Synergism between atracurium and vecuronium in infants and children during nitrous oxide-oxygen-alfentanil anaesthesia

O. A. MERETOJA, T. TAIVAINEN, L. JALKANEN AND K. WIRTAVUORI

Summary
This study was undertaken to see if infants are more sensitive than children to a combination of atracurium and vecuronium in an equipotent dose ratio: (μg:μg) 5:1 in infants and 4:1 in children. We studied 15 infants (1-11 months old) and 15 children (3-10 yr old) during nitrous oxide-oxygen-alfentanil anaesthesia. Neuromuscular function was recorded by adductor pollicis EMG. An individual dose-response curve of the atracurium-vecuronium combination was determined for every patient and its potency compared with that of the parent agents alone. The combination was significantly more potent than one parent agent, both in infants (P<0.01) and in children (P < 0.0001). However, infants were less sensitive than children to synergism produced by the atracurium-vecuronium combination: if the ED50 dose of the parent agent is defined as one dose equivalent, then the mean ED50 doses of the combination were 0.81 (SEM 0.05) and 0.64 (0.03) dose equivalents in infants and children, respectively (P<0.01). We suggest that an interaction between two binding sites of competitive neuromuscular blocking agents in postsynaptic acetylcholine receptors may explain both the synergism and sensitivity of infants to non-depolarizing neuromuscular blocking agents.

Key words

Patients and methods
After obtaining institutional Ethics Committee approval and parental informed consent, we studied 15 infants (1-11 months of age) and 15 children (3-10 yr of age). Patients were ASA I-II and were not receiving any medications or had any diseases known to affect neuromuscular transmission. Each patient was undergoing an elective surgical procedure with minimal blood loss.

Infants received methohexitone 20 mg kg⁻¹ rectally and children midazolam 0.5 mg kg⁻¹ (maximum dose 15 mg) orally as premedication. Anaesthesia was induced with thiopentone 4-6 mg kg⁻¹ and alfentanil 30-50 μg kg⁻¹ while patients were breathing 66% nitrous oxide in oxygen. The trachea was intubated without the use of neuromuscular block. General anaesthesia was maintained with 66% nitrous oxide in oxygen and a continuous infusion of alfentanil 50-100 μg kg⁻¹ h⁻¹. Ventilation was controlled to maintain an end-tidal carbon dioxide concentration of 5.0-5.5%. Volatile inhalation agents were not used during the study. Non-invasive arterial pressure, ECG and SpO₂ were monitored (Cardiocap, Datex, Helsinki, Finland).

When anaesthesia had been induced, surface electrodes were attached over the ulnar nerve near the wrist in order to stimulate the nerve by train-of-four series of supramaximal stimuli (2 Hz) at 20-s intervals (Relaxograph, Datex). Recording electrodes were attached over the adductor pollicis muscle and the base of the forefinger [10]. Palmar skin temperature was measured from the same hand and maintained at > 34 °C. A stable calibration signal of the EMG trace was present before administration of a neuromuscular blocking drug.

A cumulative dose–response curve for a combination of atracurium and vecuronium in an equipotent dose ratio was obtained for every patient. ED₅₀ doses of atracurium and vecuronium are 124 and 25 μg kg⁻¹ in infants, and 180 and 44 μg kg⁻¹ in children, respectively, when studied under similar conditions [7, 8]. This implies that an equipotent dose ratio of atracurium and vecuronium is 5:1 in infants and 4:1 in children. These dose ratios were used in this study. The first dose of the combination
Table 1  Dose–response data for atracurium (A) and vecuronium (V) [7, 8] and their combination in an equipotent dose ratio (cAV) (mean (SEM)).  P values imply significant differences in cAV between infants and children.

<table>
<thead>
<tr>
<th></th>
<th>Infants</th>
<th></th>
<th>Children</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>V</td>
<td>cAV</td>
</tr>
<tr>
<td>ED_{50} (µg kg^{-1})</td>
<td>124 (7)</td>
<td>25 (1)</td>
<td>50±10 (3(1))</td>
</tr>
<tr>
<td>Slope</td>
<td>1 (0.05)</td>
<td>0.81 (0.5)</td>
<td>0.64 (0.03)</td>
</tr>
<tr>
<td>(probit log^{-1})</td>
<td>6.0 (0.2)</td>
<td>6.7 (0.5)</td>
<td>6.2 (0.1)</td>
</tr>
</tbody>
</table>

Results

Mean age of the infants was 6.7 (range 1–11) months and weight 8.1 (SEM 0.5) (range 4.7–11.3) kg. Respective values for children were 7.1 (3–10) yr and 25.8 (2.5) (16.5–41.8) kg. Each patient received three incremental doses of a particular combination. Maximum neuromuscular block after the last incremental dose of the combination was 96.0 (SEM 0.4) (range 92–99) %. Time from administration of the first incremental dose of the combination to maximum effect after the last incremental dose did not differ between infants and children; mean value 11.4 (0.4) min. Palmar skin temperature was 34.7 (0.1) °C during construction of the dose–response curve.

