

Influence of Disease Progression on the Neuromuscular Blocking Effect of Mivacurium in Children and Adolescents with Duchenne Muscular Dystrophy

Harald Ihmsen, Ph.D.,* Joachim Schmidt, M.D.,† Helmut Schwilden, M.D., Ph.D.,‡ Hubert J. Schmitt, M.D.,§ Tino Muenster, M.D.†

Background: Studies with nondepolarizing neuromuscular blocking agents showed a delayed onset and prolonged recovery in patients with Duchenne muscular dystrophy. The objective of this study was to investigate if these alterations depend on disease progression.

Methods: The authors studied 11 children (6–9 yr) with moderate Duchenne muscular dystrophy, 11 adolescents (12–16 yr) with advanced Duchenne muscular dystrophy, and 2 age-matched control groups of 8 patients each (5–9 and 10–17 yr). Anesthesia was performed with propofol and remifentanyl. Patients received a single intravenous dose of 0.2 mg/kg mivacurium. Neuromuscular transmission was monitored by acceleromyography. The time course of neuromuscular blockade was characterized by the onset time and the times to different levels of recovery.

Results: Onset and duration of neuromuscular blockade were significantly prolonged in adolescent Duchenne muscular dystrophy patients (onset time, 4.0 min; recovery index, 12.3 min; median), as compared with Duchenne muscular dystrophy children (onset time, 2.3 min; recovery index, 6.8 min), and also as compared with young controls (onset time, 2.0 min; recovery index, 4.4 min) and adolescent controls (onset time, 2.5 min; recovery index, 4.8 min). Within the Duchenne muscular dystrophy patients, onset time and recovery index increased significantly with age. In the control group, age had no effect.

Conclusions: The neuromuscular blocking effects of mivacurium showed a significant age dependency in Duchenne muscular dystrophy patients, which was most probably caused by the progression of the disease.

DUCHENNE muscular dystrophy (DMD) is the most common myopathy in pediatric patients. This genetically determined disorder is caused by mutation of the dystrophin gene at the Xp21 locus, and results in a quantitative deficit of dystrophine. Although the complete mechanism is not yet fully understood, there is strong evidence that dystrophine and its related glycoprotein-complex contribute to the formation of normal neuromuscular junctions during development and reorganization. Clinically, DMD is characterized by ongoing degeneration of skeletal muscle. The subsequent reorga-

nization with fatty infiltration leads to progressive muscle weakness with loss of ambulation at the average age of 10 yr.^{1,2}

For the anesthesiologist, the use of muscle relaxants is of great concern in DMD patients. The use of depolarizing neuromuscular blocking drugs is contraindicated because of the risk of severe hyperkalemia with resulting cardiac arrest,^{3,4} which is probably caused by the existence of a notable number of fetal nicotinic acetylcholine receptors.^{5,6} Administration of nondepolarizing neuromuscular blocking agents, however, causes a markedly prolonged neuromuscular block (NMB).⁷⁻⁹ Noteworthy, the onset of NMB was found to be significantly delayed after administration of rocuronium,⁹ but unchanged after mivacurium in DMD patients, as compared with healthy subjects.⁸ Schmidt *et al.*⁸ speculated that the stage of the disease could be responsible for the prolonged onset of NMB in DMD after administration of rocuronium, as the patients in the rocuronium study were characterized by a more advanced stage of DMD than those in the mivacurium study. It seems conceivable that progressive reorganization including increasing fatty infiltration, fibrosis, and disorganization of the motor endplate of the skeletal muscle in DMD may lead to a changing effect of neuromuscular blocking agents with ongoing disease.

The objective of the present study was to investigate if there is a dependency between the effect of mivacurium on NMB and the progression of DMD. Therefore we compared young children with DMD who were still able to walk with adolescent exclusively wheelchair-bound DMD patients.

