Neuromuscular Blockade by Vecuronium during Induction with 5% Sevoflurane or Propofol

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This randomized trial investigated whether 5% sevoflurane potentiated neuromuscular blockade by vecuronium. General anaesthesia was induced with 5% sevoflurane in oxygen in 16 patients or with propofol in 16 patients. After loss of consciousness, vecuronium was administered to all participants at randomly assigned doses of 25, 30, 35 or 40 µg/kg. Neuromuscular blockade was assessed by use of acceleromyography to measure responses to train-of-four stimuli in the adductor pollicis and corrugator supercili muscles. Maximum blockade was significantly more intense in the adductor pollicis among patients in the sevoflurane group than in the propofol group, whereas there was no significant between-group difference at the corrugator supercili muscles. In both groups, maximum blockade at the corrugator supercili was significantly less intense than that achieved at the adductor pollicis. In the dose–response analysis, the 50% and 95% effective doses were lower for sevoflurane than for propofol in both muscles, although this did not reach statistical significance. It is concluded that induction of general anaesthesia with sevoflurane might provide improved conditions for intubation and reduce airway problems.

KEY WORDS: SEVOFLURANE; PROPOFOL; VECURONIUM; VOLATILE ANAESTHETICS; ANAESTHESIA INDUCTION; ADDUCTOR POLLICIS; NEUROMUSCULAR BLOCKADE

Introduction

General anaesthesia is usually induced with the use of intravenous or inhaled volatile agents. Sevoflurane, a commonly used inhaled agent suitable for use in adults and children, potentiates the effect of non-depolarizing neuromuscular-blockade drugs and leads to more intense outcomes than other volatile anaesthetics, such as halothane and isoflurane. This potentiating effect with sevoflurane has been demonstrated at adductor pollicis muscles after a stabilization period of 5–10 min. During induction of general anaesthesia, however, relaxation of the laryngeal muscle to facilitate tracheal intubation is a major concern of anaesthetic management and neuromuscular-blockade drugs are frequently given immediately after loss of consciousness.

The present study investigated whether sevoflurane could increase the potency of neuromuscular blockade with vecuronium, compared with intravenous propofol. The
adductor pollicis and the corrugator supercili muscles were selected for measurement of neuromuscular blockade because the profile of neuromuscular blockade in the corrugator supercili muscles is similar to that in the laryngeal muscles, and the adductor pollicis is the most popular site for neuromuscular monitoring.

Patients and methods

PATIENTS
Patients with American Society of Anesthesiology (ASA) status I or II, of age 18 – 65 years and within 20% of ideal body weight who were scheduled to undergo elective minor surgery were included in this study. Patients with hepatic, renal or neuromuscular disease or those who were receiving drugs that could interfere with neuromuscular transmission were excluded.

STUDY DESIGN
This study was conducted from September to December 2006. It was approved by the Institutional Review Board of Fukuoka University, School of Medicine, Fukuoka, Japan and written informed consent was obtained from each patient before enrolment.

Patients were randomly allocated to a sevoflurane or a propofol group. They were pre-medicated with 10 mg diazepam orally approximately 90 min before induction of anaesthesia. On arrival in the operating room, pulse oximetry, electrocardiography and non-invasive monitoring of arterial blood pressure were instituted. In the sevoflurane group, patients breathed room air before induction of anaesthesia. The circle system of the anaesthesia machine was primed for 30 s with 5% sevoflurane in oxygen at 6 l/min fresh gas flow. The face mask was then fitted and the patients were asked to take deep breaths. End-tidal sevoflurane concentration was monitored continuously with an anaesthetic gas monitor (Datex-Ohmeda AS/3™, GE Healthcare, Helsinki, Finland). In the propofol group, general anaesthesia was induced by injection of 2.0 – 2.5 mg/kg propofol and by intravenous administration at 10 mg/kg per h during the anaesthesia induction period.

Immediately after loss of consciousness, vecuronium was administered at randomly assigned single doses of 25, 30, 35 or 40 µg/kg over 5 s (one dose per patient). Loss of consciousness was defined as loss of the eyelash reflex and unresponsiveness to verbal stimulation.

In both groups, if undesirable respiratory depression occurred artificial ventilation was applied via a face mask to maintain the partial pressure of end-tidal carbon dioxide between 35 and 40 mmHg.