Dose–response data for the combinations are shown in table 1 and figure 1. The combination was more potent than one parent agent alone both in infants (P < 0.01) and in children (P < 0.0001). However, the combination was less potent in infants

Figure 1  Dose–response curves for atracurium (A), vecuronium (V) and their combinations (cAV) in infants and children (mean, SEM). The group of curves on the right consists of four superimposing curves (two parent agents and two age groups). Doses refer to dose equivalents, which are ED_{50} doses of the parent agents in the selected age groups. NMB = Neuromuscular block. * P < 0.05.

Discussion

We have shown that a combination of atracurium and vecuronium in an equipotent dose ratio was significantly more potent than one parent agent alone, both in infants and children. However, the degree of synergism was significantly less in infants than in children. Even though our study was not designed primarily to evaluate the possible mechanisms of this synergism, our results may be relevant in uncovering an explanation for the observed synergism, and for the sensitivity of infants to competitive neuromuscular blocking agents.

If two competitive neuromuscular blocking agents act only additively, then administration of a combination of 0.5 times the ED_{50} dose of both of these agents would produce 50 % neuromuscular block. This was clearly not the case with the combination. In children, 0.3 times the ED_{50} dose of atracurium and vecuronium together produced 50 % neuromuscular block. An equivalent dose of one parent...
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![Isobologram](image)

Figure 2: ED<sub>50</sub> dose of the combination of atracurium (A) and vecuronium (V) (cAV) in an equipotent dose ratio in infants (□) and children (○) as a fraction of the dose equivalent (ED<sub>50</sub> dose) of atracurium and vecuronium (mean (SEM)). cAV was synergistic both in infants and in children (symbols located left of the line of additivity (isobologram)). However, the degree of synergism was less in infants than in children.

Agent alone (0.6 times the ED<sub>50</sub> dose) would produce only less than 10% neuromuscular block. We assume that more separate acetylcholine receptors become occupied when the combination was used instead of one parent agent alone. Synergism may be explained by the hypothesis that one competitive neuromuscular blocking agent, when attached to one of the two α-subunits of a postsynaptic acetylcholine receptor, decreases the likelihood of a second agent attaching to the other α-subunit of the same receptor [5]. Decreased interaction may involve conformational change of the second α-subunit or negative cooperation between neuromuscular blockers of different molecular structures.

Why were infants less sensitive than children to the synergistic effect of the combination, even though infants are generally more sensitive to non-depolarizing neuromuscular blocking agents than children [6-9, 12]? We suggest that in infants, in contrast with children and adults, a competitive neuromuscular blocker when attached to one α-subunit of an acetylcholine receptor decreases the likelihood of other molecules of a neuromuscular blocker attaching to the other α-subunit of the same receptor. This would increase the efficacy of a blocker in infants. If this mechanism is responsible for the sensitivity of infants to non-depolarizing blockers then it would be clear that no major synergism would be expected in infants even though neuromuscular blockers of different structures were administered together.

This theory may even explain why we did not find a significant difference in ED values for tubocurarine between infants and children even though a difference existed for atracurium, vecuronium, alcuronium and pancuronium [9]. Tubocurarine is an exceptional neuromuscular blocker in that it occupies primarily only one set of α-subunits, not only in infants but also in children and adults [13]. If the sensitivity of infants to non-depolarizing blockers results from predominant receptor occupancy at only one set of α-subunits, there should not be any major difference in ED doses between infants, children and adults, as found previously [9].

Some studies on the interaction between non-depolarizing neuromuscular blocking agents proposed that synergism is produced if two blockers have different effects on pre- and postsynaptic acetylcholine receptors [1, 3, 4]. However, synergism clearly exists without the possibility of presynaptic effects [2]. Differences in pharmacokinetics between various age groups or between neuromuscular blockers cannot explain our results on reduced synergism in infants compared with children. There are no data to show that one neuromuscular blocker could affect the clearance or distribution half-life of another blocker.

References