Myopathy Following Mechanical Ventilation for Acute Severe Asthma*

The Role of Muscle Relaxants and Corticosteroids

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Background: **Acute myopathy following mechanical ventilation for near-fatal asthma (NFA) has been described recently, and some researchers have suggested that this complication is related to the use of neuromuscular blocking agents (NMBAs) and corticosteroids (CSs).**
Objectives: **To determine the incidence of acute myopathy in a group of patients and to examine the most important predictors of its development.**
Design and methods: **A retrospective cohort study over a 10-year period (1985 to 1995) of all asthma patients who received mechanical ventilation at two centers in Vancouver (designated center 1 and center 2).**
Results: **In center 1, there were 58 patients who had 64 episodes of NFA, and in center 2, there were 28 patients who had 30 episodes. NMBAs were used in 30 of 86 admissions for acute severe asthma (35%). The mean (± SD) duration of muscle paralysis was 3.1 ± 2.3 days. A total of 9 patients (10.4%) developed significant myopathy. The incidence of myopathy was 9 of 30 (30%) among patients who received NMBAs. In a multiple logistic regression model, the development of myopathy was only significantly associated with the duration of muscle relaxation. The odds ratio for the development of myopathy increased by 2.1 (95% confidence interval, 1.4 to 3.2) with each additional day of muscle relaxation. The dose and the type of the CS were not significantly associated with the myopathy in the multiple logistic regression analysis.**
Conclusion: **Our study showed that there is a high incidence of acute myopathy when NMBAs are used for NFA. The incidence of myopathy increases with each additional day of muscle relaxation.**
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Key words: corticosteroids; myopathy; severe asthma; ventilation

Abbreviations: APACHE = acute physiology and chronic health evaluation; CS = corticosteroid; HC = hydrocortisone; MP = methylprednisolone; NMBA = neuromuscular blocking agent

The majority of patients presenting with acute asthma can be successfully managed with bronchodilators, corticosteroids (CSs), and oxygen.[1] Patients who present in extremis or fail to respond to the above measures may require mechanical ventilation, which is life saving for these patients.[2] Diffuse muscle weakness following mechanical ventilation for severe asthma was first described in 1977.[3] This has been shown to be secondary to acute myopathy.[4] Both CSs and neuromuscular blocking agents (NMBAs) have been implicated in the pathogenesis of the muscle injury. Furthermore, acute myopathy has been observed with all three commonly used drugs for muscle paralysis: pancuronium, vecuronium, and atracurium.

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The exact roles of NMBAs and CSs in causing this complication are uncertain. We performed a retrospective cohort study of all asthma patients admitted to two ICUs in Vancouver during a 10-year

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period. These two ICUs had different practice patterns with regard to the way that NMBAs were administered and the type and dose of CS used in patients with near-fatal asthma. This gave us an opportunity to compare the incidence of acute myopathy in the two centers and its relationship to NMBAs and CSs.

Materials and Methods

We evaluated all asthma patients who required hospital admission and mechanical ventilation at the two centers (center 1 and center 2) over the 10-year period from 1985 to 1995. A detailed chart review was done. Demographic and clinical data were extracted using a standardized data extraction sheet. Significant muscle weakness was defined as the presence of any of the following criteria: (1) strength rating of less than 4 on a 0–5 scale in one or more major muscle groups; (2) inability to perform activities of daily living due to muscle weakness; and (3) the need for physical rehabilitation prior to discharge. Other potential causes of muscle weakness in the ICU including presence of sepsis, use of specific antibiotics, and renal or hepatic failures were specifically looked for. The assessment of neuromuscular blockade was done mainly by clinical evaluation, and peripheral nerve stimulation was not routinely used. We calculated the APACHE (acute physiology and chronic health evaluation) II score during the first 24 h after admission to the ICU to evaluate the severity of illness, as it may be a confounding factor for the development of myopathy. The calculation of APACHE II scores was performed by a trained observer who was unaware of patient outcomes.

