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Cumulative dose–response curves for atracurium in patients with myasthenia gravis

The potency of atracurium was determined in five patients with moderate to severe generalized myasthenia gravis undergoing thymectomy. Train-of-four stimulation was applied to the ulnar nerve and the force of contraction of the adductor pollicis was measured. Cumulative dose–response curves were obtained during thiopentone–nitrous oxide–fentanyl anaesthesia. The average time to complete the dose–response studies was 12.7 ± 1.5 minutes. The ED₅₀, ED₉₀ and ED₉₅ of atracurium were (mean $\pm$ SEM) 0.07 ± 0.01 , 0.12 ± 0.22 , and 0.14 ± 0.04 mg $\cdot$ kg⁻¹, respectively. The time to 25 per cent first twitch recovery was 35 ± 4 min following maximum blockade. Ten normal patients were studied in the same manner. Their ED₅₀, ED₉₀ and ED₉₅ were 0.13 ± 0.01 , 0.21 ± 0.02 and 0.24 ± 0.03 mg $\cdot$ kg⁻¹, respectively. These results demonstrated that, in patients with moderate to severe generalized myasthenia gravis, atracurium was 1.7–1.9 times as potent as in normal individuals.

Key words

PHARMACOLOGY: dose–response curves; NEUROMUSCULAR RELAXANTS: atracurium; COMPLICATIONS: myasthenia gravis.

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Myasthenia gravis is an acquired autoimmune disease associated with acetylcholine receptor deficiency at the motor end-plate.^{1–3} This deficiency is thought to be due to circulating acetylcholine receptor antibodies that result in the deposition of immune complexes (IgG and complement) on the post-synaptic membrane of the neuromuscular junction.^{4–8}

It is generally accepted that patients with myasthenia gravis may exhibit increased sensitivity to competitive nondepolarizing muscle relaxants.^{9–11} However, the response to atracurium besylate in these patients is quite variable, probably due to differences in severity of disease, concurrent drug therapy and methodology employed.^{12–19} The present study was designed to determine the potency of atracurium in patients with myasthenia gravis undergoing elective thymectomy using a cumulative dose–response technique.

Methods

After institutional approval and informed consent, five patients scheduled for elective thymectomy were studied. One hour before the scheduled surgery, patients received diazepam 0.1 mg $\cdot$ kg⁻¹ PO, and their usual oral dose of pyridostigmine and/or prednisone. After placement of an electrocardiograph, automatic blood pressure cuff and intravenous cannula, anaesthesia was induced with thiopentone, 3–5 mg $\cdot$ kg⁻¹ and maintained with nitrous oxide 66 per cent in oxygen and supplemental doses of thiopentone 0.5–1.0 mg per $\cdot$ kg⁻¹ and fentanyl 1–2 μ g $\cdot$ kg⁻¹ as required. Ventilation was provided with a bag and mask to maintain end–tidal PCO₂ between 30 and 35 mmHg (mass spectrometer). No volatile agent was given.

The ulnar nerve was stimulated supramaximally at the elbow with four square wave impulses 0.2 ms in duration delivered at a frequency of two Hz every 12 seconds using a Grass S48 stimulator and SIU 5 isolation unit. The hand and forearm were immobilized in a splint. The evoked force of contraction of the adductor pollicis muscle was measured with a Grass FT 10 force displacement transducer and recorded on paper. After stabilization of muscle twitch, cumulative doses of atracurium were administered

TABLE I Preoperative clinical characteristics of five patients with myasthenia gravis (means $\pm$ SEM are given below)

Sex	Age (yrs)	Weight (kg)	Height (cm)	Duration of myasthenia (months)	Current treatment (mg $\cdot$ day ⁻¹)	Other therapy
M	57	84	84	182	Pyridostigmine 180 Prednisone 60	Cimetidine Digoxin Moduret
M	20	55	163	26	Pyridostigmine 180 Plasmapheresis	None
M	53	91	173	22	Pyridostigmine 240 Prednisone 40	Cimetidine
F	55	83	155	7	Pyridostigmine 480 Plasmapheresis	Metoprolol Slow K Hydrochlorothiazide
F	63	54	163	10	Pyridostigmine 240 Prednisone 40	None
50 $\pm$ 8 73 $\pm$ 8 167 $\pm$ 5 18 $\pm$ 4					Pyridostigmine 264 $\pm$ 56	

until at least 95 per cent first twitch (T1) depression was observed. Each drug increment was given only after the effect of the previous dose had reached a stable response defined as three equal consecutive first twitches. The initial dose of atracurium was 0.05 mg $\cdot$ kg⁻¹. The incremental doses were 0.025 or 0.05 mg $\cdot$ kg⁻¹, depending on the response to the initial dose.

After maximal neuromuscular block, the patients' tracheas were intubated and isoflurane was introduced (end-tidal concentration 0.5–1.5 per cent as measured by a mass spectrometer). The operative procedure was then allowed to commence. No further muscle relaxant was given. Neuromuscular monitoring was continued throughout the procedure. Recovery of T1 and train-of-four ratio (T4/T1) following maximal neuromuscular blockade was noted. At the end of the surgical procedure, isoflurane and nitrous oxide were discontinued, and 100 per cent oxygen was administered. Reversal agents were not administered. If the patients were awake, cooperative, breathing well, and could sustain a head lift, their tracheas were extubated.

