**Mivacurium in the myasthenic patient**

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**Summary**

We have used mivacurium in four myasthenic patients presenting for thymectomy. Supramaximal single twitch stimulation was applied to the ulnar nerve at the wrist and the force of contraction of the adductor pollicis was measured. After an initial bolus dose of 30 μg kg⁻¹ (approximately one-fifth of the normal intubating dose), we observed a mean 37.5 (SEM 5.6)% reduction in evoked twitch tension. Neuromuscular block was increased with incremental doses and maintained with repeat bolus doses of 15 μg kg⁻¹ at 25% recovery. The interval between maintenance bolus doses remained constant (mean 5.9 (0.7) min). Spontaneous offset was rapid with a mean recovery index (T25-T75) of 11.9 (2.1) min. Provided anticholinesterase therapy is withheld in the immediate preoperative period, mivacurium would appear to be a safe and appropriate neuromuscular blocker in this variably sensitive group of patients. The cumulative dose required to establish full neuromuscular block varied between 60 and 90 μg kg⁻¹. A maintenance infusion, commencing at 3 μg kg⁻¹ min⁻¹, is recommended, guided by neuromuscular monitoring.

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**Key words**


Myasthenia gravis is an autoimmune disease in which antibodies are raised to the nicotinic cholinergic receptor at the neuromuscular junction. This results in accelerated receptor turnover, direct receptor block and complement-mediated lysis of the end-plate. The net result is a variable reduction in receptor population by 70-85%, thus impinging on the 70% safety margin for neuromuscular transmission [1]. Consequentially, these patients are resistant to suxamethonium which, in the high doses required, may lead to irreversible phase II block [2, 3]. In contrast, they are variably sensitive to non-depolarizing neuromuscular blocking agents [4-9].

Where neuromuscular block cannot be avoided, the current technique of choice is to use a reduced dose of a non-depolarizing neuromuscular blocker of intermediate action. Several studies have validated the use of both atracurium and vecuronium, deriving mean ED₅₀/ED₉₀ values of approximately 40-60% of normal controls, although individual requirements may vary considerably [4-9]. We report the use of mivacurium, a new short-acting bis-benzylosoquinolinium blocker in myasthenic patients undergoing thymectomy with a standardized anaesthetic technique.

**Patients and methods**

We studied four patients (A, B, C and D) undergoing elective trans-sternal thymectomy. Informed consent was obtained from all patients and the study was approved by the Joint Ethics Committee of the National Hospital for Neurology and Neurosurgery. All patients had electromyograms consistent with myasthenia gravis and had antibodies to acetylcholine receptors. Preoperative data are presented in table 1. All patients were first on the morning operating list. In the two patients receiving pyridostigmine at the time of operation, the morning dose was withheld. Papaveretum 10-20 mg and hyoscine 0.2-0.4 mg were administered i.m., 1 h before operation. Full routine monitoring (ECG, non-invasive arterial pressure and pulse oximetry) was commenced and blood was obtained for estimation of plasma cholinesterase [10]. Anaesthesia was induced with fentanyl 2 μg kg⁻¹ followed by propofol 2-2.5 mg kg⁻¹. Intermittent positive pressure ventilation of the lungs was carried out by hand and mask to maintain end-tidal PCO₂ at 4.5-5.5 kPa. Anaesthesia was maintained with a propofol infusion of 6-10 mg kg⁻¹ h⁻¹, supplemented with 66% nitrous oxide in oxygen [11]. Volatile anaesthetic agents were not administered.

Supramaximal single twitch stimulation of the ulnar nerve was elicited at a frequency of 0.1 Hz. The resulting contraction of the adductor pollicis was measured by a Radio Spares 2 kilo load cell with thumb piece modification, as described previously [12], amplified and transcribed onto a chart recorder. After a 10-min period of stabilization, an initial bolus of mivacurium 30 μg kg⁻¹ was injected into a fast running i.v. infusion. When a stable degree of block was attained (defined as three equal consecutive twitches) increments of either 15 or 30 μg kg⁻¹ were administered, according to the

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Results

The mean onset time for the initial bolus dose of mivacurium 30 μg kg⁻¹ was 4.2 (0.5) min producing a mean 37.5 (5.6)% reduction in evoked twitch tension (table 2). The cumulative dose required to induce full neuromuscular block with a mean 93.8 (2.2)% reduction in twitch tension from control was 60-90 μg kg⁻¹ (mean 71.3 (6.2) μg kg⁻¹). The time taken to progressively develop this level of block ranged from 7.8 to 13.4 min.

