IS VECURONIUM A LONG-ACTING NEUROMUSCULAR BLOCKING AGENT IN NEONATES AND INFANTS?

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We have previously shown that the ED$_{50}$ and ED$_{95}$ of vecuronium are 40% smaller in neonates and infants than in children aged between 3 and 10 yr [1]. The spontaneous recovery rate is also strongly dependent on age: the recovery index is 18–20 min in infants and 9–10 min in children [2–3]. The maintenance requirements for vecuronium have not been determined in paediatric patients. The aim of this study was to investigate the effect of age on the maintenance requirements and the duration of action of vecuronium during prolonged anaesthesia in infants and children.

**PATIENTS AND METHODS**

We studied 81 patients of ASA grades I and II scheduled to undergo an elective surgical procedure lasting a minimum of 90 min. The patients were healthy and were not receiving medications known to affect neuromuscular transmission or renal or hepatic function. The study was approved by the Ethics Committee of the Children’s Hospital, University of Helsinki, and consent was given by the parents.

The patients were classified into nine groups of nine, delimited by the ages 3 months, 1, 2, 3, 5, 7, 10 and 13 yr. The youngest age group included seven neonates (12–27 days old and weighing 3.3–4.2 kg) whose gestational ages had been 38–41 weeks. The average age of the second group was 6.2 months (range 3.9–8.0 months).

Dextrose 5% with sodium chloride 60 mmol litre$^{-1}$ was administered at a rate of 2–4 ml kg$^{-1}$ h$^{-1}$ throughout anaesthesia. Premedication consisted of either methohexitone 15 mg kg$^{-1}$ per rectum (3 months to 4 yr) or flunitrazepam 0.08 mg kg$^{-1}$ by mouth (maximum dose 2.0 mg) (1-16 yr). Anaesthesia was induced with fentanyl 3 µg kg$^{-1}$ and thiopentone 2–4 mg kg$^{-1}$. Ventilation was controlled with 67% nitrous oxide in oxygen to maintain the end-tidal carbon dioxide concentration at 5.0–5.5%. Body temperature was maintained between 36 and 37°C. No volatile anaesthetic agent was used.

Neuromuscular transmission was monitored by electromyography (EMG) (Relaxograph, Datex, Finland). Surface electrodes were placed over the ulnar nerve near the wrist, over the adductor pollicis muscle on the thenar eminence, and over the proximal phalanx of the middle finger. The thenar EMG was recorded with train-of-four stimulation (TOF) (2 Hz at 20-s intervals). After calibration of the equipment, vecuronium was administered in divided doses to achieve 95% depression of the first twitch response (95%
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TABLE I. $ED_{95}$ and dose requirement of vecuronium, and duration of > 90\% neuromuscular block maintained by vecuronium in paediatric patients (means (SEM)). Significant differences: †from groups < 2, < 3, < 5, < 7, < 10, < 13 and < 17 yr (Anova and Tukey test); §from groups < 3, < 5, < 7, < 10 and < 13 yr; ¶from groups < 3, < 5, < 7 and < 10 yr

