SENSITIVITY TO BOTH VECURONIUM AND NEOSTIGMINE IN A SERO-NEGATIVE MYASTHENIC PATIENT

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Myasthenia gravis is now identified as an autoimmune disease involving the destruction of acetylcholine receptors (AChR) at the postjunctional membranes of skeletal muscles. As a result of this antibody-mediated reaction, the number and half-life of receptors are diminished. Therefore, the severity of the disease is approximately related to the titre of anti-AChR antibody and the degree of destruction of the junctional membrane [1]. However, in approximately 30% of those myasthenic patients with symptoms restricted to ocular muscles, anti-AChR antibody could not be demonstrated. Mossman, Vincent and Newsome [2] suggested that this type of sero-negative myasthenia was immunologically and physiologically distinct from the AChR antibody-positive type. An immunoglobulin antibody of these sero-negative patients interferes with neuromuscular transmission by binding to determinants other than those on the AChR. In experimental autoimmune myasthenia gravis, Takamori, Okumora and Yasuda [3] showed that antibody to the receptor site near the acetylcholine (ACh) binding site may act presynaptically and may enhance the evoked release of ACh to compensate for postsynaptic failure.

We report a sero-negative ocular myasthenic patient who developed prolonged depolarizing block with apnoea following administration of neostigmine.

CASE REPORT

For 6 months before admission for thymectomy, a 35-yr-old black female had been followed up for evaluation of ptosis, involving mainly the left eyelid. The degree of ptosis was not associated with the time of day or fatigue. Detailed in-hospital investigations were performed 6 and 3 months before the present admission. Repeated edrophonium tests were equivocal. Electromyographic studies failed to show a decremental response on the right abductor pollicis brevis and the trapezius muscles to repetitive stimulation of the median and the spinal accessory nerves, respectively. The tests for AChR antibody on each admission were within the normal range. A computerized axial tomography of the chest showed a slightly prominent thymus, suggesting hyperplasia. It was concluded that the patient had sero-negative ocular myasthenia gravis. After the initial investigation the patient was given pyridostigmine 60 mg orally twice daily. Initially the medication provided some subjective improvement of the ptosis. Two months later, the medication was discontinued by the patient because she felt that it was no longer helping the...
ptosis, and this did not exacerbate the condition. During the initial investigation, hyperthyroidism was discovered. After radioactive iodine treatment, the patient became hypothyroid and required therapy with L-thyroxine 0.1 mg daily. The patient was referred to the Mayo Clinic for another opinion regarding the management of hyperplastic thymus and ocular symptoms. Further studies at the Mayo Clinic revealed the following results: electromyography showed a 17% decrement on 2-Hz stimuli in the left biceps and a lesser decrement in the left trapezius muscle; single fibre electromyography of the left common finger extensor muscles showed no abnormality; tests for AChR antibodies, including binding and modulating antibodies, were in the normal range. Diagnosis of sero-negative ocular myasthenia gravis was confirmed. The following were suggested: although her myasthenia was sero-negative, thymectomy was advised to prevent further progress of the disease; the ptosis could be improved by use of an eyelid clutch; there was no need for the use of an anticholinesterase, azathioprine, or steroid therapy.

On admission for thymectomy, the patient was a well developed and well nourished female, weighing 62 kg. Two previous general anaesthetics for bunionectomy and tubal ligation 2 and 3 years previously were uncomplicated. Current medication comprised L-thyroxine 0.1 mg daily. Muscle strength in all four extremities appeared grossly normal. Drooping of the left eyelid was noted. Preoperative laboratory studies, including complete blood count, serum chemistry and coagulation profiles, ECG and chest x-ray, were within normal ranges. Pulmonary function tests showed predicted normal values for routine spirometry and maximum voluntary ventilation. Arterial blood-gas analysis (FiO₂ = 0.2) showed pH 7.40, Pa CO₂ 5.4 kPa, Pa O₂ 14.3 kPa.

In addition to routine intraoperative monitoring devices, a Datex NMT Monitor 221 was applied to her left forearm. The NMT Monitor delivered supramaximal train-of-four stimuli to the ulnar nerve every 20 s, and measured the evoked compound action potential of the hypothenar muscles. The measured values are the ratio of the first to control twitch response (T1:T0) and train-of-four ratio (T4:T1). Anaesthesia was induced with midazolam 1 mg, fentanyl 0.05 mg and thiopentone 300 mg i.v. During ventilation of the lungs with oxygen and isoflurane by face mask, a stable 3-min control tracing of the NMT Monitor was recorded. There was no train-of-four fade. Vecuronium 2 mg was administered. The maximum twitch depression (T1:T0 = 5%) was achieved at 4 min and the trachea was intubated at 5 min. Anaesthesia was maintained with 1–2% isoflurane and 70% nitrous oxide in oxygen; fractional doses of vecuronium (total 3.5 mg), fentanyl (0.1 mg), and midazolam (2 mg) were administered also. When T1:T0 and T4:T1 recovered to 70% and 50%, respectively, at 45 min after the initial dose, the second dose of vecuronium 0.5 mg resulted in T1:T0 suppression to 18% and eliminated the T4 response. Forty minutes after the last dose of vecuronium 0.5 mg, T1:T0 and T4:T1 had recovered 70% and 100%, respectively. These values remained unchanged and the patient resumed spontaneous breathing with good tidal volume during the remaining 20 min of surgery. Even though the

