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Time course of potentiation of mivacurium by halothane and isoflurane in children

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Summary

We studied 40 children, aged 1–15 yr, to analyse the time course of potentiation of mivacurium produced by halothane and isoflurane. A steady infusion requirement of mivacurium to maintain 90 % neuromuscular block was established during thiopentone–alfentanil–nitrous oxide–oxygen anaesthesia. Patients were then allocated randomly to receive 1 MAC end-tidal concentration of either halothane (group Hal) or isoflurane (group Iso) while neuromuscular block was maintained at 90 %. Both volatile agents decreased the infusion requirements of mivacurium in an exponential manner in that maximal potentiation occurred only after 30–80 min. Maximal reduction in infusion rate (32 % in group Hal and 70 % in group Iso; $P < 0.0001$) did not depend on the age of the child but became established sooner the younger the child in the case of isoflurane ($P = 0.002$). (*Br. J. Anaesth*. 1996; **76**: 235–238)

Key words

Anaesthetics volatile, halothane. Anaesthetics volatile, isoflurane. Neuromuscular block, mivacurium. Pharmacodynamics.

Volatile anaesthetic agents reduce the dose requirements of non-depolarizing neuromuscular blocking agents by 0–70 % [1–6]. This effect may depend not only on the particular volatile anaesthetic but also on the neuromuscular blocking agent [2, 3]. The potentiation may be a time-dependent phenomenon, even though there are conflicting results [7–9]. In some early studies on the potentiation of neuromuscular blockers by volatile anaesthetic agents, the investigators maintained a steady anaesthetic concentration for more than 1 h before administering the neuromuscular blocker [1], whereas in some recent studies volatile agents were given for less than 15 min [6, 10–12]. This difference in timing may have greatly affected the results of these studies. We designed a study to evaluate the time course of potentiation of mivacurium by halothane and isoflurane in children in order to clarify the issue and to find if the age of the paediatric patient affected the magnitude or time course of this potentiation. Mivacurium was used as the neuromuscular blocker because of its short elimination half-life.

Patients and methods

The study was approved by the Ethics Committee of the Children's Hospital University of Helsinki. After obtaining parental informed consent, we studied 40 ASA I–II patients, aged 1–15 yr. Patients were undergoing elective orthopaedic or general surgery with minimal blood loss and with an anticipated duration of at least 2 h. Patients had no disease or medication known to affect neuromuscular function.

Premedication comprised oral midazolam 0.4–0.5 mg kg^{-1} (maximum dose being 15 mg), 30–60 min before induction. Anaesthesia was induced with thiopentone 4–6 mg kg^{-1} i.v. and alfentanil 50–100 μg kg^{-1} i.v., and inhalation of 66 % nitrous oxide in oxygen. The trachea was intubated without the use of neuromuscular blocker. Anaesthesia was maintained with an infusion of alfentanil 100 μg kg^{-1} h^{-1} and 66 % nitrous oxide in oxygen. End-tidal carbon dioxide was maintained at 5.0–5.5 kPa and core temperature at > 36 °C throughout the study. For peroperative fluid management, Ringer's solution was infused at a rate of 3–4 ml kg^{-1} h^{-1}. Patients did not require any volume replacement for blood loss.

Neuromuscular function was recorded as an adductor pollicis EMG evoked by supramaximal 2 Hz train-of-four responses at 20-s intervals (Relaxograph, Datex, Finland). The stimulating surface electrodes were attached over the ulnar nerve at the wrist, and the forearm was supported on a dorsal splint with the thumb abducted with a tape. Recording electrodes were attached on the adductor pollicis muscle and on the proximal volar surface of the index finger [13]. Palmar skin temperature was measured and maintained above 34 °C with a warming cover. Routine patient monitoring consisted of ECG, non-invasive arterial pressure, pulse oximetry, end-tidal carbon dioxide and halothane or isoflurane measurement (Capnomac, Cardiocap, Datex).

