Augmentation of vecuronium-induced neuromuscular block during sevoflurane anaesthesia: comparison with balanced anaesthesia using propofol or midazolam

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We have quantified the potentiating effects of 1.7% sevoflurane \( (n=12) \) on vecuronium-induced neuromuscular block and compared the results with those obtained during balanced anaesthesia with propofol \( (n=12) \) or midazolam \( (n=12) \) in 36 patients. Neuromuscular function was monitored using an accelerograph and the train-of-four responses of the adductor pollicis muscle to ulnar nerve stimulation. Vecuronium 0.1 mg kg\(^{-1}\) was administered as an intubating dose, and maintenance doses of 0.02 mg kg\(^{-1}\) were administered on three occasions when T1/T0 had recovered to 25%. Thereafter, spontaneous recovery was monitored until complete. Times to 25% recovery of T1/T0 (DUR25) after an intubating dose of vecuronium did not differ between groups (mean 44.2 (SD 18.7) min for sevoflurane, 38.3 (7.5) min for propofol and 35.5 (9.5) min for midazolam). DUR25 values after each maintenance dose were 29.8 (9.5) min, 30.3 (10.4) min and 31.6 (10.7) min during sevoflurane anaesthesia, and were significantly longer than values for propofol (21.7 (6.0) min, 21.5 (5.8) min and 21.9 (5.8) min) and midazolam (20.0 (5.9) min, 19.3 (7.7) min and 19.8 (8.0) min) \( (P<0.05 \text{ in each case}) \). Recovery index25-75% and interval from T1/T0=25% to T4/T1=0.7 after the final dose of vecuronium were significantly prolonged by sevoflurane (28.3 (13.2) min and 42.7 (16.4) min) compared with propofol (17.6 (6.1) min and 26.6 (9.8) min) or midazolam (16.3 (9.4) min and 26.0 (10.2) min) \( (P<0.05 \text{ in each case}) \).

Keywords: neuromuscular block, vecuronium; anaesthetics volatile, sevoflurane; anaesthetics i.v., propofol; hypnotics benzodiazepine, midazolam; measurement techniques, acceleromyography

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Potent inhalation anaesthetics have been reported to augment the effect of non-depolarizing neuromuscular blocking drugs to variable degrees.\(^1\)\(^-\)\(^3\) There are few reports investigating the potentiating effects of inhaled sevoflurane on neuromuscular block produced by vecuronium. In this study, we have assessed the influence of sevoflurane on vecuronium, administered as an intubating dose and in increments. We also evaluated the interaction between vecuronium and propofol or midazolam.

Methods and results

After obtaining approval from the Hospital Ethics Committee and informed consent, we studied 36 patients of both sexes, ASA I or II, aged 20–60 yr, undergoing elective ENT surgery. No patient had neuromuscular, hepatic or renal disease, and patients were not receiving any drug known to interfere with neuromuscular transmission. All patients were premedicated with pethidine 50 mg i.m. and atropine 0.5 mg i.m., approximately 45 min before induction of anaesthesia. An i.v. infusion of lactated Ringer’s solution was commenced and electrocardiography, pulse oximetry and non-invasive arterial pressure were monitored continuously from arrival in the operating theatre.

Patients were allocated randomly to one of three groups. In group S \( (n=12) \), anaesthesia was induced with fentanyl 1–2 \( \mu \)g kg\(^{-1}\) and thiamylal 4–5 mg kg\(^{-1}\) i.v., followed by controlled ventilation with 1.7–2.5% sevoflurane in oxygen via a face mask. After tracheal intubation, anaesthesia was maintained by inhalation of 1.7% sevoflurane and 67% nitrous oxide in oxygen, supplemented with i.v. fentanyl. In group P \( (n=12) \), anaesthesia was induced with fentanyl 1–2 \( \mu \)g kg\(^{-1}\) and propofol 2–2.5 mg kg\(^{-1}\) i.v., and maintained with continuous infusion of propofol 4–8 mg kg\(^{-1}\) h\(^{-1}\) during controlled ventilation with oxygen via a face mask. After tracheal intubation, anaesthesia was maintained by continuous infusion of propofol 4–8 mg kg\(^{-1}\) h\(^{-1}\), increments of fentanyl and 67% nitrous oxide in oxygen. In group M
(n=12), anaesthesia was induced with fentanyl 1–2 µg kg⁻¹ and midazolam 0.1–0.15 mg kg⁻¹. After tracheal intubation, anaesthesia was maintained with supplementary i.v. midazolam, fentanyl and 67% nitrous oxide in oxygen.

