The effects of sevoflurane are similar to those of isoflurane on the neuromuscular block produced by vecuronium

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SUMMARY

We have examined the interactions of 1 MAC of isoflurane and sevoflurane (and 66% nitrous oxide in oxygen) with vecuronium, using the EMG response of the abductor digiti minimi to train-of-four (TOF) stimulation of the ulnar nerve. We constructed dose–response curves for vecuronium in 54 patients. The curves for both isoflurane and sevoflurane had a significant leftward shift compared with that for fentanyl–nitrous oxide anesthesia ($P < 0.01$). When the amplitudes of the first response (T1) had recovered to 50% of control in another 32 patients, subsequently we compared the spontaneous recovery rate of the ratio of the fourth to the first TOF response (T4:T1) at 3-min intervals during the 15-min period, in the presence of two volatile anaesthetics or after discontinuation of administration of anaesthetic. The rate of recovery of T4:T1 was significantly greater when both anaesthetics were discontinued. However, this rate was similar for both anaesthetics, suggesting that the mechanism of action of the two anaesthetics is similar. (Br. J. Anaesth. 1994; 72: 465–467)

KEY WORDS


Isoflurane and sevoflurane are known to enhance the effects of non-depolarizing neuromuscular blocking agents to a similar degree in rats and humans [1, 2]. However, there is a great difference between isoflurane and sevoflurane in their blood-gas partition coefficients (1.4 vs 0.6) and muscle–gas partition coefficients (5.6 vs 3.13) [3, 4]. In addition, the rate of elimination of sevoflurane is greater than that of isoflurane. Therefore, we assumed that even if the neuromuscular effects of the two volatile anaesthetics are similar at a steady-state end-tidal concentration, differences in the effect on neuromuscular transmission may be detected during recovery from anaesthesia.

The aims of this study were to compare the dose–response relationships of vecuronium during anaesthesia with isoflurane and sevoflurane and to examine the spontaneous recovery rate from vecuronium-induced neuromuscular block after discontinuing administration of isoflurane and sevoflurane.

METHODS AND RESULTS

After obtaining approval from the local Ethics Committee and written informed consent, we studied 86 unpremedicated patients of physical status ASA I and II undergoing minor elective surgery.

After induction of anaesthesia, the ulnar nerve was stimulated percutaneously at the wrist using supra-maximal train-of-four (TOF) stimuli at 2 Hz for 2 s every 20 s and the resultant evoked electromyogram of the abductor digiti minimi was recorded using a Datex NMT-100 Relaxograph. Accurate baseline values (100% reference values for the amplitudes of the first response (T1) and the ratio of the fourth to the first TOF response (T4:T1)) were obtained after a 5–7 min stabilization period. Ventilation was controlled to maintain an end-tidal carbon dioxide partial pressure of 4.6–5.5 kPa and oesophageal temperature was maintained at 36.0–37.0 °C. End-tidal concentrations of carbon dioxide, oxygen, nitrous oxide, isoflurane and sevoflurane were measured continuously using a multiple gas analyser (Capnomac, Ultima). Isoflurane and sevoflurane 1 MAC were defined as 1.15 and 2.05%, respectively [3, 4].

Part 1

Fifty-four patients, aged 22–56 yr (mean 40 yr), weighing 45–65 kg (mean 59 kg), were allocated randomly to three groups: a control group (n = 18), in which patients were anaesthetized with thiopentone 4–5 mg kg⁻¹, fentanyl 5–7 μg kg⁻¹ and 66% nitrous oxide in oxygen; an isoflurane group (n = 18) and a sevoflurane group (n = 18), in which patients were anaesthetized with 66% nitrous oxide in oxygen and isoflurane or sevoflurane, respectively. In the two volatile anaesthetic groups, tracheal intubation was performed without the aid of neuromuscular block during deep isoflurane or sevoflurane anaesthesia. After at least 40 min, at 1 MAC of end-tidal concentration of each anaesthetic, the Relaxograph was recalibrated. The two groups receiving volatile anaesthetics were given a single bolus dose of...
For isoflurane, 22 (19-23) ng kg\(^{-1}\) and for sevoflurane the ED₅₀ value was 20 (19-22) ug kg\(^{-1}\). The ED₅₀ and ED₉₅ values were the doses required to produce 50% and 95% depression of T₁, respectively.

Part 2

We studied 32 patients, aged 24-62 yr (mean 36 yr), weighing 47-78 kg (mean 61 kg). Anaesthesia was induced with thiopentone 4-5 mg kg\(^{-1}\) and fentanyl 4-5 µg kg\(^{-1}\). When the EMG response was stable, a single bolus dose of vecuronium 100 µg kg\(^{-1}\) i.v. was given, after which the trachea was intubated. Anaesthesia was maintained during surgery with 66% nitrous oxide in oxygen and 1 MAC of end-tidal concentration of isoflurane or sevoflurane \((n = 16\) each group). Additional neuromuscular blockers were used to maintain T₁ at 35-45% of control. When surgery was complete, recovery from neuromuscular block was allowed to occur spontaneously in all patients.

When T₁ had recovered spontaneously to 50% of control, both groups were allocated further into two subgroups: two “stable” groups in which administration of the volatile anaesthetic was continued at 1 MAC of end-tidal concentration for 15 min and two “stop” groups in which administration of the volatile anaesthetic was discontinued \((I\) (isoflurane) (stable), \(I\) (stop), \(S\) (sevoflurane) (stable) and \(S\) (stop), respectively). Administration of nitrous oxide was continued in all patients. The T₄:T₁ values were compared at 3-min intervals during this 15-min period in the four groups. After completion of the study, residual neuromuscular block was antagonized using an appropriate dose of neostigmine with atropine.