After calibration of the EMG device and having reached a stable train-of-four response for a minimum of 5 min, a bolus dose of mivacurium 0.1 mg kg^{-1} was administered i.v. and, if needed, this was followed by a second, similar dose to establish > 95 % neuromuscular block (depression of the first EMG response from control in the train-of-four series of responses). When the first EMG response recovered to 10 % of control, an adaptive closed-loop computer controlled infusion of mivacurium was

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commenced to maintain a steady 90 % neuromuscular block [14]. Mivacurium was diluted in physiological saline to a concentration of 0.5–2.0 mg ml^{-1} depending on the patient's body weight. The computer program controlling the infusion pump was based on the patient's theoretical pharmacokinetic–dynamic variables and used continuous feedback information from the EMG monitor to adjust the infusion rate at 20-s intervals [14]. Real-time neuromuscular block, current infusion rate and cumulative amount of mivacurium infused were shown on a computer screen and stored in the computer memory.

After a steady state infusion of mivacurium of at least 30 min, a sealed envelope indicating the patient's group was opened, and either halothane (group Hal) or isoflurane (group Iso) was commenced at an inspiratory concentration of 4–5 % and then titrated individually to rapidly achieve and maintain an age-adjusted 1 MAC end-expiratory concentration of the volatile anaesthetic agent [15, 16]. At this time the infusion rate of alfentanil was reduced by 50 %. Any change in the infusion rate of mivacurium was calculated by the computer. The results were drawn on paper and the cumulative infusion dose of mivacurium was calculated for every 10-min period before and after the start of the volatile anaesthetic agent.

All between-group comparisons were made by Kruskal–Wallis and Mann–Whitney *U* tests, and the data are presented as median (range). Changes in the individual infusion rates of mivacurium for the 10-min epochs were compared by Friedman's two-way analysis of variance. Influence of age within the study groups was examined by linear regression analysis. $P < 0.05$ was regarded as significant.

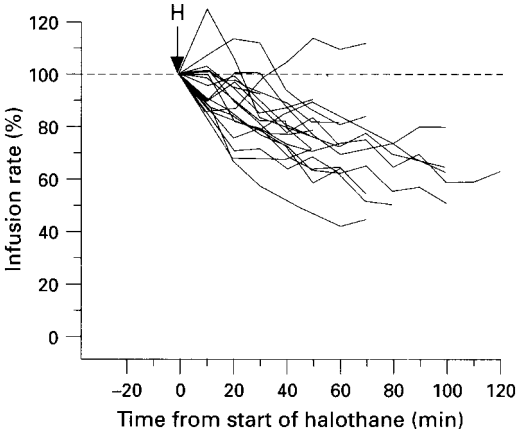

Figure 1 Individual infusion rates of mivacurium at 10-min epochs as a percentage of control from commencement of 1 MAC of end-tidal halothane (H) in children.

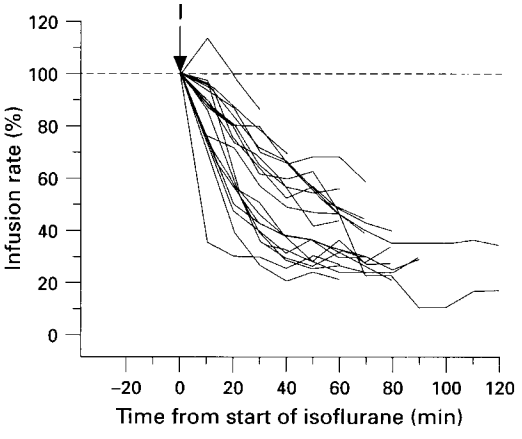

Figure 2 Individual infusion rates of mivacurium at 10-min epochs as a percentage of control from commencement of 1 MAC of end-tidal isoflurane (I) in children.

Results

Groups were matched for age, body weight, amounts of induction agents, duration of anaesthesia and steady infusion rate of mivacurium before the volatile anaesthetic agent was commenced (table 1). One MAC end-tidal concentration of the volatile agent was reached within 2–4 min from opening of the vaporizer in all patients. Figures 1 and 2 show the

Table 1 Patient characteristics and miacurium infusion rates for the study groups (median (range)). *P* values according to Mann–Whitney *U* test

