Sensitivity to vecuronium in myasthenia gravis: a dose-response study

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A cumulative dose plus infusion technique and integrated EMG monitoring of the first dorsal interosseous muscle were used to determine the potency of vecuronium in 20 normal patients and in ten patients with myasthenia gravis under thiamylal, N_2O, O_2, fentanyl anaesthesia. The mean (± SEM) values for ED_{50}, ED_{90}, and ED_{95} in the normal patients were 19 ± 1, 31 ± 1 and 36 ± 2 $\mu g \cdot kg^{-1}$, respectively. Myasthenic patients showed increased sensitivity to vecuronium, the mean values for ED_{50}, ED_{90}, and ED_{95} were 10 ± 2, 17 ± 2 and 20 ± 3 $\mu g \cdot kg^{-1}$, being 50, 55 and 56 per cent of normal, respectively. We did not demonstrate a difference in sensitivity to vecuronium between those myasthenic patients who received pyridostigmine preoperatively and those who did not, nor among those chronically treated with corticosteroids, compared with those who were not.

Une dose cumulative plus une technique de perfusion et une surveillance électromographique intégrée du muscle interosseux dorsal fut utilisée afin de déterminer la puissance du vécuronium chez 20 patients normaux et chez dix patients atteints de myasthénie grave sous thiamylal, N_2O, O_2, et fentanyl. Les valeurs moyennes (± SEM) du ED_{50}, ED_{90} et ED_{95} chez les patients normaux étaient de 19 ± 1, 31 ± 1 et 36 ± 2 $\mu g \cdot kg^{-1}$ respectivement. Les patients myasthéniques ont démontré une augmentation de la sensitivité au vécuronium, les valeurs moyennes de la ED_{50}, ED_{90} et ED_{95} furent 10 ± 2, 17 ± 2 et 20 ± 3 $\mu g \cdot kg^{-1}$ étant respectivement 50, 55 et 56 pour cent de la normale. On n'a pas démontré de différence avec les patients avant reçu de la pyridostigmine en période préopératoire et ceux qui n'en n'ont pas reçue, de même qu'on n'en a pas trouvé avec ceux qui étaient traités aux corticostéroïdes comparé à ceux qui ne l'étaient pas.

Key words
COMPLICATIONS: myasthenia gravis;
NEUROMUSCULAR RELAXANTS: vecuronium;
MEASUREMENT TECHNIQUES: electromyography, neuromuscular blockade.

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Patients with myasthenia gravis are known to be sensitive to the neuromuscular blocking effects of nondepolarizing muscle relaxants.[1,2] Vecuronium has a shorter duration of action than either d-tubocurarine or pancuronium in normal patients and has been successfully used to produce controlled neuromuscular blockade in patients with myasthenia gravis.[3-7] To date, only one study, which used a cumulative dose administration technique, has provided pharmacodynamic data on the sensitivity to vecuronium in myasthenic patients.[5] The cumulative dose technique has been shown to underestimate the potency of vecuronium in normal patients,[9-11] whereas the use of a cumulative dose plus infusion technique provides potency estimates which are similar to those obtained using a single bolus technique.[8]

The purpose of the present study was to use a cumulative dose plus infusion technique: (1) to establish the dose-effect relationship for vecuronium in normal patients and patients with myasthenia gravis, and (2) in patients with myasthenia gravis, to determine whether administration of pyridostigmine on the morning of surgery, or chronic corticosteroid therapy, would influence the sensitivity to vecuronium.

Methods

Twenty normal patients and ten patients with myasthenia gravis gave their written informed consent to participate in this institutionally approved study. The normal controls were randomly selected ASA physical status I patients, free from medications or conditions known to affect neuromuscular function, and scheduled to undergo gyn-

TABLE I Demographic data – myasthenic patients

Patient number	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Mean ± SD*
Sex	F	F	F	F	F	F	F	F	M	F	—
Age (yr)	37	49	34	43	52	63	25	21	66	22	41 ± 16
Weight (kg)	66	80	41	80	70	79	60	60	75	53	66 ± 13
MG class	IIB	IV	IV	IIB	IV	IIA	IIB	IIA	IIB	IIB	—
Pyridostigmine ($mg \cdot day^{-1}$)	180	360	210	345	540	240	300	240	225	360	300 ± 106
Pyridostigmine preop	No	Yes	Yes	No	No	Yes	No	No	No	Yes	—
Duration of disease (mo)	36	204	84	5	420	100	84	41	8	4	99 ± 128
Steroid dose (mg)	No	No	15 mg QOD	No	No	No	30 QOD	No	No	40/20 Alt. days	—
Steroids preop	No	No	Yes	No	No	No	Yes	No	No	Yes	—

