SYNERGISM BETWEEN ATRACURIUM AND VECURONIUM IN CHILDREN

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SUMMARY
In 30 children under balanced anaesthesia, we have determined dose–response curves and maintenance requirement of three dose ratio combinations of atracurium and vecuronium (10:1, 4:1 or 1.6:1 on a μg:μg basis). Neuromuscular block was monitored by adductor pollicis EMG. An equipotent dose ratio (4:1) was most potent, with a mean (SEM) ED$_{95}$ of atracurium 95 (6) μg kg$^{-1}$ with vecuronium 24 (1) μg kg$^{-1}$. The sum of these doses is only 58% of an ED$_{95}$ value of one agent (P = 0.0001). The hourly requirement to maintain a 90–95% neuromuscular block was 2.0 (0.1) times an individual ED$_{95}$ dose of any combination. Recovery index was 8.9 (0.5) min. These results indicate that a combination of atracurium and vecuronium is supra-additive compared with the effects of each drug alone. However, all combinations maintained an intermediate character of neuromuscular block. Combining atracurium with vecuronium may reduce drug requirement by 40%. (Br. J. Anaesth. 1993; 71: 440–442)

KEY WORDS

Synergism (supra-additivity) of the neuromuscular blocking effects between some competitive neuromuscular blocking agents of different molecular structure has been observed both in vivo and in vitro [1, 2]. There are also some data suggesting pure additive effects of this combination [3]. The subject is further confused because one study found non-parallel and another found parallel slopes of the dose–response curves between a combination of neuromuscular blocking agents and their parent agents [1, 2]. Our aim was to clarify the nature of the neuromuscular block produced by a combination of atracurium and vecuronium.

METHODS AND RESULTS
After obtaining Institutional Ethics Committee approval and parental informed consent, we studied 30 children (ASA I–II), aged 3–10 yr, undergoing routine general surgery, allocated randomly to three matched groups. Premedication comprised oral midazolam 0.46 (SEM 0.01) mg kg$^{-1}$. General anaesthesia was induced with thiopentone 5.2 (0.2) mg kg$^{-1}$, alfentanil 38 (2) μg kg$^{-1}$ and 66% nitrous oxide in oxygen, and maintained with nitrous oxide in oxygen and alfentanil. Neuromuscular block was monitored at 20-s intervals by the evoked adductor pollicis EMG response to supramaximal train-of-four ulnar nerve stimuli (Relaxograph, Datex). Palmar skin temperature was maintained at > 34°C and end-tidal concentrations of carbon dioxide at 5.0–5.5%.

Each patient received one of three dose ratio combinations of atracurium and vecuronium: an equipotent dose ratio of 4:1 (on a μg:μg basis), or a ratio of 10:1 or 1.6:1 (these represent geometric mean ratios for an equipotent ratio and a parent agent) (fig. IA). An individual cumulative dose–response curve of the combination was created. The first dose was atracurium 40 μg kg$^{-1}$ and vecuronium 10 μg kg$^{-1}$ in a 4:1 dose ratio group, atracurium 60 μg kg$^{-1}$ and vecuronium 6 μg kg$^{-1}$ in a 10:1 dose ratio group, and atracurium 24 μg kg$^{-1}$ and vecuronium 15 μg kg$^{-1}$ in a 1.6:1 dose ratio group. A second identical dose was administered when the maximal neuromuscular block after the first dose was reached. A third incremental dose was calculated to establish a 95% neuromuscular block. A least-square linear regression analysis of log doses and probit responses was used to determine an individual dose–response curve of each combination of atracurium and vecuronium.

During maintenance of anaesthesia, 25% of an individual ED$_{95}$ dose of combination was administered each time the neuromuscular function recovered to 10% of baseline. Neuromuscular function recovered spontaneously at the end of anaesthesia, whenever clinically appropriate. Analysis of variance and Scheffé F test were used to evaluate between-group comparisons.

