Use of Sedatives and Neuromuscular Blockers in a Cohort of Patients Receiving Mechanical Ventilation*

Alejandro Arroliga, MD, FCCP; Fernando Frutos-Vivar, MD; Jesse Hall, MD; Andres Esteban, MD; Carlos Apezteguía, MD; Luis Soto, MD; Antonio Anzueto, MD; for the International Mechanical Ventilation Study Group†

Objective: **To describe the use of sedatives and neuromuscular blocking agents (NMBs) and their impact in outcome in an international cohort of patients receiving mechanical ventilation.**
Methods: **We analyzed the database of a prospective, multicenter cohort of 5,183 adult patients who received mechanical ventilation for > 12 h. We considered that a patient received a given agent when it was administered for at least 3 h in a 24-h period.**
Results: **A total of 3,540 patients (68%; 95% confidence interval [CI], 67 to 69%) received a sedative at any time while receiving mechanical ventilation. The median number of days of use was 3 (interquartile range [IQR], 2 to 6 days). The persistent use of sedative was associated with more days of mechanical ventilation (median, 4 days [IQR, 2 to 8 days], vs 3 days [IQR, 2 to 4 days] in patients who did not receive sedatives [p < 0.001]); more weaning days (median, 2 days [IQR, 1 to 3 days], vs 2 days [IQR, 1 to 5 days] in patients who did not receive sedatives [p < 0.001]); and longer length of stay in the ICU (median, 8 days [IQR, 5 to 15 days], vs 5 days [IQR, 3 to 9 days] in patients who did not receive sedatives [p < 0.001]). Six hundred eighty-six patients (13%; 95% CI, 12 to 14%) received an NMB for at least 1 day. The median number of days of use was 2 (IQR, 1 to 4 days). The administration of an NMB was independently related with age, a normal previous functional status, main reason of mechanical ventilation (patients with ARDS received more NMBs), and with patient management (patients requiring permissive hypercapnia, prone position, high level of positive end-expiratory pressure, and high airways pressure).**
Conclusions: **The use of sedatives is very common, and their use is associated with a longer duration of mechanical ventilation, weaning time, and stay in the ICU. NMBs are used in 13% of the patients and are associated with longer duration of mechanical ventilation, weaning time, stay in the ICU, and higher mortality.** ***(CHEST 2005; 128:496–506)***

Key words: ICU; mechanical ventilation; neuromuscular blocking agents; sedatives

Abbreviations: CI = confidence interval; IQR = interquartile range; NMB = neuromuscular blocking agent; OR = odds ratio; PEEP = positive end-expiratory pressure; SAPS = simplified acute physiology score

Sedatives, analgesics, and neuromuscular blocking agents (NMBs) are drugs commonly used in the ICU, mainly in patients requiring mechanical ventilation.[1] Sedatives and analgesics are often used to facilitate patient tolerance of invasive mechanical ventilation. The goals of sedation/analgesia in this context include decreasing pain and anxiety, reducing the stress response, and facilitating nursing care.[2,3] Studies[4–7] have suggested that we need to pay attention to the way we provide sedation/analgesia because of the potential impact on patient outcomes such as length of stay in the ICU, days of mechanical ventilation, and rate of self-extubation.

*From the Cleveland Clinic Foundation (Dr. Arroliga), Cleveland, OH; Hospital Universitario de Getafe (Drs. Frutos-Vivar and Esteban), Spain; University of Chicago (Dr. Hall), Chicago, IL; Hospital Profesor Posadas (Dr. Apezteguía), Buenos Aires, Argentina; University of Texas Health Science Center at San Antonio (Dr. Anzueto) and Instituto Nacional del Tórax (Dr. Soto), Santiago, Chile.
†For members of the Mechanical Ventilation Study Group, see the Appendix.
This study was supported by grant 98/0233 from the Fondo de Investigación Sanitaria, Spain, Red GIRA (G03/063) and Red RESPIRA (C03/11) from Instituto de Salud Carlos III, Spain.

Manuscript received June 21, 2004; revision accepted January 7, 2005.

Correspondence to: Antonio Anzueto MD, University of Texas Health Science Center at San Antonio, 111E, 7400 Merton Minter Blvd, San Antonio, TX 78229; e-mail: anzueto@uthscsa.edu

Furthermore, the use of sedatives and NMBs have being shown to correlate with the subsequent presence of depression and posttraumatic stress disorder symptoms[8,9] and protracted neuromuscular weakness syndromes.[10]

The current data related to the pattern of use of sedatives, analgesics, and NMBs during mechanical ventilation are limited and derived largely from mail survey reports.[11–16] Only a few studies[17–19] have tracked drug use over time, and then for brief intervals. Recently, Bertolini et al[18] reported on 2,932 patients enrolled in a multicentric study in Italy, and noted that 60% received at least one sedative during the first week in the ICU. Although 51% of the patients in the study were receiving mechanical ventilation at the time of admission to the ICU and 71% received mechanical ventilation at any time during the ICU stay, it is unclear of the type of drugs and pattern of administration in patients receiving mechanical ventilation.