	Group Hal	Group Iso	*P*
Age (yr)	6.4 (1.0–15.5)	7.8 (2.0–14.4)	ns
Body weight (kg)	19.4 (10.6–64.8)	27.7 (9.9–65.0)	ns
Duration of anaesthesia (min)	140 (105–390)	148 (105–330)	ns
Duration of volatile agent (min)	70 (30–200)	70 (37–235)	ns
Infusion rate of mivacurium			
Before volatile agent			
No. of patients	20	20	
μg kg^{-1} min^{-1}	11.0 (6.7–26.3)	12.6 (5.5–25.1)	ns
Percentage of control	100.0	100.0	
30 min after volatile agent			
No. of patients	20	20	
μg kg^{-1} min^{-1}	9.0 (5.4–19.0)	5.8 (2.4–20.1)	<0.01
Percentage of control	81.9 (57.3–112.0)	54.5 (27.3–86.3)	0.0001
60 min after volatile agent			
No. of patients	13	17	
μg kg^{-1} min^{-1}	7.4 (6.4–10.8)	4.1 (1.7–17.2)	<0.01
Percentage of control	72.1 (42.2–109.9)	37.0 (22.0–68.3)	0.0001
90 min volatile agent			
No. of patients	5	4	
μg kg^{-1} min^{-1}	6.1 (5.0–10.9)	3.1 (0.7–4.8)	<0.05
Percentage of control	67.5 (57.0–79.9)	30.3 (11.7–36.1)	<0.01

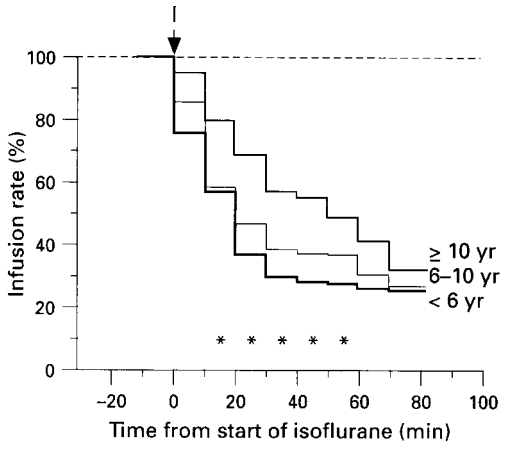

Figure 3 Median infusion rates of mivacurium at 10-min epochs as a percentage of control from commencement of 1 MAC of end-tidal isoflurane (I) in three age groups of children. Potentiation becomes maximal sooner in the youngest children.*$P < 0.05$.

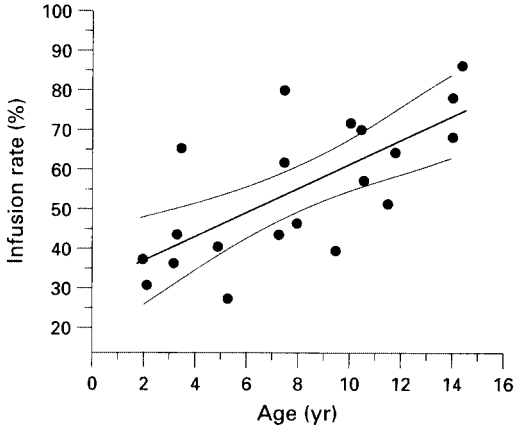

Figure 4 Significant correlation between the age of a child and infusion rate of mivacurium as a percentage of control after 30 min of inhalation of 1 MAC of end-tidal isoflurane. Regression line has been drawn with 95 % confidence intervals ($y = 30 + 3 \times$ age, $n = 20$, $r = 0.705$, $P = 0.0005$).

individual time course of the effect of halothane and isoflurane on the infusion rate of mivacurium to maintain 90 % neuromuscular block. Within 10 min of inhalation of the selected volatile anaesthetic agent the infusion rate had decreased in group Iso (fig. 2, $P < 0.001$). At all intervals between 10 and 90 min from the start of the volatile anaesthetic, the infusion rate of mivacurium had decreased more in group Iso than in group Hal (table 1).

The maximum effect of halothane or isoflurane in reducing the infusion requirement of mivacurium to maintain 90 % neuromuscular block did not depend on the age of the patient. However, the time course of this potentiation depended on age in group Iso in that maximum potentiation was established sooner the younger the child (time (min) to maximum potentiation = $32 + 3 \times$ age ($r = 0.663$, $P = 0.002$)). Figure 3 illustrates the time course of potentiation of mivacurium by isoflurane in three age groups of children. A similar age-related correlation was not detected in group Hal.

The effect of isoflurane on reducing the requirement for mivacurium was age-dependent within 10–60 min from the start of isoflurane inhalation (r values from 0.515 ($P = 0.02$) to 0.705 ($P < 0.001$)). Figure 4 shows the effect of isoflurane on the infusion requirement of mivacurium in children after 30 min of inhalation of 1 MAC of isoflurane. The younger the child, the smaller was the infusion requirement related to the control 100 % infusion rate before isoflurane (infusion rate (%) = $30 + 3 \times$ age ($r = 0.705$, $P = 0.0005$)). Group Hal did not show similar significant correlations (r values from 0.013 ($P = 0.96$) to 0.227 ($P = 0.34$) within the time interval 10–60 min from the start of halothane inhalation).