Statistical Analysis

To compare patient characteristics between groups of those patients who developed myopathy and those who did not, simple *t*-tests were used for continuous variables (such as age), and the χ^2 test was used for categorical variables such as the indicator of treatment with NMBAs. The results were expressed as mean ± SD. Multiple logistic regression was used for the analysis of myopathy (binary outcome, yes or no). The variables considered were the following: NMBA usage; duration of muscle relaxation; dose and duration of CS administration; type of CS (hydrocortisone [HC]) or methylprednisolone [MP]); treating center; and APACHE II score. The analysis was done on 68 patients who had complete data on all the examined variables.

Results

Over the 10-year period, there were 58 patients who had 64 episodes of acute severe asthma in center 1 and 28 patients who had 30 episodes of acute asthma in center 2. The characteristics of all 86 patients were as follows: mean age 47 ± 16 years, men 48 (56%), duration of asthma 18 ± 15 years, and APACHE II score 14.3 ± 6.2. All patients in both centers received inhaled salbutamol by nebulizer, and patients admitted after 1990 received a combination of salbutamol and ipratropium bromide. IV MP was used in 55 of 86 (64%), and the rest of the patients were given HC. The mean initial dose of CS as MP or equivalent was 260 ± 154 mg/d. NMBAs were used for 30 of 86 patients (35%) admitted for acute severe asthma. The mean duration of muscle paralysis was 3.1 ± 2.3 days. Three different NMBAs (pancuronium, vecuronium, and atracurium) were used alone or in combination at both centers.

Nine patients (30% of those patients who received NMBAs) developed significant myopathy: eight patients from center 1, and one patient from center 2. None of the patients with myopathy had sepsis or renal or hepatic failure prior to the development of myopathy. Six of these patients had all three criteria used to define myopathy, and three had the first criterion, which is muscle weakness ≤ grade 3 in one or more muscle groups. The clinical characteristics of these nine patients are presented in Table 1. None of these patients received aminoglycosides or vancomycin during their stay in the ICU. Six of these patients had electromyography, which showed abnormalities consistent with myopathy. Those patients had normal results from sensory nerve conduction

Table 1—*Clinical Characteristics of Patients Who Had Muscle Weakness

Patient	Age, yr	Gender	CS/Dose, mg/d	NMBA	Duration of NMBA, d	Duration of Mechanical Ventilation, d	Duration of Hospital Stay, d
1	57	M	MP/120	Pancuronium	3	6	35
2	42	F	MP/500	Pancuronium	3	20	34
3	62	M	MP/500	Pancuronium	5	7	25
4	60	M	MP/425	Pancuronium	7	11	37
5	52	F	MP/250	Pancuronium	3	5	30
6	32	F	MP/500	Pancuronium	3	10	27
7	41	M	MP/500	Pancuronium	7	14	30
8	57	F	MP/375	Pancuronium + vecuronium	6	27	49
9	60	F	HC/800	Pancuronium	2	7	26

*M = male; F = female.

studies, and motor nerve conduction velocities were normal, while needle electromyography showed abnormal spontaneous activity including fibrillation potentials. None of these patients underwent muscle biopsy. There were 41 patients (48%) who required mechanical ventilation for >24 h. The median duration of hospitalization was 7 days (range, 2 to 49 days). The patients who had muscle weakness and received NMBAs required a longer duration of mechanical ventilation and had a longer hospital stay compared to the rest of the patients (Table 2).

The multiple logistic regression analysis showed that the duration of muscle paralysis was the only strong independent predictor of the development of myopathy. The odds ratio for the development of myopathy increases by 2.1 (95% confidence interval, 1.4 to 3.2) with each additional day of muscle relaxation (Fig 1). The use of NMBAs, the type and dose of CS, the treatment center, and the severity of illness determined at presentation (APACHE II score) were not statistically significant independent predictors of the development of myopathy. The incidence of myopathy among patients who received NMBAs was 8 of 20 patients (40%) for center 1 and 1 of 10 patients (10%) for center 2 ($p = 0.09$).

