Clinical use of atracurium in myasthenia gravis: a case report

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A patient with myasthenia gravis was anaesthetized for thymectomy utilizing atracurium for maintenance of muscle relaxation. The patient was not taking anticholinesterase medications before surgery. Neuromuscular function was monitored by recording the train-of-four response to supramaximal stimulation of the ulnar nerve. Anaesthesia was induced with thiopentone and maintained with isoflurane and N₂O in oxygen. Following complete recovery from a succinylcholine block for intubation, the patient developed complete neuromuscular block within two minutes after atracurium (5 mg) was administered. Evidence of recovery commenced 12 minutes later and was complete at 72 minutes. This rate of recovery is consistent with the recovery rate from atracurium during isoflurane anaesthesia in normal patients. Atracurium appears to offer an advantage over other nondepolarizing muscle relaxants in patients with myasthenia gravis due to its shorter duration and less cumulative effect at the neuromuscular junction.

Key words

NEUROMUSCULAR RELAXANTS: atracurium;
MYASTHENIA GRAVIS.

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Myasthenia gravis is an autoimmune disease characterized by a reduction of functional acetylcholine receptors at the neuromuscular junction. Antibody attack leads to accelerated destruction of the receptors, as well.^{1,2} This results in a decreased neuromuscular margin of safety in affected patients who are extremely sensitive to nondepolarizing muscle relaxants. Most patients show clinical improvement with anticholinesterase agents. Cortico-steroids are also efficacious by interfering with the immunologic mechanisms central to the disease. Due to its shorter clinical duration of action and more rapid clearance from plasma via Hofmann elimination, atracurium poses theoretical advantages compared to longer acting nondepolarizing relaxants in the anaesthetic management of patients with myasthenia gravis. We report the successful use of atracurium in a myasthenic patient treated only with steroids.

Case report

A 34-year-old male with myasthenia gravis diagnosed one year earlier was admitted for elective thymectomy. His symptoms included diplopia, hand weakness and easy fatigability. After a positive test with edrophonium he began medical treatment that included both pyridostigmine and neostigmine with atropine. He was unable to tolerate the side effects of these and they were discontinued. He was placed on prednisone at a maximum dose of 60 mg/day that had been tapered to 7.5 mg every other day at the time of admission. He had undergone repeated plasmapheresis without improvement. Additionally, the patient had mild hypertension, moderate obesity (87 kg, 175 cm) and a history of oesophagitis ten months prior to admission that was asymptomatic since that time. Admission laboratory values were normal except for a serum glucose of 223 mg·dl⁻¹.

FIGURE Train of four response following 5 mg ($57 \mu\text{g}\cdot\text{kg}^{-1}$) bolus ($\uparrow$) of atracurium in a patient with myasthenia gravis. T_1 = first response in train of four as per cent of control. T_4 is ratio of fourth response to first response in a given train.

Following a preoperative explanation of the relative advantages and disadvantages of muscle relaxants in the setting of his disease, the patient consented to receive atracurium to facilitate anaesthetic management while its effects on his neuromuscular function were monitored. He received cimetidine (300 mg) the night before surgery and was premedicated with oral diazepam (10 mg) and cimetidine (300 mg) as well as intramuscular hydrocortisone (100 mg) 75 minutes prior to induction of anaesthesia. Utilizing one per cent lidocaine for local anaesthesia a 14-gauge intravenous catheter was started in his right arm as well as a 20-gauge arterial cannula in his right radial artery. A blood gas while breathing room air at rest revealed PaO_2 83 mmHg, PaCO_2 36 mmHg, pH 7.45, and HCO_3^- 24.2 $\text{mEq}\cdot\text{L}^{-1}$.

