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Complication profiles of adult asthmatics requiring paralysis during mechanical ventilation

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Abstract *Objective*: To assess the characteristics and the incidence of morbidity of intubated asthmatic patients who received long-term paralysis.
Design: Retrospective cohort study.
Setting: Five intensive care units (ICUs) in Paris and the surrounding suburbs.
Patients and participants: The NMB group consisted of patients who received neuromuscular blocking agents for more than 12 h (NMB group) versus sedation alone (SED).
Interventions: None.
Measurements and results: The incidence of post-extubation muscle weakness and/or myopathy was 18 % in the NMB group compared to 2 % in the SED group ($p = 0.01$). The occurrence of ventilator-associated pneumonia was higher in the NMB group (42 % versus 4 %; $p < 0.0001$). The duration of ICU stay and of mechanical ventilation were significantly greater in the NMB group. Multiple logistic regression analysis showed that inclusion in the NMB group was the only independent predictor of the presence of the overall morbidity [odds ratio 6.4 (2.09; 19.64)].
Conclusion: While greater initial severity of respiratory compromise in the NMB group may explain part of the difference, use of NMB agents appears to be strongly related to the presence of significant complications among mechanically-ventilated asthmatic patients.

Keywords Paralysis · Morbidity · Mortality · Mechanical ventilation · Near fatal asthma

Introduction

During the last decade, both the rate of hospitalization for asthma and asthma-related mortality are reported to have increased [1, 2, 3, 4]. Thus, it is anticipated that increasing numbers of patients with near fatal asthma will require mechanical ventilation and sedation [5].

Effective sedation is crucial to the improvement of patient comfort during intubation and to ensure patient-ventilator synchrony. Sedation decreases oxygen consumption (VO_2) and carbon dioxide (CO_2) production, helps to control exaggerated respiratory efforts and may decrease the risk of barotrauma [6]. A number of consensus guidelines have been developed for seda-

tion in critically ill patients [7], although it is unclear whether any of them have become widely followed. Classically, the addition of paralytic agents is reserved for sufficiently sedated patients in whom it is difficult to achieve adequate ventilation at reasonable inflation pressures. Like sedation, neuromuscular blockade reduces VO_2, CO_2 production and lactate accumulation [8]. Up to 10% of intensive care unit (ICU) patients now receive continuous administration of neuromuscular blocking (NMB) agents for at least 24 h [9]. However, prolonged neuromuscular blockade may be associated with several adverse effects, such as prolonged myopathy, increased duration of mechanical ventilation and nosocomial pneumonia [9].

The decision whether or not to use a NMB agent as a part of the overall therapeutic strategy is generally based on the clinician's judgment that paralysis is needed to maintain stable respiratory parameters and ensure patient safety. Nevertheless, a complete assessment of the risk/benefit of this adjunct is lacking, its having never been submitted to a randomized clinical trial. The aims of this study were to profile the characteristics of adult asthmatic patients who initially required continuous infusion of NMB agents during their ICU stay and to evaluate the morbidity in this group as compared with patients receiving intravenous sedation alone. An appreciation of this profile may help the clinician to judge the relative benefits and risks of NMB prior to the decision to use this specific treatment.

Materials and methods

Our study involved five clinical centers in Paris and the surrounding suburbs: the ICUs of Jean Verdier University Hospital, Ambroise Paré University Hospital, Henri Mondor University Hospital, Avicenne University Hospital and the Hospital of Poitiers. This study was performed in accordance with the French Medical Ethics law (Loi Huriet). We retrospectively studied all patients with the diagnosis of status asthmaticus requiring mechanical ventilation and admitted to one of these hospital ICUs between January 1995 and January 1999.

A computerized search was carried out for all ICU admissions with primary admission diagnosis codes of asthma and mechanical ventilation. Patients who had a primary discharge diagnosis of chronic obstructive pulmonary disease and patients with cardiac arrest before admission were subsequently excluded from the study. The patients were divided into two groups: the NMB group was composed of patients who received pharmacologic paralysis lasting more than 12 h. The SED group consisted of the remaining intubated patients who did not fulfil these criteria. Patients paralyzed only for the purpose of intubation were allocated to the SED group.