TABLE II Demographic Data – Normal Patients

n = 20	*Mean ± SD*
Males/females	4/16
Weight (kg)	59 ± 20
Age	38.5 ± 13.2
ASA physical status	All ASA I

aecological or orthopaedic surgical procedures. The myasthenic patients were ASA physical status II or III, Osserman Class IIA–IV,[12] and scheduled to undergo transcervical thymectomy as a surgical treatment for their myasthenia.[13] The patient demographic data are shown in Tables I and II. Although both groups were studied concurrently, patients were not age or sex matched. All of the myasthenic patients were being treated with pyridostigmine (Mestinon), but only four of the ten received it on the morning of surgery, 60–90 minutes before induction of anaesthesia. Three of the ten were receiving chronic corticosteroid therapy and were given supplementation with hydrocortisone 100 mg IV on the morning of surgery. In all patients with myasthenia gravis, the diagnosis had been confirmed preoperatively by electromyography (EMG) or pharmacological testing.

All of the patients received diazepam, 5–10 mg PO for premedication. Anaesthesia was induced with thiamylal, and maintained with nitrous oxide (66 per cent) in oxygen and incremental doses of thiamylal and fentanyl. Potent inhaled agents were not used during the study period. Ventilation was controlled with a bag and facemask to maintain end-tidal CO_2 within the normal range as measured by a mass spectrometer (Perkin-Elmer Advantage 1100, Pomona, CA). Train-of-four stimulation was applied to the ulnar nerve at the wrist every ten seconds and the integrated EMG responses of the first dorsal interosseous muscle were recorded using a Datex 221 neuromuscular transmission monitor (Puritan-Bennett Co., Wilmington, MA). Stimulation and recordings were made via surface electrodes. After calibration of baseline EMG response values to 100 per cent by the Datex monitor, patients received a vecuronium bolus dose of 5 or 10 $\mu g \cdot kg^{-1}$ followed by similar incremental doses together with an infusion of vecuronium, the rate of which was adjusted to replace eliminated drug.[8] An initial bolus dose and subsequent incremental doses of 5 $\mu g \cdot kg^{-1}$ were used in the myasthenic patients, and 10 $\mu g \cdot kg^{-1}$ in the normal controls. Incremental doses were administered and the vecuronium infusion rates increased, when three consecutive equal first responses (T1/C) were observed in the continuously recorded EMG. The vecuronium infusion rate was calculated as follows. Based upon the work of Smith *et al.*,[8] it was assumed that if a vecuronium bolus dose of V $\mu g \cdot kg^{-1}$ produced a certain degree of depression of T1/C response, then an infusion rate of 2 × V $\mu g \cdot kg^{-1} \cdot hr^{-1}$ would be needed to maintain that level of T1/C depression. In the myasthenic patients, a bolus dose of 5 $\mu g \cdot kg^{-1}$ was administered and, when the T1/C decrement was stable for 20–30 seconds (three equal consecutive T1/C responses), an incremental dose of vecuronium 5 $\mu g \cdot kg^{-1}$, was given and an infusion of (5 × 2 × body weight in kg) per hour commenced. With each incremental dose of vecuronium, 5 $\mu g \cdot kg^{-1}$, the vecuronium infusion rate was increased using multiples of the above. Additional doses and infusion rate increases were continued until a 95–99 per cent decrease in T1/C had been achieved. At this time the trachea was intubated and ventilation was controlled. Each patient received between three and eight incremental doses of vecuronium and the total duration of the study period in each patient was between 10 and 15 minutes. Following completion of the dose–response study, anaesthesia and relaxation were maintained with nitrous oxide, fentanyl, and isoflurane. Upon completion of surgery any residual neuromuscular blockade was reversed with incremental doses of edrophonium titrated against the EMG response or until clinical signs of adequate reversal were evident.

Linear regressions were derived for each individual patient between the logit transformation of the neuromuscular blockade (i.e., (100 − T1/C) per cent) and the logarithm of the cumulative dose of vecuronium. Only the

