Effect of antagonism of mivacurium on recovery of extraocular muscle function

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Summary

We have measured extraocular muscle function in 41 patients who received neuromuscular block with mivacurium 0.2 mg kg\(^{-1}\) during anaesthesia with propofol, ketorolac, fentanyl and isoflurane in nitrous oxide and oxygen, which was antagonized at the end of surgery with neostigmine 0.05 mg kg\(^{-1}\) and glycopyrronium 0.01 mg kg\(^{-1}\) in 21 of these patients. Extraocular muscle function was measured before and after surgery in each group with the Maddox Wing apparatus and compared with a control group (n = 20) who breathed spontaneously the same gaseous anaesthetic mixture via a reinforced laryngeal mask airway. In patients where the action of mivacurium was antagonized, extraocular muscle function was improved significantly 20 min after antagonism (P < 0.001) compared with those who received no antagonism. At 60 min after antagonism, there were no differences between the groups. There were no differences between patients who received no neuromuscular blockers and those who received blocker and antagonist. (Br. J. Anaesth. 1996; 76: 621–623)

Key words


Mivacurium is a new non-depolarizing neuromuscular blocking agent with a short duration of action and rapid offset of effect because of its rapid metabolism by plasma cholinesterase. This occurs \textit{in vitro} at approximately 80% of the rate at which suxamethonium is degraded [1, 2]. The rapid recovery from mivacurium-induced neuromuscular block allows patients to recover from the block without the use of anticholinesterase drugs [3]. However, there is wide inter-patient variability in response to neuromuscular block with mivacurium [2] and neuromuscular monitoring should be used to demonstrate satisfactory antagonism of its effects before termination of anaesthesia.

Traditionally, recovery from neuromuscular block is monitored by train-of-four stimulation. However, in clinical anaesthesia, the train-of-four is observed visually and is a relatively poor indicator of recovery [4]. The ability of neostigmine to antagonize neuromuscular block produced by mivacurium has been demonstrated [1] using train-of-four stimulation and electromyogram recording or adductor pollicis force transduction [3]. However, neostigmine blocks the metabolism of mivacurium \textit{in vivo} in a dose-dependent manner [5]. This has been demonstrated \textit{in vivo} with prolongation of intense mivacurium-induced block by administration of neostigmine [6]. Faced with the difficulty of measuring subtle degrees of muscular weakness, many anaesthetists use neostigmine to antagonize any residual effects of mivacurium after anaesthesia. Our study aimed to demonstrate the benefit of this practice, using the Maddox Wing apparatus to detect residual neuromuscular dysfunction.

Patients and methods

After obtaining Ethics Committee approval and informed consent, we studied 61 patients undergoing day-case anaesthesia for minor oral surgery. Patients were allocated randomly to one of three groups by choosing sealed envelopes.

The Maddox Wing is a device used by orthoptists to measure latent squint. It consists of a black metal screen with baffles to present an image of two perpendicular arrows to the right eye. The left eye is presented with an image of two perpendicular scales. These are graduated in prism diptres and the amount of esophoria or exophoria is the number on the horizontal scale where the arrow is superimposed onto the scale. Before surgery, the visual function of each subject was tested with the Maddox Wing apparatus. Esophoria and exophoria were recorded, as measured on the horizontal scale of the Maddox Wing. No results were recorded from the vertical scale. No premedication was used and patients requiring spectacles for refractive correction were allowed to use them.

After attaching full monitoring, anaesthesia was induced with propofol 2.5 mg kg\(^{-1}\) i.v. Each 20-ml syringe of propofol contained lignocaine 10 mg to relieve pain on injection. Each patient received fentanyl 1 \(\mu\)g kg\(^{-1}\) and ketorolac 10 mg i.v. At termination of anaesthesia, ketorolac 20 mg was administered.

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Patients in groups MIV and REV were given mivacurium 0.2 mg kg$^{-1}$ at induction of anaesthesia. The trachea was intubated via the nasal route and the lungs ventilated to normocapnia with 1–2 % inspired isoflurane and 66 % nitrous oxide in oxygen. The time of administration of mivacurium was recorded as time A. At termination of surgery, isoflurane was discontinued and neostigmine 0.05 mg kg$^{-1}$ and glycopyrronium 0.01 mg kg$^{-1}$ administered to group REV. The time of antagonism and discontinuing isoflurane was recorded as time B.

Patients in the laryngeal mask airway (LMA) group were used as a control; these patients did not receive mivacurium or a reversal agent. Time A was recorded as the time of administration of propofol 2.5 mg kg$^{-1}$. Fentanyl 1 μg kg$^{-1}$ and ketorolac 10 mg, followed by 20 mg after operation, were administered and an LMA inserted. Patients breathed a mixture of 1–2 % isoflurane and 66 % nitrous oxide in oxygen. Time B was recorded at termination of surgery when isoflurane was discontinued.

At the end of anaesthesia in groups MIV and REV, neuromuscular function was assessed using a peripheral nerve stimulator before waking the patient to ensure against prolonged neuromuscular block caused by atypical plasma cholinesterase. A train-of-four count of four twitches with no fade was taken as demonstrating adequate antagonism.

