The pharmacodynamics and pharmacokinetics of mivacurium in children

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Background: In children, onset time and duration of action of mivacurium are shorter than in adults. Some suggest that this is due to differences in plasma cholinesterase (pChe), whereas others indicate that there is no difference. The purpose of this study was to evaluate the pharmacodynamics and pharmacokinetics of mivacurium in phenotypically normal children aged 3–6 and 10–14 years old, respectively.

Methods: Ten children aged 3–6 years and 10 children aged 10–14 years were studied during halothane anaesthesia. Before induction of anaesthesia, a blood sample was drawn to measure the pChe activity and phenotype. The neuromuscular block was monitored at the thumb using train-of-four (TOF) nerve stimulation every 12 s and mechanomyography. The times to different levels of neuromuscular recovery following mivacurium 0.2 mg/kg were recorded. The concentrations in venous blood of the three isomers and the metabolites of mivacurium were measured.

Results: No statistically significant difference was found in pChe activity or in the pharmacodynamics of mivacurium. The onset time was 1.4 min (0.8–1.9) median (range) and 1.3 min (1.1–1.9) and the time to first response to TOF nerve stimulation was 9.6 min (6.5–12.6) and 10.5 min (7.0–14.0) in young and older children, respectively. The pharmacokinetic data were too sparse to allow analysis of the two age groups separately (8 and 8 patients), hence the data were pooled. The median clearances of the cis-cis, the cis-trans, and the trans-trans isomer were 5.5, 51.0 and 30.5 ml/kg/min, respectively.

Conclusion: Our data indicate that there are no major differences in pharmacodynamics or pharmacokinetics of mivacurium between young (3–6 years) and older (10–14 years) children.

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Key words: butyrylcholinesterase; children; cholinesterase; mivacurium; neuromuscular relaxants; pharmacodynamics; pharmacokinetics; pseudocholinesterase.

IN CHILDREN, ED95 of mivacurium is larger and the onset time and the duration of action shorter than in adults (1–4). This difference between children and adults is often explained by an age-dependent variation in volume of distribution and in differences in plasma cholinesterase activity (pChe) (5, 6). Some studies in children have indicated that pChe is low at birth, increases to a maximum at the age of 3–6 years, and decreases to adult level at puberty (7, 8), but other studies indicate that no such differences exist (9–12). No studies have, however, evaluated the pharmacodynamics together with the pharmacokinetics of mivacurium in young and older children and generally pharmacokinetic data following mivacurium are sparse (10, 13).

The purpose of the present study was to evaluate the pharmacodynamics and pharmacokinetics of a single dose of mivacurium 0.2 mg/kg in two groups of phenotypically normal children, aged 3–6 years and 10–14 years, respectively.

Patients and methods

Ten randomly selected children aged 3–6 years and 10 aged 10–14 years were included in the study. All patients (ASA physical status 1) were scheduled for elective surgery. Informed consent was obtained from the children’s parents and the study was approved by the local Ethics Committee. Before induction of anaesthesia, a blood sample was taken for later determination of pChe activity and phenotype. Subsequent analysis showed all patients to have a normal phenotype and low to normal pChe activity according to the reference values of the Danish Cholinesterase Research Unit (9). Children with a history of neuromuscular, cardiovascular, renal or hepatic disorders were not included in the study, as were children receiving drugs that might affect the neuromuscular transmission.

Premedication consisted of diazepam 0.3 mg/kg rectally (young children) or orally (older children). An-
Aesthesia was induced with an inhalation with halothane 2% and 50% N₂O in oxygen in the majority of the small children (7 out of 10) and with a single bolus dose of thiopentone i.v in the majority of the older children (7 out of 10). Immediately following the induction with thiopentone, halothane 2% and 50% N₂O in oxygen were applied. Anaesthesia was maintained normocapnia (end-tidal CO₂ 4.5–5.6 kPa). The rectal temperature was measured every min for the first 3 min following induction of anaesthesia, a second intravenous catheter was inserted for blood sampling in the arm used for administration of anaesthetics and fluid were kept greater than 35°C and 32°C, respectively (14). After induction of anaesthesia, a second intravenous catheter was inserted for blood sampling in the arm used for monitoring.

