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## The Response of Myasthenia Gravis to Atracurium

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Patients with myasthenia gravis generally are believed to have increased sensitivity to nondepolarizing muscle relaxants. However, some authors do not agree with this conclusion. For example, two clinical reports described the response of one myasthenic patient each, receiving steroids and pyridostigmine therapy. In the first, the author concluded that myasthenic patients are quite sensitive to *d*-tubocurarine and require greatly reduced doses.<sup>1</sup> However, in the second report the authors did not find an increased sensitivity to *d*-tubocurarine.<sup>2</sup> Other authors reported on the use of very small doses of pancuronium 5.0 µg/kg, which produced 90% twitch suppression with uneventful recovery. On the other hand, resistance and early appearance of phase II block have been reported following the administration of succinylcholine.<sup>4</sup> Recently, the use of the new intermediate-acting nondepolarizing relaxant atracurium has been reported in six patients with myasthenia gravis.<sup>5-7</sup> The unique mode of elimination of atracurium may offer an advantage over the previously available long-acting muscle relaxants.

We present two additional case reports of the anesthetic management of two myasthenic patients using atracurium. Our findings are compared with previous reports.

### REPORT OF TWO CASES

*Case 1.* A 64-year-old woman, weighing 76 kg, was scheduled for an elective sigmoid colectomy for diverticulitis. She presented with a 2-year history of myasthenia gravis manifested with bulbar symptoms and progressive limb weakness. She first was diagnosed in 1982 with electromyography and a positive edrophonium test. The patient also had a history of hypertension and insulin-dependent adult-onset diabetes mellitus. Initially she was taking pyridostigmine with improvement of her symptoms. However, increasing gastrointestinal symptoms as well as dysphagia and a questionable history of aspiration of gastric contents caused her physician to begin her on a regimen of steroids, tapering her dose of pyridostigmine to none by January 1983. The patient underwent plasmapheresis in August 1983. She experienced marked improvement of her symptoms. Upon admission, her pulmonary function tests were 85% of normal, with a vital capacity of 2.5 l. Prior computerized axial tomography and chest roentgenography were negative for thymoma. Her prednisone dosage had been decreased to 12 mg per day. Preoperatively, she received 5 mg diazepam, po, 30 U NPH insulin, subcutaneously, and 100 mg hydrocortisone, iv. Anesthesia was induced using a total of 300 µg fentanyl, 10 mg diazepam, and 200 mg thiopental, iv. Force of thumb adduction was monitored in response to ulnar nerve stimulation (0.2 ms at a frequency of 0.15 Hz) at the wrist via two percutaneous needle electrodes using a Grass FT-10® force transducer and a Grass® polygraph. Incremental doses of atracurium 0.065 mg/kg (5 mg) each were given every 4 min until the twitch height was depressed to 5% of control. A total dose of 25 mg (0.33 mg/kg) was required to achieve 95% depression of the control response (fig. 1). Two incremental doses of atracurium, 5.0 mg each, were given further as clinically indicated over the next hour. One hour after induction of anesthesia, halothane was added at an inspired concentration of 1.0%, and up to 20 mg hydralazine was given to control hypertension. After the last 5-mg dose of atracurium, the twitch was allowed to recover spontaneously to 95% of control. The pH was maintained between 7.43 and 7.46, with a PaCO<sub>2</sub> from 33 to 38 mmHg. Serum sodium and potassium concentrations were normal, and blood sugar was 233 mg/dl. The 5-95% recovery time was estimated to be 83 min. The recovery index (25-75% recovery time) was 32 min (fig. 1). Four hours after induction of anesthesia, clinical relaxation was required, and further incremental doses of atracurium to a total of 20 mg were given over the next half hour without complete ablation of the first twitch of the train-of-four. The patient was taken to the intensive care unit 6 h after induction of anesthesia. At this time she was arousable and had a tidal volume of 300 ml.