First twitch responses for the adductor pollicis muscle were compared with control values to construct dose-response curves. Linear regressions were obtained between the logit transformation of T1 depression at the adductor pollicis and log dose using the method of least-squares analysis.²⁰ A regression line was calculated for each patient, from which a mean dose-response curve was constructed. The calculated doses expected to produce 50, 90 and 95 per cent T1 depression (ED50, ED90, ED95) and their standard errors were determined from the

regression. The results were compared with those obtained for atracurium in ten normal individuals using the same cumulative dose technique during thiopentone-fentanyl-nitrous oxide anaesthesia.²¹ In the case of normal patients, however, the initial dose of atracurium was 0.1 mg $\cdot$ kg⁻¹, followed by 0.05 mg $\cdot$ kg⁻¹. Results are expressed as mean values $\pm$ SEM.

Results

All patients were suffering from moderate to severe generalized myasthenia (Osserman grade 2B)²² which was characterized by moderate to severe skeletal and bulbar involvement in the absence of respiratory crises. In addition to pyridostigmine therapy, four of the five patients were treated with oral steroids, and two received preoperative plasmapheresis. Patient information is summarized in Table I.

A total of three to four doses of atracurium was required to achieve 95 per cent or greater T1 depression. Maximum effect from the initial dose occurred within five minutes after its injection and within three minutes after the subsequent doses. The average time to complete the dose-response studies was 12.7 $\pm$ 1.5 min. In normal individuals, this time was 10.2 $\pm$ 0.8 min, which required three to four doses of atracurium. Patients with myasthenia gravis were 1.7 to 1.9 times more sensitive to atracurium than normal individuals (Figure). The regression lines were parallel (slope = 4.40 $\pm$ 0.50 myasthenia versus 4.85 $\pm$ 0.27 normal individuals). The potency estimates derived from the regression from patients with myasthenia gravis and normal individuals are compared

FIGURE Dose-response relationships for atracurium in patients with myasthenia gravis ($n = 5$, cumulative dose technique) and in normal individuals ($n = 10$, cumulative dose technique).²¹ The logit transformation of first twitch depression is plotted as a function of the logarithm of the dose. Error bars represent SEM.

in Table II. The recovery characteristics are summarized in Table III. It was not possible to monitor recovery of the adductor pollicis in all patients due to surgical positioning. The recovery index (25–75 per cent T1 recovery) was 19 ± 6 minutes. The tracheas of all patients were extubated at the conclusion of surgery while still in the operating room. The average duration of surgery was 106 ± 2.4 minutes. The postoperative courses were uneventful.

Discussion

This study demonstrated the increased sensitivity of patients with myasthenia gravis to the nondepolarizing muscle relaxant atracurium. This is presumably due to the deficiency of acetylcholine receptors at the neuromuscular junction.¹ Acetylcholine receptor deficiency may result from complement mediated lysis of the junctional folds on the postsynaptic membrane of the motor end plate, accelerated internalization and destruction of the acetylcholine receptor cross linked by antibody (modula-

TABLE III Time to achieve recovery (first twitch- T1 and train-of-four-T4/T1) following maximal atracurium blockade in myasthenic patients (means $\pm$ SEM)

T1/Contro	T4/T1	Time (min)	Number of patients
5%	0	24 ± 4	4
10%	0	28 ± 4	4
25%	23 ± 4	35 ± 4	3
50%	45 ± 6	43 ± 5	3
75%	71 ± 2	55 ± 4	2
90%	74 ± 6	66 ± 2	2
95%	82 ± 9	75 ± 6	2

tion), and to a lesser degree by antibodies which block the binding of acetylcholine to the acetylcholine receptor.^{2-6,23-25}

The ED90 estimates obtained in this study were somewhat lower than those obtained by Baraka and Dajani in patients with myasthenia gravis undergoing thymectomies.¹² In their study of three patients, the cumulative dose of atracurium required to abolish the fourth to second twitch of the train-of-four (which corresponds to approximately 75–90 per cent block) ranged from 0.09 to 0.21 $\text{mg} \cdot \text{kg}^{-1}$. On the other hand, the ED90 obtained in the present study ($0.12 \text{ mg} \cdot \text{kg}^{-1}$) was greater than in previous case reports describing the use of atracurium in patients with myasthenia. For example, Bell *et al.*¹⁵ found that, in four of five patients studied, atracurium 0.1 $\text{mg} \cdot \text{kg}^{-1}$ was sufficient to produce abolition of twitch response during thiopentone-fentanyl-nitrous oxide anaesthesia. However, the difference in potency may partly be because their patients did not receive their anticholinesterase therapy on the morning of surgery and only received two-thirds of their usual oral dose of pyridostigmine the evening before surgery, whereas all patients in the present study received their usual oral dose of pyridostigmine up to and including the morning of surgery. The patient in Ramsey and Smith's study also exhibited increased sensitivity to atracurium compared with our patients, with complete neuromuscular blockade occurring after two minutes with only 0.06 $\text{mg} \cdot \text{kg}^{-1}$ of atracurium¹⁷. However, succinylcholine had been employed for tracheal intubation which may have altered the sensitivity of their patient's neuromuscular junction. Vacanti *et al.*¹⁶ reported two myasthenic patients who were given cumulative doses of atracurium. One required 0.35 $\text{mg} \cdot \text{kg}^{-1}$ while the other needed only 0.05 $\text{mg} \cdot \text{kg}^{-1}$ for 90 per cent blockade. Our results lie between these two extremes.