During surgery the patients were monitored continuously with electrocardiogram, pulseoximetry and capnography. Also, the end-tidal halothane concentration was monitored continuously. Blood pressure was measured every min for the first 3 min following administration of mivacurium, and every 5 min thereafter. The blood pressure cuff and the intravenous line were on the same arm. Ventilation was adjusted to maintain normocapnia (end-tidal CO₂ 4.5–5.6 kPa). The rectal and peripheral skin temperatures were measured and kept greater than 35°C and 32°C, respectively (14). After induction of anaesthesia, a second intravenous catheter was inserted for blood sampling in the arm used for monitoring.

The mechanical twitch was recorded using a Myograph 2000 (Biometer International, Denmark). The ulnar nerve was stimulated at the wrist using surface electrodes and 1 Hz single twitch stimulation. When supramaximal stimulation was achieved and the response to stimulation was stable for 5 min, the stimulation pattern was changed to train-of-four (TOF) stimulation every 12 s and a single bolus dose of mivacurium 0.2 mg/kg was given over 20 s. Tracheal intubation was performed at 100% twitch (T₁) suppression. The neuromuscular block was allowed to recover spontaneously.

**Pharmacodynamic analysis**

Onset (time from beginning of injection of mivacurium to 95% T₁ depression) and recovery data were determined using start control values, and monitoring was continued until at least 90% T₁ recovery and a TOF ratio of 0.8 were obtained. The period of no twitch response (from 100% T₁ depression to first response to TOF stimulation), the duration to 10, 25, 90% T₁ recovery and to a TOF ratio of 0.8 and the interval 25–75% (time from 25 to 75% twitch height recovery) were recorded (14).

**Measurement of plasma cholinesterase activity**

Plasma cholinesterase activity was measured using benzoylcholine as substrate and the phenotype was determined using the dibucaine number (DN), the fluoride number (FN), the urea number (UN) and the Ro-2-0683 number (Ro) (9). However, only the results concerning the DN are given.

**Plasma concentrations of mivacurium**

Venous blood samples (3 ml) were collected immediately prior to the administration of mivacurium and 1, 2, 3, 4, 6, 10, 15, 20, 40 and 60 min after the start of injection. In less than 10 s the blood was transferred into a vacutainer containing a cholinesterase inhibitor (phospholine iodide). The samples were centrifuged, plasma decented and frozen at -70°C. The ratio of cis, cis-trans and trans-trans isomers in the clinical trial material used are approximately 6.2, 37.3 and 58.8%, respectively (Data from certificate of analysis, Glaxo Wellcome). The concentration of each isomer and metabolite of mivacurium was determined by a stereospecific high performance liquid chromatographic method (HPLC) with fluorometric detection and a stepped gradient (15) (modified by Glaxo Wellcome, UK). The drug assay was automated (ASPEC, Gilson). The coefficient of variation was 10% at all concentrations except for the lowest level of quantification (5 ng/ml) (15%). Extraction efficiency was 75%. Calibration was linear over the range 5–1000 ng/ml.

**Pharmacokinetic analysis**

A two compartment model was fitted separately to the plasma concentrations of each isomer using ADAPT II (16) with numerical integration of differential equations. The following parameters were fitted: Volume of the central compartment (V₁), the elimination rate constant describing elimination from the central compartment (kₑ), and the rate constants describing the intercompartmental transport (k₁₂ and k₂₁). As the nature of the data did not allow for use of a ‘standard two stage method’, the fitting was done in the way that concentrations from all patients were treated as if they originated from a single patient. The goodness of fit was evaluated from visual inspection and from plots of residuals.

The following secondary parameters were calculated: Clearance (CL) as kₑ *V₁, λ₁ and λ₂ according to the equation:

\[ \lambda_1 = \frac{1}{2} \left[ \frac{(k_e + k_{12} + k_{21}) + \sqrt{(k_e + k_{12} + k_{21})^2 - 4k_{21}k_e}}{2k_{21}} \right] \]

\[ \lambda_2 = \frac{1}{2} \left[ \frac{(k_e + k_{12} + k_{21}) - \sqrt{(k_e + k_{12} + k_{21})^2 - 4k_{21}k_e}}{2k_{21}} \right] \]

and \( t_{1/2} = \ln 2 \lambda_2 \).
Table 1
Demographic and biochemical data.

