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The Response of Patients with Duchenne's Muscular Dystrophy to Neuromuscular Blockade with Vecuronium

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Background: **The authors hypothesized that patients with Duchenne's muscular dystrophy (DMD) are more sensitive to nondepolarizing muscle relaxants.**

Methods: **Eight children with DMD and eight healthy children having orthopedic procedures were studied. Anesthesia consisted of thiopental, 60% nitrous oxide in 40% oxygen, and intravenous fentanyl and midazolam. Using electromyography, the ulnar nerve was stimulated and the electromyographic train-of-four ratio (TOFr) of the first dorsal interosseous muscle was recorded every 60 s. After baseline TOFr recording, all patients received 50 μg/kg vecuronium and the TOFr at 3 min was compared. Vecuronium (10 μg/kg) was then administered every minute until TOFr was ≤0.1. The TOFr was followed until TOFr was ≥0.01. Then 10 μg/kg of vecuronium were administered to maintain TOFr ≤ 0.1. At the conclusion of the procedure, TOFr was allowed to recover to 0.25, and then neostigmine and glycopyrrolate were administered. Data are presented as medians and ranges.**

Results: **The initial dose of vecuronium resulted in greater TOFr depression in patients with DMD than in controls (0.14 *vs.* 0.86). Less vecuronium was needed to produce TOFr ≤0.1 in the patients with DMD than in the control patients (55 μg/kg *vs.* 95 μg/kg). Recovery time for the TOFr to ≥0.1 after the initial dose was longer in the patients with DMD than in the controls (28 *vs.* 20 min; $P = 0.03$), and the maintenance dose of vecuronium was less in patients with DMD (0.6 *vs.* 1.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$; $P < 0.01$). The time for TOFr recovery from 0.1 to 0.25 was 36 min in the patients with DMD and 6 min in the controls ($P < 0.01$). After neostigmine, the TOFr was 1.0 in the controls and 0.91 ($P = 0.03$) in the patients with DMD.**

Conclusion: **There is increased sensitivity to vecuronium from neuromuscular blockade in patients with DMD. (Key words: Children; muscle relaxant; neuromuscular disorders.)**

DUCHENNE'S muscular dystrophy (DMD) is the most common type of X-linked muscular dystrophy. It is characterized by severe proximal muscle weakness, progressive degeneration, fat infiltration of muscle, and gradually deteriorating motor function. The progressive nature of the disorder results in multiple contractures, kyphoscoliosis, restrictive pulmonary disease, and nonambulation in early preadolescence. These patients often require surgical intervention to maintain the greatest degree of comfort and function.[1] Specific anesthetic complications in persons with DMD are related to administration of succinylcholine and volatile anesthetics.[2-9] However, little information is available about the response to nondepolarizing muscle relaxants.

Reports of the response of patients with DMD to nondepolarizing muscular relaxants are conflicting (normal or increased sensitivity), and information on dosing and antagonism of nondepolarizing muscle relaxants is lacking.[10-14] In clinical practice, we subjectively observed a greater effect of vecuronium in DMD and therefore hypothesized that persons with DMD are more sensitive to nondepolarizing muscle relaxants. In this article, we used vecuronium to characterize the neuromuscular blockade of patients with DMD and compared the response to that of controls.

Methods

Approval for the study was obtained from the committee on clinical investigations at The Children's Hospital. Sixteen male patients between the ages of 8 and 18 yr were entered into the study after written, informed consent was obtained from parents. Eight patients had

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DMD and eight male patients classified as American Society of Anesthesiologists physical status 1 served as controls. All patients underwent orthopedic surgery either of the spine or of the lower extremities. The procedures lasted longer in patients with DMD than in the controls because scoliosis cases were included in DMD and not the controls. Intraoperative body temperature (esophageal) was maintained between 35.5 and 37°C.

An intravenous catheter was placed before surgery. Twenty minutes before arrival in the operating room, the skin was cleansed with alcohol and electrodes were placed to obtain the electromyograph response of the first dorsal interosseus muscle. The Relaxograph (Datex Medical Instrumentation Inc., Helsinki, Finland) was used to stimulate the ulnar nerve and to record the train-of-four ratio (TOFr; ratio of T_4:T_1) electromyographic response.[15,16] The hand was immobilized in anatomic position and maintained normothermic by being wrapped in gauze and plastic bag. No intravenous catheters or blood pressure cuffs were placed on the study arm. All patients were premedicated with 0.1 mg/kg intravenous or 1 mg/kg oral midazolam.

All patients received 10 μg/kg glycopyrrolate followed by preoxygenation and induction of anesthesia with 4 mg/kg thiopental and 5 - 10 μg/kg fentanyl. Anesthesia was maintained with 60% nitrous oxide in oxygen by mask before intubation. After induction, a baseline electromyographic recording was observed until three consistent, consecutive readings were obtained for the supramaximal stimuli and the TOFr was recorded every 60 s. After the baseline TOFr was obtained, 50 μg/kg vecuronium was administered intravenously. After 3 min, 10 μg/kg vecuronium was administered at the hub of the intravenous catheter every 60 s until a TOFr ≤0.1 was reached. Tracheal intubation was then performed after intravenous administration of an additional 2 mg/kg thiopental. Anesthesia was maintained with 60% nitrous oxide in oxygen and 2 - 5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ fentanyl. Patients received additional 0.03 mg/kg midazolam every 2 h.

