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Dose–response and time-course of the effect of rocuronium bromide during sevoflurane anaesthesia

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Summary

To evaluate the influence of sevoflurane on the dose–response relationship and on the time-course of the effect of rocuronium, 60 adult patients undergoing elective plastic surgery were randomly allocated to either the control or the sevoflurane group. Anaesthesia was maintained with 60% nitrous oxide in oxygen and thiopentone in the control group and with 60% nitrous oxide in oxygen and an end-tidal concentration of 1.75% sevoflurane in the sevoflurane group. Neuromuscular function was assessed mechanomyographically with train-of-four stimulation at the wrist every 12 s and the percentage depression of the first twitch of the train-of-four was used as the study parameter. The dose–response relationship of rocuronium in the two groups was determined by the cumulative dose–response technique. The dose–response curve of rocuronium in the sevoflurane group was shifted to the left compared to the control group, indicating a potentiation of rocuronium-induced neuromuscular block. The effective doses of rocuronium required to produce 50%, 90% and 95% twitch depression in the sevoflurane group were decreased by 30.5%, 26.7% and 25.2%, respectively, compared to the control group. Following the administration of a total dose of rocuronium of 400 $\mu g.kg^{-1}$, the duration of action of, and the recovery from, rocuronium were both significantly prolonged by sevoflurane. There were significant differences in the duration of peak effect, clinical duration, recovery index and the total duration of action between the control and the sevoflurane groups.

Keywords *Neuromuscular relaxants*; rocuronium. *Anaesthetics, volatile*; sevoflurane. *Interactions, drug.*

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Rocuronium bromide is a new nondepolarising muscle relaxant that has a monoquaternary aminosteroid molecular structure similar to that of vecuronium bromide. Its main advantage compared to other currently available relaxants is its shorter onset time. Other time-course characteristics are similar to vecuronium. Further advantages are its lack of side-effects such as histamine release and its minimal interaction with cardiac muscarinic receptors [1, 2]. Factors possibly influencing the pharmacokinetics and pharmacodynamics of rocuronium, such as age [3], hepatic [4] and renal [5] insufficiency, hypothermia [6] and obesity [7], have been studied extensively. Its interactions with some intravenous and volatile anaesthetics [8–11], opioids [7, 8], suxamethonium [12], anticholinesterases [13] and antibiotics [14] have also been studied. Several publications show that anaesthetic agents potentiate the neuromuscular effects of rocuronium in the same order as for other nondepolarising neuromuscular blocking agents, namely: enflurane and isoflurane > halothane > intravenous anaesthetic agents. It has been demonstrated that such potentiation is not evident during induction and only becomes significant as anaesthesia becomes more prolonged [15]. However, there is no information on the dose–response relationship and the time-course of the effect of rocuronium during sevoflurane anaesthesia in adult patients. The purpose of this study was to determine the effects of sevoflurane anaesthesia on the dose–response relationship and on the pharmacodynamics of rocuronium in healthy adult patients.

Methods

After institutional ethics committee approval and written informed consent, 60 ASA Grade I adult patients, aged between 17 and 52 years and scheduled for elective plastic surgery of an anticipated duration of > 120 min under general anaesthesia, were included in this study. Patients were not studied if they had cardiac, pulmonary, renal, hepatic, neurological, psychiatric, muscular, inflammatory, malignant or endocrine diseases, as were pregnant women and patients with recent exposure (< 72 h) to medications known to interfere with neuromuscular transmission. Patients with a body weight more than 10% more than the ideal for their age and height were also excluded. Patients were randomly allocated to either the control or the sevoflurane group.

