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Onset and Duration of Rocuronium-induced Neuromuscular Blockade in Patients with Duchenne Muscular Dystrophy

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Background: **In patients with Duchenne muscular dystrophy (DMD) the response to nondepolarizing muscle relaxants is scarcely documented and conflicting. The current study was conducted to determine the time to peak effect and the time for complete spontaneous recovery after a single dose of 0.6 mg/kg of rocuronium in patients with DMD.**

Methods: **Twenty-four patients (12 with DMD, 12 controls, aged 10–16 yr) were studied. All patients were anesthetized with propofol and fentanyl/remifentanil. Neuromuscular transmission was monitored by acceleromyography. After induction all patients received a single dose of 0.6 mg/kg of rocuronium. The complete time course of onset and spontaneous recovery were recorded**

Results: **Significant ($P < 0.01$) increase in the onset times to 95% neuromuscular block was observed in DMD patients (median, 203 s; range, 90–420 s) compared with controls (median, 90 s; range, 60–195 s). The time between rocuronium administration and recovery of first twitch of the train-of-four to 90% was significantly ($P < 0.01$) prolonged in DMD compared with controls (median, 132 min; range, 61–209 min *versus* 39 min; 22–55 min). The recovery index was also significantly prolonged in the DMD group compared with controls (median, 28 min, range, 15–70 min *versus* 8 min; 3–14 min).**

Conclusions: **The most striking and surprising result of this study is the delayed onset of blockade in DMD after a standard dose of rocuronium. This effect should be kept in mind in situations when a rapid airway protection is necessary in DMD patients. The documented very long recovery from rocuronium-induced block emphasizes the need for careful assessment of neuromuscular function in DMD patients.**

DUCHENNE muscular dystrophy (DMD) is the most common and severe muscular dystrophy; it is caused by a mutation in the dystrophin gene located on chromosome Xp21. This mutation results in a deficit of dystrophin, an important sarcolemmal structural protein in muscle cells. The clinical course of DMD is severe and there is no causative therapy available. This disorder is characterized by progressive skeletal muscle weakness with an early onset in childhood. Muscle reorganization with fatty infiltration and increase in fibrous tissue leads to loss of ambulation by the age of 10 yr. Most of these patients require corrective orthopedic surgery in the early stage of the disease for foot deformities and later for severe scoliosis to improve quality of life. The main anesthetic concern in the treatment of patients with DMD is the use of depolarizing relaxants because of the potential for hyperkalemic cardiac arrest and rhabdomyolysis. Administrations of various nondepolarizing neuromuscular blocking agents (NMBA) at different stages of the disease are anecdotally reported. Documented responses to nondepolarizing NMBA are inconsistent and range from normal to an increased sensitivity.[1–6] Accordingly, a reduction to a standard dosage of NMBA is recommended. Most importantly, however, in nearly all cases reversal agents have been used and, therefore, the complete spontaneous recovery of neuromuscular blockade (NMB) in DMD patients remains unclear.

The objective of this study was to investigate the response of patients with DMD to rocuronium-induced NMB. We hypothesized that rocuronium, with its usually short onset time, could be a suitable alternative to succinylcholine in DMD patients when clinical conditions require rapid muscle relaxation for airway protection. Thus, the aims of this study were to determine onset time and to determine complete spontaneous recovery of NMB after a standard dose of rocuronium of 0.6 mg/kg in patients with advanced DMD in comparison with controls.

Materials and Methods

After approval of the local ethics committee and obtained written consent, 24 male patients, aged 10–16 yr, scheduled for elective surgery were consecutively enrolled in the study. Twelve patients (DMD group, ASA physical status III) suffering from DMD underwent orthopedic surgery of the spinal column using Isola Spinal Implant System (AcroMed, Cleveland, OH). All DMD patients suffered from advanced stage of the disorder and were wheelchair-bound. Eight of the DMD patients were in part genotyped. Three of them had deletion in exons 46–51 and one had deletion in exons 8–17. In another four patients deletions were excluded by genetic testing; however, other possible mutations were not specified. Four patients were not genetically tested. Twelve gender-matched and age-matched patients (control group, ASA physical status I) without any neuromuscular disease served as controls. These children underwent urological or lower limb surgery that required

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tracheal intubation. None of the patients received any medication known to influence neuromuscular function. Several days before the planned surgery in all DMD patients an echocardiography and a lung function test were performed to evaluate cardiopulmonary risk.