The ED₅₀ and ED₉₅ values are expressed as mean (95% confidence limits (CL)). Other results are expressed as mean (SEM). The Scheffe F test or a paired t test was used to test significance, as appropriate. P < 0.05 was considered statistically significant.

All groups were comparable in age and weight. In part 2 of the study, there were also no significant differences in total doses of vecuronium \((mean\ 150 \mu g \text{ kg}^{-1})\) and inhalation time \((mean\ 85\ min)\) required until the T₁ values recovered to 50% of control. Isoflurane and sevoflurane enhanced the effects of vecuronium to an approximately similar degree; that is, the mean ED₅₀ value was 10.5 (95% CL 9-12) µg kg\(^{-1}\) for isoflurane, 11 (9-13) µg kg\(^{-1}\) for sevoflurane and 21 (18-25) µg kg\(^{-1}\) for fentanyl anaesthesia \((P < 0.01,\ compared\ with\ fentanyl\ anaesthesia)\); the ED₅₀ value was 20 (19-22) µg kg\(^{-1}\) for isoflurane, 22 (19-23) µg kg\(^{-1}\) for sevoflurane and 47 (42-51) µg kg\(^{-1}\) for fentanyl anaesthesia \((P < 0.01,\ compared\ with\ fentanyl\ anaesthesia)\).

In part 2 of the study, the final T₁ and T₄:T₁ values were similar in all four groups and were greater than 96 and 98%, respectively. The end-tidal concentrations of isoflurane and sevoflurane (MAC concentration) were plotted every 1 min during a 7-min period. The end-tidal concentration of sevoflurane decreased more rapidly than the isoflurane concentration after discontinuation of the anaesthetic \((P < 0.01\ at\ 2\ and\ 7\ min,\ P < 0.05\ at\ 3-6\ min)\) (data not shown). However, the difference was minimal, within 0.3 MAC. The T₄:T₁ values were almost identical in the four groups (mean...
21.7%) when T1 had recovered spontaneously to 50% of the control value, indicating similarity in spontaneous recovery from vecuronium-induced neuromuscular block (see 0 min in fig. 1B). Figure 1B shows the effects of discontinuation of the two anaesthetics on T4:T1 values. The T4:T1 values recovered more rapidly in both stop groups than in both stable groups (P < 0.05). There were no significant differences in the spontaneous T4:T1 recovery rate between the I (stop) and S (stop) groups or between the I (stable) and S (stable) groups.

We have used two experimental designs to elucidate the interactions of isoflurane and sevoflurane with vecuronium. The dose–response curves for both isoflurane and sevoflurane had a significant leftward shift compared with that for fentanyl–nitrous oxide anaesthesia (P < 0.01) (fig. 1A). The T4:T1 values were also found to recover more rapidly in the two stop groups than in the two stable groups (fig. 1B). Thus we have confirmed the neuromuscular effects of isoflurane and sevoflurane. However, we failed to detect any differences in the neuromuscular effects of isoflurane and sevoflurane during the anaesthetic recovery period, because of more rapid elimination of sevoflurane compared with isoflurane. Because of the rapid elimination of both anaesthetics [3, 4], the difference in MAC concentrations observed during the alveolar anaesthetic washout period was too small to produce any difference in the recovery rate of T4:T1 values. In addition, the faster recovery rates of the T4:T1 values in both the stop groups were found at 9, 12 and 15 min (fig. 1B). For the remainder of the 15-min observation period, there was an extremely small difference (if any) in MAC concentrations of both anaesthetics. Another reason for our findings may be related to the use of vecuronium. Vecuronium shows greater fade during recovery of block than during onset [7] and during recovery it is difficult to determine any difference in the neuromuscular effects of anaesthetic agents.

From the similarity of the dose–response curves and the similar recovery rates for the two anaesthetics, we conclude that the mechanisms of action of sevoflurane and isoflurane at the neuromuscular junction are not dissimilar.

COMMENT

We have used two experimental designs to elucidate the interactions of isoflurane and sevoflurane with vecuronium. The dose–response curves for both isoflurane and sevoflurane had a significant leftward shift compared with that for fentanyl–nitrous oxide anaesthesia (P < 0.01) (fig. 1A). The T4:T1 values were also found to recover more rapidly in the two stop groups than in the two stable groups (fig. 1B). Thus we have confirmed the neuromuscular effects of isoflurane and sevoflurane. However, we failed to detect any differences in the neuromuscular effects of isoflurane and sevoflurane during the anaesthetic recovery period, because of more rapid elimination of sevoflurane compared with isoflurane. Because of the rapid elimination of both anaesthetics [3, 4], the difference in MAC concentrations observed during the alveolar anaesthetic washout period was too small to produce any difference in the recovery rate of T4:T1 values. In addition, the faster recovery rates of the T4:T1 values in both the stop groups were found at 9, 12 and 15 min (fig. 1B). For the remainder of the 15-min observation period, there was an extremely small difference (if any) in MAC concentrations of both anaesthetics. Another reason for our findings may be related to the use of vecuronium. Vecuronium shows greater fade during recovery of block than during onset [7] and during recovery it is difficult to determine any difference in the neuromuscular effects of anaesthetic agents.

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REFERENCE

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