Materials and Methods

Patients and Anesthesia

After approval by the Ethics Committee of the Medical Faculty of the University of Erlangen-Nuremberg (Erlangen, Germany) and obtaining written consent, 38 male patients were enrolled in this study. Of 22 boys with the diagnosis of DMD, 11 children aged 6 to 9 yr were still able to walk, whereas 11 adolescent boys aged 12 to 16 yr suffered from advanced stages of the disease and were wheelchair-bound. They were scheduled for elective corrective orthopedic surgery of the lower limbs or elongation and stabilization of the spinal column, respectively. Sixteen patients without neuromuscular disease aged 5 to 17 yr served as controls and underwent uro-

* Research Scientist, † Associate Professor of Anesthesiology, ‡ Professor of Experimental Anesthesiology, § Professor of Anesthesiology, Department of Anesthesiology, Friedrich-Alexander University Erlangen-Nuremberg.

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Address correspondence to Dr. Muenster: Department of Anesthesiology, Friedrich-Alexander Universität Erlangen-Nuremberg, Krankenhausstrasse 12, 91054 Erlangen, Germany. muenster@kfa.imed.uni-erlangen.de. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

logical surgery. None of the patients received any medication known to influence neuromuscular function. We recorded age, height, weight, and body mass index for each patient.

The patients were visited the day before surgery for a physical examination and review of laboratory test results, including plasma cholinesterase. In addition, we performed a lung function test and an echocardiography in all boys of the adolescent DMD group. After weight-adapted premedication with midazolam orally 45 min before anesthesia, placement of an intravenous line, and preoxygenation with pure oxygen, anesthesia was induced with 2 $\mu\text{g}/\text{kg}$ fentanyl and 3 mg/kg propofol. The patient's trachea was intubated without any use of neuromuscular blocking agents. For maintenance of anesthesia we used a continuous intravenous infusion of 8 mg/kg propofol and remifentanyl titrated to effect. Standard monitoring included electrocardiography, automatic blood pressure, capnometry, pulse oxymetry, and a temperature probe. In adolescent DMD patients, an intraarterial and a central venous line were also placed. The lungs were ventilated with a mixture of oxygen in air; minute volume ventilation was set to obtain end-tidal carbon dioxide levels of 35–40 mmHg. The central body temperature was kept between 35.5 and 37°C using warmed fluids and a warm forced-air device.

Neuromuscular Monitoring

Neuromuscular transmission was monitored by acceleromyography using TOF Watch SX equipment (Organon Ireland Ltd., a part of Schering-Plough Corporation, Dublin, Ireland) within the guidelines of the Copenhagen Consensus Conference.¹⁰ After final positioning (adolescents, prone position; children and controls, supine position), the right forearm was prepared for neuromuscular 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 IV 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 (4 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 acceleromyography probe fixed to the volar surface of the distal phalanx of the thumb. The TOF monitor was connected to a portable computer for online data recording and processing. After calibration and signal stabilization of the control response, 0.2 mg/kg of mivacurium was administered intravenously over 5 s. The time from administration of mivacurium to complete clinical recovery was monitored. The following parameters of NMB were measured: maximal depression of the first twitch,

time from injection to the first of three consecutive twitches with the same or increasing amplitude (onset time), time between injection and recovery of first twitch to 25% and to 90%, time between 25% and 75% recovery of first twitch (recovery index), and time between 25% recovery of first twitch and recovery of TOF ratio to 90% (recovery time).

Statistics

All data were tested for normal distribution with the Shapiro-Wilks test, and for homogeneity of variances with the Levene test. The groups were tested for statistically significant differences either by two-way ANOVA with the factors age (young and adolescent) and group (control and DMD), followed by the Scheffé *post hoc* test or by the nonparametric Mann-Whitney U-test with Bonferroni correction, if appropriate. For a 2 \times 2 ANOVA, the required sample size per group to detect a standardized effect of 1.0 (*i.e.*, a difference with a magnitude of one SD) with $P < 0.05$ and a power of 0.80 is $n = 5$ for the factor effects and $n = 9$ for the interaction effect. The effect of age was assessed by linear regression analysis, and the regression coefficient was tested for statistical significance using the F test. A value of $P < 0.05$ was considered statistically significant for all analyses. Statistical analysis was performed using Statistica 6.0 (StatSoft Inc., Tulsa, OK).