![Fig. 1. Tracing of evoked hypothenar electromyographic responses to train-of-four stimuli in a patient with myasthenia gravis. Two different types of neuromuscular block, one resulting from vecuronium and the other resulting from antagonizing agents, are shown. The former is a typical non-depolarizing block, but the latter resembles a depolarizing block. Two (T1 and T4) train-of-four twitch responses are printed. The light lines are T1 twitch responses, and the overlapped darker lines are T4 twitch responses. Elapsed times were recorded every 15 min.](http://bja.oxfordjournals.org/)
DISCUSSION

Because the normal neuromuscular end-organ has a large excess of receptor sites, transmission in response to single pulses or tetanic pulses at 30 Hz is not altered until 70–80% of receptors are occupied by non-depolarizing blockers [4]. This margin of safety is reduced in myasthenic patients, depending upon the severity of the disease. However, non-depolarizing neuromuscular blockers of intermediate duration (atracurium and vecuronium) have been used safely for surgical relaxation in patients with varying degrees of myasthenic impairment [5–8]. Following antagonism of atracurium-induced residual neuromuscular block with neostigmine 5 mg, none of a series of five myasthenic patients suffered respiratory embarrassment [8].

We used an NMT Monitor to titrate the dose of vecuronium. The observed hypersensitive responses to the initial dose of vecuronium (2 mg) were unexpected because the extensive preoperative investigation suggested that the myasthenia gravis was limited primarily to the ocular muscles, with negligible somatic involvement. As a result of more cautious titration of subsequent doses, neuromuscular transmission recovered spontaneously at the end of surgery. However, the antagonists were administered to increase the margin of safety. The resultant neuromuscular block showed a well maintained train-of-four ratio (except for the significant train-of-four fades on the first three responses during onset), suggesting a depolarizing block.

The i.v. regional curare test on the isolated arm described by Foldes [9] could not only help to confirm diagnosis, but also disclose hypersensitive reaction to a non-depolarizing neuromuscular blocker. The administration of isoflurane could potentiate the neuromuscular blocking effect of vecuronium in this case. However, the potentiation by isoflurane is reported to be much less with vecuronium than with tubocurarine and pancuronium [10]. In addition, when the end-tidal concentration of an inhalation agent is low at the beginning of anaesthesia, potentiation may not be manifested. Therefore, the dose of blocker needed to establish block at this time should not be altered, regardless of the type of anaesthesia [11]. The reduced number of AChR in myasthenic muscles cannot explain how anticholinesterases improve muscle strength. In contrast, the presence of a relative excess of ACh on the remaining fewer receptors could induce nicotinic responses. Certainly, cholinergic crisis is a well known complication in myasthenic patients, caused by an overdose of anticholinesterase. Depolarizing neuromuscular block observed in our patient indicated that cholinergic crisis was the most likely cause of muscle paralysis. Rolbin and colleagues [12] described a myasthenic patient who became apnoeic acutely following i.v. administration of neostigmine 2.0 mg and atropine 0.4 mg to treat the myasthenic crisis which developed after delivery of a fetus. Similar long-lasting depolarizing block was reported in a patient with dystrophia myotonia when pancuronium-induced residual block was antagonized with neostigmine [13]. Payne, Hughes and Azawi [14] reported that first administration of neostigmine 2.5 mg antagonized non-depolarizing block in anaesthetized patients, whereas a second dose given 2–5 min later depressed the peak tetanic contraction and re-established tetanic fade. In their further studies on non-paralysed patients, one or two injections of neostigmine 2.5 mg caused a substantial reduction in the peak tetanic contraction and severe tetanic fade. These neostigmine-induced tetanic responses were antagonized by gallamine and potentiated by suxamethonium. They concluded that neostigmine, in sufficient dose, produces an ACh-induced depolarizing block, and cautioned that when full recovery has been achieved, a further dose of neostigmine could be hazardous, because a prolonged depolarizing block with apnoea could ensue.

This report shows that a cholinergic crisis can result with indiscriminate use of anticholinester-
erase; therefore, administration of antagonizing agents should also be titrated carefully in patients with myasthenia.

REFERENCES