The timing between equal maintenance doses, administered at 25% recovery, was remarkably constant for each patient (fig. 1), with bolus doses of mivacurium 30 μg kg⁻¹ lasting a mean of 5.9 (0.7) min. The maintenance doses for patient D were 30 μg kg⁻¹. Equivalent maintenance infusion rates were derived, with a mean value of 2.9 (0.3) μg kg⁻¹ min⁻¹.

Recovery was rapid in all patients with a mean recovery index (T25–T75) of 11.9 (2.1) min (table 2).

Discussion

The decrease in receptor population in myasthenia gravis is similar to that induced when “priming” normal patients with non-depolarizing neuromuscular blocking agents. Thus the speed of onset of neuromuscular block may be expected to be accelerated in myasthenic patients, as demonstrated by Baraka [13]. The mean onset time of a 30-μg kg⁻¹ bolus of mivacurium was 4.2 min in this study compared with 5.6 [14], 5.8 [15] and 5.6 [16] min in normal subjects.

The generation of individual cumulative dose–response curves is inappropriate for a drug with a short clinical half-life such as mivacurium in assessing mean ED₉₀/ED₉₅ values [17]. In the absence of hepatic failure, Cook and colleagues [18]...
have demonstrated rapid clearance of mivacurium with undetectable plasma concentrations of both active isomers 15 min after a bolus dose of 150 μg kg⁻¹. A significant proportion of the initial doses in this study should therefore have been cleared in the 7.8–13.4 min taken to incrementally establish full neuromuscular block. Silverman and Brull [19] demonstrated this clinically by comparing the effect of a single bolus of 150 μg kg⁻¹ with that of two 75-μg kg⁻¹ bolus doses administered 60 s apart. A significant reduction in maximum twitch depression attained was observed with the divided doses. Individual ED indices derived from the cumulative dose–response data in this study would therefore significantly overestimate the true values. Unfortunately, the innovative cumulative dose–response in addition to infusion (to match clearance) technique, as described for vecuronium [4], cannot be applied to mivacurium because of its variable and unpredictable clearance. In addition, the small number of myasthenic patients presenting for elective surgery precludes the design of a large single bolus study.

Therefore, in this study we aimed to increase neuromuscular block safely to an evoked twitch tension of 10% or less of control, to monitor the duration of action of equal increments and to follow the spontaneous recovery profile. An initial bolus dose of 30 μg kg⁻¹ (40% of the normal ED₉₀ value) was chosen. From previous studies with atracurium and vecuronium [4–9], this would be unlikely to represent an overdose. Using single twitch stimulation with a balanced anaesthetic technique, Savarese and co-workers [14] found that this dose produced a mean 9.4% depression of evoked twitch tension in normal patients. Similarly, Caldwell and colleagues [15] found a mean 24% depression, but using a train-of-four pattern. In our myasthenic patients, this dose produced a mean 37.5%, decrease in twitch tension.

The mode of action of pyridostigmine in myasthenia gravis is to inhibit synaptic acetylcholinesterase, thereby overcoming the deficit in receptor density. One might therefore expect high pyridostigmine concentrations to reduce the sensitivity of these patients to non-depolarizing neuromuscular blockers. This is difficult to investigate in individual patients and with the variability of disease severity in myasthenia, small comparative studies may be misleading. A report of two myasthenics, only one of whom was receiving pyridostigmine, supports this hypothesis [20]. Nilsson and Meretoja [5], in 11 myasthenics, found conversely that higher daily pyridostigmine doses were associated with increased sensitivity to vecuronium. However, anticholinesterase therapy was withdrawn 12 h before surgery in all patients and its activity would therefore have largely decayed. This apparent increase in sensitivity may reflect the fact that, in general, as disease severity increases, so does the amount of anticholinesterase prescribed. Eisenkraft, Book and Papatestas [4] compared four patients given pyridostigmine on the morning of surgery with those from whom it was withheld and failed to demonstrate any difference in sensitivity to vecuronium.