Patients were visited the day before surgery for a physical examination and review of laboratory test results. Patients were premedicated with 3.75 mg midazolam orally 45 min before anesthesia. Standard intraoperative monitors were used, including electrocardiography, automatic blood pressure, and pulse oximetry. After placing a peripheral intravenous line and preoxygenation with 100% oxygen, anesthesia was induced with fentanyl 2–3 μg/kg and propofol 3 mg/kg. Mask ventilation was secured and patients were intubated without the use of neuromuscular blocking agents. In addition, in the DMD group intra-arterial and central venous catheters were placed for continuous pressure recordings. Anesthesia was maintained with continuous intravenous infusion of propofol 8–12 mg/kg and remifentanil was titrated to effect. No volatile drugs were used. The patients received no NMBA until final placement and until baseline calibration was made. Lungs were ventilated with a mixture of oxygen in air and minute volume ventilation was set to obtain end-tidal carbon dioxide concentrations of 35–40 mmHg. Central body temperature, monitored in the DMD group by means of bladder probes and in the control group by means of ear probes, was kept closely to 36°C in the control group and higher than 35.5°C in the DMD group using a warm forced-air device and warmed fluid infusion.

Neuromuscular transmission was monitored by acceleromyography using TOF watch SX equipment (Organon, Nijmegen, The Netherlands) within the guidelines of the Copenhagen Consensus Conference.[7] Patients were placed for surgery; DMD subjects were set into prone position and control subjects mostly stayed in a supine position. After final positioning, the right forearm was prepared for acceleromyographic monitoring. The hand and the forearm were immobilized in a splint allowing free mobility of the thumb. Skin temperature was monitored and maintained above 32°C throughout the study. The monitoring arm was kept free from arterial and intravenous indwelling catheters and from the blood pressure cuff.

The ulnar nerve was stimulated at the wrist *via* surface electrodes by supramaximal square wave impulses of 0.2 ms duration in a train-of-four-sequence (TOF; four consecutive impulses with 2 Hz). These stimuli were delivered every 15 s throughout the investigation. Response of the adductor pollicis muscle was quantified using an acceleromyographic probe fixed to the volar surface of the distal phalanx of the thumb. The TOF monitor was connected to a personal computer for online data recording and processing (TOF watch SX monitor program, Organon). After calibration and signal stabilization of the control response for at least 5 min, 0.6 mg/kg of rocuronium was administered over 5 s into a peripheral intravenous line. The time from administration of rocuronium to complete clinical recovery was monitored. The following times of NMB were measured: i) maximal depression of the first twitch; ii) time between rocuronium administration and the first change of TOF response (lag time); iii) time between injection of rocuronium and more than 95% depression of the first twitch (onset time); iv) time between rocuronium 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 demographic description we recorded age, height, and weight of the patients and calculated body mass indices.

Table 1. Demographic Data

	Age (yr)	Body weight (kg)	Height (cm)	BMI
DMD Group	13.3 ± 2.0	49.8 ± 13.6	157 ± 11	20.0 ± 3.7
Control Group	13.8 ± 3.0	54.5 ± 15.9	165 ± 18	20.50 ± 2.6

Values are mean ± SD.

BMI = body mass index; Control Group = controls; DMD Group = patients with Duchenne Muscular Dystrophy.

Comparison of the time course of NMB between the DMD group and the control group was performed with the Mann–Whitney U test. A P value < 0.05 was considered statistically significant.

Results

We studied 24 patients, 12 with DMD and 12 without neuromuscular disease. Patients did not differ with respect to age, height, weight, or body mass index. Demographic data are shown in Table 1. Preoperative echocardiography of DMD patients revealed beginning cardiomyopathy in two patients, and in two other patients one mitral valve insufficiency (grade I) and one beginning left ventricular hypertrophy were discovered, respectively. The vital capacity of DMD patients evaluated by lung function testing ranged from 31% to 64% of the reference value. The serum creatine kinase value varied between 345 and 1886 U/L (normal value, <174 U/L).

