

## CLINICAL PRACTICE

# Onset and duration of mivacurium-induced neuromuscular block in patients with Duchenne muscular dystrophy<sup>†</sup>

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**Background.** To determine the response to mivacurium, we prospectively studied onset time and complete spontaneous recovery from mivacurium-induced neuromuscular block in patients with Duchenne muscular dystrophy (DMD).

**Methods.** Twelve boys with DMD, age 5–14 yr, seven of them wheelchair-bound, ASA II–III, and 12 age- and sex-matched controls (ASA I) were enrolled in the study. Anaesthesia was induced with fentanyl 2–3  $\mu\text{g kg}^{-1}$  and propofol 3–4  $\text{mg kg}^{-1}$  titrated to effect, and maintained by continuous i.v. infusion of propofol 8–12  $\text{mg kg}^{-1}$  and remifentanyl as required. The lungs were ventilated with oxygen in air. Neuromuscular transmission was assessed by acceleromyography using train-of-four (TOF) stimulation every 15 s. After baseline readings, a single dose of mivacurium 0.2  $\text{mg kg}^{-1}$  was given. The following variables were recorded: (i) lag time; (ii) onset time; (iii) peak effect; (iv) recovery of first twitch from the TOF response to 10, 25 and 90% ( $T_{10}$ ,  $T_{25}$ ,  $T_{90}$ ) relative to baseline; (v) recovery index (time between 25 and 75% recovery of first twitch); and (vi) recovery time (time between 25% recovery of first twitch and recovery of TOF ratio to 90%). For comparison between the groups the Mann–Whitney *U*-test was applied.

**Results.** There were no differences between the groups in lag time, onset time and peak effect. However, all recorded recovery indices were significantly ( $P < 0.05$ ) prolonged in the DMD group. The median (range) for time points  $T_{10}$ ,  $T_{25}$  and  $T_{90}$  in the DMD and control group was 12.0 (8–16) vs 8.4 (5–15) min, 14.1 (9–20) vs 10.5 (7–17) min and 26.9 (15–40) vs 15.9 (12–23) min, respectively. The recovery index and recovery time were similarly prolonged in the DMD group.

**Conclusions.** These results support the assumption that mivacurium-induced neuromuscular block is prolonged in patients with DMD.

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Duchenne muscular dystrophy (DMD) is the most common myopathy in paediatric patients. DMD is caused by mutations in the dystrophin gene located on the X chromosome.<sup>1,2</sup> These mutations result either in an abnormal protein or in a very low concentration of dystrophin. Normally dystrophin and its related proteins (dystrophin–glycoprotein complex) play an important role as part of the cytoskeleton of muscle cells. The complete function of dystrophin and its related proteins is not fully understood, but these proteins seem to be necessary for the regular formation of the postsynaptic membrane of the neuromuscular junction.<sup>3,4</sup>

One concern for the anaesthetist when managing DMD patients is the use of depolarizing neuromuscular blocking agents, because of the risk of hyperkalaemia, rhabdomyolysis or even cardiac arrest. The effect of non-depolarizing muscle relaxants, however, remains to be elucidated in these patients. Though the effect of various muscle relaxants has been reported anecdotally,<sup>5–11</sup> these reports are conflicting

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and indicate either normal or increased sensitivity to non-depolarizing muscle relaxants. In a recent investigation in DMD patients we recorded a prolonged onset time and a markedly prolonged spontaneous recovery after a single standard dose of rocuronium.<sup>12</sup> This observation raises the question of whether this altered response to rocuronium could be applied accordingly to other non-depolarizing muscle relaxants in DMD patients.

Thus, the aims of this study were (i) to determine onset time and complete spontaneous recovery after administration of a bolus dose of mivacurium  $0.2 \text{ mg kg}^{-1}$ , a non-depolarizing muscle relaxant with a short duration of action; and (ii) to compare these data with data from children without neuromuscular diseases.