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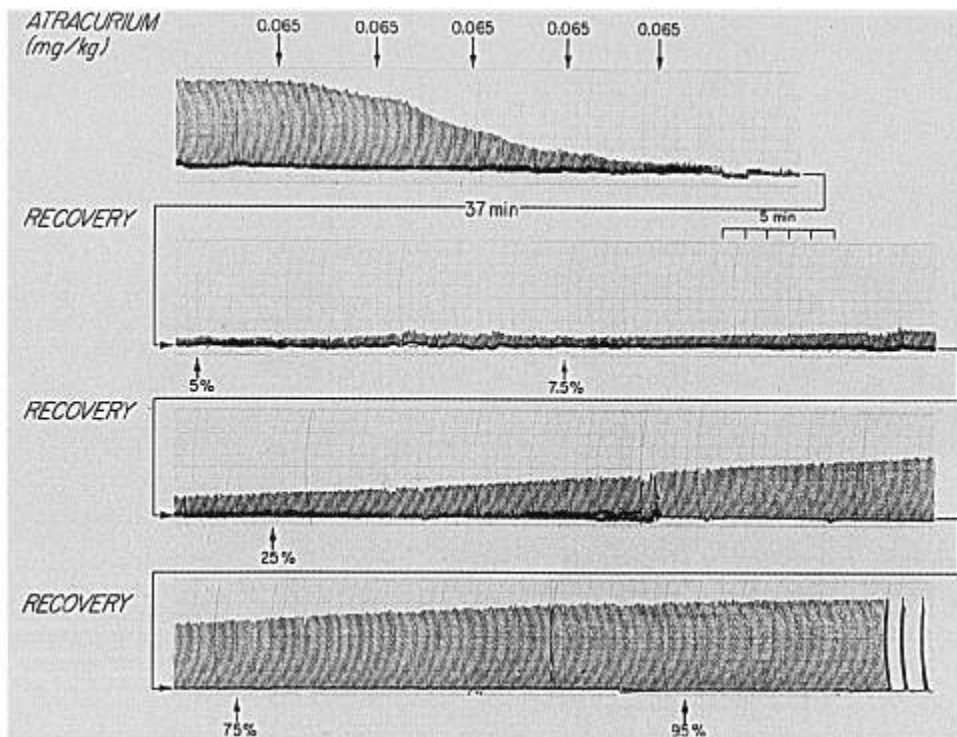
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FIG. 1. Evoked thumb adduction in response to ulnar nerve stimulation at 0.15 Hz. Upper panel demonstrates the response to five increments of atracurium of 0.065 mg/kg each. In the second panel from above, two further increments of 0.65 mg/kg were given 15 min after the arrow, denoting 5% with minimal effect. At the second arrow (7.5%), spontaneous recovery was followed up as, in the third and fourth panels. The following three arrows denote 25, 75, and 95% recovery of the single twitch as compared with the control. Note at the end of the last panel (right side) train-of-four response showed almost complete recovery. See details in the text.



She became more alert over the next hour, and her tidal volume increased to 400 ml, with a vital capacity of 1,600 ml and a negative inspiratory pressure of 40 cmH<sub>2</sub>O. Decreasing rates of intermittent mandatory ventilation (IMV) were instituted, after which a trial of spontaneous ventilation with continuous positive airway pressure (CPAP). Four-and-a-half hours postoperatively, her trachea was extubated without difficulty with a vital capacity of 1,500 ml. Postoperatively she did very well and was discharged on a daily dose of 12.5 mg prednisone. Muscle function upon discharge was reported to be good.