Before administration of rocuronium the control TOF ratio varied between 90% and 106% in the DMD group with slight variations within the single patient. Rocuronium 0.6 mg/kg caused complete NMB (100% twitch suppression) in 21 patients (88%). In one child of the DMD group and in two patients in the control group, only 95% reduction of twitch response was achieved. In the DMD group, first twitch height recovered to only 85% in two patients compared with baseline. Time course of NMB is presented in Table 2. Whereas lag time showed no difference between the groups, time to onset

Table 2. Neuromuscular Effects of a Bolus Dose of 0.6 mg/kg of Rocuronium in Patients with Duchenne Muscular Dystrophy (DMD group) and Controls (Control group)

	Lag time (sec)	Onset time (sec)	T_{10} (min)	T_{25} (min)	T_{90} (min)	Recovery index (min)	Recovery time (min)
DMD group	45 (30–75)	203 (90–420)*	54.7 (32–124)*	64.5 (41–140)*	131.5 (61–209)*	27.5 (15–70)*	71.0 (39–144)*
Control group	45 (30–60)	90 (60–195)	22.5 (11–30)	26.3 (14–34)	38.5 (22–55)	8.3 (3–14)	16.8 (13–36)

Data are median (range).

Control Group = controls; DMD Group = patients with Duchenne Muscular Dystrophy; Lag time = time between rocuronium administration and first change of train-of-four response; Onset time = time between injection of rocuronium and more than 95% depression of the first twitch; Recovery index = time between 25 and 75% recovery of first twitch; Recovery time = time between 25% recovery of first twitch and recovery of train-of-four ratio to 90%; T_{10}, T_{25}, T_{90} = time between rocuronium administration and recovery of first twitch of the train-of-four response to 10, 25 and 90%.

* $P < 0.01$ versus patients without neuromuscular disease.

of NMB was significantly prolonged in the DMD group compared with the control group ($P < 0.01$) (Table 2).

Recovery from NMB was significantly prolonged in the DMD group compared with the control group. The duration of complete spontaneous recovery in the DMD group was increased threefold to fourfold compared with the control group, and it differed significantly at all recorded time points ($P < 0.01$) (Table 2).

Duration of surgery varied between 5 and 7 h in the DMD group and 2 and 3 h in the control group. Patients of the DMD group were mechanically ventilated overnight and weaned from the respirator the next morning. All patients from the control group breathed spontaneously at the end of surgery.

Discussion

There are two major findings in this study: the administration of a standard dosage of rocuronium (0.6 mg/kg) in patients with advanced DMD leads to 1) a prolonged onset time and 2) a prolonged recovery from NMB compared with unaffected controls. Documented by the very long persisting NMB, our results in part support the hypothesis that patients with DMD are more sensitive to nondepolarizing NMBA, especially rocuronium. The recorded prolonged onset time is in contrast to a suspected higher sensitivity and contradicts our hypothesis that in patients with DMD rocuronium might be an alternative drug to succinylcholine in situations where rapid muscle relaxation is required.

In 1975 Brown and Charlton, studying the sensitivity to curare in patients with advanced DMD using the isolated forearm technique, found that the response to curare differed from unaffected controls in that the regional NMB persisted after tourniquet release.[8] A previous investigation of the effect of nondepolarizing NMBA in DMD patients during anesthesia reported a higher sensitivity to vecuronium, evidenced by smaller dose requirements to achieve equipotent NMB compared with controls.[2] Our finding of markedly prolonged recovery times confirms the assumption of a higher sensitivity against NMBA in DMD patients. However, comparison to our study is limited. In contrast to our protocol, vecuronium was administered according to the degree of NMB and, most importantly, at the end of surgery the NMB was antagonized with neostigmine. Besides the study design, the measurement technique also differed between these two investigations. We used acceleromyography, a method measuring acceleration, for monitoring of NMB whereas the previous study used electromyography, a method recording the evoked compound action potential of a muscle group. There are no data available indicating which of the methods correlates better to clinical tests assessing complete recovery in patients with DMD.

The response of DMD children to other nondepolarizing NMBA is controversial. In a retrospective study, response to mivacurium in DMD patients ranging in age from 8 to 14 yr was found to be prolonged with a wide interpatient variability.[4] In a case report of a 5-yr-old DMD child mivacurium was reported to effect a normal response.[5] Although atracurium was administered in a 12-yr-old boy, data concerning the recovery are lacking.[3] Recovery from rapacuronium-induced NMB in two DMD children was noted to be prolonged.[6] Our results together with the published data strongly indicate that the response of patients with DMD to a standard dosage of available nondepolarizing NMBA differ from that in normal patients.[9,10]

We can only speculate concerning the reasons for the two seemingly contradictory findings (prolonged onset and prolonged recovery) of our study. One reason for the prolonged duration of NMB in these patients could be the known degradation of muscle fibers and its replacement by fatty and fibrous tissue with progression of the disorder. These structural changes are obviously accompanied by a decrease in the total number of neuromuscular junctions (NMJs) and receptors. Consistently, in an experimental study in mdx mice, an accelerated degradation of the adult nicotinic acetylcholine receptors (nAChRs) was observed.[11] Such a situation with a reduced number of receptors would strongly influence the dose-response relationship of administered nondepolarizing NMBA. With this assumption, the conflicting results of reported normal and prolonged durations of nondepolarizing NMBA could be sufficiently explained.