Immediately after induction of anaesthesia, the ulnar nerve was stimulated at the wrist with square-wave supra-maximal stimuli of 0.2 ms duration, delivered in a train-of-four (TOF) mode at 2 Hz every 15 s using a TOF guard (Organon Teknika NV, Turnhout, Belgium), and contraction of the ipsilateral adductor pollicis muscle was measured using accelerometry. After evoked responses had been stable for at least 5 min, all patients were given vecuronium 0.1 mg kg⁻¹ via a running infusion. Tracheal intubation was performed when maximum depression of the first twitch response (T1/T0) had occurred. Ventilation was adjusted to maintain end-tidal carbon dioxide partial pressure at 4.7–5.1 kPa using a Capnomac Ultima (Datex, Helsinki, Finland). Oesophageal temperature was maintained greater than 36°C with a heating mattress. Three maintenance doses of vecuronium 0.02 mg kg⁻¹ were administered when T1/T0 had recovered to 25%. After the final increment of vecuronium, spontaneous recovery (T4/T1 >0.7) of neuromuscular function was allowed to occur. Variables measured were: maximum depression of T1/T0 (%); time (min) from end of injection of vecuronium to maximum depression of T1/T0 (onset time); clinical duration (min) from injection of vecuronium to spontaneous recovery of T1/T0 to 25% (DUR25); time to recovery of T1/T0 from 25% to 75% (recovery index (RI)); interval from T1/T0=25% to T4/T1=0.7; T4/T1 at the time when T1/T0 had recovered to 50% and 75%; and skin temperature on the monitored thenar muscles.

Statistical analysis was performed using analysis of variance (ANOVA). P<0.05 was considered statistically significant. If ANOVA gave a significant P value, further group comparisons were made using Scheffe’s F test. Data are presented as mean (SD).

Results are shown in Table 1. Patient characteristics and skin temperature over the thenar muscles measured at the beginning and end of the study did not differ between groups. The intubating dose of vecuronium abolished the TOF response in all patients. Onset time and initial DUR25 did not differ between groups. After each incremental dose, DUR25 values in group S (29.8 (9.5), 30.3 (10.4) and 31.6 (10.7) min) were significantly longer than those in groups P (21.7 (6.0), 21.5 (5.8) and 21.9 (5.8) min) and M (20.0 (5.9), 19.3 (7.7) and 19.8 (8.0) min) (P<0.05). Similar findings were observed for RI and the interval from T1/T0=25% to T4/T1=0.7 (28.3 (13.2) and 42.7 (16.4) min for group S; 17.6 (6.1) and 26.6 (9.8) min for group P; and 16.3 (9.4) and 26.0 (10.2) min for group M, respectively; P<0.05).

During spontaneous recovery after the final dose of vecuronium, T4/T1 at the time when T1/T0=50% and 75%, was significantly lower in group S (0.20 (0.08) and 0.41 (0.08), P<0.01) than in groups P (0.41 (0.12) and 0.66 (0.20)) and M (0.40 (0.15) and 0.60 (0.15)). There was no difference in any variable between groups P and M.

**Comment**

We have demonstrated the marked potentiating effect of sevoflurane on vecuronium-induced neuromuscular block. The marked prolongation of DUR25 observed after increments of vecuronium in patients anaesthetized with sevoflurane contrasted with DUR25 after the initial intubating dose of vecuronium. This effect may be caused by the very slow equilibration of sevoflurane between blood and muscle (more than 1 h). DUR25 of the intubating dose (44.2 min) was probably not prolonged significantly by sevoflurane.

A non-depolarizing neuromuscular blocking drug induces fade of the TOF response to indirect repetitive nerve stimulation. Fade has been suggested to be caused by presynaptic inhibition of acetylcholine release from motor nerve terminals. Potent inhalation anaesthetics have been used in combination with the non-depolarizing blocking drugs to counteract fade produced by the non-depolarizing blocking drugs.4
reported to inhibit presynaptic acetylcholine release. In this study, we found that sevoflurane significantly increased TOF fade when T1/T0 = 50% and 75%, compared with balanced anaesthesia.

In summary, sevoflurane had a marked potentiating effect on vecuronium-induced neuromuscular block and augmentation was more evident after incremental doses.

References