After obtaining TOFr ≤0.1, the TOFr was allowed to recover to ≥0.1. Vecuronium (10 μg/kg) was administered in repeated boluses as needed to maintain the TOFr at ≤0.1 throughout the surgery. A maintenance dose was calculated for a 90-min period from these data. At the end of surgery, the TOFr was allowed to recover to 0.25. At that point, the patient was given 70 μg/kg neostigmine and 15 μg/kg glycopyrrolate. The TOFr was monitored until it reached 1.0 or until it had not changed for 3 min. This took an average of 5 min in controls and 9 min in patients with DMD.

The TOFr at 3 min after 50 μg/kg of vecuronium, the dose of vecuronium required to achieve a TOFr ≤0.1, time to recovery of the TOFr to ≥0.1, the maintenance dose of vecuronium per minute, the time for recovery from 0.1 - 0.25 TOFr, and the TOFr after reversal were determined.

All parameters were compared between groups using the Wilcoxon rank sum test. Data are presented as medians with ranges.

Results

The median age of the patients with DMD was 12 yr (range, 11 - 15 yr), and for control patients it was also 12 yr (range, 8 - 18 yr). Of the patients with DMD, six underwent scoliosis surgery, and two had heel cord lengthening procedures. All of the control patients underwent lower extremity orthopedic procedures: two for resection of osteochondroma, two for open reduction and internal fixation of fractures, two for removal of hardware, and two for anterior cruciate ligament reconstruction.

Three minutes after 50 μg/kg vecuronium was given, the TOFr was less in patients with DMD ($P = 0.04$), and the dose to attain a TOFr ≤0.1 was less in the patients with DMD compared with controls ($P < 0.01$; all data are shown in table 1). After this level of neuromuscular blockade, the time for TOFr to recover ≥0.1 was greater in the patients with DMD than in controls ($P = 0.03$). The maintenance dose of vecuronium was less in the patients with DMD ($P = 0.01$) and the recovery of TOFr from 0.1 to 0.25 was slower in the patients with DMD ($P = 0.01$). In patients with DMD, the TOFr remained below control values after administering the reversal agent neostigmine ($P = 0.03$).

Discussion

This study supports our hypothesis that patients with DMD are more sensitive to vecuronium as measured by a greater suppression of the evoked electromyographic response to a given dose as well as a smaller dose requirement to achieve a given degree of neuromuscular blockade. The vecuronium maintenance dose was also less and the time to spontaneous recovery was longer in patients with DMD.

No previous systematic investigation of the response

Table 1. Comparison of Duchenne's Muscular Dystrophy (DMD) and Control Patients

Parameter	DMD	Control	*P* Value
n	8	8	—
Median age (yr)	12 (11–15)	12 (8–18)	NS
TOFr after 50 μg/kg	0.14 (0–0.94)	0.86 (0.1–0.98)	0.04
Vecuronium dose to achieve TOFr ≤ 0.1 (μg/kg)	55 (50–60)	95 (50–120)	0.01
Time to TOFr ≥ 0.1 (min)	28 (15–43)	20 (14–33)	0.03
Dose for maintenance of TOFr ≤ 0.1 ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.6 (0.2–1.2)	1.3 (0.9–7)	0.01
Time to TOFr 0.1–0.25 recovery (min)	36 (14–52)	6 (4–9)	0.01
TOFr after reversal	0.91 (0.51–1.0)	1.0 (0.97–1.1)	0.03

TOFr (ratio of T4:T1) in DMD patients and control patients. Values are the median value (with ranges). Statistical significance was tested using Wilcoxon Rank Sum. $P < 0.05$ was considered significant.

NS = not significant.

to vecuronium in patients with DMD has been reported, and no clear conclusions on the effects of nondepolarizing neuromuscular blocking agents in DMD have been formed.[10] Previous reports on the response of children with DMD to nondepolarizing neuromuscular blocking agents have been conflicting. The response to gallamine and d-tubocurarine during surgery have been reported as "normal"[11,12] using nonquantitative assessment of neuromuscular blockade. In a regional test of sensitivity to curare, 11 patients with DMD showed a normal block onset time but significantly longer duration compared with patients without neuromuscular disorders (controls).[13] Prolongation of block in this study is consistent with our findings. Onset of block measurements with curare were only obtained at 1 and 11 min and missed intermediate time points, when the difference we observed may have occurred.

There is no satisfactory explanation for the altered sensitivity to neuromuscular blockade in DMD. Preliminary data in human DMD suggest that the release of and the postsynaptic responsiveness to acetylcholine are intact, but the activity of the acetylcholinesterase is impaired in dystrophic myotubules.[17,18]

In this study, we did not make a formal T_1:T_c ratio measurement; instead we used TOFr to assess neuromuscular blockade. Although the T_1:T_c ratio is the ideal parameter to quantify neuromuscular blockade, the use of TOFr has also been firmly established in clinical practice to reliably determine the degree of muscle paralysis.[19] We chose to use TOFr to assess the degree of paralysis produced by vecuronium in children with DMD and compare it with controls during a standardized routine anesthetic.

Patients with DMD need smaller initial and maintenance doses of vecuronium and increased time for recovery or incomplete recovery from blockade during nitrous oxide-fentanyl anesthesia. Therefore, titration of vecuronium dosing while closely monitoring the neuromuscular blocking responses is more crucial in children with DMD than in healthy children. Further studies are needed to better understand the pharmacokinetic profile of vecuronium, to correlate the clinical effect to plasma levels, and to better characterize the vecuronium-acetylcholine interaction in DMD.

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