Indeed, the normal response to mivacurium is reported in a 5-yr-old boy, an age where the disease becomes clinically manifest corresponding to an early stage. However, a decrease in the total number of NMJs and receptors alone would not explain the prolonged onset time. Assuming a smaller number of receptors, as in myasthenia, a shorter onset time would be expected, thus indicating a higher sensitivity against rocuronium.[12]

We are not aware of any data regarding the number and subtypes (mature or fetal) of nAChRs from patients with DMD. Regarding the increasing immobilization with progression of the disease, up-regulation of nAChRs might be possible with a shift of the dose-response curve of nondepolarizing NMBA to the right. The very long recovery period in our study clearly contradicts such a theory in DMD. Although an experimental investigation in mdx mice found fetal and adult nAChRs in mouse muscle,[13] data are lacking for DMD patients. Therefore, it remains unclear whether changes of nAChRs are causally involved in the observed response to rocuronium.

To interpret our data, possible changes of the microstructure of the NMJ in DMD patients must be considered. It is now accepted that NMJs underlie lifelong permanent remodeling in response to muscle activity.[14,15] Recent basic investigations have enlightened the involvement of dystrophin as a major component of the dystrophin-protein complex in synaptogenesis. This dystrophin-protein complex and dystrophin-related proteins (*e.g.*, α1-syntrophin) play an important role not only for stabilization of the muscle cytoskeleton but also for maturation and regeneration of the neuromuscular synapse.[16] The absence of dystrophin, the leading feature in DMD, is accompanied by secondary deficiency of several dystrophin-protein complex-associated proteins including dystroglycans and α1-syntrophin.[17] Mice lacking α1-syntrophin develop the typical muscle hypertrophy known from DMD and also aberrant formation of NMJs during regeneration.[18,19] These recent animal studies confirmed one previous investigation in which an atrophy of the postsynaptic region of NMJs in DMD was documented.[20] Considering these data, one can imagine that an aberrant microstructure of NMJs in DMD may change binding characteristics of rocuronium to nAChRs. This concept could reconcile our data of prolonged onset time and prolonged recovery. In addition, this assumption would also explain that response to nondepolarizing NMBA is normal in the early stage of DMD but becomes modified by reduction of structural integrity in NMJs with progression of the disorder. However, this remains purely speculative.

Besides speculation about structural changes at the level of NMJs, possible pharmacokinetic effects must be considered as a cause for the altered response to rocuronium in DMD patients. However, there are no data available concerning pharmacokinetics of rocuronium or other nondepolarizing NMBA in DMD patients.

There are several clinical implications of the current study. First, the prolonged onset time of rocuronium in DMD must be kept in mind in situations where rapid intubation is necessary for airway protection. From our study design we cannot estimate the required dosage for rocuronium for rapid tracheal intubation. The question of whether other nondepolarizing NMBA have a shorter onset time and should be preferred in DMD patients requires further investigation.

Second, if rocuronium is administered in DMD patients, assessment of complete neuromuscular recovery (TOF ratio = 0.9) by quantitative measurement such as acceleromyography is mandatory. In addition, because it is not known whether a TOF ratio of 0.9 is sufficient for adequate respiratory function in these patients, clinical testing such as the head lift should be applied to eliminate the possibility of residual paralysis. The generally prolonged recovery and the wide interpatient variability do not allow estimation of the time needed for complete recovery in a single patient.

Third, even after the administration of a reversal agent, monitoring of muscle strength in the recovery room either quantitatively or clinically should be performed. Regarding the prolonged recovery time, special attention must be paid to the effect of the reversal agent used. Depending on the time of reversal, it may be possible that the duration of residual block after rocuronium exceeds the duration of antagonism by the reversal agent. Therefore, using reversal agents in this situation involves the risk of possible "recurarization."

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