In-hospital clinical records for all patients were reviewed. The data included were: (1) demographic information – age, gender, weight, dates of ICU admission and discharge; (2) arterial blood pressure (systolic and diastolic) and pulse oximetry. In-hospital laboratory evaluation included arterial blood gases (recorded once a day, including the initial (admission) values and the first blood sample obtained after 8 a.m. each day during the initial 8 days. Peak pressure was defined as the mean of three measurements obtained near the time of arterial blood gas sampling. Morbidity factors included in-hospital mortality, cardiovascular failure (defined as systolic blood pressure < 90 mmHg or continuous infusion of vasopressor or inotropic agents), renal failure (defined as serum creatinine > 300 μmol/l and/or urine output < 500 ml/24 h or 180 ml/8 h and/or the need for hemodialysis or peritoneal dialysis), neurologic failure (defined as a Glasgow Coma Scale of 6 without sedation or sudden onset of confusion or psychosis), hematologic failure (defined as hematocrit = 20% and/or total leukocyte count < 2000/mm^3 and/or a platelet count < 40,000/mm^3), sepsis (defined as clinical evidence of infection and two or more positive blood cultures or the presence of pus in a closed space or a source of infection determined during hospitalization) [10]. The Simplified Acute Physiology Score (SAPS) was recorded [11]. The presence of barotrauma (pneumothorax and/or pneumomediastinum) during the ICU course were documented. Duration of mechanical ventilation was also recorded.

The diagnostic criteria for ventilator-associated pneumonia (VAP) were taken from the work of Kollef et al. [12]. VAP was defined as the occurrence of a new (more than 48 h after the onset of mechanical ventilation) and persistent roentgenographic infiltrate with presence of one of the following four criteria: positive pleural/blood cultures for the same organism as in the tracheal aspirate; roentgenographic cavitation; histopathologic evidence of pneumonia; or new fever *and* leukocytosis *and* purulent tracheal aspirate. Multi-organ failure (MOF) is defined as the presence of more than two organs in failure [10]. We defined prolonged neuromuscular weakness in the ICU as that requiring a significantly longer than expected recovery period (e.g., greater than 12 h after discontinuation of any sedation or NMB agent) and the presence of any of the following criteria: (1) inability to perform activities of daily living (e.g., bathing, eating, dressing, walking), (2) strength rating of less than 4 on a 0–5 scale in one or more major muscle groups and (3) the need for in-patient rehabilitation [13, 14]. Myopathy was defined as the clinical triad of persistent clinical paresis with abnormal motor unit electromyography, but normal sensory nerve conduction studies, after ICU administration of sedative (with or without NMB) agents [9].

We further defined a composite morbidity end point (CME) as the occurrence of any one of the following events: death in the ICU, presence of MOF, pneumonia, muscle weakness (and/or myopathy) or barotrauma (pneumothorax and/or pneumomediastinum). The nature and duration of infusion of drugs employed in sedation protocols was also collected.

In the statistical analysis, all data are described as mean ± SD for Gaussian distributions or as median, (25th,75th percentiles) for non-Gaussian distribution. The chi-squared test and Fisher's exact test were used to find differences among dichotomous variables. The unpaired Student's *t*-test was used to analyze continuous variables for significant differences. For variables that were not normally distributed, the Mann-Whitney U test was used. Multiple logistic regression was used for the analysis of the CME (binary outcome, yes or no); The analysis was performed in 101 patients who had complete data on all the variables examined. Probability less than 0.05 was considered significant. Statistical analysis was performed using the Statview software (Version 5; SAS Institute; Cary, N.C.).