Discussion

We have found that potentiation of mivacurium by halothane and isoflurane was strongly time-dependent and took at least 30 min before maximum potentiation was established. In addition, the magnitude of the potentiation did not depend on the age of a child but became established more quickly in younger children when isoflurane was used. We found that conditions for neuromuscular block were unstable for at least the first 30 min of anaesthesia with volatile anaesthesia. This implies that potentiation was decreased with a shorter duration of anaesthesia. Thus it may not be possible to compare data from different studies on neuromuscular blockers if the duration of inhalation anaesthesia is not standardized. Potentiation of mivacurium by isoflurane was greater the younger the child if the duration of anaesthesia was less than 1 h. This suggests that not even a standard duration or concentration of isoflurane guarantees the same degree of potentiation at all ages in children.

There are relatively few studies on the time dependence of the effects of volatile agents on non-depolarizing neuromuscular blockers. Miller, Crique and Eger concluded in 1976 that duration of halothane anaesthesia had no effect on neuromuscular block produced by tubocurarine within 10–160 min [7]. However, their data on cumulative dose–response curves showed that ED_{50} values were greater within 10–20 min than within 40–160 min of halothane anaesthesia (4.6 *vs* 3.1 mg m^{-2}, respectively). Withington and colleagues designed a study with patients as their own controls to evaluate the time course of potentiation of atracurium by enflurane [9]. They found a clear time-dependent reduction in the plasma concentrations of atracurium needed to maintain 90 % neuromuscular block.

We found that halothane and isoflurane produced maximal neuromuscular effect in not less than 30–80 min from onset of administration. Our average infusion rate of mivacurium to maintain 90 % neuromuscular block before the volatile agent was 12 μg kg^{-1} min^{-1} (700 μg kg^{-1} h^{-1}). This rate and its variation are comparable with those described for children to maintain 95 % or 89–99 % neuromuscular block [14, 17, 18]. Brandom and colleagues, and Alifimoff and Goudsouzian found that halothane reduced infusion requirements of mivacurium by 20 % [17, 18]. This reduction in infusion require-

ments was smaller than that in the present study. However, both of these earlier studies included infusion analysis within the first 15 min of halothane anaesthesia, even though Brandom and colleagues reported that later infusion rates were smaller [18]. Thus it may be that the average infusion rates calculated in these studies did not represent maximal potentiation of neuromuscular block by halothane in children. Our finding of 32 % maximal potentiation produced by halothane is very similar to the 36 % reduction in vecuronium infusion to maintain 90 % neuromuscular block by at least 60 min of halothane anaesthesia in adults [4].

There are no previous paediatric data on infusion requirements for mivacurium during isoflurane anaesthesia. In adults, more than 1 h of isoflurane anaesthesia reduced the bolus dose requirements for tubocurarine by 70 % [1] and the infusion requirements for vecuronium to maintain 90 % neuromuscular block by 67 % [5]. These results for isoflurane-induced potentiation are close to our finding of 70 % maximal reduction in infusion requirement of mivacurium during isoflurane anaesthesia. When shorter exposures of isoflurane were studied, less potentiation was observed for mivacurium: 20–30 % reduction in dose requirement by 10–15 min of isoflurane [10, 19] and 40 % reduction in infusion requirement when infusion data for the first 15 min of isoflurane anaesthesia were included [20]. These results are consistent with our results on the time course of potentiation of mivacurium infusion produced by isoflurane (fig. 2).

A key question in paediatric neuromuscular pharmacology is how infants, children and adults differ in their dose requirements for different neuromuscular blockers [21, 22]. Our study casts doubt on many previous studies on the subject as several studies have been carried out during anaesthesia with unknown duration of volatile anaesthetic agents. Our results indicate that if the timing of the volatile agent has not been controlled, then neuromuscular studies cannot be compared because of unknown potentiation, and comparisons between age groups may be questionable. A serious problem arises if isoflurane has been used; in this case, unstable neuromuscular conditions last for at least 30 min in the youngest children and for even 60 min in older children.

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