Monitoring of vital signs included blood pressure by arterial line, heart rate and temperature by a mid-oesophageal probe and continuous recording of the electrocardiogram. The arterial waveform was transduced with a Gould P23ID transducer and displayed on a Hewlett Packard 8805C monitor. Temperature, measured with a Monatherm monitor, was maintained at 36.5 – 36.6°C with the aid of a HumidiventTM placed between the endotracheal tube and the semiclosed breathing circuit. Ventilation during the procedure was controlled mechanically with a tidal volume of 900 cc at a frequency of eight breaths per minute. Arterial blood gas values during surgery were obtained in the following ranges: PaO_2 (105–178 mmHg), PaCO_2 (40–46 mmHg), pH (7.33–7.40), HCO_3^- (23.0–24.0 $\text{mEq}\cdot\text{L}^{-1}$). Neuromuscular function was monitored by recording the evoked twitch responses

with a Grass FT-10 force displacement transducer to train of four (T_4) stimulation of the ulnar nerve. Trains of four ($2\text{Hz} \times 2\text{sec}$) supramaximal stimuli were delivered from a Grass S88 nerve stimulator and SIU5 isolation unit via 25-gauge stainless steel needle electrodes placed subcutaneously in the forearm. The T_4 response was recorded every ten seconds on a Grass polygraph (model 7D).

After preoxygenation, anaesthesia was induced with thiopentone (350 mg). Following succinylcholine (100 mg) complete neuromuscular block occurred in 45 seconds and the trachea was intubated without difficulty. Maintenance anaesthesia consisted of isoflurane (1–2.5 per cent inspired) and N_2O in 50 per cent O_2 . Complete neuromuscular block lasted seven minutes and full recovery to control train of four required an additional 15 minutes. Atracurium (5 mg) was then administered and complete neuromuscular block recurred in 2 min. Spontaneous recovery of T_4 over the next 72 min is shown in the Figure. No additional muscle relaxants were used. Thymectomy was accomplished via a median sternotomy and proceeded uneventfully except for sudden bradycardia to 35/min and hypotension to 60/30 associated with surgical traction. This was treated effectively with atropine (0.4 mg) and did not recur. At the conclusion of surgery, although the T_4 equalled the control response, the patient was given edrophonium (10 mg) and atropine (0.4 mg) with a small enhancement (5 per cent) of all four responses. A second dose of edrophonium (10 mg) had no effect on T_4 . Arterial blood gas results during spontaneous ventilation of 50 per cent O_2 were PaO_2 175 mmHg, PaCO_2 45 mmHg, pH 7.33, HCO_3^- 24

mEq·L⁻¹. The patient was transported to the recovery room intubated and given 100 per cent O₂ to breathe. Fifteen minutes later he was extubated fully responsive with good motor strength. He was given 60 per cent O₂ by faceshield and continued to have excellent blood gases. A postoperative chest x-ray confirmed bilateral lung expansion. He recovered uneventfully during 24-hour observation in the intensive care unit.

Discussion

As expected, this patient exhibited a marked sensitivity to atracurium, a nondepolarizing muscle relaxant. This is consistent with the sensitivity to curare in a steroid treated myasthenic described by Lake.³ In addition to the patient's disease a steady state of isoflurane anaesthesia⁴ and prior use of succinylcholine⁵ for intubation have been reported to potentiate the effects of atracurium. The 5 mg bolus (0.057 mg·kg⁻¹) of atracurium that our patient received produced a rapid and complete neuromuscular block comparable to the block produced in normal patients following 0.3 mg·kg⁻¹ atracurium during isoflurane anaesthesia reported by Sokoll *et al.*⁴ These authors found the ED₉₅ of atracurium during isoflurane anaesthesia to be 0.13 mg·kg⁻¹. At 2.3 × ED₉₅ (0.3 mg·kg⁻¹) the mean onset time to complete block in Sokoll's study was two minutes, very comparable to the onset time we observed in our patient. Despite the patient's marked sensitivity to atracurium he regained neuromuscular function at a rate similar to the normal patients in Sokoll's study. Following 0.3 mg·kg⁻¹ atracurium, 95 per cent recovery occurred in 67.3 ± 5.9 min in Sokoll's study. This compares favourably with our patient's 95 per cent recovery time of 62 minutes.