Extraocular muscle function was tested 45 min after time A, and 20 and 60 min after time B. Visual function was tested by the same observer who performed the preoperative test, who was blinded to the anaesthetic technique used.

As the data were not from a normally distributed population, visual disturbance in prism dioptres for the three treatment groups was tested with the Kruskal–Wallis one-way analysis of variance and the Mann–Whitney U test. As the data were not from a normally distributed population, visual disturbance in prism dioptres for the three treatment groups was tested with the Kruskal–Wallis one-way analysis of variance and the Mann–Whitney U test. $P < 0.05$ was considered significant.

### Results

Three patients were excluded from the study, one because of uniocular blindness, one because of severe squint, unsuccessfully corrected by surgery and one because of excessive sleepiness after anaesthesia. The mean duration of anaesthesia was 23 min and there were no significant differences in operative time between the groups (table 1). The values obtained 45 min after time A and 20 min after time B were similar.

The mean preoperative degree of exophoria did not differ significantly between the three groups (Kruskal–Wallis) (table 1).

Table 1 shows the degree of exophoria measured after operation. The values shown were corrected by subtracting the degree of pre-existing exophoria from the postoperative result. A45 is the change at 45 min after induction time A. B20 and B60 are the changes at 20 and 60 min after reversal time B.

When group MIV and both groups REV and LMA were compared, there were significant differences at both times A45 and B20. There were no significant differences between groups REV and LMA. There were no significant differences between the groups at time B60.

### Discussion

The Maddox Wing apparatus has been used in several studies of postoperative recovery. Its use as a test of recovery from general anaesthesia was first described in 1970 [7]. It is a simple, non-painful test to perform in the immediate postoperative period. Recovery from anaesthesia is a multidimensional phenomenon in the same way that a balanced anaesthetic consists of components of anaesthesia, analgesia and paralysis. The Maddox Wing has been used as an indicator of residual paralysis [8, 9] comparing one neuromuscular blocker with another. In an analysis of six recovery tests [10] the Maddox Wing was used as an indicator of sedation. It has been used to assess sedation after propofol infusions [11] and alcohol consumption [12]. As far as we are aware, the Maddox Wing has not been used to monitor the effects of reversal drugs on extraocular muscle function.

In designing a study to demonstrate neuromuscular dysfunction using the Maddox Wing, it is crucial to eliminate the effects caused by sedative agents. For this reason we included a control group (LMA) who received neither mivacurium nor reversal agents, breathing spontaneously the same gaseous anaesthetic mixture via a reinforced laryngeal mask airway.

Our results demonstrated significant changes in extraocular muscle function in the hour after anaesthesia. Of note was the significant ($P < 0.001$) difference in the early postoperative period between those treated with mivacurium and those who received mivacurium and antagonism. This was demonstrated at 20 min after termination of anaesthesia (B20) and at 45 min after the start of anaesthesia (A45). At 20 min after operation, there was significantly less exophoria in the LMA group than in those who received mivacurium alone ($P < 0.001$).
Our results suggest an improvement in extraocular muscle function in the first hour after operation in patients whose mivacurium block was antagonized by neostigmine and glycopyrronium. This improvement may result from antagonism of acetylcholinesterase at the neuromuscular junction.

Neostigmine is well known to have central effects on cholinergic receptors, despite poor penetration of the blood–brain barrier. It also has an effect on cholinergic transmission in the eye [13]. It is not possible to rule out the central, analptic effects of neostigmine, the peripheral cholinergic effects of miosis and accommodation caused by neostigmine as explanations of our findings. Glycopyrronium should antagonize these effects but it also poorly penetrates the blood–brain barrier.

Recovery of neuromuscular function has been shown to be more rapid after antagonism with neostigmine from both bolus doses and infusions of mivacurium [2]. However, there is evidence to support withholding anticholinesterase drugs. Patients undergoing laparoscopic surgery receiving mivacurium followed by antagonism with neostigmine have been shown to have a greater incidence of nausea and vomiting compared with patients receiving no antagonism [14]. This effect was also demonstrated in children [15]. We did not specifically examine postoperative nausea and vomiting in our study. In another study using mivacurium without antagonism for outpatient dentoalveolar surgery, the incidence of nausea and vomiting was 6% [unpublished results].

In addition, neostigmine antagonizes plasma cholinesterase [5, 16]. Thus in the presence of high degrees of block, corresponding to high concentrations of unmetabolized mivacurium, administration of neostigmine may paradoxically increase recovery time. This effect may result from development of channel block.

In each of our three groups, extraocular muscle function was the same 1 h after anaesthesia, which indicates spontaneous recovery from minor degrees of neuromuscular block. Spontaneous recovery of mivacurium-induced neuromuscular block has been demonstrated to be safe, allowing adequate neuromuscular function for spontaneous respiration and airway maintenance [3]. However, our results showed that antagonism of an intubating dose of mivacurium significantly improves extraocular muscle function during the first hour after operation, which indicates improved antagonism of subtle degrees of neuromuscular block. The clinical benefit of achieving this degree of antagonism of a single dose of mivacurium in patients undergoing day-case surgery is debatable.

References