COMPARISON OF ATRACURIUM-INDUCED NEUROMUSCULAR BLOCKADE IN NEONATES, INFANTS AND CHILDREN

G. MEAKIN, E. A. SHAW, R. D. BAKER AND P. MORRIS

Atracurium is a non-depolarizing neuromuscular blocking drug, the duration of action of which is suitable for many paediatric surgical procedures. In view of reports suggesting that the newborn are sensitive to this type of myoneural blockade [1-5], we wished to compare the effects of atracurium in neonates, infants and children. In the present study the ED$_{50}$ and the ED$_{95}$ of atracurium were determined for each of the above groups during thiopentone-fentanyl-nitrous oxide in oxygen anaesthesia. In addition, we determined the speed of onset, and the duration of action, of a standard intubating dose.

PATIENTS AND METHODS

The design of the study was reviewed and approved by the District Ethics Committee. Sixty-three paediatric surgical patients consisting of 21 neonates (median age 9 days, range 1-27), 21 infants (median age 4 months, range 1.3-10.9), and 21 children (median age 4.3 yr, range 1.4-5.7) were the subjects of the study. All were ASA class I and none was receiving drugs known to interfere with neuromuscular transmission.

No premedication was given. In all patients anaesthesia was induced with thiopentone 6-8 mg kg$^{-1}$ and fentanyl 5 µg kg$^{-1}$. Anaesthesia was maintained with 70% nitrous oxide in oxygen, supplemented with thiopentone, as required. With the exception of four neonates who had the trachea intubated while awake, intubation of the trachea was performed following induction of anaesthesia but without the aid of a neuromuscular blocking drug. Ventilation was controlled using the paediatric attachment of the Blease ventilator. End-tidal carbon dioxide tension was monitored using a Datex capnograph, and maintained in the range 5.0-5.5 kPa. Rectal temperature was maintained between 36.5 and 37.5 °C.

Neuromuscular transmission was monitored using the method of Ali, Utting and Gray [6]. The ulnar nerve was stimulated supramaximally at the wrist via small silver electrodes applied to the skin with adhesive electrode paste. Trains-of-four with square pulses of 0.2 ms duration at a frequency of 2 Hz were repeated every 10 s using

**SUMMARY**

The potency of atracurium was determined in neonates, infants and children during thiopentone-fentanyl-nitrous oxide in oxygen anaesthesia using single dose-response curves. The effective doses producing 50% depression of the first twitch of the train-of-four were significantly lower in neonates and infants than in children (82 and 112 v. 135 µg kg$^{-1}$). Following a standard dose of atracurium 0.5 mg kg$^{-1}$, 95% depression of the first twitch occurred more rapidly in neonates than in children (0.9 v. 1.4 min), while recovery to 10% of the control twitch height occurred more rapidly in neonates than in the other two groups (22.7 v. 29.7 and 28.6 min). It is concluded that neonates and infants require less atracurium to produce a given degree of neuromuscular blockade compared with older children. However, prompt recovery can be expected in all healthy paediatric patients following a standard intubating dose of atracurium 0.5 mg kg$^{-1}$.
The hand and forearm were immobilized in a splint and the force of thumb adduction was measured using a strain gauge transducer (Grass FT03) and recorded on a pen-and-ink recorder (Grass polygraph).

Following a period of 8–12 min to allow stabilization of the train-of-four responses, atracurium was administered by rapid (5-s) i.v. injection. In order to construct dose–response curves, 15 patients from each age group were allocated randomly to three sub-groups of five. Patients in each sub-group received one of three doses of atracurium (table I), which were chosen following a preliminary trial to determine the approximate position of the dose–response curves. The remaining six patients from each group received atracurium 0.5 mg kg$^{-1}$ to determine the onset and duration of a standard dose suitable for intubation. Onset times were measured from injection to 95 % and 100 % depression of the first twitch of the train-of-four. Recovery times were measured from injection until the initial twitch had recovered to 10 % and 25 % of the control twitch height.

Before regression analysis, doses were transformed into logarithms and depression of twitch height was transformed into probit values. These transformations convert the sigmoid dose–response relationship for neuromuscular blockade into a straight line [7,8]. Log–probit regression lines were calculated using the iterative least squares method of Finney [9]. Calculations were performed on a PRIME 9955 computer using a Rothamstead statistical package, GLIM 3.77. The fitted lines were tested for parallelism and identity using the goodness-of-fit Chi square, so these were not significantly different. When the positions of the lines (intercepts) were compared using the F ratio test, these were found to be significantly different ($P < 0.001$), indicating that the groups differed significantly in their sensitivity to atracurium.