MEASUREMENT OF NEUROMUSCULAR BLOCKADE
Neuromuscular blockade was assessed by acceleromyographic measurement of evoked responses to train-of-four stimuli at the adductor pollicis and the corrugator supercili muscles, using a TOF-Guard™ neuromuscular transmission monitor (Organon Instruments, Oss, The Netherlands).

The temporal branch of the facial nerve was stimulated supramaximally every 15 s at the external part of the superciliary arch and an acceleration transducer was fixed to the left medial eyebrow. Another pair of electrodes was applied to the left wrist to stimulate the ulnar nerve supramaximally every 15 s and the acceleration transducer was fixed to the volar side of the distal phalanx of the left thumb. Responses were measured every time each muscle was stimulated; since responses from the
corrugator supercilii are low, the signal from the acceleration transducer was amplified five times.

Stabilization for >10 min or preconditioning with tetanic stimulation for 5 s is recommended before acceleromyography, but these procedures were omitted in the present study to enable assessment of the effects of vecuronium immediately after induction of general anaesthesia. Thus, baseline measurements of neuromuscular responses at both muscles were obtained just after loss of consciousness. Maximum blockade was defined as the first twitch response in the train of four being the same or increased height on three consecutive measurements.

STATISTICAL ANALYSIS

Previous studies have shown that the SD for maximum blockade after a single dose of 20–40 µg/kg vecuronium was 14–21%. With an assumed SD of 21%, therefore, a sample size of 14 patients/group was calculated as required to detect a 20% difference in maximum blockade at a 5% significance level with a power of 80%.

Differences in maximum blockade at both muscles between the sevoflurane and propofol groups were compared by analysis of covariance. Differences in maximum blockade between the adductor pollicis and the corrugator supercilii muscles were compared by repeated measures analysis of variance (StatView 5.0 software for Windows; SAS Institute, Cary, NC, USA). All tests were two-sided, with \( P < 0.05 \) considered significant. The relationship between dose of vecuronium and maximum neuromuscular blockade was assessed by transformation to log-dose and probit-response values, respectively. Responses of 0% or 100% were adjusted, respectively, by adding or subtracting 0.5%. The 50% and 95% effective doses (ED\(_{50}\) and ED\(_{95}\), respectively) for the adductor pollicis and the corrugator supercilii in both groups were derived from least-square linear regression analysis.

Results

Of the 32 patients with ASA status I or II who were enrolled into this study, 16 were assigned to the sevoflurane group and 16 to the propofol group. The groups did not differ significantly with regards to sex ratio, age, height or weight (Table 1). Mean ± SD end-tidal sevoflurane concentrations at loss of consciousness and at maximum blockade were 3.1% ± 0.4% and 3.9% ± 0.3%, respectively. Maximum blockade achieved with vecuronium at the adductor pollicis was significantly more intense in the sevoflurane group than in the propofol group (\( P = 0.02 \)). At the corrugator supercilii, however, maximum blockade did not differ significantly between the groups. In both

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<th>TABLE 1: Demographic data for the patients in the study</th>
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Data show mean ± SD or number of patients. No significant between-group differences (\( P > 0.05 \)).
groups the maximum neuromuscular blockade in the corrugator supercilii was significantly less intense than that in the adductor pollicis ($P < 0.01$).

The dose–response relationships for the sevoflurane and propofol groups are shown in Fig. 1. In the sevoflurane group, the $ED_{50}$ and $ED_{95}$ were 20 and 31 µg/kg, respectively, for the adductor pollicis and 31 and 51 µg/kg, respectively, for the corrugator supercilii. The $ED_{50}$ and $ED_{95}$ in the propofol group were 26 and 37 µg/kg, respectively, for the adductor pollicis and 35 and 58 µg/kg, respectively, for the corrugator supercilii. Comparisons of $ED_{50}$ and $ED_{95}$ between the sevoflurane and propofol groups or between the adductor pollicis and corrugator supercilii showed no statistically significant differences.

Mean ± SD arterial blood pressure and heart rate at the time nearest maximum blockade at which these were measured were similar in the propofol and sevoflurane groups (84 ± 14 mmHg and 75 ± 15 beats/min versus 92 ± 17 mmHg and 69 ± 13 beats/min).