## Patients and methods

After approval from the local ethics committee and written informed consent from their parents, 24 boys between the ages of 5 and 14 yr were enrolled in the study. The 12 patients suffering from DMD (DMD group, ASA I–III) underwent elective orthopaedic surgery of the lower extremities. Twelve age- and sex-matched patients scheduled for elective orthopaedic or surgical procedures (control group, ASA I) served as controls. None of the patients was being treated with any medication known to influence neuromuscular function. Before surgery, all patients of the DMD group were screened by echocardiography and lung function test to evaluate cardiopulmonary risk.

The patients were visited the day before surgery for a physical examination and review of laboratory test results, including determination of plasma cholinesterase activity. The children were fasted overnight and premedicated orally with midazolam  $0.375 \text{ mg kg}^{-1}$ . Standard intraoperative monitors were applied, including electrocardiography, non-invasive blood pressure, and pulse oximetry. A standardized anaesthetic technique was used in both groups. After placing a peripheral i.v. line, the administration of glycopyrrolate  $0.004 \text{ mg kg}^{-1}$  and preoxygenation with 100% oxygen, anaesthesia was induced with fentanyl  $2\text{--}3 \mu\text{g kg}^{-1}$  and propofol  $3\text{--}4 \text{ mg kg}^{-1}$  titrated to effect. Mask ventilation was secured and the trachea of the patients intubated without neuromuscular paralysis. Tidal volume and respiratory rate were controlled to keep the end-tidal carbon dioxide pressure at  $4.25\text{--}4.65 \text{ kPa}$ . Anaesthesia was maintained with continuous i.v. infusion of propofol  $8\text{--}12 \text{ mg kg}^{-1}$  and remifentanyl as required. No patient received any volatile anaesthetics during the procedure. Cephazolin  $30 \text{ mg kg}^{-1}$  was administered i.v. for the perioperative prophylaxis of infection. The patients did not receive any muscle relaxant until baseline calibration had been made. A warm forced air device was used to maintain temperature at  $36^\circ\text{C}$ , which was monitored with an ear probe.

Neuromuscular function was assessed by acceleromyography using TOF-Watch SX equipment (Organon, Oss,

The Netherlands) within the guidelines of the Copenhagen Consensus Conference.<sup>13</sup> One forearm was prepared for acceleromyographic monitoring and immobilized in a splint, allowing free mobility of the thumb. The monitoring arm was kept free from i.v. indwelling catheters and from the blood pressure cuff. Skin temperature was monitored and maintained above  $32^\circ\text{C}$  throughout the study.

Stimulating electrodes were applied to the skin over the ulnar nerve, and the recording acceleromyographic probe was fixed to the volar surface of the distal phalanx of the thumb. Supramaximal square-wave impulses of  $0.2 \text{ ms}$  duration were delivered to the ulnar nerve in a train-of-four-sequence (TOF; four consecutive impulses,  $2 \text{ Hz}$ ). These stimuli were delivered every  $15 \text{ s}$  throughout the investigation. The acceleromyographic response of the adductor pollicis muscle was recorded by the TOF monitor and the data were transferred to a portable PC for further processing (TOF-Watch SX monitor program; Organon). After calibration and  $5 \text{ min}$  of stable baseline response, mivacurium  $0.2 \text{ mg kg}^{-1}$  was administered over  $15 \text{ s}$  into a rapidly flowing i.v. infusion of a balanced salt solution.

With reference to baseline twitch height, the following times of onset and recovery of neuromuscular block were measured: (i) time between mivacurium administration and the first change of TOF response (lag time); (ii) time between injection of mivacurium and more than 95% depression of the first twitch (onset time); (iii) maximal depression of the first twitch (peak effect); (iv) time between mivacurium administration and recovery of first twitch of the TOF response to 10, 25 and 90% ( $T_{10}$ ,  $T_{25}$ ,  $T_{90}$ ); (v) time between 25 and 75% recovery of first twitch (recovery index); and (vi) time between 25% recovery of first twitch and recovery of TOF ratio to 90% (recovery time). For clinical assessment of recovery of neuromuscular function at the end of surgery, every patient was asked to lift their head and protrude their tongue. If the patient could follow these instructions the tracheal tube was removed.