For editorial comment see page 477

The main objective of this study is to describe the use of sedatives and NMBs in an international cohort of patients receiving mechanical ventilation. Furthermore, we want to study their impact on patient outcomes such as duration of mechanical ventilation, length of ICU stay, and length of hospital stay. We analyzed the factors associated with their use and the association with selected outcomes, such as duration of mechanical ventilation, weaning, ICU stay, and mortality.

Materials and Methods

We analyzed the database of a prospective, multicenter, international cohort of 5,183 adult patients who received mechanical ventilation for > 12 h at 361 ICUs in 20 countries.[20] The general physiologic and clinical characteristics of these patients were previously described and reported.[20] The institutional review board at each center approved the study protocol. For the purpose of this study, we collected the following information: demographic data (age, gender, simplified acute physiology score [SAPS] II), previous functional status, medical or surgical condition, date of admission to the ICU, date of initiation of mechanical ventilation, and primary indication for mechanical ventilation: acute on chronic respiratory disease (COPD, asthma, chronic pulmonary disease other than COPD), neurologic disease (coma, neuromuscular disease), or acute respiratory failure (ARDS, postoperative, congestive heart failure, aspiration, pneumonia, sepsis, trauma, cardiac arrest), date of starting weaning of mechanical ventilation, date of extubation, and date and status at discharge from the ICU.

After starting mechanical ventilation, every day for the first 28 days we recorded the use of sedatives, analgesics, and/or NMBs. We considered that a patient received one of these drugs when it was administered for at least 3 h in a 24-h period. The presence or absence of the following variables were evaluated: (1) patient management, including mode or level of ventilatory support (full support defined as ventilation with controlled volume or pressure-controlled modes or when patients received synchronized intermittent mandatory ventilation but mandatory frequency was similar to the total respiratory rate; partial support defined as ventilation with pressure support or synchronized intermittent mandatory ventilation with mandatory frequency lower than total respiratory rate; noninvasive ventilation; inverse ratio ventilation; permissive hypercapnia; prone position; and administration of inhaled nitric oxide); tidal volume (categorized as < 6 mL/kg, from 6 to 10 mL/kg, and > 10 mL/kg); applied positive end-expiratory pressure (PEEP), categorized as < 5 cm H_2O, from 5 to 10 cm H_2O, and > 10 cm H_2O; peak pressure > 50 cm H_2O; and plateau pressure > 35 cm H_2O; and (2) complications that developed over the course of the mechanical ventilation: ARDS, ventilator-associated pneumonia, sepsis, shock, acute renal failure, hepatic failure, coagulopathy, metabolic acidosis, respiratory acidosis and hypoxemia defined as a ratio of PaO_2 to fraction of inspired oxygen < 200 mm Hg. The ARDS, ventilator-associated pneumonia, and sepsis were considered as events only if they appeared > 48 h after mechanical ventilation was started. Each of these conditions has been previously defined.[20] The arterial blood gases corresponded to the values obtained once daily at approximately 8 AM. The ventilator variables corresponded to the time that the arterial blood gases were obtained.

Statistical Analysis

Data are expressed as mean (SD), median (interquartile range [IQR]), or proportions as appropriate. Continuous variables were compared with Student *t* test or Mann-Whitney *U* test if the distribution was nonparametric. Categorical variables were compared using χ^2 test or Fisher Exact Test; all p values are two-sided.

Primary outcome were use of sedatives or NMBs. To estimate the effects of multiple factors on these outcomes, a logistic regression analysis was performed using a backward stepwise selection method. The criterion for entering variables tested in the model were selected at $p < 0.10$. All variables were analyzed separately in three groups: variables previous to start mechanical ventilation (age and SAPS II were dichotomized taking as cut-off point the value that best correlated with the use of sedatives and NMBs), variables related with patient management, and complications appearing during mechanical ventilation. Significant variables ($p < 0.05$) from each group were entered to construct the final model.

Linear regression analysis was used to estimate the adjusted relation between the use of sedatives and NMBs with days of mechanical ventilation, days of weaning, and length of stay in the ICU. Similar methods were used to determine the variables associated to the use of benzodiazepines compared with propofol, taking as cohorts the patients who only received benzodiazepines or only propofol.

Results

Use of Sedatives

Of the 5,183 ICU patients admitted during the study period, 3,540 patients (68%; 95% confidence interval [CI], 67 to 69%) received a sedative at any time while receiving mechanical ventilation. For these patients, the median number of days receiving a sedative was 3 days (IQR, 2 to 6 days). Figure 1 shows the daily percentage of patients who received