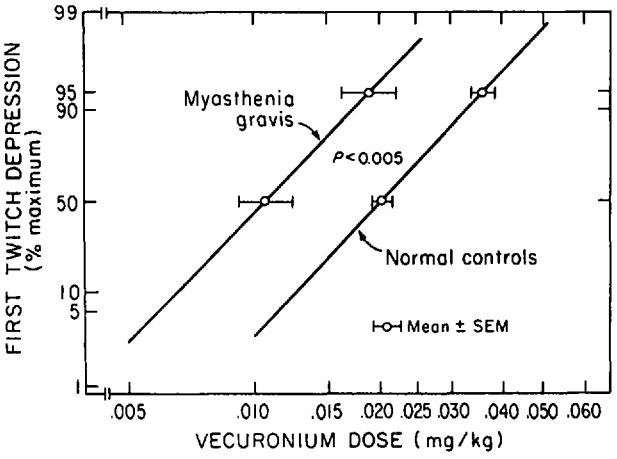

FIGURE 1 Mean log dose–logit response curves for vecuronium in 20 normal controls and ten myasthenic patients obtained using a cumulative dose plus infusion technique.[8] The equations to the regression lines are: normals: logit response = 4.61 × log dose + 7.93; myasthenics: logit response = 4.66 × log dose + 9.16.

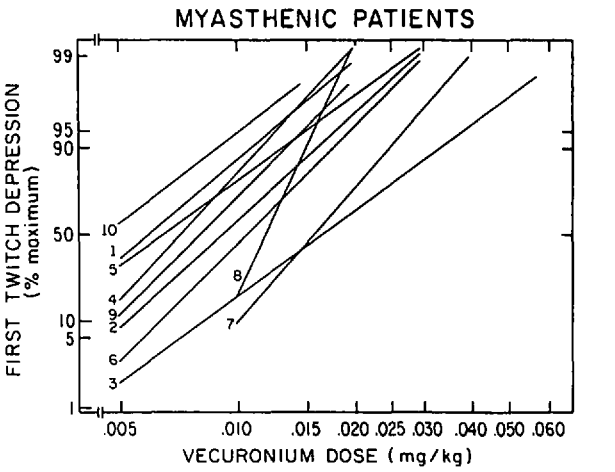

FIGURE 2 Individual log dose–logit response curves for the ten myasthenic patients. The numbers identify the individual patients in Table I. patients 2, 3, 6 and 10 received preoperative pyridostigmine. Patients 3, 7 and 10 were being chronically treated with prednisone and received hydrocortisone preoperatively (see Table I).

dose administered in bolus form was considered in the derivations of the dose–response regression curves because the amount of vecuronium given by infusion was to replace drug which had been eliminated.[8] From the individual dose–response curves, each of which was calculated using at least three data points, mean dose–response curves were constructed for each group. From these curves, the mean effective doses producing 50, 90 and 95 per cent block (ED_{50}, ED_{90}, ED_{95}) were calculated. The group mean slopes, intercepts and ED values were compared using a Student's t test for unpaired data. A difference was considered to be significant if $P < 0.05$.

Results

No complications were associated with the administration of vecuronium in either group. Residual neuromuscular blockade was adequately reversed in all of the patients, whose tracheas were extubated either in the operating room or in the recovery room. None required prolonged postoperative ventilation.

TABLE III Mean ED values with 95% confidence limits for normal and myasthenic patients

	Normals $n = 20$	*Myasthenics* $n = 10$	*P*
ED_{50}	19	10	0.0001
(95% confidence limits)	(17–21)	(7–14)	
Range	14–33	5–19	
ED_{90}	31	17	0.0001
(95% confidence limits)	(28–34)	(13–22)	
Range	24–52	9–35	
ED_{95}	36	20	0.0001
(95% confidence limits)	(33–40)	(15–27)	
Range	28–61	11–44	

Although the normal and myasthenic patients were not age or sex matched, we found no significant difference between the two groups in mean age or weight. The mean (±SD) ages of the myasthenia and control groups were 41.2 (±16.2) and 38.5 (±13.2) yr, respectively, and the weights were 66.4 (±13.0) and 59 (±20) kg, respectively. The male:female ratio was 1:9 in the myasthenia group and 4:16 in the control group.

The mean dose–response curves are shown in Figure 1. Compared with the curve in normal patients, the curve for the myasthenic patients was shifted to the left but there were no significant differences between the groups in slope. The myasthenic patients were approximately twice as sensitive as the normal patients, the ED_{50}, ED_{90} and ED_{95} values of 10, 17, 20 $\mu g \cdot kg^{-1}$ representing 52, 55 and 56 per cent of control, respectively (Table III). The differences between these mean values for the myasthenic and normal patient groups were highly significant ($P = 0.0001$). The individual dose–response curves for each of the ten myasthenic patients are shown in Figure 2, and for each of the 20 normal control patients in Figure 3. There was considerable individual variability in the ED values within each group and the ranges of the ED values for the two groups are seen to overlap (Table III, Figures 2, 3).

