Neuromuscular Effects of Pipecuronium during Sevoflurane Anesthesia Compared with Isoflurane and Enflurane Anesthesia

Yasuo NAKAO, Mikio OHNO, Makoto IMAI and Osamu KEMMOTSU

We evaluated the neuromuscular effects of pipecuronium during anesthesia with equipotent concentrations of either sevoflurane, isoflurane or enflurane.

Twenty-seven patients scheduled for minor elective otolaryngeal or plastic surgery were studied and randomly assigned to 3 groups, one group per anesthetic agent. Anesthesia was induced with thiamylal 5 $mg \cdot kg^{-1}$ and the trachea was intubated with succinylcholine 1 $mg \cdot kg^{-1}$, then anesthesia was maintained with 60% nitrous oxide in oxygen and sevolfurane, isoflurane or enflurane, depending on the group. Neuromuscular blocking effects were monitored by recording the electromyographic activity of the adductor pollicis muscle from supramaximal stimulation of the ulnar nerve at 10-s intervals. Pipecuronium 40 $\mu g \cdot kg^{-1}$ was administered when electromyographic activity had reached a stable state, 30 min after succinylcholine administration. The maximum effect (% block of control) and clinical duration (time to 25% recovery) of pipecuronium were 99.1 ± 1.4% and 63.7 ± 14.7 min (mean ± S.D.) for sevoflurane, 99.0 ± 2.0% and 60.9 ± 20.5 min for isoflurane, and 98.0 ± 2.5% and 62.8 ± 28.7 min for enflurane, respectively. There were no significant differences in these values between the anesthetics. Cardiovascular stimulant effects were not observed in any of the groups.

We conclude that the effect of pipecuronium under seveflurane anesthesia is similar to that under isoflurane and enflurane anesthesia.
(Key words: pipecuronium, nondepolarizing neuromuscular blockade, twitch response, sevoflurane, isoflurane, enflurane).

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Pipecuronium is a bisquaternary derivative of pancuronium and a long-acting nondepolarizing steroidal muscle relaxant similar to pancruonium[1,2]. It has little or no cardiovascular and histamine releasing effects[3]. Enflurane and isoflurane anesthesia prolong the clinical duration of the neuromuscular blocking effects of pipecuronium[4–6], while sevoflurane has a stronger potentiation of the neuromuscular effects of vecuronium and pancuronium

Department of Anesthesiology, Hokkaido University, Sapporo, Japan

Address reprint requests to Dr. Nakao: Department of Anesthesiology, Hokkaido University School of Medicine, N-15, W-7, Kitaku, Sapporo, 060 Japan

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than halothane and enflurane[7]. However, the effect of pipecuronium under sevoflurane anesthesia has not been reported. In this study, we examined the effect of pipecuronium under sevoflurane anesthesia and compared it with those under isoflurane and enflurane anesthesia.

Methods

Institutional Human Ethics Committee approval was obtained for the study protocol. Twenty-seven ASA physical status 1 or 2 adult patients (18 females and 9 males, 22–60 yr-old) scheduled for elective otolaryngeal or plastic minor surgery gave informed written consent, and were admitted to the study. Patients were excluded from the study if they had known kidney, liver, or neuromuscular disorders or if they were taking any medication known to interfere with the action of neuromuscular blocking agents.

All patients were premedicated with oral diazepam 0.15 $mg \cdot kg^{-1}$ 90 min before induction of anesthesia. The patients wre randomly assigned into three groups: sevoflurane (n=9); isoflurane (n=9); and enflurane (n=9). Anesthesia was induced with thiamylal 5 $mg \cdot kg^{-1}$ IV and the trachea was intubated with succinylcholine 1 $mg \cdot kg^{-1}$ IV, then anesthesia was maintained with 60% nitrous oxide in oxygen and inspired 1–4% sevoflurane, 1–3% isoflurane or 1–3% enflurane, according to the need of the patient until the end of the surgical procedure.

In all patients electrocardiography, blood pressure, heart rate were monitored wtih Sirecust 1281 patients monitoring system (Siemens, Erlangen, Germany), and Sa_{O_2} by pulseoximetry, end-tidal CO_2 and end-tidal anesthetic concentration were monitored with 5250 Respiratory Gas Monitor (Ohmeda, Louis Ville, USA). Ventilation was controlled to maintain the end-tidal CO_2 at 35–40 mmHg, and body temperature were monitored during anesthesia and was maintained at 36–37°C with a warmer blanket.