Results are presented as median and range. Patient characteristics and pharmacodynamic data measured for the two groups were compared using the Mann–Whitney *U*-test. Observed differences were considered significant if *P* was less than 0.05.

## Results

There were no differences between the groups with respect to patient characteristics (Table 1). Seven children of the DMD group were wheelchair-bound and unable to walk more than a short distance. Preoperative laboratory testing yielded normal plasma cholinesterase activity in both groups (Table 1). In the DMD group the serum creatine kinase values varied between 366 and  $6810 \text{ U litre}^{-1}$  (normal value  $<174 \text{ U litre}^{-1}$ ). Preoperative echocardiography of DMD patients revealed early cardiomyopathy in three patients and normal global function in all patients. Results of lung function testing were available in only seven of the

**Table 1** Characteristics of patients with DMD and controls. Data are mean (SD) or (for plasma cholinesterase) mean (range). Normal plasma cholinesterase range 5320–12 920 U litre<sup>-1</sup>

	Age (yr)	Height (cm)	BMI	Plasma cholinesterase activity (U litre <sup>-1</sup> )	Duration of anaesthesia (min)
DMD group	9.5 (2.4)	135 (0.17)	18.4 (3.6)	8654 (6870–10 478)	103 (25)
Control group	8.3 (3.7)	135 (0.24)	17.4 (3.2)	8871 (7662–11 064)	95 (35)

**Table 2** Neuromuscular effects of a bolus dose of mivacurium 0.2 mg kg<sup>-1</sup> in patients with DMD and controls. Data are median (range). Lag time is time between mivacurium administration and first change of TOF response; onset time is time between injection of mivacurium and more than 95% depression of the first twitch; T<sub>10</sub>, T<sub>25</sub>, T<sub>90</sub> are times between mivacurium administration and recovery of first twitch of the TOF response to 10, 25 and 90%; recovery index is time between 25 and 75% recovery of first twitch; recovery time is time between 25% recovery of first twitch and recovery of TOF ratio to 90%. \**P* < 0.05 vs patients without neuromuscular disease

	Lag time (s)	Onset time (s)	T <sub>10</sub> (min)	T <sub>25</sub> (min)	T <sub>90</sub> (min)	Recovery index (min)	Recovery time (min)
DMD group	45 (30–60)	135 (90–225)	12.0* (8–16)	14.1* (9–20)	26.9* (15–40)	6.8* (4–13)	13.9* (10–27)
Control group	45 (30–75)	143 (75–210)	8.4 (5–15)	10.5 (7–17)	15.9 (12–23)	4.1 (2–6)	8.4 (7–14)

DMD patients. The vital capacity ranged from 51 to 76% of the reference value.

Three patients (two in the DMD group and one in the control group) developed mild cutaneous erythema of the infusion arm, and one DMD boy developed a mild flush over the upper part of the chest in response to administration of mivacurium. None of the children received a second dose of mivacurium. At the end of surgery the tracheal tube was removed from all children without the use of a reversal agent.

In both groups, mivacurium induced a peak effect of more than 95% of twitch depression. The lag time and onset time did not differ between the two groups (Table 2). However, all recorded times of recovery were significantly prolonged in the DMD group compared with controls. Accordingly, the deduced recovery index was also significantly increased in the DMD group (Table 2).

## Discussion

The results of the present study support our hypothesis that patients with DMD respond in a different way to various non-depolarizing muscle relaxants. After a standard dose of mivacurium, recovery was prolonged by approximately 50% in DMD patients.

