CLINICAL PHARMACOLOGY OF VECURONIUM IN CHILDREN

Studies During Nitrous Oxide and Halothane in Oxygen Anaesthesia


Vecuronium is a non-depolarizing neuromuscular blocker with a potency slightly greater than that of pancuronium, and a short duration of action. It is devoid of cardiovascular side-effects in adults (Agoston et al., 1980; Fahey et al., 1981). The aim of the present study was to determine the dose–response relationship for vecuronium in children, its duration of action, its potential for cumulative inhibition and its cardiovascular effects, during nitrous oxide–halothane anaesthesia.

PATIENTS AND METHODS

Forty-seven children, aged between 4 and 8 yr and in ASA grades I or II, were studied. No patient had received any medication within the 7 days before surgery; no child had evidence of renal or hepatic failure nor of any disease known to alter neuromuscular function. The study was approved by the local ethics committee and informed consent was obtained from a parent. Premedication was not given. Anaesthesia was induced with a 60% nitrous oxide in oxygen mixture plus 1% inspired halothane. Once the child was asleep, a cannula was inserted to a vein. Halothane was vaporized in a new calibrated vaporizer; the same vaporizer was used for all the patients. After induction, the ulnar nerve was stimulated at the wrist with surface electrodes. A single supramaximal square-wave stimulus, 0.2 ms duration 0.1 Hz, was used. The electromyographic response was monitored through electrodes placed over the adductor pollicis muscle and the evoked electromyogram was amplified and recorded by a DISA apparatus. After 10 min to permit stabilization of the electromyographic recording, vecuronium was injected i.v. After tracheal intubation, ventilation was controlled and anaesthesia was maintained with 60% nitrous oxide in oxygen, plus 1% inspired halothane and phenoperidine 20 μg kg⁻¹. End-tidal PCO₂ was measured by capnography and maintained between 4.7 and 5.3 kPa. Body temperature was maintained between 35 and 37 °C.

To determine the dose–response curve and the time course of action, a single bolus of vecuronium 40, 55 or 70 μg kg⁻¹ was administered i.v. to 33 patients and the time course of action was determined. The dose–response curve for vecuronium was determined after the injection of a single bolus (40, 55 or 70 μg kg⁻¹) to 33 patients. The ED₅₀ and ED₉₀ were 31 and 64 μg kg⁻¹ respectively. Fourteen children received a larger dose (100 μg kg⁻¹); good intubating conditions were obtained in all of these within 2 min. After a single bolus (100 μg kg⁻¹) the duration of action was 36.5 min and the recovery index was 9.3 min. In patients who received small maintenance doses (25 μg kg⁻¹) after a single bolus (100 μg kg⁻¹) the recovery index after the last maintenance dose was not increased. There were no significant changes in heart rate or arterial pressure. In children, vecuronium has a short duration of action and lacks cumulative or cardiovascular side effects.

SUMMARY

Forty-seven children (ASA I or II) were studied during nitrous oxide–oxygen, halothane anaesthesia. The dose–response curve for vecuronium was determined after the injection of a single bolus (40, 55 or 70 μg kg⁻¹) to 33 patients. The ED₅₀ and ED₉₀ were 31 and 64 μg kg⁻¹ respectively. Fourteen children received a larger dose (100 μg kg⁻¹); good intubating conditions were obtained in all of these within 2 min. After a single bolus (100 μg kg⁻¹) the duration of action was 36.5 min and the recovery index was 9.3 min. In patients who received small maintenance doses (25 μg kg⁻¹) after a single bolus (100 μg kg⁻¹) the recovery index after the last maintenance dose was not increased. There were no significant changes in heart rate or arterial pressure. In children, vecuronium has a short duration of action and lacks cumulative or cardiovascular side effects.
patients (table I). The following were measured: onset time (the time from the end of the injection until the maximum effect); duration of action (the time from the end of the injection to spontaneous recovery to 90% of the control value); recovery index (the time required for recovery between 25% and 75% of the control value); peak effect (maximum percentage depression of EMG twitch height).

The dose–response curve was determined by log probit transformation of the data and calculation by least-squares regression.

To determine the safety and the time course of action of a larger dose, 14 patients received a single bolus of vecuronium 100 µg kg⁻¹ i.v. In nine patients of this group, as surgical conditions warranted, the bolus injection was followed by small maintenance doses (25 µg kg⁻¹) when the electromyographic response had returned to 25% of its control value. The recovery index after the last maintenance dose was measured.