After intubation, the electromyographic activity of the adductor pollicis muscle was monitored using a Relaxograph™ (Datex, Helsinki, Finland) neuromuscular transmission monitor. Surface stimulation electrodes were placed adjacent to the ulnar nerve at the wrist and recording electrodes were placed on the radial surface of the palm. Supramaximal pulses at the rate of 0.1 Hz were continuously delivered through the stimulation electrodes, and the twitch response was monitored until the end of anesthesia.

After induction of anesthesia and administration of succinylcholine, 30 min were allowed for stabilization of anesthesia and of the twitch response before pipecuronium (0.04 $mg \cdot kg^{-1}$ administration. Control electromyographic activity was established and recorded just before pipecuronium administration. The maximum effect (% block of control), onset time (from the administration of pipecuronium to the maximum effect) and clinical duration (time to 25% recovery) were recorded in all patients. In some cases, when twitch response indicated 25% recovery, additional pipecuronium (0.01 $mg \cdot kg^{-1}$) was administered. In most patients, residual neuromuscular block was antagonized with edrophonium 0.5 $mg \cdot kg^{-1}$ and atropine 8 $\mu g \cdot kg^{-1}$, and the mixture of neostigmine 40 $\mu g \cdot kg^{-1}$ and atropine 15 $\mu g \cdot kg^{-1}$ were added for antagonization if needed.

All values are expressed as mean ± S.D. Statistical analyses were performed by ANOVA, and $P < 0.05$ was considered statistically significant.

Results

The average age, body weight and height of the patients in the three groups did not differ as shown in table 1. Blood pressure and heart rate

Table 1. Patients characteristics

		sevoflurane	isoflurane	enflurane
n		9	9	9
Sex	(M/F)	4/5	2/7	3/6
Age	(yr)	43.4 ± 12.3	38.7 ± 10.7	39.3 ± 12.7
Weight	(kg)	63.8 ± 9.9	56.0 ± 10.0	62.4 ± 11.6
Height	(cm)	162.0 ± 6.7	157.7 ± 10.4	162.6 ± 8.8

mean ± SD

Table 2. Changes of blood pressure and heart rate before and 5 min after administration of pipecuronium

		Before	5 min
Sevoflurane			
Systolic blood pressure	(mmHg)	103 ± 9	104 ± 13
Diastolic blood pressure	(mmHg)	62 ± 11	62 ± 12
Heart rate	(beat·min^{-1})	74 ± 14	74 ± 15
Isoflurane			
Systolic blood pressure	(mmHg)	110 ± 16	123 ± 30
Diastolic blood pressure	(mmHg)	63 ± 13	72 ± 16
Heart rate	(beat·min^{-1})	80 ± 19	91 ± 26
Enflurane			
Systolic blood pressure	(mmHg)	102 ± 15	98 ± 13
Diastolic blood pressure	(mmHg)	60 ± 14	59 ± 13
Heart rate	(beat·min^{-1})	71 ± 6	68 ± 6

mean ± SD

Table 3. The maximum effect, time to maximum effect and clinical duration of pipecuronium under sevoflurane, isoflurane and enflurane anesthesia

		sevoflurane	isoflurane	enflurane
Maximum effect	(%)	99.1 ± 1.4	99.0 ± 2.0	98.0 ± 2.5
Onset time	(min)	3.4 ± 1.6	2.8 ± 1.2	3.5 ± 1.1
Clinical duration	(min)	63.7 ± 14.7	60.9 ± 20.5	62.8 ± 28.7

mean ± SD

before and 5 min after administration of pipecuronium 40 $\mu g \cdot kg^{-1}$ are summarized in table 2. There were no significant differences in hemodynamic variables between the three groups.

The end-tidal concentration anesthetic agents were 2.5 ± 0.5% for sevoflurane, 1.6 ± 0.4% for isoflurane, and 1.7 ± 0.3% for enflurane.