It has been suggested for many years that in patients with DMD the response to muscle relaxants may differ from subjects without neuromuscular disease. Normal and prolonged neuromuscular recovery together with higher sensitivity has been documented in only a few case reports.<sup>5–7 10 11</sup> For the first time Ririe and colleagues<sup>9</sup> investigated systematically the response to vecuronium in a larger number of DMD patients and found increased sensitivity to vecuronium, manifested as a smaller dose necessary to induce a TOF less than 10%. In a recent investigation with rocuronium, we found significantly prolonged recovery in DMD patients with an advanced state of the disease.<sup>12</sup>

In this special situation, mivacurium, a non-depolarizing muscle relaxant with a normally short duration of action and fast spontaneous recovery, might offer an advantage over other muscle relaxants. Retrospectively reviewing the anaesthetic records of seven boys with DMD, Tobias and Atwood<sup>8</sup> assumed increased sensitivity to mivacurium in these patients. Their assumption was based on a moderate decrease in infusion requirements for single-twitch depression. Comparability with our study, however, is very limited because of differences in study design (infusion vs single bolus, retrospective vs prospective, qualitative vs quantitative monitoring), anaesthetic technique (isoflurane vs propofol infusion), and the use of reversal agents in the study of Tobias and Atwood. In our study, the altered response to mivacurium was clearly demonstrated as a significantly delayed spontaneous recovery at all given time points relative to controls. Despite these differences, the data of both investigations strengthen the presumption of a delayed recovery from mivacurium-induced neuromuscular block in DMD patients.

We found a normal onset time after the standard dose of mivacurium. This documented normal onset time is in contrast to a recent investigation with rocuronium, in which a significantly prolonged onset time was found.<sup>12</sup> This difference in onset time (normal vs prolonged) may have been a result of the stage of the disease of the patients in the rocuronium study. All patients in this former study were wheelchair-bound and needed surgical correction of severe scoliosis corresponding to late-stage DMD.

The exact reason for the altered response of DMD patients to non-depolarizing muscle relaxants is still unclear and remains speculative. In principle, two possibilities must be considered: (i) possible changes in pharmacokinetics; and (ii) alterations at the neuromuscular junction due to the underlying disease. Concerning pharmacokinetics, we are not aware of any data about deviant pharmacokinetic parameters in DMD. In none of the DMD patients did

preoperative echocardiography reveal any major impairment of cardiac function, and we can therefore exclude different circulation times as the cause of the altered response. Congruently, lag and onset times were similar in both groups. Although we can say nothing about tissue perfusion in these patients, the normal onset time contradicts the presumption of poorly perfused muscle.

We speculate that structural changes at the neuromuscular junction are likely to be responsible for the altered behaviour of the DMD muscle against muscle relaxants. The degeneration of muscle tissue and its reorganization by fatty infiltration makes it most likely that the total number of acetylcholine receptors will be lowered continuously with the progression of the disease, although no evidence has been provided yet. The second important aspect to be mentioned concerns possible changes in the microstructure of the subsynaptic membrane at the neuromuscular junction. Recent basic investigations have highlighted the important role of dystrophin and its related protein complex (e.g. dystroglycan) for the normal development, formation and organization of the neuromuscular junction.<sup>14,15</sup> These newer findings have shown dystrophin to be necessary for normal acetylcholine receptor–cytoskeleton interaction.<sup>3</sup> One can imagine that increasing alterations of the microstructure of the neuromuscular junction with the progression of the disease may cause an altered response of the DMD muscle against any type of muscle relaxant. Such a concept would explain the reported normal response to muscle relaxants in early stages and the prolonged recovery in late stages of the disease.

The result of this study, together with data from rocuronium- and vecuronium-induced neuromuscular block, clearly indicate that the administration of muscle relaxants induces a prolonged neuromuscular block in patients with manifest DMD. Compared with aminosteroids with their very long recovery times, one potential advantage of using mivacurium in these patients is that its use makes the administration of anticholinesterases unnecessary. If muscle relaxants are used in DMD patients, careful quantitative monitoring of neuromuscular transmission is mandatory.

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