The values of $ED_{50}$ and $ED_{95}$ obtained from the regression analysis are shown in table II. It will be seen that the neonates had the lowest goodness-of-fit Chi square, so these were not significantly different. When the positions of the lines (intercepts) were compared using the $F$ ratio test, these were found to be significantly different ($P < 0.001$), indicating that the groups differed significantly in their sensitivity to atracurium.

**RESULTS**

Figure 1 illustrates the fit of the regression lines with the mean dose–response data for the three groups of patients. The weighted regression coefficient (common slope) was 4.44 probits log$^{-1}$. Allowing the slopes to differ did not improve the goodness-of-fit Chi square, so these were not significantly different. When the positions of the lines (intercepts) were compared using the $F$ ratio test, these were found to be significantly different ($P < 0.001$), indicating that the groups differed significantly in their sensitivity to atracurium.

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<table>
<thead>
<tr>
<th>TABLE I. Subgroups and doses (μg kg$^{-1}$)</th>
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<tr>
<td>$n$</td>
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<tr>
<td>5</td>
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</tbody>
</table>

**Table II. Calculated values of $ED_{50}$ and $ED_{95}±SE$. The initials $N$ = neonates, $I$ = infants, $C$ = children indicate significant differences between sub-groups of five patients.**

<table>
<thead>
<tr>
<th>$ED_{50}$ (μg kg$^{-1}$)</th>
<th>Neonates</th>
<th>Infants</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P &lt; 0.001$</td>
<td>82±4.5</td>
<td>112±4.0</td>
<td>135±4.5</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>$ED_{95}$ (μg kg$^{-1}$)</th>
<th>Neonates</th>
<th>Infants</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P &lt; 0.01$</td>
<td>119±8.6</td>
<td>163±10.1</td>
<td>195±10.6</td>
</tr>
<tr>
<td>$P &lt; 0.001$</td>
<td>C</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>
Onset and recovery times following atracurium 0.5 mg kg\(^{-1}\) are shown in tables III and IV, respectively. The speed of onset was significantly more rapid in neonates compared with children (\(P < 0.05\)), whilst recovery was more rapid in neonates compared with the other two groups (\(P < 0.05\)).

**DISCUSSION**

The differences between the ED\(_{50}\) and ED\(_{95}\) values of atracurium for patients in the present study (table II) indicate that neonates and, to a lesser extent, infants are sensitive to atracurium when compared with older children. These findings agree with earlier reports of sensitivity to other non-depolarizing neuromuscular blocking agents [1-5]. Although the basis of this sensitivity is still not fully understood, it seems likely to be immaturity of neuromuscular transmission. Churchill-Davidson and Wise [10] showed that neuromuscular transmission fatigued more readily in neonates than in adults, while experimental evidence suggests that there is a reduction in the amount of acetylcholine available for release at the neuromuscular junction in the very young. From an analysis of neuromuscular transmission in rat phrenic nerve–diaphragm preparations, Kelly and Roberts [11] estimated that the rate at which acetylcholine was made available for release in 30-day-old rats was less than one-half of that in 110-day-old rats. Furthermore, they calculated that the safety factor in neuromuscular transmission in young rats—that is the number of times the amount of acetylcholine released exceeded the minimum necessary to produce a muscle action potential—was only 70-80\% of that in older rats. They suggested that a similar loss of safety factor in infants could account for the observed sensitivity to the non-depolarizing myoneural blockers.

The safety factor in neuromuscular transmission may also help to explain a discrepancy between the results of the present study and those of Goudsouzian and colleagues [12,13]. Using a similar method for measuring neuromuscular transmission in paediatric patients, but plotting cumulative rather than single dose–response curves, these authors failed to demonstrate any difference in sensitivity to tubocurarine or metocurine between neonates, infants and children. However, because twitch height is depressed only after the safety factor has been overcome, the cumulative dose–response method underestimated the neuromuscular blocking effect of the first dose of a test drug. The error introduced to the dose–response relationship will vary with the size of the safety factor. A further practical

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**TABLE III. Onset times (mean±SEM) following atracurium 0.5 mg kg\(^{-1}\). The initials N = neonates, C = children indicate one significant difference between groups**

