It was encouraged to adjust mechanical ventilator parameters to maintain pH between 7.35 and 7.45 during MV. Patients' attending physicians were not involved with the study. Respiratory weaning protocol and a sedoanalgesia protocol were applied to all patients.

2.4. Data collection

The baseline characteristics recorded were age, gender, weight, height, SAPS 3 [25], SOFA score [34] on the day of inclusion, previous treatment with diuretics, presence of comorbidities as heart failure, NYHA functional classification [9], COPD, obesity (body mass index $\geq$ 30 kg/m^2), OHS, FEV1 and FVC in stable period, previous out-of-hospital $PaCO_2$ and plasmatic bicarbonate levels in stable condition, diuretic chronic treatment and home non-invasive ventilation.

Variables recorded during invasive MV were blood gas analysis previous to intubation, at inclusion and daily during MV, minute ventilation, respiratory rate, FiO_2, etiology of the acute respiratory failure, daily blood laboratory tests with hemogram, ionogram (sodium, potassium, chloride, calcium, magnesium), creatinine, urea, albumin, bilirubin, lactate, and prothrombin activity.

Other variables collected were daily readiness to wean, daily diuresis and volume intake, doses of corticosteroids and diuretics and total number of study capsules administered, need of vasoactive drugs, presence of ventilator associated pneumonia or