We failed to demonstrate any difference in sensitivity to vecuronium between those myasthenic patients who had received pyridostigmine (#s 2, 3, 6 and 10) on the

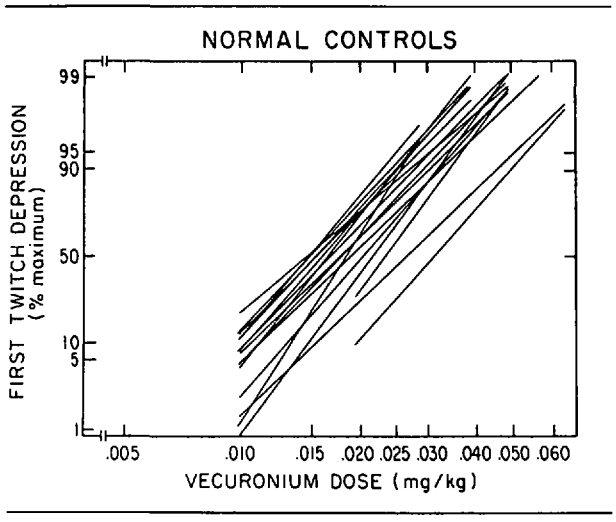

FIGURE 3 Individual log dose-logit response curves for the 20 normal control patients for comparison with Figure 2.

morning of surgery compared with those myasthenic patients who had not. The mean (±SEM) ED_{50} and ED_{95} for patient numbers 2, 3, 6 and 10 were 12.0 (±3.0) and 21.6 (±5.6) $\mu g \cdot kg^{-1}$, respectively, compared with mean ED_{50} and ED_{95} values of 10.4 (±2.0) and 15.6 (±2.1) $\mu g \cdot kg^{-1}$, respectively for those patients (#1, 4, 5, 7, 8, 9) who did not receive pyridostigmine. We also failed to demonstrate any difference in sensitivity to vecuronium between those myasthenic patients receiving chronic steroid therapy (ED_{50} and ED_{95} of 11.0 ± 3.7 and 20.8 ± 7.6 $\mu g \cdot kg^{-1}$, respectively) and those who were not (ED_{50}, ED_{95} of 11.0 ± 1.7 and 17.4 ± 2.4 $\mu g \cdot kg^{-1}$, respectively).

Discussion

There are several reports of the use of vecuronium in patients with myasthenia gravis,[3-7] on the basis of which the range of values for ED_{80}-ED_{98} is 11–80 $\mu g \cdot kg^{-1}$. The reasons for this broad range include the small number of patients and individual reports, variability in the perioperative medical management (pryidostigmine, corticosteroids, immunosuppressants) and the variety of methods whereby neuromuscular blockade was assessed in the patients studied.

The single bolus (SB) dose technique is generally considered to be the best method for constructing dose–response curves.[9] Use of this technique in myasthenic patients would be difficult, however, because of the small number of patients available for study. In the only other published dose–response study of vecuronium in myasthenic patients, Buzello *et al.*[5] used a cumulative dose–response (CDR) technique and mechanomyographic monitoring of the adductor pollicis. They reported mean (ranges) ED_{50} and ED_{90} values of 7 (0.3–14) $\mu g \cdot kg^{-1}$ and 19 (5–31 $\mu g \cdot kg^{-1}$), respectively in myasthenics. Their control values were 18 (6–28) and 44 (34–52) $\mu g \cdot kg^{-1}$. Several groups have shown, however, that the potency estimates for vecuronium using the CDR technique in normal patients overestimate ED_{50} values by 25–33 per cent when compared with a SB technique.[9-11] These authors recommended that the CDR technique not be used for potency determination of muscle relaxants of medium and short duration.[9-11] The reason for the overestimation of ED values with CDR is that some of the administered drug is redistributed or eliminated before the next incremental dose takes effect. The cumulative dose thus represents both drug producing the observed effect plus that which has been redistributed or eliminated. Therefore, the ED values for vecuronium reported by Buzello *et al.*[5] may represent overestimates.