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of patients</th>
<th>Male/Female</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Plasma cholinesterase activity (U/l)</th>
<th>Dibucaine number</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3–6 years)</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Older children</td>
<td>10</td>
<td>8/2</td>
<td>(10–14 years)</td>
<td>(10–14)</td>
<td>(22–70)</td>
<td>(449–1544)</td>
<td>(82–86)</td>
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<tr>
<td>(10–14 years)</td>
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</table>

Medians (ranges) are given. Reference values of the Danish Cholinesterase Research Unit for plasma cholinesterase activity and dibucaine number are 660–1620 U/l and 79–87, respectively (9).

Table 2
Onset time (time to 95% block), duration of action and recovery data following mivacurium 0.2 mg/kg in young and older children.

<table>
<thead>
<tr>
<th>Group</th>
<th>Onset time</th>
<th>Reappearance of T₁</th>
<th>10%</th>
<th>25%</th>
<th>90%</th>
<th>Duration</th>
<th>TOF 0.80</th>
<th>Interval 25–75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young children</td>
<td>1.4 (0.8–1.9)</td>
<td>9.6 (6.5–12.6)</td>
<td>11.5 (8.9–14.7)</td>
<td>13.3 (9.8–16.6)</td>
<td>22.7 (17.5–30.4)</td>
<td>20.6 (17.1–27.8)</td>
<td>6.5 (4.6–8.0)</td>
<td></td>
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<tr>
<td>(3–6 years)</td>
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</tr>
<tr>
<td>Older children</td>
<td>1.3 (1.1–1.9)</td>
<td>10.6 (7.0–14.0)</td>
<td>11.8 (8.3–16.1)</td>
<td>13.6 (9.4–18.0)</td>
<td>23.9 (15.7–30.3)</td>
<td>22.7 (16.1–27.3)</td>
<td>6.0 (4.1–14.5)</td>
<td></td>
</tr>
<tr>
<td>(10–14 years)</td>
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</table>

Values are given as median and ranges (min).
TOF = train of four ratio.
Data are presented according to the GCRP rules for pharmacodynamic studies of neuromuscular blocking agents (14).

Statistical analysis
All pharmacodynamic results are presented as medians and ranges and all pharmacokinetic results are presented as means (±SD) and compared using the non-parametric Mann–Whitney U-test. \( P < 0.05 \) was considered statistically significant. The necessary number of patients was calculated to be 20, based on an accepted risk of type I error of 5%, a type II error of 20%, a minimum relevant difference (MIREDIF) (17) of 5 min on recovery data, and an SD of 4 min (recovery time to 25% T₁), known from a previous study (3).

Results
Table 1 summarizes the demographic and biochemical data. All patients were within 20% of their ideal body-weight.

Plasma cholinesterase activity
All children were phenotypically normal, as indicated by normal inhibitor numbers. Two children, however, had low pChe activity, one in each group. There was no significant difference in pChe activity between young and older children (Table 1).

Pharmacodynamics
One older child was excluded from the pharmacodynamic part of the study as the twitch height did not recover to 80% of the control twitch height (14). No significant differences were seen in any of the pharmacodynamic variables between the two groups of patients (Table 2). The relationship between pChe activity and time to first reappearance of T₁ is presented in Fig. 1.

All patients were able to maintain headlift for 5 s before leaving the operation theater and at discharge from the recovery room.

Pharmacokinetics
Four children (2 young and 2 older) were excluded from the pharmacokinetic analysis due to insufficient blood sampling.

The plasma concentrations of the active isomers of mivacurium decreased rapidly in both groups, and only a few data points could therefore be included in the pharmacokinetic analysis. It was therefore not possible to analyze the data separately for the two groups of children, and data were pooled.

Figure 2 shows the individual plasma concentrations of each of the three isomers over time and
Table 3

Clearances (CL) (ml kg⁻¹ min⁻¹), rate constants kₑ, k₁₂, k₂₁ (min⁻¹), terminal elimination half-lives (t₁/₂), initial volumes of distribution (V₁) and the volumes of distribution at steady state (VDss) (L kg⁻¹) estimated from the pooled data of young and older children.