The maximum effect, onset time and clinical duration of pipecuronium were 99.1 ± 1.4% 3.4 ± 1.6 min and 63.7 ± 14.7 min under sevoflurane anesthesia, 99.0 ± 2.0%, 2.8 ± 1.2 min and 60.9 ± 20.5 min under isoflurane anesthesia and 98.0 ± 2.5%, 3.5 ± 1.1 min and 62.8 ± 28.7 min under enflurane anesthesia respectively, and summarized in table 3. And these data were not significantly different between inhalational

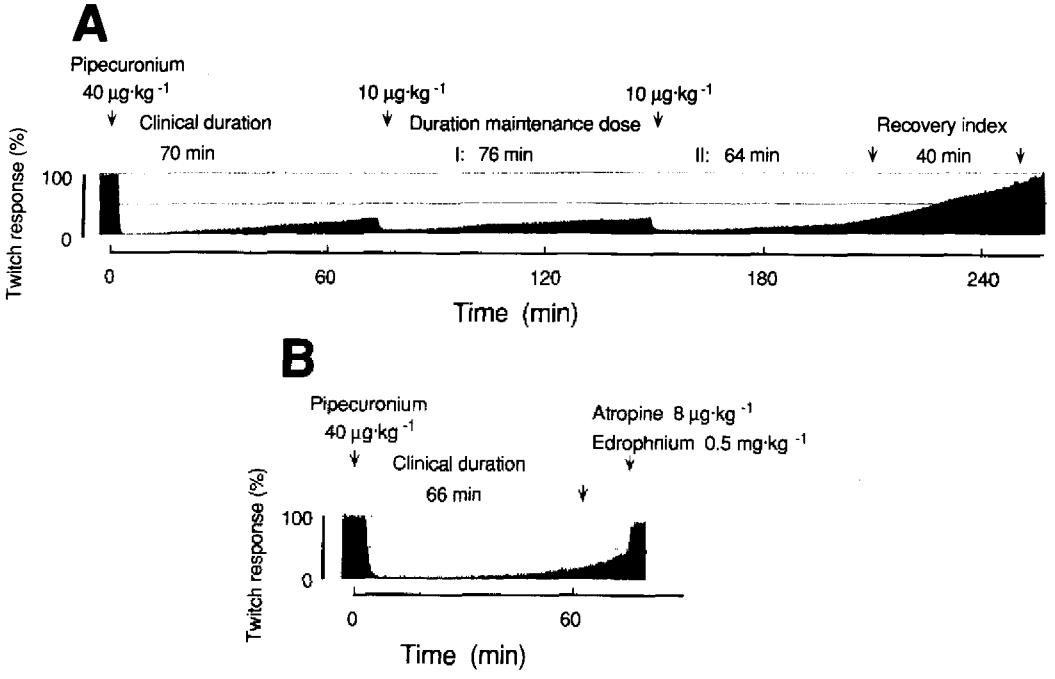

Fig. 1. Time course of the neuromuscular blocking effect of pipecuronium 40 $\mu g \cdot kg^{-1}$ under sevoflurane anesthesia.

A: additional pipecuronium 10 $\mu g \cdot kg^{-1}$ was administered after 25% recovery of twitch response and recovery index was obtained.

B: Atropine 8 $\mu g \cdot kg^{-1}$ and edrophonium 0.5 mg antagonized residual pipecuronium neuromuscular blocking effects at the 40% twitch response.

anesthetics. Figure 1A shows a typical example of the data under sevoflurane anesthesia in this study protocol. Two additional doses were administered and no reversal of neuromuscular blockade was needed for this patient. In 6 patients in the sevoflurane group, 7 in the isoflurane group and 5 in the enflurane group, pipecuronium 40 $\mu g \cdot kg^{-1}$ completely suppressed the electromyographic activity of the adductor pollicis muscle, in other patients pipecuronium suppressed activity to more than 93% of the control. Recovery index (time from 25% recovery to 75% recovery) was measured in 8 patients, and the values were 40 and 45 min in sevoflurane, 44 and 45 min in isoflurane and 20, 25, 25 and 35 min in enflurane. In most patients, edrophonium 0.5 $mg \cdot kg^{-1}$ successfully reversed the residual pipecuronium block as shown in figure 1B. Neostigmine 40 $\mu g \cdot kg^{-1}$ was administered to only two patients, one in the sevoflurane group and the other in the enflurane group, for additional pipecuronium reversal.