**Case 2.** A 28-year-old woman weighing 60 kg presented with a 3-year history of myasthenia gravis. She was admitted to undergo transradial thymectomy for treatment of her disease. At the time of her admission, the patient was well controlled with a daily dose of 480 mg pyridostigmine and steroid therapy. She had no bulbar symptoms or limb weakness. The night before surgery she was given a long-acting spansule containing 180 mg of pyridostigmine. Anesthesia was induced with 250 mg thiopental iv and maintained with 60% nitrous oxide in oxygen and 1.5% inspired concentration of isoflurane. Her trachea was intubated without the use of muscle relaxants after spraying the vocal cords and trachea with 4% lidocaine. Anesthesia was maintained thereafter with isoflurane 0.7% (end-tidal concentration) and 60% nitrous oxide in oxygen and controlled ventilation. Thumb twitch was monitored visually in response to ulnar nerve stimulation at the wrist via percutaneous needle electrodes using a train-of-four nerve stimulator. Initially, 1 mg atracurium was administered iv, with no visible effect. Five minutes later, an additional 2 mg atracurium was given (a total dose of 0.05 mg/kg). This resulted in approximately 95% depression of evoked thumb twitch adduction based on the train-of-four response. Twenty-five minutes later, the train-of-four appeared to have recovered completely. Upon completion of surgery, 90 min after induction, the patient received 10 mg pyridostigmine iv, and her trachea was extubated shortly thereafter in the operating room. She was returned to the intensive care unit in stable condition. Her postoperative course was uneventful.

## DISCUSSION

Previous reports<sup>1-3</sup> suggest that the response of patients with myasthenia gravis to nondepolarizing relaxants (pancuronium and *d*-tubocurarine) is variable, probably depending on the stage of the disease, the preoperative control, and whether the patient is in remission. The use of the new intermediate-acting nondepolarizing relaxant atracurium has been reported recently in six myasthenic patients.<sup>5-7</sup> In the first report<sup>5</sup> approximately 0.18 mg/kg of atracurium administered incrementally was required to suppress the evoked twitch tension to 95% of control response. In the second report, a total dose of 0.25 mg/kg atracurium given in three increments was required to depress the evoked compound action potential of the adductor pollicis muscle to 90% of control, and 0.1 mg/kg in the third report. In our cases the dose required to suppress evoked thumb adduction varied between 0.33 and 0.05 mg/kg, respectively. It appears that, as with other nondepolarizing relaxants reported, the response of myasthenic patients to atracurium (onset and depth of block) is also variable. In three of eight patients who received atracurium, the ED<sub>95</sub> (the effective dose to 95% twitch suppression) was not different from that reported in normal nonmyasthenic patients (*e.g.*, 0.2 mg/kg).<sup>8,9</sup> The important finding in these case reports is that myasthenic patients who were given atracurium recovered spontaneously from their neuromuscular blockade within a reasonably and relatively short time. In our first case, the recovery

index (25–75% recovery time) and the 5–95% recovery time were 32 min and 83 min, respectively, compared with approximately 12 min and 30 min, respectively, in normal patients.<sup>9</sup> The recovery time was even much shorter in the other myasthenic patients. This relatively rapid spontaneous recovery from atracurium neuromuscular blockade as compared with the older muscle relaxants, *d*-tubocurarine and pancuronium, may be related to its mode of biodegradation and elimination. Atracurium under normal body temperature of 37° C and pH of 7.4 spontaneously is broken down at the two quaternary nitrogens to inactive metabolites (Hofmann elimination) and enzymatic ester hydrolysis independent of plasma cholinesterase.<sup>10</sup> It should be realized that the 5–95% recovery time of 83 min in our first patient followed a total dose of atracurium of 0.46 mg/kg. The latter dose is equivalent to two times the ED<sub>95</sub>.<sup>9</sup> A comparable dose of *d*-tubocurarine and pancuronium would be approximately 1.0 mg/kg and 0.14 mg/kg, respectively.<sup>11</sup> It is conceivable that if either of the latter two doses of *d*-tubocurarine or pancuronium were administered to this myasthenic patient, the recovery from neuromuscular blockade would have been prolonged markedly in comparison with atracurium. This is based on the finding that the recovery from injection of *d*-tubocurarine 0.6 mg/kg and pancuronium 0.1 mg/kg to only 25% of control is 80.5 ± 6.9 min and 99.3 ± 15.0 (mean ± SEM), respectively, in normal patients.<sup>11</sup>

In summary, atracurium appears to be a reasonable choice for myasthenic patients to provide surgical relaxation when clinically indicated. This is primarily because

of the relatively rapid rate of recovery. Still, the use of atracurium does not alleviate the need for monitoring neuromuscular function. Obviously, the key to the proper and safe use of not only atracurium, but any other muscle relaxant, is monitoring neuromuscular function.

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