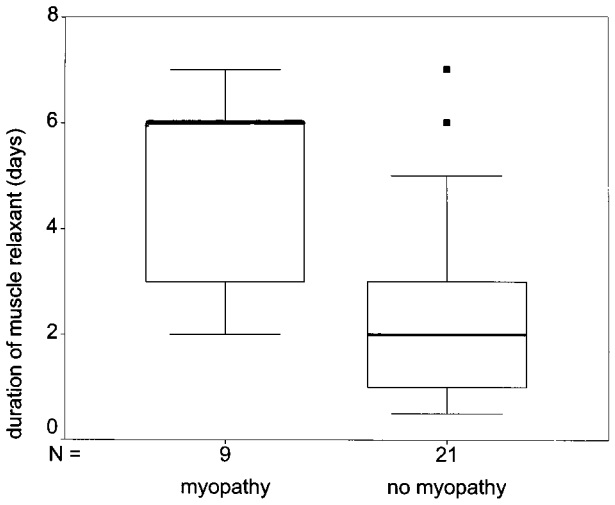

FIGURE 1. A box plot graph of the duration of muscle relaxation in patients with myopathy and patients without myopathy who received NMBAs ($p < 0.001$).

DISCUSSION

In this retrospective study of acute severe asthma requiring mechanical ventilation, we found that the incidence of myopathy was 10.4% among all patients and 30% among patients who received NMBAs. The duration of muscle relaxation was the only independent predictor for the development of myopathy. Our results confirm and extend the results of previous studies.[4,6] However, we performed a multivariate analysis and controlled for severity of illness using the APACHE II score, which had not been done in previous studies.

There are isolated case reports indicating that acute myopathy may develop when CSs are used alone in the setting of acute severe asthma.[3,5] However, in studies with relatively large numbers of patients, diffuse muscle weakness in acute asthma followed the use of both CSs and NMBAs.[4,6–8] Several of these reports included electrophysiologic and histologic examinations of skeletal muscles. These studies confirm that the muscle weakness is secondary to a myopathic process, and a muscle biopsy usually shows myonecrosis.[4,8] In these studies, different CSs were used in variable doses. These CSs included MP, HC, and dexamethasone. Our study shows that myopathy may develop when either MP or HC is used in combination with an NMBA for the treatment of acute severe asthma. The dose of CS did not seem to act as a strong independent predictor of myopathy in our study. The optimal dose of CS to be used in severe acute asthma is controversial. There are some studies that support

Table 2—*Comparison of Patients Who Had Muscle Weakness vs Those Who Did Not

Patient Characteristics	Myopathy	No Myopathy	p Value
Age, yr	51.4 ± 10.6	46 ± 16.4	0.3
Duration of asthma, yr	19.0 ± 16.3	18 ± 14.8	0.8
APACHE II score	16 ± 6.4	13.7 ± 6.1	0.2
Initial dose of CS, mg/d†	332 ± 157	250 ± 149	0.16
Patients receiving NMBA, No. (%)	9/9 (100)	21/77 (27)	< 0.001
Duration of NMBA, d‡	4.8 ± 2.0	2.5 ± 2.1	0.01
Duration of mechanical ventilation, d	12.4 ± 7.1	2.4 ± 3.0	< 0.001
Duration of hospital stay, d	32 ± 10.4	9.2 ± 7.2	< 0.001

*Values are expressed as mean ± SD.
†The dose of CS is expressed as milligrams of MP or equivalent.
‡For patients who received only NMBA.

the use of moderate or high doses of CSs,[9] while other studies have not found a difference in outcome when low doses of a CSs were compared to moderate or high doses of CSs.[10] The overall consensus is that a dose of 120 mg/d of MP or the equivalent is adequate.[11,12]