In our study we failed to demonstrate any difference in sensitivity to mivacurium between the two patients receiving pyridostigmine and the two who were not. The constant interval between equal incremental doses (fig. 1) indicates that mivacurium would be suitable for infusion in these patients. The lack of cumulation of mivacurium has been reported previously [14,21,22]. In normal subjects during balanced anaesthesia, Diefenbach and co-workers [21] demonstrated no significant difference in the cumulative dose requirements of mivacurium between a continuous infusion to maintain twitch tension at 5% of control and bolus dosing at 25% recovery. The bolus maintenance doses represented an equivalent infusion rate of 5.0 (1.3) μg kg⁻¹ min⁻¹. The mean derived infusion rate from bolus dosing at 25% recovery in this study was 2.9 (0.3) μg kg⁻¹ min⁻¹, representing a reduction of 40%.

Mivacurium is hydrolysed rapidly by plasma cholinesterase [14] which may be inhibited by residual pyridostigmine, thus prolonging the duration of neuromuscular block. Baraka and colleagues [23] demonstrated that while maximum inhibition of plasma cholinesterase by an i.v. bolus of pyridostigmine 0.25 mg kg⁻¹ reaches 70% at 5 min, its effect decays rapidly and by 120 min is less than 20%. As is common practice in our institution, the morning dose of those patients receiving pyridostigmine was withheld, leaving a minimum 10-h interval before surgery. The terminal elimination half-life of pyridostigmine in myasthenics is 97 min [24]. It is perhaps not surprising that there was little difference between the plasma cholinesterase activities of the two patients in this study receiving pyridostigmine and the two who were not.

Variations in plasma cholinesterase activity within or slightly below the normal range correlated poorly with the clinical duration of action of mivacurium [14, 25], except at the high dose of 200 μg kg⁻¹ [26]. There is a clearer correlation when comparing plasma cholinesterase activity with steady state infusion rates where distribution processes are constant [22]. The relation between plasma cholinesterase activity and the derived infusion rate in our patients is presented in figure 2.

Studies examining the pharmacokinetics of mivacurium in patients with hepatic failure [18, 27], who exhibited profoundly reduced plasma cholinesterase activity, have demonstrated approximately threefold increases in neuromuscular recovery indices. For this reason we would not recommend the use of mivacurium in those patients where the morning dose of pyridostigmine cannot be withheld.

The mean T25–T75 recovery index during balanced anaesthesia in normal patients has been reported as 5.4–7.6 min, regardless of the total cumulative dose [14, 16, 25, 28]. By comparison, in this study the mean recovery index was 11.9 min, reflecting both the increased sensitivity of myasthenic patients to small concentrations of non-depolarizing neuromuscular blockers and the apparent inverse relationship between recovery index and plasma cholinesterase activity (fig. 3).
Mivacurium in the myasthenic patient

The safety in relative overdose of mivacurium is illustrated by a case report in which 150 μg kg⁻¹ was administered to a myasthenic patient for a course of multiple monitored electroconvulsive therapy [29], a procedure lasting up to 20 min. As the patient had just undergone two plasmaphereses in addition to receiving pyridostigmine 180 mg twice daily, plasma cholinesterase activity may have been reduced (it was not assayed). Surprisingly, a maintenance bolus dose of 100 μg kg⁻¹ was required after 10 min and, after neostigmine 2.5 mg and atropine 1 mg, the patient’s trachea was extubated without problem at the end of the procedure.

In summary, mivacurium would appear to be safe and appropriate for use in myasthenic patients provided immediate preoperative anticholinesterases are withheld. In this variably sensitive group of patients, it offers the advantage of a readily titratable degree of neuromuscular block with comparatively small maintenance requirements in patients with myasthenia gravis. Anesthesiology 1987; 42: 950–957.

References

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