Tracheal intubation was attempted at 2 min following the administration of vecuronium. The same investigator attempted the intubation in each patient and was unaware of the dose. The conditions at intubation were studied for patients who received 40, 55, 70 or 100 µg kg⁻¹; they were judged to be either excellent (relaxation of jaw muscles and no movement of the vocal cords, diaphragm or abdominal muscles), good (relaxation of jaw muscles, but some movement of the vocal cords or abdominal muscles) or poor.

Arterial pressure and heart rate were measured and recorded (Dinamap), and the electrocardiogram monitored. Measurements were performed before the induction of anaesthesia, at the end of the injection (55, 70 or 100 µg kg⁻¹), and 2 and 5 min after the administration of the vecuronium.

The results are expressed as mean ± SEM. Analyses of variance (Anova) based on the F-test and Student–Newman–Keuls test were used to examine significant differences.

RESULTS

All groups (table I) were similar in regard to age and weight. The estimated ED₅₀, ED₉₀ and ED₆₀ were 31 µg kg⁻¹, 55 µg kg⁻¹ and 64 µg kg⁻¹, respectively (fig. 1). The correlation of the log probit curve was 0.98. The indices of neuromuscular function are summarized in table II. Following a dose of vecuronium 100 µg kg⁻¹, 12 of the 14 patients developed complete neuromuscular blockade (mean 99% ± 2). After a single bolus of 100 µg kg⁻¹, the duration of action was 36.5 ± 5.3 min and the recovery index was
9.3 ± 1.7 min. In patients who required additional doses of vecuronium the recovery index after the last maintenance dose (table III) did not differ significantly from the recovery index after a single bolus of vecuronium 100 µg kg⁻¹.

Excellent intubating conditions were obtained in all patients after a bolus of 100 µg kg⁻¹. In patients receiving 70 µg kg⁻¹, conditions were considered as excellent in four patients, good in six patients and poor in one. For children receiving a bolus of 55 µg kg⁻¹, the conditions at intubation were excellent in seven patients and good in five patients. In those receiving 40 µg kg⁻¹, intubating conditions were excellent in only two children (table IV).

Changes in heart rate and arterial pressure are summarized in table V. There were no significant differences between the control values and the values measured after the administration of the three doses of vecuronium. No side effects such as skin rash, bronchospasm or facial flushing were observed.

**DISCUSSION**

The ED₅₀ and ED₉₀ are dependant on the anaesthetic technique and the method by which the dose–response curves are constructed. Since all the children received halothane—a drug known to potentiate the intensity and duration of action of neuromuscular blockade, all were studied while receiving the same inspired concentration of halothane (1 %) delivered from the same calibrated vaporizer during comparable clinical situations. During nitrous oxide–halothane anaesthesia, Fisher and Miller (1983) found a lower ED₅₀ (19 µg kg⁻¹) in children—a difference which could be partly explained by the time elapsing between the induction of anaesthesia and the administration of vecuronium. The concentrations of halothane were similar, but vecuronium was administered on an average 10 min after induction in the present study as against 20–30 min after intubation in the study by Fisher and Miller (1983). Although halothane potentiates the intensity of neuromuscular blockade, it could also have an effect by decreasing hepatic blood flow (Gelman, 1976) and so alter the distribution and elimination of vecuronium by the liver. Also, the smaller ED₅₀ found by Fisher and Miller (1983) could be explained by a difference in the ages of children in their study (1–8 yr) (mean age 3.9 yr) as compared with a mean age of 6.2 yr in our group. Last, we studied the electromyographic response which is likely to be decreased less than the mechanical twitch during halothane anaesthesia (Epstein and Epstein, 1973). Moreover, in the study by Fisher and Miller (1983) the slope of the
regression of electromyographic twitch height \( v \). Mechanical twitch height was less than 1.0. Goudsouzian and colleagues (1983), using a higher inspired concentration of halothane (1.5%), obtained ED\textsubscript{50} and ED\textsubscript{95} values comparable to ours, when one would have expected lower values. These results can be explained by the use of a cumulative method for producing a dose–response curve (by Goudsouzian and colleagues), a method that overestimates the ED\textsubscript{95} when compared with that obtained by the single bolus method (Fisher et al., 1982). In the study by Goudsouzian and colleagues, the higher inspired concentration of halothane and the use of the cumulative method countered each other and resulted in values for ED\textsubscript{50} and ED\textsubscript{95} which were comparable to those in our study. When compared with studies of the dose–response curve of vecuronium in adults during halothane anaesthesia, the ED\textsubscript{50} obtained in this study seems to be slightly higher than that observed in adults. Ording and Viby-Mogensen (1981) found that the ED\textsubscript{50} was 26 \( \mu \text{g kg}^{-1} \) in adults during halothane anaesthesia—a decrease of 20% in comparison with our results in children. Fisher and Miller (1983) demonstrated that the dose–response curve of vecuronium in children was shifted to the right of that in adults and, even if the difference was not significant, the ED\textsubscript{50} in adults (15 \( \mu \text{g kg}^{-1} \)) was decreased by 20% in comparison with the ED\textsubscript{50} in children (19 \( \mu \text{g kg}^{-1} \)). A similar tendency was also observed by Goudsouzian and colleagues (1983); the derived ED\textsubscript{50} was 33 \( \mu \text{g kg}^{-1} \) in children when the ED\textsubscript{50} was 23 \( \mu \text{g kg}^{-1} \) in adolescents. These differences between children and adults could be the result of age-related differences in the pharmacokinetics or pharmacodynamics of vecuronium.