Discussion

The results of this study show that, the onset time, maximum effect and clinical duration of pipecuronium during anesthesia with nitrous oxide in oxygen and sevoflurane, isoflurane or enflurane were not influenced by these three anesthetics.

Katz[8] reported prior administration of succinylcholine potentiated the effects of pancuronium, although subsequent studies[9] failed to demonstrate any interaction. Dubois et al.[10] demonstrated that prior adminis-

tration of succinylcholine shortened the onset time of pancuronium and pipecuronium but did not modify the clinical duration. In his study, the nondepolarizing neuromuscular blocking agents pipecuronium and pancuronium were administrated before full succinylcholine recovery, and the twitch height was 75% of the control level. In our study, there was little influence of succinylcholine, because pipecuronium was administrated when a steady state of twitch response was obtained, 30 min after administration of the succinylcholine. The onset time to maximum effects of 2.8 to 3.5 min in our study were similar to those of previous reports[6,10–12], and we corroborated the previous findings that the anesthetic agents did not affect the onset time of pipecuronium[4,6]. Onset time of pipecuronium under sevoflurane anesthesia was the same as those under isoflurane and enflurane anesthesia.

Folder et al.[12] reported that the ED_{95} (the dose of 95% block) values of pipecuronium was 23.6 $\mu g \cdot kg^{-1}$ during enflurane anesthesia and the clinical duration of pipecuronium under enflurane anesthesia was longer than balanced anesthesia. Additionally, the ED_{95} values of pipecuronium under isoflurane anesthesia were 42.3 $\mu g \cdot kg^{-1}$ from Pittet et al.[5] and 44.6 $\mu g \cdot kg^{-1}$ from Wierda et al.[4]. In this study, maximum effects of pipecuronium ranged from 98.0 to 99.1% as shown in table 3, thus suggesting that the ED_{95} values of pipecuronium were less than 40 $\mu g \cdot kg^{-1}$ under sevoflurane, isoflurane and enflurane anesthesia.

In this study, the clinical duration of 60.9–63.7 min by pipecuronium 40 $\mu g \cdot kg^{-1}$ was similar to that of the previous report by Wierda et al. of pipecuronium 50 $\mu g \cdot kg^{-1}$ under isoflurane anesthesia[4]. The clinical duration of pipecuronium under sevoflurane anesthesia did not differ from those under isoflurane and enflurane anesthesia in our study.

Enflurane-potentiated neuromuscular blocking effects of pipecuronium were compared with balanced anesthesia[12] and with halothane and balanced anesthesia[6]. Isoflurane enhanced the neuromuscular blocking effects of pipecuronium compared with balanced and halothane anesthesia[4,5]. Itagaki et al.[7] reported that sevoflurane had a strong potentiating effect on neuromuscular block by pancuronium and vecuronium. Previous papers reported minimum alveolar concentration (MAC%) of sevoflurane, 1.71%[13], is higher than either that of isoflurane at 1.15%[14], or that of enflurane at 1.68%[15]. In this study, the end-tidal concentration of sevoflurane was significantly higher than that of isoflurane and enflurane. However, the end-tidal concentrations of anesthetics in this study were 1.5 ± 0.3 MAC of sevoflurane, 1.4 ± 0.4 MAC of isoflurane and 1.0 ± 0.2 MAC of enflurane, respectively. There were significant differences between sevoflurane versus enflurane and isoflurane versus enflurane. Thus it is suggested that the potentiation of neuromuscular blocking effects of pipecuronium by sevoflurane is similar to or less than those by isoflurane and enflurane.

Residual pipecuronium block reversal was performed by edrophonium 0.5 $mg \cdot kg^{-1}$ IV in this study. An additional reversal dose of neostigmine was needed in only two patients. Abdulatif et al.[16] reported that edrophonium 1 $mg \cdot kg^{-1}$ did not consistently antagonize residual pipecuronium neuromuscular block at 20% recovery of T1. In our study, however, edrophonium was administered after 25% recovery, and before extubation we checked routinely that the train of four ratio was higher than 80%. Thus, there were no problems caused by residual pipecuronium blocking effects in this study.

In conclusion, the neuromuscular blocking effects with pipecuronium under sevoflurane anesthesia with nitrous oxide in oxygen are similar to those of isoflurane and enflurane anesthesia.

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