The incidence of clinically detectable muscle weakness following mechanical ventilation for acute asthma has been reported to be 36% in one study[4] and 19% in another study.[6] However, a rise in creatine kinase in patients being ventilated for acute asthma has been observed in as many as 76% of patients.[4] In our study, the incidence of muscle weakness was 10.4% among all patients ventilated for bronchial asthma and 30% among patients who received NMBAs. Because of the retrospective nature of our study and the fact that creatine kinase was not measured systematically in our patients, we were only able to detect clinically significant muscle weakness. Furthermore, we used strict criteria to define muscle weakness so that its presence was indicative of a clinically significant complication associated with the need for prolonged ventilatory support and hospitalization. As shown in a previous study,[6] the incidence of myopathy increases as the duration of muscle relaxation increases. In that study, there was no difference between the aminosteroid NMBAs (pancuronium and vecuronium) and the benzylisoquinolinium NMBA (atracurium) with regard to the incidence of myopathy.

In an attempt to identify the most important predictors of the development of myopathy, we compared the group of patients who had myopathy to the group of patients who did not. The baseline characteristics of age and duration of asthma were not significantly different between the two groups (Table 2). To evaluate the severity of illness at presentation to the ICU, we calculated the APACHE II score for each patient.[13] To our surprise, the APACHE II scores were not significantly different between the groups of patients who had and did not have myopathy (Table 2). We evaluated the possible explanatory variables in a multivariate analysis using logistic regression. The potential explanatory variables included the duration of muscle relaxation, the use of NMBAs, the treating center, the dose and type of CS used, and the APACHE II score. The duration of muscle relaxation was the only strong independent predictor for the development of myopathy. We included the treating center as a variable because there was a trend of higher incidence of myopathy in center 1 (8 of 58 patients [13.8%]) compared to center 2 (1of 28 patients [3.6%]; $p = 0.1$). This trend may be explained by the fact that NMBAs were mainly used as continuous IV infusion in center 1 compared to center 2. Hence the duration of muscle relaxation was longer in center 1 (3.8 ± 2.3 days) compared to center 2 (2.0 ± 1.6 days; $p = 0.04$).

As expected, our study showed that patients who developed myopathy suffered a great deal of morbidity as a result of their muscle weakness. The duration of mechanical ventilation and the duration of hospitalization for patients with muscle weakness were 7 to 27 days and 25 to 49 days, respectively. Six patients needed an intensive rehabilitation program during their stay in the hospital, and three patients were transferred to an in-patient rehabilitation institution for further treatment. We estimated that the direct medical costs associated with each admission in which myopathy developed ranged from $21,000 to $56,500 (in Canadian dollars). This estimate is based on a previous study that we performed regarding the health-care costs associated with admissions for acute bronchial asthma.[14] The cost calculation did not include the indirect costs. In a case-control study, Rudis et al[15] found that the development of muscle weakness secondary to the use of NMBAs was associated with disproportionate health-care expenditures $> $66,000 per patient.

Our study and others[4,6] emphasize the increased risk of myopathy associated with the use of NMBAs in combination with CSs in patients who are receiving mechanical ventilation. All patients who developed significant muscle weakness had received NMBAs for ≥ 48 h, and the majority of those patients had received NMBAs as a continuous infusion. The use of peripheral nerve stimulation for monitoring the degree of neuromuscular blockade vs clinical assessment has been shown to result in a lower total dose of the NMBA and a faster recovery of neuromuscular function.[16] Whether the use of peripheral nerve stimulation leads to a reduction in the incidence of significant muscle weakness in settings of combined use of NMBAs and CSs needs to be evaluated. The pathogenesis of this muscle weakness is unclear. However, animal studies suggest that an interaction between NMBAs and CSs can lead to CS-induced myopathy, which is augmented by pharmacologic denervation of the muscles involved.[17,18] Because all patients who are mechanically ventilated for severe acute asthma receive CSs, it follows that the use of NMBAs should be avoided as much as possible. When NMBAs are used, the duration of muscle paralysis should be kept to a minimum by using an intermittent dosage schedule to allow partial return of muscle function and to evaluate the need for further paralysis.[19]