Results

Patients' data are summarized in table 1. Within both the control and the DMD patients, the adolescents were significantly older, taller, and heavier, as compared with the children, whereas there were no demographic differences between the DMD patients and the controls in the corresponding age classes. The plasma cholinesterase activity was within the normal range in all subjects (data not shown). The train-of-four ratio at baseline before injection of mivacurium was 1. A maximum NMB effect of 100% was achieved in 6 of 8 young controls, in

Table 1. Patient Data

	Control Group Children	Control Group Adolescents	DMD Group Children	DMD Group Adolescents
N	8	8	11	11
ASA class	I	I	II	III
Age (yr)	6.3 \pm 1.6	13.5 \pm 2.6*	7.9 \pm 1.2	13.8 \pm 1.5†
Body weight (kg)	25 \pm 8	54 \pm 9*	27 \pm 6	54 \pm 20†
Height (cm)	120 \pm 15	168 \pm 16*	127 \pm 10	162 \pm 29†
BMI (kg/m ²)	17 \pm 2	19 \pm 2	17 \pm 2	20 \pm 7

Data are given as mean \pm SD.

* $P < 0.05$ adolescents vs. children in the control group. † $P < 0.05$ adolescents vs. children in the DMD group.

ASA = American Society of Anesthesiologists; BMI = body mass index; DMD = Duchenne muscular dystrophy.

Table 2. Neuromuscular Effect Parameters

	Control Group Children	Control Group Adolescents	DMD Group Children	DMD Group Adolescents
Onset time (min)	2.0 (1.3–3.0)	2.5 (2.0–3.5)	2.2 (1.5–4.7)	4.0 (1.8–7.0)*
T ₂₅ (min)	11 (7.3–18)	12 (9.3–18)	12 (8.8–19)	19 (12–44)*†
T ₉₀ (min)	18 (12–27)	18 (14–27)	25 (20–31)	40 (25–63)‡
Recovery index (min)	4.4 (2.5–6.8)	4.8 (3.5–7.5)	6.8 (4.0–10)	12 (6.5–23)‡§
Recovery time (min)	8.5 (6.5–12.0)	9.1 (7.5–9.8)	12 (3.0–21)	18 (4.5–45)†
Maximum effect (%)	100 (94–100)	100 (97–100)	100 (98–100)	100 (75–100)

Data are given as median and range.

* $P < 0.05$ DMD adolescents vs. DMD children. † $P < 0.05$ DMD adolescents vs. control adolescents. ‡ $P < 0.01$ DMD adolescents vs. DMD children.

§ $P < 0.005$ DMD adolescents vs. control adolescents.

DMD = Duchenne muscular dystrophy; onset time = time between injection of mivacurium and onset of neuromuscular block; recovery index = time between 25% and 75% recovery of first twitch; recovery time = time between 25% recovery of first twitch and train-of-four ratio of 90%; T₂₅ = time between injection of mivacurium and 25% recovery of first twitch; T₉₀ = time between injection of mivacurium and 90% recovery of first twitch.

7 of 8 adolescent controls, in 10 of 11 young DMD children, and in 6 of 11 adolescent DMD patients.

Table 2 summarizes the neuromuscular effects of mivacurium in the four groups. Within the control group there were no significant differences between young and adolescent patients, whereas onset and recovery of NMB were significantly delayed in the DMD adolescents, as compared with the DMD children and the adolescent controls. The young DMD patients did not differ significantly from the young controls.

There was a significant age-related increase of the onset time ($r^2 = 0.30$, $P = 0.0089$) and the recovery index ($r^2 = 0.34$, $P = 0.0047$) within the DMD patients (fig. 1 and 2), whereas the age dependency in the control group was insignificant for onset time ($r^2 = 0.13$, $P = 0.18$) and recovery index ($r^2 = 0.03$, $P = 0.49$).