Results

Between January, 1995, and January, 1999, 118 patients with acute severe asthma requiring mechanical ventila-

Table 1 Baseline characteristics of all patients and study groups

Characteristics	NMB group ($n = 55$)	SED group ($n = 46$)	p value
Age (years) ± SD	40 ± 16	52 ± 16	0.0005
Weight (kg) ± SD	67 ± 11	46 ± 8	0.154
Male patients (%)	51	43	0.456
History of previous mechanical ventilation (%)	23	26	0.768
Pre-admission therapy			
Chronic inhaled steroids (%)	58	60	0.836
Oral steroids (%)	24	35	0.241
Chronic inhaled terbutaline (%)	85	88	0.649
Oral theophylline (%)	34	27	0.530
ICU therapy			
Parenteral beta-mimetics (%)	100	100	1
Parenteral steroids (%)	100	100	1
Epinephrine (%)	50	30	0.185
Magnesium (%)	40	28	0.305

Table 2 Sedation protocols infused used in the two groups during the 1st day of ICU (*MDZ* midazolam, *FTL* fentanyl, *PPF* propofol)

Nature of sedation protocol	NMB group ($n = 55$)	SED group ($n = 46$)	p value
MDZ alone (%)	9	24	
Dose MDZ ± SD (mg/kg per h)	0.11 ± 0.05	0.18 ± 0.10	0.183
Combination MDZ/FTL (%)	72	67	
Dose MDZ ± SD (mg/kg per h)	0.10 ± 0.04	0.12 ± 0.07	0.197
Dose FTL ± SD (μg/kg per h)	2.1 ± 1.0	2.6 ± 1.8	0.158
PPF alone (%)	6	0	
Dose PPF ± SD (mg/kg per h)	3.9 ± 3.1		
Combination PPF/MDZ (%)	13	9	
Dose PPF ± SD (mg/kg per h)	1.9 ± 0.7	2.5 ± 1.8	0.556
Dose MDZ ± SD (mg/kg per h)	0.13 ± 0.06	0.14 ± 0.10	0.779
Halothane (%)	10	0	0.02

tion were enrolled in the five ICUs involved in this study. Seventeen patients were excluded, nine due to cardiac arrest prior to ICU admission and eight due to a discharge diagnosis of chronic obstructive pulmonary disease. Thus, 101 patients with the final diagnosis of severe acute asthma were retained. Data points were complete for all patients with the exception of peak pressure, which was available for only 82 patients. The study group consisted of 53 females (52.5 %) and 48 males with ages ranging from 16 to 88 years (mean ± SD: 45 ± 17 years). Fifty-five (54 %) patients were included in the NMB group and 46 in the SED group. All patients were intubated by an intensivist prior to ICU admission either during prehospital care (mobile ICU) or in the emergency department. The decision to employ adjunct NMB agents always occurred during the initial period of hospitalization; patients not requiring paralysis during the 1st day did not require paralysis during their ICU stay.

Baseline characteristics for all patients, NMB and SED groups, are summarized in Table 1. There were no significant differences in baseline characteristics for the two groups except for age: patients included in the NMB group were significantly younger than those included in the SED group. The in-hospital therapy did not differ between the two groups; in particular, 100 % of patients received i. v. corticosteroids and beta-mimetic agents. The median (25th; 75th percentile) duration of use of NMB agents was 46 (20; 91) h. There was no significant difference ($p = 0.168$) in the type of sedation used during the 1st day of admission among patients in either group, except for halothane (Table 2). The most frequent sedation used was the combination of continuously infused midazolam and fentanyl. Inhalational anesthetic agents (halothane) were used in ten patients (all in the NMB group). Sedative doses administered were not significantly different between groups (Table 2). All NMB agents were infused continuously without breaks in drug administration. The initial in-hospital characteristics of the study groups are summarized in Table 3. The evolution of $PaCO_2$, pH and mean peak pressure in patients in who remained pharmacologically

Table 3 Initial clinical features of the two groups at presentation (*SAPS* Simplified Acute Physiology Score)