References

1 FitzGerald JM, Grunfeld A. Status asthmaticus. In: Lichtenstein LM, Fauci AS, eds. Current therapy in allergy, immu-

nology and rheumatology. St. Louis, MO: Mosby, 1996; 63–67
2 Fitzgerald JM, Macklem PT. Proceedings of a workshop on near fatal asthma. Can Respir J 1995; 2:113–125
3 MacFarlane IA, Resenthal FD. Severe myopathy after status asthmaticus [letter]. Lancet 1977; 2:615
4 Douglass JA, Tuxen DV, Horne M, et al. Myopathy in severe asthma. Am Rev Respir Dis 1992; 146:517–519
5 Williams TJ, O'Hehir RE, Czarny D, et al. Acute myopathy in severe acute asthma treated with intravenously administered corticosteroids. Am Rev Respir Dis 1988; 137:460–463
6 Leatherman JW, Fluegel WL, David WS, et al. Muscle weakness in mechanically ventilated patients with severe asthma. Am J Crit Care Med 1996; 153:1686–1690
7 Griffin D, Fairman N, Coursin DB, et al. Acute myopathy during treatment of status asthmaticus with corticosteroids and steroidal muscle relaxants. Chest 1992; 102:510–514
8 Giostra E, Magistris MR, Pizzolato G, et al. Neuromuscular disorder in intensive care unit patients treated with Pancuronium Bromide: occurrence in a cluster group of seven patients and two sporadic cases, with electrophysiologic and histologic examination. Chest 1994; 106:210–220
9 Haskell RJ, Wong BM, Hansen JE. A double-blind randomised clinical trial of methylprednisolone in status asthmaticus. Arch Intern Med 1983; 143:1324–1327
10 Bowler SD, Mitchell CA, Armstrong JG. Corticosteroids in acute severe asthma: effectiveness of low doses. Thorax 1992; 47:584–587
11 Rowe BH, Keller JL, Oxman AD. Effectiveness of steroid therapy in acute exacerbation of asthma: a meta analysis. Am J Emerg Med 10; 1992:301–310
12 Leatherman J. Life-threatening asthma. Clin Chest Med 1994; 15:453–479
13 Day AC, Rankin AP, Judson JA. Grading asthma severity: using the APS component of the APACHE II System. Intensive Care Med 1993; 19:221–226
14 Awadh N, Grunfeld A, FitzGerald JM. Health care costs associated with acute asthma [abstract]. Am J Respir Crit Care Med 1994; 149(suppl 2):A1076
15 Rudis MI, Guslits BJ, Peterson EL, et al. Economic impact of prolonged motor weakness complicating neuromuscular blockade in the intensive care unit. Crit Care Med 1996; 24:1749–1755
16 Rudis MI, Sikora CA, Angus E, et al. A prospective, randomized, controlled evaluation of peripheral nerve stimulation versus standard clinical dosing of neuromuscular blocking agents in critically ill patients. Crit Care Med 1997; 25:575–583
17 Dubois DC, Almon RA. A possible role for glucocorticoids in denervation atrophy. Muscle Nerve 1981; 4:370–373
18 Rouleau G, Karpati G, Carpenter S, et al. Glucocorticoid excess induces preferential depletion of myosin in denervated skeletal muscle fibers. Muscle Nerve 1987; 10:428–438
19 Hansen-Flaschen J, Cowen J, Raps EC. Neuromuscular blockade in the intensive care unit: more than we bargained for. Am Rev Respir Dis1993; 147:234–236