After an overnight fast, patients were premedicated with diazepam 0.2 $mg.kg^{-1}$, pethidine 1 $mg.kg^{-1}$ and atropine 0.01 $mg.kg^{-1}$ given intramuscularly 1 h before anaesthesia. On arrival in the operating room, an intravenous catheter was inserted and general anaesthesia was induced with intravenous thiopentone 4–6 $mg.kg^{-1}$ and fentanyl 2–4 $\mu g.kg^{-1}$. After topical anaesthesia with 2% lignocaine, the patients' tracheas were intubated without the aid of a muscle relaxant. General anaesthesia was maintained with 60% nitrous oxide in oxygen and intravenous thiopentone in the control group and with 60% nitrous oxide in oxygen and 1 minimum alveolar concentration (MAC) of sevoflurane in the sevoflurane group. Bolus doses of fentanyl 2 $\mu g.kg^{-1}$ were administered if clinical signs of inadequate analgesia were present (i.e. heart rate or mean arterial pressure > 120% of baseline values). The patients' lungs were ventilated during surgery and the end-tidal partial pressure of CO_2 was kept in the range 4–5 kPa.

During surgery the electrocardiogram, blood pressure, heart rate, temperature and peripheral oxygen saturation were monitored continuously (Cardiocap II, Datex Instrumentarium, Helsinki, Finland). Inspired and end-tidal concentrations of oxygen, carbon dioxide, sevoflurane and nitrous oxide were measured continuously and displayed digitally with an anaesthetic gas analyser (Capnomac Ultima, Datex). The gas analyser was calibrated regularly using a calibrating gas (Quick Cal, Datex). Thenar skin temperature was monitored using a thermocouple placed on the dorsum of the hand from which the response to ulnar nerve stimulation was recorded. Skin temperature over the thenar muscles was maintained above 32 °C throughout the study period by wrapping the arm in cotton wool.

After 40 min of stable end-tidal anaesthetic concentrations (within 5% of the target values), we started neuromuscular function monitoring using mechanomyography of the thenar muscles. The ulnar nerve was stimulated at the wrist with a nerve stimulator in train-of-four (TOF) mode (Myotest Mark II, Biometer, Odense, Denmark) through surface electrodes. Supramaximal square-wave impulses of 0.2 ms duration at 2 Hz, were administered every 12 s. The hand and forearm were immobilised in supination and abduction on a splint and the fingers were strapped in extension. Evoked muscle contractions of the adductor pollicis brevis were measured isometrically by a force displacement transducer, amplified and recorded continuously on a polygraph (Gould brush recorder 220, Cleveland, Ohio, USA). The first twitch (T1) of the TOF stimulus was used as the parameter for pharmacodynamic measurements.

The dose–response relationship of rocuronium in the two groups was evaluated using a cumulative dose–response technique according to Donlon *et al.* [16]. A total dose of 250 $\mu g.kg^{-1}$ of rocuronium was given in four doses (an initial dose of 100 $\mu g.kg^{-1}$ followed by three increments of 50 $\mu g.kg^{-1}$ each). Each dose of rocuronium was injected as an intravenous bolus over < 5 s into a rapidly running infusion. Ten minutes were allowed for stabilisation of the response to TOF stimulation before administration of the first dose of rocuronium. The mean of 10 T1 responses immediately preceding the first administration of rocuronium became the control to which all subsequent T1 responses were compared. Each dose increment was given only after the effect of the previous dose had reached a stable response, defined as three equal (±1%) consecutive T1 responses or when 5 min had passed with no decrease in T1 from control. If 90% or more of twitch depression was achieved following the second incremental dose, the third incremental dose was not used. The individual dose–response relationships were examined by least-squares linear regression of the logarithm of each dose against a probit transformation of the depression of T1 response, from which the doses required for 50%, 90% and 95% T1 depression (ED_{50}, ED_{90} and ED_{95}, respectively) were calculated. The regression lines were tested to determine if they deviated from parallelism [17]. If they did not, ED_{50}, ED_{90} and ED_{95} values were recorded and compared between the groups.

When maximal depression of T1 occurred after the final dose increment, additional doses of 150 $\mu g.kg^{-1}$ or 200 $\mu g.kg^{-1}$ rocuronium (to produce a total dose of 400 $\mu g.kg^{-1}$) were given. If the resulting depression of T1 was 100%, the duration of the peak effect (time from injection of a total dose of 400 $\mu g.kg^{-1}$ to the recovery of T1 to 5% of control), clinical duration (time from injection to 25% recovery of T1), total duration (time from injection to 90% recovery of T1) and recovery index (time from 25 to 75% recovery of T1) were measured.