<table>
<thead>
<tr>
<th>Isomer</th>
<th>CL (ml/min/kg)</th>
<th>kₑ (min⁻¹)</th>
<th>k₁₂ (min⁻¹)</th>
<th>k₂₁ (min⁻¹)</th>
<th>t₁/₂ (min)</th>
<th>V₁ (ml/kg)</th>
<th>VDss (ml/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cis–cis</td>
<td>5.5 ± 0.5</td>
<td>0.121 ± 0.014</td>
<td>0.243 ± 0.030</td>
<td>0.085 ± 0.014</td>
<td>28.7 ± 5.5</td>
<td>46 ± 3</td>
<td>176 ± 36</td>
</tr>
<tr>
<td>Cis–trans</td>
<td>51.1 ± 4.0</td>
<td>0.760 ± 0.082</td>
<td>0.245 ± 0.037</td>
<td>0.102 ± 0.033</td>
<td>9.3 ± 3.3</td>
<td>67 ± 9</td>
<td>229 ± 52</td>
</tr>
<tr>
<td>Trans–trans</td>
<td>30.5 ± 2.5</td>
<td>0.620 ± 0.072</td>
<td>0.190 ± 0.035</td>
<td>0.074 ± 0.033</td>
<td>12.6 ± 6.2</td>
<td>49 ± 6</td>
<td>177 ± 38</td>
</tr>
</tbody>
</table>

Mean (±SD) are given.

Table 3 summarizes the pharmacokinetic data. The cis–cis isomer had the lowest clearance, the cis–trans isomer the highest, i.e. 1.7 times that of the trans–trans isomer. The volumes of distribution were small for all isomers.

Metabolites
The plasma concentration of the cis quaternary alcohol metabolite was too low to allow for reliable estimate of the half-life or AUC data (Table 4). For the three other metabolites, no significant differences were found between young and older children in time to maximum concentration (tₘₐₓ), maximum concentration (Cₘₐₓ) or elimination half-lives.

In one patient injection of mivacurium caused cutaneous flushing. No other adverse reactions that might be related to mivacurium were observed.

Discussion
Our findings suggest that there are no differences in the pharmacodynamics or pharmacokinetics of mivacurium in children aged 3–6 and 10–14 years, respectively. However, due to the small sample size, minor differences in a larger population cannot be excluded; although no significant differences were shown in our study.

Plasma cholinesterase activity
We found no significant difference in pChe activity between the two groups of children. This is in accordance with the findings of Markakis et al. (10, 12) and Bevan et al. (11), and with our own findings in 6.688 children and adults in the Danish Cholinesterase Research Unit (DCRU) (9). It is, however, in contrast to traditionally held views (7, 8). In earlier studies, different age groups of children were investigated by different research groups (6, 7), whereas the data from the DCRU represent a larger group of a Danish population of both children and adults (9). Also, in recent clinical trials with mivacurium both children and adults were included and pChe activity measured and compared (10–12). Longitudinal studies, where pChe
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Fig. 2 (a)–(c). Plasma concentrations (ng/ml) of the cis-cis, cis-trans, and trans-trans isomers over time (min) in young children (full line symbols), and older children (broken line). The thick line is the result of fitting all concentrations.

activity is measured in the same person over time (years), have not been published.

Figure 1 shows the relationship between pChe activity and the time to reappearance of T1 following mivacurium. The figure suggests that there is a relationship between pChe activity and time to reappearance of T1. The higher the pChe activity, the shorter the time to reappearance of T1. This is in accordance with previous findings in children (18) and adults (19). However, the relationship in the present study is only due to three patients, two patients with a pChe activity below the normal range and one with pChe activity in the upper normal range.

Pharmacodynamics

No significant difference was seen in onset and recovery data between the two groups of patients (Table 2). The duration of action of mivacurium in our study is in accordance with results published by Goudsouzian et al. (3), Bevan et al. (11) and Kaplan et al. (20), but slightly longer than reported by McCluskey et al. (21). The shorter onset time in children than in adults (19) is probably due to the fact that young children circulate their blood volume faster (22).

Pharmacokinetics

The plasma clearances of the three isomers of mivacurium found in our study are comparable to the clearances described by Simhi et al. (13), but much lower than reported by Markakis et al. (10) during a continuous infusion. This may be due to different sampling times and procedures as well as different modes of administration. We used venous sampling and only relatively few samples were taken immediately after the injection of mivacurium because we considered it problematic to obtain permission to use an arterial line in otherwise healthy children and, further, to obtain larger volumes of blood from small children. Our venous sampling procedure and the relative few samples might cause an underestimation of the initial area under the plasma concentration time curve (23). Markakis et al. (10) also used venous sampling, but only for 8 min, which might explain the higher clearances in their study. The clearances found in our study are comparable to the clearances found in adult patients (19).

