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 ED₉₀ dose of the parent agent is defined as one dose equivalent, then the mean ED₉₀ 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. (Br. J. Anaesth. 1994; 73: 605–607)

Key words

Synergism (potentiation) exists between some competitive neuromuscular blocking agents of different molecular structure [1–4]. The magnitude of this synergism was found to be maximal when competitive neuromuscular blockers were administered in an equipotent dose ratio rather than in a dose ratio favouring one parent agent [5]. Infants are known to be more sensitive than children to competitive neuromuscular blockers when either ED₉₀ doses or plasma concentrations maintaining 50% neuromuscular block are assessed [6–9]. This study was undertaken to see if this sensitivity applied also to a combination of atracurium and vecuronium when administered in an equipotent dose ratio.

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 1–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. ED₉₀ 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.

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<thead>
<tr>
<th></th>
<th>Infants</th>
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<td>50 ± 10</td>
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<td>0.81</td>
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<td>(0.05)</td>
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<td>6.7</td>
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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 comprised atracurium 40 µg kg⁻¹ and vecuronium 8 µg kg⁻¹ in infants, and atracurium 40 µg kg⁻¹ and vecuronium 10 µg kg⁻¹ in children. These doses were administered from two different syringes into a freely running i.v. infusion. After maximum neuromuscular responses, a second similar dose combination was administered and a maximum response awaited. Thereafter, a third dose combination was calculated individually to establish 95% neuromuscular block using a log-probit paper [11].

Doses of atracurium and vecuronium were transformed to log values and maximum neuromuscular blocks to probit values. A least square linear regression analysis was used to determine individual ED₁₀, ED₅₀ and ED₉₀ values of the atracurium–vecuronium combination and the slope of the dose–response curve. These data were compared with respective data for atracurium and vecuronium alone, determined under similar conditions [7, 8]. The possible potentiation of the combinations compared with the parent agents alone was determined from an isobologram by analysis of variance. In order to quantitate possible potentiation of the combination, we defined an EDₙ₀ dose of each of the parent agents in infants or children as one dose equivalent. The magnitude of the potentiation was compared between children and infants using the two-tailed Student’s t test for unpaired data. P < 0.05 was regarded as significant. Values are expressed as mean (SEM).

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 ED₅₀ dose of both of these agents would produce 50% neuromuscular block. This was clearly not the case with the combination. In children, 0.5 times the ED₅₀ dose of atracurium and vecuronium together produced 50% neuromuscular block. An equivalent dose of one parent...
exceptional neuromuscular blocker in that it occupies
a significant difference in ED values for tubocurarine
administered together.

Figure 2

Synergism between atracurium and vecuronium

<table>
<thead>
<tr>
<th>Fraction of ED50 of A</th>
<th>Fraction of ED50 of V</th>
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<tbody>
<tr>
<td>0.25</td>
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<td>0.75</td>
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\[ P < 0.01 \]
\[ P < 0.001 \]
\[ P < 0.0001 \]

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

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