Discussion

This study generally confirmed our previous finding that the administration of mivacurium in patients with DMD led to a significantly prolonged duration of NMB, as compared with controls.⁸ Whereas in the previous study patients with an age between 5 and 14 yr were pooled, the separation into children and adolescents in the present study allowed investigation of the effect of the DMD progress on the neuromuscular blocking effect of mivacurium. The young DMD children with a moderate degree of DMD showed no significant differences, as compared with the control group; whereas in the adolescents with advanced DMD there was a significantly prolonged duration and also a significantly prolonged onset of NMB. The regression analysis of all DMD data

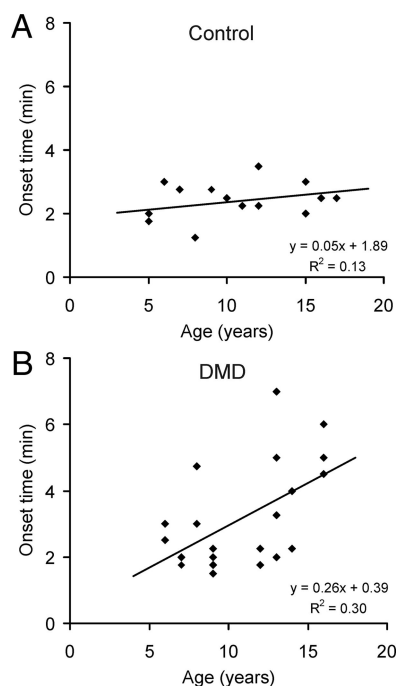


Fig. 1. Onset time versus age in the control group (A) and in Duchenne muscular dystrophy (DMD) patients (B). Shown are the individual values (dots) and the linear regression lines.

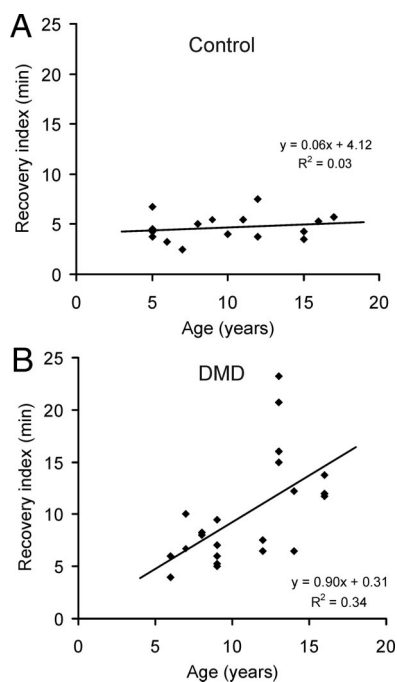


Fig. 2. Recovery index versus age in the control group (A) and in Duchenne muscular dystrophy (DMD) patients (B). Shown are the individual values (dots) and the linear regression lines.

confirmed this age dependency of mivacurium effects in DMD patients. In the control groups, which covered comparable ranges of age, we did not find an influence of age. The slightly smaller size of the control groups may be a limitation, but our results for the control group are in agreement with the findings of Østergaard *et al.*, who showed that onset and duration of NMB after administration of mivacurium were not different between younger (3-6 yr) and older (10-14 yr) children.¹¹ The recovery index for the control group in the present study was also in accordance with the results of other authors, who found values between 4.1 and 7.3 min for mivacurium in children.¹¹⁻¹⁶ This suggests that the age dependency in DMD patients found in the present study is indeed an effect of the DMD progression and not simply of age.

The origin of the observed alterations in DMD patients is still unclear. As we did not measure mivacurium concentrations, it was not possible to discriminate pharmacokinetic and pharmacodynamic changes. A change in pharmacokinetics seems, however, less probable, as the plasma cholinesterase activity was not changed in DMD patients. In a recent pharmacokinetic-dynamic study on rocuronium in DMD patients, we found unchanged pharmacokinetics, whereas the equilibration between plasma and effect site concentration was significantly slower (*i.e.*, a smaller k_{e0}), and the half maximum effect site concentration EC_{50} was significantly smaller in DMD patients.¹⁷ Possible physiologic mechanisms for such alterations are structural changes in the nicotinic acetylcholine receptor and/or its signal transduction.

In conclusion, administration of mivacurium in DMD patients led to an age-dependent delay of onset and recovery, as compared with controls. These findings support our hypothesis that neuromuscular blocking effects of neuromuscular blocking agents in DMD patients depend on the stage of the disease. Although the age of the DMD patients is only a surrogate parameter for the stage of the disease, it seems to be adequate for clinical practice as a more precise and easy-to-determine marker

is still missing. For clinical practice it is important that the bolus dose to achieve maximum NMB is not different for DMD patients and controls, and is also not changed with increasing age and ongoing disease.

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