Two other case reports have described the successful use of atracurium in patients with myasthenia gravis. Ward and Wright⁶ titrated 2 mg increments of atracurium to a total dose of 8 mg to achieve 80–90 per cent block during halothane anaesthesia. Their patient was on chronic anticholinesterase therapy and received both neostigmine and pyridostigmine the morning of surgery. MacDonald *et al.*⁷ described a patient on both anticholinesterase and steroid therapy who required near normal doses of atracurium during balanced anaesthesia. Spontaneous recovery of twitch in both these patients did not differ from that expected in the

normal population. Our patient differed from these two reported cases in that he was not on chronic anticholinesterase therapy nor did he receive an anticholinesterase as part of the preanaesthetic regimen. Thus, his sensitivity to atracurium was greater and more clearly approximated the virginal myasthenic state. Had he been undiagnosed and not treated with steroids, we expect he would have demonstrated even greater sensitivity to atracurium.

Based on the known pharmacokinetics of atracurium and these three reports of normal recovery from given degrees of block from atracurium in myasthenia, it is tempting to speculate about the consequences of giving a patient with myasthenia a typical intubating dose of atracurium. The 5 mg our patient received was approximately 1/8 the 40 mg dose one might routinely administer. Weatherly *et al.*⁸ found the elimination half life of atracurium to be 20.0 ± 0.6 min (n = 19). Since 1/8 = (1/2)³ it would require three half lives or approximately 60 minutes for a plasma level achieved with 40 mg to diminish to a plasma level achieved with 5 mg. The extended two compartment open model developed by Weatherly *et al.* predicts that the neuromuscular effects of atracurium parallel the concentration of drug at the receptor sites which lags behind the plasma level described by pharmacokinetic parameters. Thus, a longer clinical half life than plasma half life might be expected with atracurium. Complete neuromuscular block requires blockade of approximately 90 per cent of the post-synaptic receptors at the neuromuscular junction. Minimal peripheral block occurs with 75 per cent receptor blockade. Waud⁹ has shown that the concentration of antagonist required to provide nearly a complete block is roughly twice that required for minimal block. Thus, an individual patient's clinical half life is approximated by the time required for complete recovery of twitch to occur once recovery commences. In our patient this was approximately 42 minutes. Therefore, although three plasma half lives occur in one hour, three clinical half lives require two hours. We believe the actual recovery would have been somewhere between these two extremes. This is supported further by Weatherly's model which predicts the concentration in the effect compartment and that in the plasma equilibrate in about one hour. Therefore, had we mistakenly given the patient 40 mg atracurium he should

only have required approximately an additional 90 minutes to fully recover.

We agree with Ward and Wright⁶ and MacDonald *et al.*⁷ that atracurium offers a significant advantage over longer-acting nondepolarizing relaxants in the anaesthetic management of patients with myasthenia gravis. Although one should anticipate the required dose of atracurium to be less in myasthenic patients compared to normal patients, the spontaneous rate of recovery appears to be normal. The severity of the patient's disease, concurrent drug therapy, other anaesthetic agents, as well as inherent individual sensitivity, all interact in a complex way to determine the patient's response. Clinical monitoring of neuromuscular function permits safe titration of atracurium in patients with myasthenia gravis.

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Résumé

Un patient atteint de myasthénie a été anesthésié pour une thymectomie utilisant l'atracurium pour le relachement musculaire. Le patient n'était pas traité avec les anticholinestérasiques avant la chirurgie. La fonction neuromusculaire a été surveillée par l'enregistrement du "train-of-four" (ondée de quatre) après stimulation supramaximale du nerf cubital. L'anesthésie a été induite avec du thiopentone et maintenue avec l'isoflurane et protoxide d'azote/oxygène. Après la reprise de la fonction neuromusculaire suite à l'administration de succinylcholine pour l'intubation, le patient a développé un bloc neuromusculaire complet en dedans de deux minutes post-administration d'atracurium (5 mg). Un début de reprise de la fonction neuromusculaire a été noté 12 minutes plus tard et complété à 72 minutes. La vitesse de reprise de la fonction neuromusculaire est similaire à celle observée lors de l'utilisation de l'atracurium durant l'anesthésie à l'isoflurane chez les patients normaux. L'atracurium semble offrir un avantage sur les autres relaxants musculaires non dépolarisants chez les patients atteints de myasthénie à cause de sa courte durée d'action et du moindre effet cumulatif à la jonction neuromusculaire.