There was little deviation from the linear regression of log doses and probit responses ($r^2 = 0.995$ (0.001)). Slopes of the individual dose–response curves did not differ between groups (P = 0.27) and averaged 7.0 (0.1) probit/log. This did not differ from that of parent agents [4]. An ED$_{10}$ and an ED$_{95}$ value of an equipotent dose-ratio combination were 0.62 (0.04) and 0.58 (0.04) times
the corresponding ED-value of one parent agent \( (P = 0.0001) \) (fig. 1A). Respective values for a non-equipotent dose ratio combination of the two neuromuscular blockers were 0.78 (0.02) and 0.74 (0.02) \( (P = 0.0001) \).

Hourly requirement of a combination of atracurium and vecuronium to maintain a 90–95 % neuromuscular block was 1.84 (0.08), compared with 2.14 (0.05) times, an individual ED\(_{95}\) dose in patients who received an equipotent or a non-equipotent dose ratio combination \( (P = 0.0002) \). Spontaneous recovery of neuromuscular function was observed in 20 patients. Time to recover from 10 % to 90 % neuromuscular function and the recovery index did not differ between the groups and were, on an average, 17.0 (1.8) min and 8.9 (0.5) min, respectively. These values were similar to those produced by a single agent \([4]\).

## COMMENT

Our results confirm synergism between atracurium and vecuronium, and may provide some data to explain this effect. We found no difference between the slopes of the dose–response curves of any of the combinations of atracurium and vecuronium or their parent agents. When atracurium and vecuronium were used in an equipotent dose ratio, only 29 % of an ED\(_{95}\) dose of each agent was required to establish a 95 % neuromuscular block.

A relation between concentration of a neuromuscular blocking agent \( (C) \) and receptor occupancy \( (Y) \) is characterized by the formula:

\[
Y = \frac{C}{(C + K_D)}
\]

where \( K_D \) = a drug–receptor dissociation constant \([5]\). This formula can be used to estimate receptor occupancy at different degrees of neuromuscular block. Accordingly, 95 % neuromuscular block is produced by 93 % receptor occupancy. When synergism between atracurium and vecuronium was greatest, 0.29 times an ED\(_{95}\) dose of each parent compound administered simultaneously produced a 95 % neuromuscular block. If either atracurium or vecuronium alone is administered, then increasing a dose from 0.29 to 2 x 0.29 of an ED\(_{95}\) increases receptor occupancy only from 79 to 88 %. Therefore, one assumes that more acetylcholine receptors are occupied when a combination of atracurium and vecuronium is used instead of a single agent \( (93 \text{ vs } 88 \%) \).

As binding by a competitive antagonist to one of the two \( \alpha \)-units on the postsynaptic acetylcholine receptor is sufficient to block activation of the receptor, synergism may depend on decreased interaction of a second drug with the other \( \alpha \)-unit when a different drug occupies one \( \alpha \)-unit. For example, the presence of a benzylisoquinolinium molecule may reduce the likelihood of a steroid molecule interacting with the second \( \alpha \)-unit of the same receptor. This can explain simply the observed synergism. Non-equipotent dissociation constants of the two \( \alpha \)-units \([2, 6]\) cannot explain this synergism.

Our theory may also explain a lesser (though significant) degree of synergism produced by a non-equipotent dose ratio combination. In a non-equipotent dose ratio, a greater dose of one drug is administered and part of this may become “wasted” to occupy those \( \alpha \)-units on the acetylcholine receptors, the counterunits of which are already occupied by the same drug.

Maintenance requirements of combinations of neuromuscular blocking drugs have not been evaluated before. Long-, intermediate- and short-acting competitive neuromuscular blocking agents are required on average 0.4–0.6 times, 1.8–2.0 times and 6–8 times their ED\(_{95}\) dose per hour, respectively, to maintain a 90–95 % neuromuscular block \([4]\). For each combination of atracurium and vecuronium we examined, 1.8–2.1 times an ED\(_{95}\) dose of that combination maintained a 90–95 % neuromuscular block for 1 h. Also, the rate of spontaneous recovery from the neuromuscular block produced by any combination was similar to those of a parent agent \([4]\). Thus each combination had the character of an intermediate acting myoneural blocker.

In summary, we have found that the combination of atracurium and vecuronium was synergistic and more potent in an equipotent dose ratio than in a
dose ratio favouring one parent agent. These synergistic combinations may be used as one intermediate acting competitive neuromuscular blocking agent. Maximal reduction of drug requirement would be about 40%.

REFERENCES