<table>
<thead>
<tr>
<th></th>
<th>Neonates ((n = 6))</th>
<th>Infants ((n = 6))</th>
<th>Children ((n = 6))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from injection to 95 % block (min)</td>
<td>0.9±0.1 C</td>
<td>1.0±0.1 N</td>
<td>1.4±0.1 N</td>
</tr>
<tr>
<td>Time from injection to 100 % block (min)</td>
<td>1.1±0.2 C</td>
<td>1.2±0.2 N</td>
<td>1.7±0.1 N</td>
</tr>
</tbody>
</table>

**TABLE IV. Recovery times (mean±SEM) following atracurium 0.5 mg kg\(^{-1}\). The initials N = neonates, I = infants, C = children indicate significant differences between groups**

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Injection to 10 % control twitch height (min)</td>
<td>22.7±1.5 IC</td>
<td>29.7±2.4 N</td>
<td>28.6±0.6 N</td>
</tr>
<tr>
<td>Injection to 25 % control twitch height (min)</td>
<td>28.7±1.9 IC</td>
<td>35.9±2.5 N</td>
<td>33.7±1.2 N</td>
</tr>
</tbody>
</table>

values and almost all the differences between the groups were statistically significant.
problem in determining cumulative dose–response curves is the delay in obtaining maximum effect following subclinical doses of neuromuscular blocking drugs. In the present study the maximum effect of small doses of atracurium commonly occurred 3–4 min after administration. It is difficult to see how previous investigators could have been sure of determining the maximum effect of incremental doses of neuromuscular blockers when four or five of these were given within 8 min.

The most comparable studies with atracurium in adults give values of ED$_{50}$ of 83 $\mu$g kg$^{-1}$ and 100 $\mu$g kg$^{-1}$ [14,15]. These values are similar to our results in neonates, but less than those obtained in infants and children (table II). On this basis, it would appear that neonates require the same dose of atracurium as adults, whilst infants and children require slightly higher doses. The apparent lack of sensitivity in neonates and resistance in our older patients when compared with adults can be explained by the gradual reduction in the volume of distribution of the neuromuscular blockers (that is the extracellular fluid volume) throughout infancy and childhood. Cook [16] has shown that these differences can be resolved by expressing the doses of the myoneural blocking drugs in $\mu$g m$^{-2}$. Using his table of mean weights and surface areas to convert the ED$_{50}$ values of our patients to $\mu$g m$^{-2}$ gives the following approximate values: neonates 1212 $\mu$g m$^{-2}$, infants 1925 $\mu$g m$^{-2}$, and children 3385 $\mu$g m$^{-2}$. The equivalent adult value (mean of the two results presented above) is 3768 $\mu$g m$^{-2}$. Thus on a $\mu$g m$^{-2}$ basis, children require about the same dose of atracurium as adults, whilst infants require half as much and neonates one-third. The results in infants and children are comparable to those obtained by Brandsom and colleagues [17,18].

Complete depression of the initial twitch of the train-of-four occurred in all patients given atracurium 0.5 mg kg$^{-1}$ (table III). The trend towards faster onset times in neonates and infants compared with children may be explained by the rapid circulation time in these patients [19] and the shorter distribution half-life of atracurium in infants [20]. Time to 95% depression of twitch height is important because intubation can easily be carried out at this degree of neuromuscular blockade [21]. Our results indicate that atracurium 0.5 mg kg$^{-1}$ should provide good intubating conditions in neonates and infants in about 90 s, and in children in less than 2 min. The time to 100% depression in children (1.7 min) was identical to that previously obtained in adults given atracurium 0.5 mg kg$^{-1}$ by rapid i.v. injection [15].

Plasma clearance of atracurium is significantly greater in infants aged less than 6 months compared with children, and its elimination half-life tends to be shorter [20]. The extrapolation of these results to neonates in the present study could explain their more rapid recovery following atracurium 0.5 mg kg$^{-1}$ (table IV). The 10% recovery time of 22.7 min in our neonatal group aged 5–27 days agrees closely with the data of Nightingale [22] on the clinical duration of effect of atracurium in neonates aged 3–28 days. Although in this earlier study clinical duration was found to be increased to 32.4 min in neonates aged less than 3 days, this is still comparable to the 10% recovery times of our infants and children and we would not regard this as an indication for reducing the initial dose of atracurium. Recovery of the first twitch to 25% of the control value was more rapid in all groups in the present study than in adults given the same dose of atracurium (43.6 min) [23].

In summary, neonates and infants require less atracurium to produce a given degree of neuromuscular block compared with older children. However, in view of the prompt rates of recovery it should be convenient to use the same initial dose of atracurium, 0.5 mg kg$^{-1}$, for all paediatric surgical patients.

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REFERENCES