**Discussion**

In this study, the maximum neuromuscular blockade in the adductor pollicis induced by

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**FIGURE 1:** Dose–response curves at the adductor pollicis and corrugator supercilii for: (A) vecuronium in the sevoflurane-treated group and (B) vecuronium in the propofol-treated group (black filled circles show the maximum depression in the first twitch response (T1) in the train of four for each patient; solid straight lines show the mean; dashed curved lines show 95% confidence intervals)
Sevoflurane and potency of neuromuscular blockade

Vecuronium was significantly more intense after administration of 5% sevoflurane than that achieved with propofol induction. This potentiation, despite the short duration (30 s) of exposure to sevoflurane, could be partly due to a strong inhibitory effect of sevoflurane on neuromuscular transmission. For example, Suzuki et al. compared the neuromuscular blocking effects of sevoflurane, isoflurane and halothane in cats by measurement of muscular compound action potentials and showed that sevoflurane had the most potent neuromuscular inhibitory effect through both pre- and post-synaptic inhibitory mechanisms. In addition, sevoflurane has been shown in humans to potentiate the effects of non-depolarizing neuromuscular blockers to a greater degree than other volatile anaesthetics, such as halothane and isoflurane.

In the present study, sevoflurane led to significantly more intense blockade at the adductor pollicis than did propofol, whereas the maximum blockade at the corrugator supercilii did not differ significantly between the two groups. The cause of this difference in outcome is not clear. A greater variability in the maximum blockade at the corrugator supercilii might, however, be the reason for this discrepancy, since the sample size for the study was calculated on the basis of the SD for maximum blockade at the adductor pollicis muscle from previous studies.

When maximum blockade was compared between the two different muscles, blockade of the corrugator supercilii was significantly less than that of the adductor pollicis in both treatment groups. This is in accordance with previous studies with muscle relaxants other than vecuronium. In addition, Donati et al. showed that the maximum blockade with vecuronium was less at the orbicularis oculi than at the adductor pollicis. Since they applied electrodes to the medial and the central portions of the eyebrow, the responses attributed to the orbicularis oculi in their study might also be considered to be those of the corrugator supercilii.

In the present study, the ED50 of vecuronium at the adductor pollicis muscle was 20 µg/kg, which is higher than reported in previous studies (10.6 – 16.8 µg/kg, dependent on duration of exposure to sevoflurane which varied from 60 min down to 15 min, respectively). This decreased effect of vecuronium in the present study is mainly due to the short duration of exposure to sevoflurane because of the study design. Duration-dependent potentiation of neuromuscular blockade associated with exposure to volatile inhaled anaesthetic agents has been reported with enflurane, halothane, isoflurane and sevoflurane. Low-level cardiovascular effects of sevoflurane owing to the short exposure time might also account for the reduced potency of vecuronium in the present study; decreased cardiac output and increased muscle blood flow can increase the intensity of neuromuscular blockade, although arterial blood pressure and heart rate near to maximum blockade were similar in the two groups.

The ED50 of vecuronium at the adductor pollicis muscle in the propofol group was 26 µg/kg in the present study. This contrasts with that found by Plaud et al., who showed that propofol administered alone or with nitrous oxide for 15 min before injection of muscle relaxant increased mivacurium-induced neuromuscular blockade, yet is similar to that after a 10 min stabilization period reported by McCarthy et al. (ED50 24 µg/kg) and to previous studies that used thiopental, fentanyl and nitrous oxide during the stabilization period. The different duration of stabilization, the
different muscle relaxant used or weak neuromuscular effects of propofol at clinical concentrations\textsuperscript{17} might be reasons for the discrepancy between the present study and that of Plaud et al.\textsuperscript{11}

In summary, compared with propofol, induction of general anaesthesia with 5% sevoflurane resulted in potentiation of neuromuscular blockade by vecuronium at the adductor pollicis muscle but not at the corrugator supercilii muscle. The corrugator supercilii muscle was more resistant to the action of vecuronium than was the adductor pollicis in both treatment groups. Induction of general anaesthesia with sevoflurane might provide improved conditions for intubation and reduce airway problems.

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**Conflicts of interest**

The authors had no conflicts of interest to declare in relation to this article.

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