Parameters	NMB group ($n = 55$)	SED group ($n = 46$)	p value
Initial blood gases			
PaO_2:FIO_2 (mmHg) ± SD	314 ± 150	331 ± 131	0.561
$PaCO_2$ (mmHg) ± SD	77 ± 36	60 ± 20	0.006
HCO_3 (mmol/l) ± SD	25.7 ± 3.8	25.2 ± 4.8	0.599
pH	7.14 ± 0.15	7.23 ± 0.10	< 0.001
Circulatory parameters			
Systolic blood pressure (mmHg) ± SD	138 ± 40	140 ± 29	0.793
Diastolic blood pressure (mmHg) ± SD	81 ± 18	79 ± 19	0.633
Heart rate (beats/min)	119 ± 31	124 ± 26	0.547
Peak pressure (cmH_2O)[a]	49 ± 15	35 ± 9	< 0.0001
SAPS	9.7 ± 2.7	9.1 ± 2.7	0.464

[a] Data for 82 patients were considered in this analysis

paralyzed, compared to patients not paralyzed, is shown in Fig. 1.

In-hospital morbidity and mortality

Six (5.9 %) patients died during their ICU hospitalization. Median (25th; 75th percentiles) length of ICU stay was 7 (3; 12) days and duration of mechanical ventilation was 68 (20; 160) h. Thirty-five (35 %) patients met criteria for the composite morbidity end point (CME). While SAPS scores did not differ significantly between NMB and SED groups, the CME was present in a significantly greater number of patients requiring NMB ($p < 0.0001$; Table 4). The incidence of muscle weakness and/or myopathy was 10/55 (18 %) among patients who received neuromuscular blockade compared to 1/46 (2 %) in the SED group ($p = 0.01$). The presence of muscle weakness is significantly ($p < 0.01$) related to the duration of paralysis and not to the paralytic agent used (Table 5). The incidences of CME and VAP are significantly ($p < 0.01$) associated with prolonged use of NMB agents as well. The occurrence of ventilator-associated pneumonia was significantly higher in the NMB group (42 % versus 4 %; $p < 0.0001$). The duration of ICU stay and of mechanical ventilation were significantly greater among patients in the NMB group (Table 4).

Statistical analysis

In an univariate analysis, four factors were found to be significantly related to the presence of the CME: initial hypercapnia and acidosis ($p = 0.002$ and $p = 0.001$, respectively), initial mean peak pressure ($p = 0.03$) and inclusion in the NMB group ($p < 0.0001$). Multiple logistic regression analysis showed that inclusion in the NMB group was the only strong independent predictor of the presence of the CME. The odds ratio was 6.403 (95 % confidence interval, 2.09–19.64).

Discussion

The focus of this study was to determine (1) the characteristics of patients with near fatal asthma who were pharmacologically paralyzed during their ICU course and (2) to determine if associated morbidity was related to the use of NMB agents.

There are few true consensus guidelines for the use of adjunctive NMB agents in ICU sedation protocols [7]. It is often difficult, when faced with the inability to ventilate an asthmatic patient adequately, objectively to determine the need for adjunctive paralytic agents versus a simple increase in the depth of sedation. Thus, the decision is most frequently made on the basis of "clinical judgment". Experience with NMB drugs in critical care has been reported in numerous small series but has not been subjected to randomized or prospective large clinical trials. Thus, the risk/benefit ratio is not known. Nonetheless, chemical paralysis is frequently employed in patients in whom adequate ventilation at reasonable inflation pressures is difficult to obtain [8].

The potential benefits include a reduction in oxygen consumption and lactic acid generation, and perhaps prevention of barotrauma. Moreover, elimination of expiratory effort may also be associated with less airway collapse [6]. The potential adverse effects of NMB agents include prolonged muscle weakness and myopathy, venous thromboembolism, central nervous system toxicity with prolonged administration (speculative), decreased lymphatic flow, decreased respiratory clearance, accumulation of drug metabolites and cardiovascular interactions [9]. Hsiang et al. suggested that the routine, long-term use of NMB agents in patients with head injuries was associated with increased morbidity (occurrence of pneumonia, sepsis, prolonged ICU stay) without improvement in overall prognosis [15]. Even the benefit on oxygen consumption in deeply sedated patients has not been convincingly documented [16, 17].