<table>
<thead>
<tr>
<th>Age group</th>
<th>$ED_{95}$ ((\mu g \text{ kg}^{-1}))</th>
<th>Requirement in 60 min ((\mu g \text{ kg}^{-1}))</th>
<th>Duration 100 (\mu g \text{ kg}^{-1}) (min)</th>
<th>Duration 150 (\mu g \text{ kg}^{-1}) (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3 months</td>
<td>49 (6)§</td>
<td>106 (7)§</td>
<td>60 (7)†</td>
<td>111 (13)†</td>
</tr>
<tr>
<td>3 months—&lt; 1 yr</td>
<td>47 (3)§</td>
<td>104 (3)§</td>
<td>57 (3)†</td>
<td>109 (5)†</td>
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<tr>
<td>1–&lt; 2 yr</td>
<td>58 (6)</td>
<td>134 (9)¶</td>
<td>39 (4)¶</td>
<td>72 (6)¶</td>
</tr>
<tr>
<td>2–&lt; 3 yr</td>
<td>69 (4)</td>
<td>185 (12)</td>
<td>24 (3)</td>
<td>49 (6)</td>
</tr>
<tr>
<td>3–&lt; 5 yr</td>
<td>80 (4)</td>
<td>207 (10)</td>
<td>19 (2)</td>
<td>39 (3)</td>
</tr>
<tr>
<td>5–&lt; 7 yr</td>
<td>75 (5)</td>
<td>223 (19)</td>
<td>18 (2)</td>
<td>37 (4)</td>
</tr>
<tr>
<td>7–&lt; 10 yr</td>
<td>84 (5)</td>
<td>221 (19)</td>
<td>18 (3)</td>
<td>38 (6)</td>
</tr>
<tr>
<td>10–&lt; 13 yr</td>
<td>74 (7)</td>
<td>185 (18)</td>
<td>25 (4)</td>
<td>48 (6)</td>
</tr>
<tr>
<td>13–&lt; 17 yr</td>
<td>52 (3)¶</td>
<td>143 (7)¶</td>
<td>37 (3)¶</td>
<td>68 (6)¶</td>
</tr>
</tbody>
</table>

neuromuscular block) over 5–8 min, and the trachea was intubated. Incremental doses of vecuronium 10–15 \(\mu g \text{ kg}^{-1}\) were given whenever the first twitch of the TOF recovered to 10\% of the control value. If increments were needed at regular intervals, vecuronium was administered by continuous infusion. Neuromuscular blockade was maintained between 90 and 98\% throughout the study period in every patient.

Three or four doses of vecuronium were given during establishment of the initial 95\% blockade. The individual $ED_{95}$ doses for vecuronium were determined after log-probit analysis was used to determine the individual vecuronium dose–response curves. The individual vecuronium requirement during the first 1 h of anaesthesia was calculated and the duration of neuromuscular blockade > 90\% maintained by cumulative doses of vecuronium 100 and 150 \(\mu g \text{ kg}^{-1}\) measured. Analysis of variance, with Welch modification in cases of unequal variances, was used for statistical analysis (BMDP Statistical Software 7D, Berkeley, California). The Tukey studentized range method was used to compare the mean $ED_{95}$ doses, and the between-group requirements and durations of effect of vecuronium. $P < 0.05$ was considered statistically significant. Values are expressed as mean (SEM).

RESULTS

In patients younger than 1 yr the $ED_{95}$ of vecuronium was 40\% less than in patients aged 3–10 yr ($P < 0.01$), but comparable to the $ED_{95}$ for adolescents (table I). During the first 1 h of anaesthesia, vecuronium requirements of neonates and infants were identical, but were only 48\% and 73\% of the requirements for children aged 3–10 yr and adolescents, respectively (table I). The cumulative 100-\(\mu g \text{ kg}^{-1}\) dose of vecuronium maintained neuromuscular blockade > 90\% in infants for 58 min, compared with only 18 min in children aged 3–10 yr ($P < 0.001$) and 37 min in adolescents ($P < 0.01$) (fig. 1). There were similar differences in the durations of blockade > 90\% maintained by the cumulative 150-\(\mu g \text{ kg}^{-1}\) dose of vecuronium.

![Fig. 1. Mean (SEM) duration of the > 90\% neuromuscular blockade maintained by cumulative doses of vecuronium 100 and 150 \(\mu g \text{ kg}^{-1}\) in different age groups of paediatric patients. Note the marked prolongation of effect in infants compared with older children and adolescents.](image-url)
DISCUSSION

The present study is the first to analyse of the maintenance dose requirements of vecuronium in different age groups of paediatric patients. Requirements for vecuronium in neonates and infants (aged up to 1 yr) were approximately 50% of those in children aged 3–10 yr. Furthermore, cumulative 100- and 150-μg·kg⁻¹ doses of vecuronium could maintain surgical neuromuscular blockade in infancy for almost 1 and 2 h, respectively, while the duration was less than 20 and 40 min in children aged 3–10 yr. Vecuronium is clearly not an intermediate-acting neuromuscular blocking agent in infancy compared with childhood. In contrast, the steady-state infusion requirement for atracurium is similar in children of all ages greater than 1 month [4, 5].