All data were stored on a computer and were analysed with POMS statistical software Version 2.00 (Shanghai

Table 1 Demographic data. Values are given as mean (SD) [range].

	Control group	Sevoflurane group
Gender; M: F	16: 14	13: 17
Age; years	29.2 (10.1) [17–52]	30.5 (7.7) [19–51]
Weight; kg	59.6 (11.8) [46–86]	59.1 (10.2) [48–75]
Height; cm	166.3 (9.3) [158–186]	167.8 1(10.2) [156–175]
Duration of surgery; h	3.40 (1.11) [2.0 –6.9)	3.62 (1.28) [2.6–5.7]
Temperature; ℃	36.5 (0.37) [36.2–37.0]	36.4 (0.38) [36.2–37.0]
Haemoglobin; $g.dl^{-1}$	14.7 (1.5) [12.5–16.8]	14.9 (1.5) [13.1–16.5]

Scientific and Technical Publishers, Shanghai, People's Republic of China). The Chi-squared test was used to compare sex distribution between the two groups. Analysis of covariance was used to compare the dose–response data of the two groups. Other statistical analyses were made with Student's *t*-test. Data are expressed as mean (SD). A probability value of <0.05 was considered to be significant.

Results

The two groups of patients were comparable with respect to the demographic data (Table 1). All patients had stable haemodynamic parameters and were normothermic throughout the study. The mean end-tidal concentration of sevoflurane in the sevoflurane group during the study period was 1.75 (0.02)%.

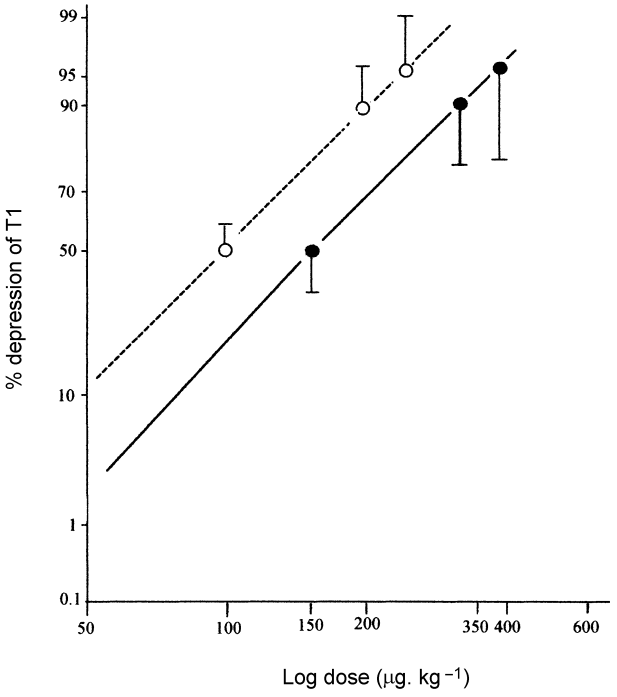

Figure 1 Log dose–response curves for rocuronium in the two groups. Error bars indicate 1 SD. Control group (—); sevoflurane group (– – –).

Table 2 Dose–response data for rocuronium. Values are given as mean (SD).

	Control group ($n=30$)	Sevoflurane group ($n=30$)
ED_{50}; $\mu g.kg^{-1}$	153.11 (48.55)	106.39 (36.25)*
ED_{90}; $\mu g.kg^{-1}$	297.15 (116.02)	217.91 (63.28)*
ED_{95}; $\mu g.kg^{-1}$	361.17 (152.82)	270.18 (81.81)*
Slope; probit/log	5.07 (1.61)	4.33 (1.32)

* $p<0.01$ compared with Control group.

The times from the administration of the initial dose of rocuronium to the administration of the first, second and third dose increments were 2.5 (0.5), 4.6 (1.3) and 8.2 (2.8) min, respectively, in the control group and 2.2 (0.3), 4.4 (1.1) and 8.0 (2.1) min in the sevoflurane group. These values did not differ significantly between the two groups. During sevoflurane anaesthesia, the cumulative dose–response curve of rocuronium was shifted to the left (Fig. 1), indicating potentiation of rocuronium-induced neuromuscular block. There were significant differences in ED_{50}, ED_{90} and ED_{95} between the two groups. The slope of the dose–response curve of rocuronium for the sevoflurane group was not significantly different compared to the control group (Table 2).