Our inclusion criteria (patients pharmacologically paralyzed for at least 12 h) was chosen in order to avoid

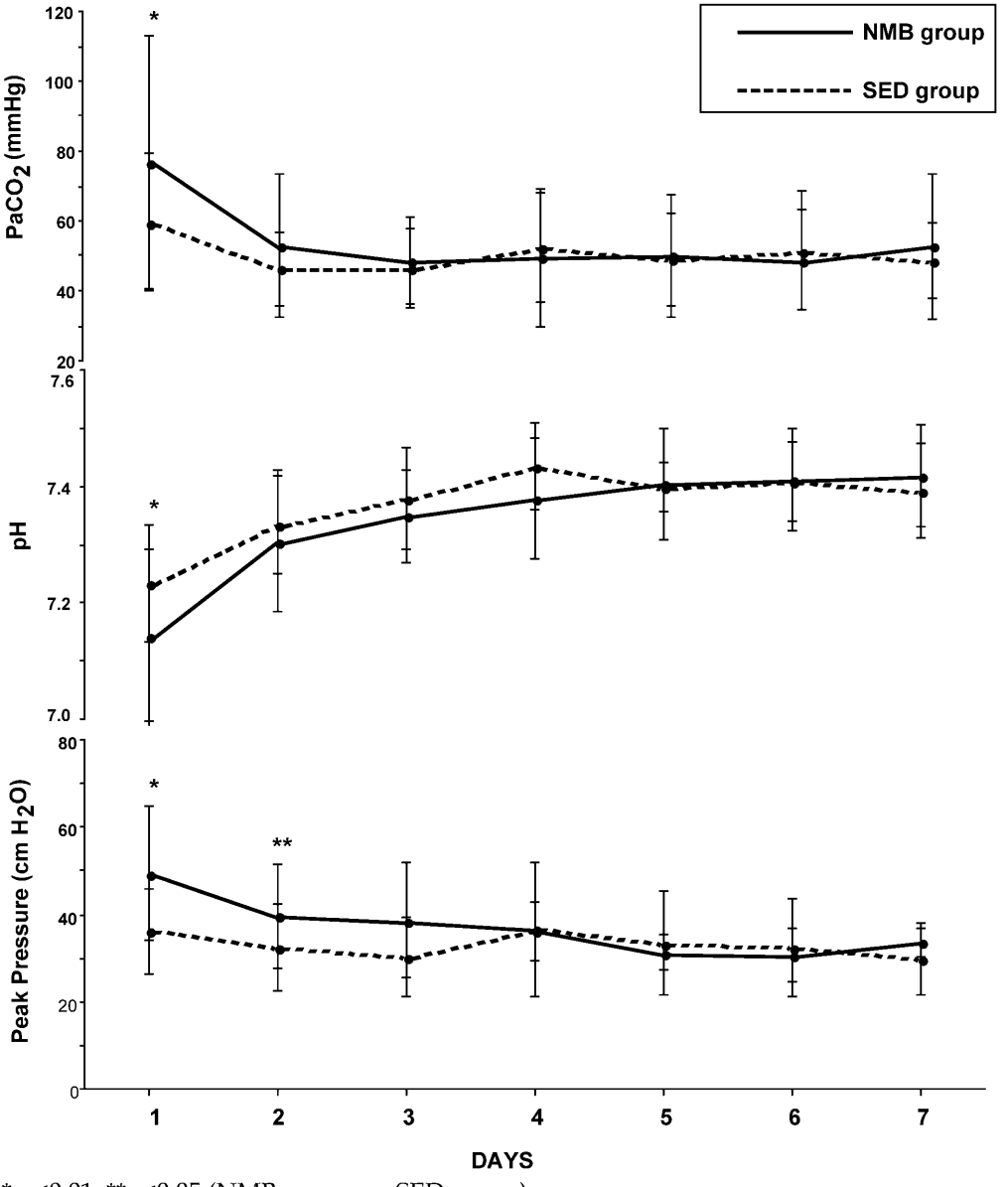

Fig. 1 Evolution of arterial partial pressure of carbon dioxide ($PaCO_2$), pH and mean peak pressure (PP) in patients who remained pharmacologically paralyzed (NMB group), compared to patients not paralyzed (SED group)

* p<0.01; **p<0.05 (NMB group vs. SED group)

including patients who received NMB agents only during intubation or during transport from the scene to the ICU, as has been recommended [18].