The cumulative dose-response technique is extremely helpful in evaluating the potency of neuromuscular blocking agents.^{26,27} The technique is especially well suited for determining dose-response relationships in

TABLE II Potency estimates of atracurium in five patients with myasthenia and 10 normal individuals²¹ (means $\pm$ SEM)

	Myasthenia	Normals
ED50 ($\text{mg} \cdot \text{kg}^{-1}$)	0.07 ± 0.01	0.13 ± 0.01
ED90 ($\text{mg} \cdot \text{kg}^{-1}$)	0.12 ± 0.02	0.21 ± 0.02
ED95 ($\text{mg} \cdot \text{kg}^{-1}$)	0.14 ± 0.04	0.24 ± 0.03

patients with neuromuscular abnormalities such as myasthenia gravis, since a dose-response curve can be obtained in a single individual²⁸ and, therefore, fewer patients are required to produce statistically reliable potency estimates. The cumulative dose-response technique may underestimate potency due to the relatively rapid elimination and/or redistribution of atracurium during administration of incremental doses.^{29,30} For atracurium, the ED50 and ED95 can be calculated to be 14 per cent and 26 per cent greater with cumulative compared with single dose-response curves.²¹ However, because the duration of the study and the number of doses given were approximately the same in myasthenics and in normals, the error involved is likely to be the same in both groups. Thus, although the actual values of ED50 and ED95 might have been slightly lower than reported here, this would not alter the potency ratio between myasthenics and normals.

The spontaneous recovery of neuromuscular function following greater than 95 per cent T1 depression with atracurium in the present study was similar to that of normal individuals who received the same anaesthetic.^{31,32} The recovery index (25 to 75 per cent recovery of T1) was 17 min in our patients compared with 21 min in normal individuals under isoflurane-nitrous oxide anaesthesia.³¹ This indicates that once recovery starts, time to return to full neuromuscular function is not prolonged in myasthenics. All patients in the study recovered neuromuscular function spontaneously without the need for reversal agents, and were able to be extubated at the end of the surgical procedure. The fact that no patient in the present study required postoperative ventilatory support is in agreement with the scoring criteria of Leventhal *et al.*³² who applied multivariate discriminant analysis retrospectively to preoperative physical, historical and laboratory data of 24 myasthenic patients in order to identify risk factors that would predict the need for postoperative mechanical ventilation. None of the patients in the present study had any preoperative risk factor. For example, the duration of myasthenia gravis was 7–26 months, the total daily dose of pyridostigmine was 180–480 mg and no patient had any history of respiratory disease or evidence of impaired vital capacity.

Although the clinical course of myasthenia gravis can vary greatly between patients due to severity of the disease process and the response to drug therapy, the present study suggests that atracurium is 1.7–1.9 times more potent in patients with moderate to severe generalized myasthenia gravis compared with normal individuals. We conclude that atracurium may be safely employed for muscle relaxation in patients with myasthenia. However, since the potency of atracurium is increased in these patients, and the duration of action may be slightly

prolonged, clinical monitoring of neuromuscular function is strongly recommended.

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Résumé

On a étudié la relation dose-effet de l'atracurium chez cinq sujets atteints de myasthénie grave subissant une thymectomie. On a enregistré la force de contraction de l'adducteur du pouce suite à l'application d'une stimulation en train-de-quatre appliquée au nerf cubital, pendant une anesthésie au thiopental, protoxyde d'azote et fentanyl. On a donné des doses successives d'atracurium pendant une période de 12.7 ± 1.5 minutes, pour étudier la relation dose-effet. Les DA50, DA90 et DA95 étaient de (moyenne $\pm$ ETM) 0.07 ± 0.01 , 0.12 ± 0.02 et 0.14 ± 0.04 mg $\cdot$ kg⁻¹, respectivement. Le temps entre le bloc maximum et 25 pour cent de récupération du premier twitch était de 35 ± 4 minutes. On a étudié dix sujets normaux de la même manière. Leur DA50, DA90 et DA95 s'établissaient à 0.13 ± 0.01 , 0.21 ± 0.02 et 0.24 ± 0.03 mg $\cdot$ kg⁻¹, respectivement. On en conclut que l'atracurium est de 1.7 à 1,9 fois plus efficace chez les myasthéniques modérés à graves que chez les sujets normaux.