Twenty-six patients in the control group and all patients in the sevoflurane group had 100% depression of T1 following an intravenous administration of a total dose of rocuronium 400 $\mu g.kg^{-1}$. Rocuronium-induced neuromuscular block was significantly prolonged by sevoflurane. There were significant differences in the duration of peak effect, clinical duration, recovery index and the total block duration between the control and the sevoflurane groups (Table 3).

Table 3 Pharmacodynamic data for patients with 100% neuromuscular block following the administration of rocuronium 400 $\mu g.kg^{-1}$. Values are given as mean (SD).

	Control group ($n=30$)	Sevoflurane group ($n=30$)
Duration of peak effect; min	9.00 (3.44)	20.15 (9.14)*
Clinical duration; min	14.90 (5.80)	31.31 (13.88)*
Recovery index; min	13.60 (5.76)	25.44 (12.96)*
Total duration; min	38.3 (11.10)	69.16 (25.65)*

* $p<0.01$ compared with Control group. Duration of peak effect = time from injection of rocuronium to recovery of T1 response to 5% of control. Clinical duration = time from injection to 25% recovery of T1. Total duration = time from injection to 90% recovery of T1. Recovery index = time from 25 to 75% recovery of T1.

Discussion

The goal of this study was to determine the influence of the new volatile anaesthetic sevoflurane on the dose–response relationship and on the pharmacodynamics of rocuronium. In the population studied, the MAC of sevoflurane in 100% oxygen was taken to be 1.71% [18]. Therefore, the mean concentration of sevoflurane in our study was calculated to be 1 MAC, omitting the MAC contribution of nitrous oxide (60%) and 1.6 MAC including the MAC contribution of 60% nitrous oxide. Our results show that sevoflurane significantly potentiates and prolongs rocuronium-induced neuromuscular block. Compared to the control group, the ED_{50}, ED_{90} and ED_{95} of rocuronium in the sevoflurane group were decreased by 30.5%, 26.7% and 25.2%, respectively, and the duration of peak effect, clinical duration, recovery index and total duration after administration of a total dose of 400 $\mu g.kg^{-1}$ were prolonged by 123.9%, 109.5%, 87.1% and 80.6%, respectively.

The incremental cumulative dose technique was used to evaluate the dose–response relationship of rocuronium in the current study. Some investigators have found that the cumulative dose technique may underestimate the potency of neuromuscular blocking agents with rapid distribution and elimination [19–22]. However, administration of rocuronium was consistent throughout the study and the patients were chosen randomly, thus the degree of redistribution would have been similar in the two groups of patients. To improve the accuracy of the cumulative dose–response technique for rocuronium, we also restricted ourselves to the use of three cumulative doses. Additionally, the aim of this study was to determine the effect of sevoflurane on the neuromuscular block produced by rocuronium and not to provide an absolute potency estimate. To allow for the slow penetration of the inhaled anaesthetics into the muscle compartment during anaesthesia [23, 24], rocuronium was administered 30–45 min after the start of sevoflurane administration in our study, allowing time for muscle tissue to equilibrate with the partial pressure of sevoflurane in the alveoli and blood.

The measured potency of rocuronium (ED_{50} and ED_{90}) in different studies varies considerably because of differences in the mode of stimulation employed (single twitch or TOF), the method of constructing the dose–response curves (single or cumulative dose), patient selection and the type of anaesthesia. The average ED_{50} and ED_{90} from previous studies are around 200 $\mu g.kg^{-1}$ (range: 125–220 $\mu g.kg^{-1}$) and 300 $\mu g.kg^{-1}$ (range: 230–419 $\mu g.kg^{-1}$), respectively, when combined with a balanced anaesthetic technique (nitrous oxide/opioid) that did not include the use of volatile anaesthetic agents [1–5]. The mean ED_{50} and ED_{90} of the control group in our study were 151.78 $\mu g.kg^{-1}$ and 297.15 $\mu g.kg^{-1}$, which is comparable to previously published data. One study found that the clinical duration and recovery index of rocuronium 600 $\mu g.kg^{-1}$ during balanced anaesthesia were 24–40 min and 8–17 min, respectively, being similar to those of atracurium and vecuronium using equipotent doses [2]. The clinical duration found in the present study was shorter because of the smaller dose of rocuronium used (400 $\mu g.kg^{-1}$).