Although the two groups (NMB and SED) have similar severity scores (SAPS), paralyzed patients were characterized by a more severe initial bronchospasm, as demonstrated by increased peak pressure and respiratory acidosis. However, the SAPS scores do not take into account pH or blood gas values [11]. Since serum bicarbonate values were the same for the two groups, SAPS categorization failed to detect the gravity associated with the initial difficulty to ventilate these patients mechanically. Thus, the increase of severity in NMB group appears to have been masked by the significantly increased age in the SED patients, as SAPS scores were similar. SAPS II scoring might better demonstrate the difference in initial gravity between the two groups. Unfortunately, SAPS II scores were not performed in most of our patients. Moreover, there was no significant difference between paralyzed and non-paralyzed patients in terms of sedation drug choices or doses. Thus, the decision to employ chemical paralysis appears to be less closely related to depth of sedation than to the ventilatory parameters of these patients. This is in keeping with current recommendations for the ventilatory management of asthma patients [6, 8].

Table 4 Comparison of the incidence of complications between the two groups of patients (*MOF* multi-organ failure, *MV* mechanical ventilation, *VAP* ventilator-associated pneumonia)

Complication	NMB group ($n = 55$) n (%)	SED group ($n = 46$) n (%)	p value
Death	4 (7)	2 (4)	0.844
Extrapulmonary organ failure	21 (38)	12 (26)	0.281
Renal failure	7 (13)	1 (3)	0.068
Cardiovascular failure	14 (25)	10 (22)	0.839
Sepsis	7 (13)	1 (2)	0.103
MOF	8 (14)	0 (0)	0.007
VAP	23 (42)	2 (4)	< 0.0001
Muscle weakness and/or myopathy	10 (18)	1 (2)	0.010
Barotrauma	5 (9)	1 (2)	0.143
Pneumothorax	3 (5)	0 (0)	0.308
Pneumomediastinum	3 (5)	1 (2)	0.742
ICU stay (days), median (25th; 75th percentile)	9 (7; 15.75)	4.5 (2; 7)	< 0.0001
Duration of MV (h), median (25th; 75th percentile)	144 (72; 192)	48 (24; 72)	< 0.0001
Composite Morbidity End Point	29 (3)	6 (13)	< 0.0001

Table 5 Determinants of the presence of muscle weakness or myopathy (Weak group) among patients included in NMB group

	Weak ($n = 10$)	Not weak ($n = 45$)	p value
Duration of paralysis (h), median (25th; 75th percentile)	101 (70; 148)	22 (46; 70)	0.007
Type of NMB agent	0.179		
Pancuronium, n (%)	6 (60)	17 (38)	
Vecuronium, n (%)	2 (20)	25 (55)	
Atracurium, n (%)	1 (10)	1 (2)	
Cisatracurium, n (%)	1 (10)	2 (4)	

The in-hospital mortality rate observed in our patients is consistent with previously published data regarding patients undergoing mechanical ventilation for status asthmaticus [19, 20, 21, 22]. Despite the occurrence of complications in our patients, the mortality rate was relatively low (5.9 %) compared with the predicted mortality based on the SAPS score (about 20 %) [11]. Our criteria for exclusion included cardiac arrest before ICU admission. Most mortality associated with asthma requiring mechanical ventilation is due to brain anoxia secondary to cardiac arrest. Thus, our low mortality was partially explained by our exclusion criteria.

Nevertheless, the global incidence of morbidity is relatively high in our study, since 35 % of the patients presented at least one major complication, thus meeting criteria for the CME. This study evaluated the overall morbidity rather than individual aspects. In the study by Scoggin et al., 86 % of patients who were mechanically ventilated for asthma had at least one major complication during their ICU stay [20]. The incidence of barotrauma, pneumonia or hypotension in our study is consistent with those previously described [20, 21, 22, 23, 24, 25].