The elimination half-lives of the cis-trans and the trans-trans isomers of mivacurium were 9.3 ± 3.3 min and 10.6 ± 6.2 min, respectively, which is longer than those found by Simhi et al. (13) and Markakis et al. (10) following a continuous infusion in children. This difference might also be due to the short sampling period used in the latter study. The elimination half-lives of
the active isomers in children are longer than previously presented in adults (4, 19). The elimination half-life of the cis-cis isomer was estimated to be about 29 min in our study, which is longer than reported by Simhi et al. (13). Because the method is only briefly described in the short communication of Simhi et al. (13), we cannot explain the different results in the two studies. The elimination half-life of the cis-cis isomer in children found by us is shorter than is found in adults (19). Again, this might be due to a short sampling period. A sampling period of 60 min, as used in the present study, is too short for an isomer with an expected half-life of about 50 min.

The initial volume of distributions and the rate constant $k_e$ and $k_{12}$ found by us were not different from those seen in adults. The rate constants $k_{21}$ for the active isomers were, however, lower than in adults (19). This might be due to a higher volume of distribution in the second compartment (VD$_2$) in children (unpublished data from (19) and calculations in the present study), which correlates well with the higher extracellular volume in children than in adults.

The elimination half-lives of the metabolites of mivacurium are shorter than reported in adults by Lacroix et al. (24). These differences might be due to a shorter sampling period in our study.

In summary, we found no significant differences in onset or recovery between the two age groups, nor did we find any difference in pChe activity. Due to sparse data immediately following the injection of mivacurium, we were unable to evaluate whether there were any differences in the pharmacokinetics of the isomers of mivacurium. We did not, however, find any differences in the pharmacokinetics of the metabolites. Therefore, taking all results into account, i.e. no difference between the two groups of children in pharmacodynamics, no difference in pChe activity or in pharmacokinetics of the metabolites, we find it improbable that there should be a difference in the pharmacokinetics of the isomers.

In conclusion, our data indicate that there are no differences in pharmacodynamics or pharmacokinetics of mivacurium between young (3–6 years) and older (12–14 years) phenotypically normal children.

Acknowledgements
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References
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Table 4

Estimated time to maximum concentration ($t_{\text{max}}$) (min), maximum plasma concentration ($C_{\text{max}}$) and elimination half-life ($t_{1/2}$) (min) of the three major metabolites of mivacurium.

<table>
<thead>
<tr>
<th></th>
<th>$t_{\text{max}}$ (min)</th>
<th>$C_{\text{max}}$ (ng/ml)</th>
<th>$t_{1/2}$ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cis 879 (monoester)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young (3–6 years)</td>
<td>1.0 (1.0–2.0)</td>
<td>473 (323–707)</td>
<td>42.8 (35.8–63.6)</td>
</tr>
<tr>
<td>Older (10–14 years)</td>
<td>1.0 (0.8–1.0)</td>
<td>581 (352–872)</td>
<td>43.8 (35.8–63.1)</td>
</tr>
<tr>
<td><strong>Trans 879 (monoester)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young (3–6 years)</td>
<td>1.0 (1.0–2.0)</td>
<td>713 (574–948)</td>
<td>30.2 (22.9–71.6)</td>
</tr>
<tr>
<td>Older (10–14 years)</td>
<td>1.0 (1.0–2.0)</td>
<td>622 (440–989)</td>
<td>34.5 (24.4–43.8)</td>
</tr>
<tr>
<td><strong>Trans 141 (alcohol)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young (3–6 years)</td>
<td>2.0 (1.0–2.5)</td>
<td>898 (566–1427)</td>
<td>22.9 (16.2–29.7)</td>
</tr>
<tr>
<td>Older (10–14 years)</td>
<td>1.0 (1.0–3.0)</td>
<td>796 (563–1466)</td>
<td>27.4 (14.5–45.4)</td>
</tr>
</tbody>
</table>

Medians and ranges are given.
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