Smith *et al.*[8] have introduced a cumulative dose–response with infusion (CDI) technique to determine the potency of atracurium and vecuronium. They concluded that the use of an infusion to compensate for drug lost by redistribution or elimination resulted in the generation of dose–response curves that were indistinguishable from curves obtained with SB methods. Using the CDI technique and integrated EMG monitoring of the first dorsal interosseous muscle, we obtained mean ED_{50} and ED_{90} values for vecuronium of 19 and 31 $\mu g \cdot kg^{-1}$ in normal patients, compared with the values of 23 and 34 $\mu g \cdot kg^{-1}$ (SB) and 21 and 36 $\mu g \cdot kg^{-1}$ (CDI), respectively, reported by Smith *et al.*[8]

We employed integrated EMG monitoring of the first dorsal interosseous muscle because this technique is simple to apply and it may be used in patients whose arms are adducted during surgery. Although the evoked adductor pollicis mechanomyogram is the response most commonly monitored, Kopman[14] has reported that the first dorsal interosseous EMG may be used interchangeably with it in determining depth of non-depolarizing neuromuscular blockade. Kopman[14] also found that calculating the ED_{95} (of metocurine) from the EMG resulted in a very slight overestimate of that drug's potency. That our ED values (by EMG) were slightly less than those of Smith *et al.*[8] (by mechanomyography) is consistent with the observations reported by Kopman.[14] We therefore believe that the methodology which we used to derive the potency (ED) data for vecuronium is valid.

While the mean ED_{50} value in our control group (19 $\mu g \cdot kg^{-1}$) was essentially the same as that (18 $\mu g \cdot kg^{-1}$) reported by Buzello *et al.*, our mean value for ED_{90} (31 $\mu g \cdot kg^{-1}$) was much lower than theirs (44 $\mu g \cdot kg^{-1}$). This difference is probably due to our use of the CDI technique while they used the CD method. In comparing ED_{90} values for the myasthenic patients, the difference was much less, our value being 17 $\mu g \cdot kg^{-1}$ and theirs, 19

$\mu g \cdot kg^{-1}$. Both our study and that of Buzello *et al.*[5] found that the ED_{90} for vecuronium in myasthenic patients was approximately 55 per cent of control and, therefore, that patients with myasthenia gravis are approximately twice as sensitive to the neuromuscular blocking effects of vecuronium than are normal patients.

The administration of pyridostigmine to four of our myasthenic patients (#s 2, 3, 6, 10) on the morning of surgery produced a nonsignificant decrease in their sensitivity to vecuronium, the mean (±SEM) ED_{50} and ED_{90} values for these four patients being 12 ± 3 and 22 ± 6 compared with 10 ± 2 and 16 ± 2 $\mu g \cdot kg^{-1}$, in the other six myasthenic patients (NS), respectively. Compared with the 20 normal patients, these four myasthenic patients were still significantly more sensitive to vecuronium than were normal controls. In our institution, pyridostigmine is administered on the morning of surgery only to those myasthenic patients who require it and who would otherwise be markedly weak and therefore also psychologically uncomfortable.[13] One cannot therefore assume that pyridostigmine administered preoperatively on the morning of surgery has no effect on the sensitivity to vecuronium, but rather, that without it these four patients might have demonstrated increased sensitivity.

The three myasthenic patients who were receiving chronic therapy with corticosteroids and who received hydrocortisone on the morning of surgery also showed no significant difference from the other seven in their sensitivity to vecuronium (mean ± SEM, ED_{50}, ED_{95}, were 11 ± 4 and 21 ± 8 $\mu g \cdot kg^{-1}$ compared with 11 ± 2 and 17 ± 2 $\mu g \cdot kg^{-1}$, respectively). In our hospital, corticosteroids are used to treat those patients who have more severe symptoms of generalized myasthenia gravis.[13] The mechanism whereby corticosteroids improve the clinical condition of patients with myasthenia gravis is thought to be immunosuppression.[15] The interactions of corticosteroids at the neuromuscular junction in humans is unclear[16] and, in particular, conclusive data for their effects in patients with myasthenia gravis are not available.

Buzello *et al.*[5] also reported that the recovery times from vecuronium neuromuscular blockade were significantly prolonged in myasthenic patients. We were not able to study this aspect of vecuronium since in our patients isoflurane was used intermittently after the study period as described, and patients with myasthenia gravis have been shown to have an increased sensitivity to the neuromuscular blocking effects of the potent inhaled agents.[17] Clinically, however, all of our patients demonstrated adequate neuromuscular function following their surgery and anaesthesia.

In conclusion, we have used a cumulative dose plus infusion (CDI) technique and integrated EMG monitoring of the first dorsal interosseous muscle to determine the potency of vecuronium in 20 normal patients and in ten patients with myasthenia gravis. The myasthenic patients were more sensitive to vecuronium, the mean ED_{50}, ED_{90} and ED_{95} being 50, 55 and 56 per cent of normal, respectively. Vecuronium may be safely used in myasthenic patients provided that neuromuscular blockade is carefully monitored. There is a wide variability in the ED_{90} values among myasthenic patients so that if vecuronium is to be used, incremental doses of 5 $\mu g \cdot kg^{-1}$ titrated against quantified effect are recommended for these patients.

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