Post-extubation muscle weakness was directly related to the administration of NMB in our series. All of our patients, however, were treated daily with corticosteroids in similar doses (data not shown). The incidence of myopathy in previously published studies of chemically paralyzed patients not receiving steroids is limited to a few case reports, whereas the incidence in patients receiving steroids alone or in association with NMB agents appears to be much more significant [13, 14, 26]. We found an incidence of muscle weakness of 18 % in patients who had received corticosteroids and NMB agents. Leatherman et al. found an incidence of muscle weakness in asthmatic patients treated with steroids and NMB of 29 % [14]. Curiously, none of their patients had reported sepsis, MOF or evidence of renal or hepatic dysfunction. Our results are quite different and, although there was no significant difference of incidence of MOF or renal failure between patients with or without weakness, the incidence of these complications was not negligible in the NMB group.

Nevertheless, in agreement with the Leatherman study, we found that the occurrence of muscle weakness is strongly related to the duration of paralysis and not to the paralytic agent used (Table 5) [14]. The only patient who developed severe muscle weakness in the SED group received a single dose of vecuronium to facilitate intubation. The association of severe myopathy and a single dose of a paralytic agent has been previously described [14]. Behbehani et al. found an incidence of acute myopathy of 30 % among patients who received NMB agents and steroids for near fatal asthma [13]. In a multiple logistic regression model they found that the development of myopathy was only significantly associated with the duration of muscle relaxation (odds ratio: 2.1). Unfortunately, no respiratory functions were evaluated and, in particular, the authors did not state whether there was a greater respiratory illness severity in patients who received NMB agents and those who did not. Douglass et al. found an incidence of 9/22 patients who developed a clinically detectable myopathy and es-

tablished a positive correlation between the dose of vecuronium and the frequency of myopathy [27].

None of our patients were monitored with a twitch stimulator using the train-of-four method and we were therefore unable to evaluate the benefit of using a twitch stimulator to titrate the dose of the NMB agent and its influence on the development of morbidity. Whether the use of peripheral nerve stimulation leads to a reduction in the incidence of significant muscle weakness in the setting of the combined use of NMBA and corticosteroids should be evaluated.

We found that global morbidity is associated with NMB use. A multivariate analysis shows clearly that inclusion in the NMB group is the only strong independent factor related to morbidity, with an odds ratio of 6.4. Hsiang et al., in a retrospective study, suggested that the long-term use of NMB agents to manage the intracranial pressure in patients with severe head injuries not only does not improve the outcome, but is also associated with an increase in morbidity [15]. In particular, they found an incidence of pneumonia of 29 % and an incidence of sepsis of 11 % in the NMB group, much higher than in the non-NMB group. Moreover, the ICU stay was significantly longer in the patients who required paralysis.

The weakness of this study is due to its observational methodology and because NMB patients had a more serious clinical presentation than the SED patients, thus the two groups are not comparable in terms of severity of illness. Nevertheless, the goal of this study was not to demonstrate a "*cause-effect*" between the use of paralysis and morbidity, but rather to describe the morbidity associated in NMB patients. Since we found a very strong association between NMB use and morbidity, the continuous infusion of NMB agents should be recognized as a marker of severe morbidity in this sub-group of patients. Another weakness of our study was that clinicians are more likely to expect and seek muscle weakness in patients who have received NMB, given the general information available on this association, but all patients had a neurologic evaluation before discharge from the ICU, and all medical records were analyzed in this study.

In summary, we found that morbidity is associated with the paralysis of mechanically ventilated asthmatic patients. It must be noted, however, that the NMB group appeared to have more severe bronchospasm, justifying the decision to utilize paralytic agents. The true risk/benefit ratio of the use of paralytic agents in life-threatening asthma would probably be discerned only after a prospective randomized study comparing NMB plus sedation with sedation alone. Such a study would be difficult to perform, given the ethical dilemma of withholding paralytic agents in the setting of difficult mechanical ventilation. Nonetheless, this study underscores the need for physicians to consider the likelihood of increased complications among asthmatic patients undergoing neuromuscular blockade.

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