We have shown previously that the ED₉₅ of vecuronium is identical in neonates and older infants (47 μg·kg⁻¹), but significantly less than in children aged 3–10 yr (81 μg·kg⁻¹) [1]. The present results are comparable to these values. The lesser ED₉₅ in infancy may result from the immaturity of neuromuscular transmission in these subjects. Marked differences have been found in the pharmacodynamics of vecuronium between infants and children [2, 3]. The rate of spontaneous recovery of neuromuscular blockade was halved in infants compared with children. Clearance of vecuronium has been found to be comparable in infants and children, but the distribution volume was greater in infants [6]. This leads to a slower rate of recovery from neuromuscular blockade in infants compared with children. In contrast, the spontaneous recovery rate of atracurium is only slightly slower in neonates and infants than in children [7].

The ED₉₅ values for pancuronium, tubocurarine and dimethyltubocurarine are identical in infants and children [8–10]. Furthermore, the rates of recovery from neuromuscular blockade induced by pancuronium and dimethyltubocurarine are similar in infants and children [8, 10], indicating that both are long-acting non-depolarizing neuromuscular blockers in both groups. Tubocurarine, however, may be a more long-acting agent in infants than in children [9, 11, 12]. In contrast, prolongation of effect and diminished dose requirement in neonates and infants appear to be features unique to vecuronium. The mean hourly maintenance requirement of a long-acting neuromuscular blocking agent, such as pancuronium, is 60% of the ED₉₅ [13]. In the present study, the 150-μg·kg⁻¹ dose of vecuronium maintained neuromuscular blockade > 90% for 20 min longer than the 100-μg·kg⁻¹ dose in children aged 3–10 yr. The hourly maintenance requirement of these children was thus 210% of the ED₉₅, which is appropriate for an intermediate-acting neuromuscular blocking agent. However, in neonates and infants the hourly requirement was 130% of the ED₉₅. This difference, together with the marked prolongation of the spontaneous recovery rate in infancy, suggests that the neuromuscular blocking effects of vecuronium in neonates and infants tend to similarities with those of a long-acting neuromuscular blocking agent.

The ED₉₅ of vecuronium in adolescents was less and the duration of blockade > 90% longer following both 100 and 150 μg·kg⁻¹, compared with the values in children aged 3–10 yr. These findings may be clinically important, but do not indicate that vecuronium is not an agent of intermediate duration of action in this age group. Vecuronium 150 μg·kg⁻¹ maintained neuromuscular blockade > 90% for 31 min longer than did 100 μg·kg⁻¹ in adolescents. The calculated hourly maintenance requirement would then be 200% of the ED₉₅, confirming an intermediate duration of effect. Although children aged 3–10 yr showed the shortest duration of blockade > 90%, their vecuronium requirement was comparable to the requirements of other children and adolescents when related to individual ED₉₅ values.

Prolonged duration of action of vecuronium is thus seen only in neonates and infants. A dose of 100 μg·kg⁻¹ corresponds with 1.9 mg·m⁻² in neonates and infants. The same dose per unit body surface area would correspond with 75 and 57 μg·kg⁻¹ in children aged 3–10 yr and adolescents, respectively. Therefore, if vecuronium is administered by calculating dose on the basis of body surface area instead of body weight, the differences in duration of effect between different age groups is accentuated.

The maintenance dose requirement for vecuronium is related to the age of the paediatric patient. A dose of 100 μg·kg⁻¹ produces neuromuscular blockade > 90% of almost 1 h duration in infancy, but of only 18 min in children aged 3–10 yr. Vecuronium tends to have an effect in neonates and infants which is similar to that of a long-acting neuromuscular blocking agent.

ACKNOWLEDGEMENTS

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