The duration of action of vecuronium in children is short compared with that of other non-depolarizing agents in equivalent doses. The increase in dose from 40 to 70 \( \mu \text{g kg}^{-1} \) decreased the onset time by 32% \( (P < 0.01) \) and prolonged the duration of action by 44% \( (P < 0.01) \). Even with vecuronium 100 \( \mu \text{g kg}^{-1} \), a dose close to twice the ED\textsubscript{50}, the duration of action and the recovery index were short and allowed satisfactory recovery without undue delay. Moreover, adequate recovery from a single bolus of vecuronium was achieved in less than 45 min in all the patients without the administration of neostigmine or edrophonium.

The duration of action after a bolus of 70 \( \mu \text{g kg}^{-1} \) was 27 min during halothane anaesthesia in children. This was shorter than the duration of action observed by Fisher and Miller (1983) in adults (53 min) using the same dose during halothane anaesthesia. Even if the anaesthetic conditions were not quite comparable, the recovery index obtained by Fisher and Miller (1983) following vecuronium 70 \( \mu \text{g kg}^{-1} \) was very similar (9 min) to that obtained in this study (8.3 min). The recovery index was shorter than in adults, this index being close to 14 min in adults during halothane anaesthesia (Fisher and Miller, 1983). The shorter recovery index in children than in adults could result from a larger volume of distribution or a higher plasma clearance in children than in adults.

Lack of cumulation following repeated doses of vecuronium has been described in adults (Buzello and Noldge, 1982). In the children, there was no evidence of prolonged blockade, and the recovery index was not increased in those children receiving several supplementary doses of vecuronium. Bencini (1983), has suggested that this lack of cumulation could be attributable to the pharmacokinetic properties of vecuronium, in particular to a greater apparent volume of distribution and a higher plasma clearance than with other non-depolarizing blockers such as pancuronium.

Although intubating conditions were studied during halothane anaesthesia, it must be accepted that halothane can potentiate the neuromuscular effects of non-depolarizing neuromuscular blockers (Miller et al., 1972) and facilitate intubation. However, a 1% inspired concentration of halothane is seldom sufficient to provide good or excellent intubating conditions, even if the halothane is administered for 10 min. Intubating conditions were not tested in controls not receiving vecuronium, because the study was performed to find the ideal dose of vecuronium in children to allow excellent intubating conditions 2 min after its injection during halothane anaesthesia. A dose of 40 \( \mu \text{g kg}^{-1} \) has a duration of action of less than 20 min, but intubating conditions were seldom excellent 2 min after the injection—as a result of the inadequacy of the neuromuscular blockade obtained with this dose. Intubation was possible with 70 \( \mu \text{g kg}^{-1} \), but it was necessary to wait for more than 2 min to obtain excellent intubating conditions in all the patients, as described also in adults with this dose (Krieg et al., 1980). If satisfactory and rapid intubating condi-
tions are required in children during halothane anaesthesia, a dose of 100 μg kg\(^{-1}\) allows excellent intubating conditions 2 min after the injection of vecuronium. In children, vecuronium can be used for intubation when a long duration of neuromuscular blockade is not required, but vecuronium does not appear to be an alternative to suxamethonium.

There were no significant changes in heart rate or arterial pressure associated with the administration of any of the doses (55, 70, 100 μg kg\(^{-1}\)) of vecuronium studied. The modest, but not significant, increases in systolic arterial pressure and heart rate 2 min after injection were most probably a consequence of intubation rather than a cardiovascular effect of vecuronium per se. Similar findings have been observed in adults (Gregoretti, Sohn and Sia, 1982; Engbaek et al., 1983) and confirm the cardiovascular stability of vecuronium.

In conclusion, in children receiving 1.0% halothane, vecuronium is a potent non-depolarizing neuromuscular blocking drug with a short duration of action and lack of cardiovascular and cumulative effects. A dose of 100 μg kg\(^{-1}\) provides good intubating conditions 2 min after administration and sufficient muscle paralysis for surgical procedures of less than 45 min duration.

REFERENCES