In other studies of the interaction of volatile anaesthetics with rocuronium, the potentiating effects of isoflurane, enflurane and halothane were investigated [1–4, 25]. These studies yielded data that showed wide variation in the extent of potentiation. In cats anaesthetised with intraperitoneal chloralose, halothane and enflurane statistically significantly shifted the dose–response curves for rocuronium to the left and a small increase in the time from maximum block to 90% recovery was seen. The ED_{50} of rocuronium was decreased by 27% under halothane and enflurane anaesthesia [8]. In one of the studies of the use of rocuronium in humans [10], the dose–response curves were found to be different when propofol/alfentanil, halothane, enflurane and isoflurane anaesthesia were compared. Compared to the propofol/alfentanil group, the ED_{50} and ED_{90} of rocuronium were decreased by 20.4% and 16.7%, respectively, in the halothane group, by 29.3% and 33.0% in the enflurane group, and by 58.7% and 26.7% in the isoflurane group. The clinical duration of rocuronium following administration of the total dose of 500 $\mu g.kg^{-1}$ was prolonged by 42.9% in the halothane group, 87.7% in the enflurane group and 78.9% in the isoflurane group when compared with the propofol/alfentanil group.

Various studies in the past have shown that, at equal MAC values, isoflurane and sevoflurane potentiate the neuromuscular blocking potency and increase the duration of action of vecuronium to an approximately similar degree [26, 27]. The degree of potentiation by sevoflurane of the dose–response relationship of rocuronium in our study appeared to be similar to that of enflurane and isoflurane in the above study [10] at 1 MAC but to be greater than that of halothane. However, the prolonging effect of sevoflurane on the duration of action of rocuronium in our study was greater than that of enflurane, isoflurane and halothane in spite of total doses of rocuronium of 500, 600 and 900 $\mu g.kg^{-1}$ [2, 10] being administered in the interaction studies with other volatile anaesthetics. This effect may be related to methodological differences in our study, since in the previous studies the exposure time to the inhalational agents was $\approx$ 5–7 min. After this short exposure, alveolar concentrations of the anaesthetic agents usually approximate to only a fraction of the inspired concentration. Thus, during long-lasting

procedures more significant potentiation may occur. This is best illustrated by the difference in rocuronium dose requirements when administered by continuous infusion aiming to maintain a stable (90%) twitch height depression. The infusion rate of rocuronium for the maintenance of neuromuscular block at this degree of twitch depression was 9.8 (3.7) $\mu g.kg^{-1}.min^{-1}$ with intravenous anaesthesia and was found to be 40% lower during enflurane (5.9 (3.1) $\mu g.kg^{-1}.min^{-1}$) and isoflurane (6.1 (2.7) $\mu g.kg^{-1}.min^{-1}$) [11] anaesthesia.

In contrast to the results of our study and others [8–11], Lambalk *et al.* [24] did not demonstrate that the degree of rocuronium-induced neuromuscular block was significantly different between droperidol/fentanyl, propofol/fentanyl, halothane, enflurane and isoflurane anaesthesia. The onset time, clinical duration and recovery index of rocuronium were also similar in the five experimental groups. This finding is not surprising since, besides the short exposure time to inhalational agents, the total dose of rocuronium (300 $\mu g.kg^{-1}$) was less than in our study and another [10] with resulting clinical durations ranging between 8 and 13 min, which is too short a time to demonstrate significant potentiation of the rocuronium-induced neuromuscular block by volatile anaesthetic agents. A tendency towards a longer duration of action of rocuronium in the enflurane and isoflurane groups could be deduced from the duration of the maintenance doses but the extent of prolongation in the isoflurane and enflurane groups as compared with the other groups did not reach statistical significance. This might be also related to the wide range in individual response within the different groups and the small number of patients in each group.

In conclusion, the neuromuscular blocking potency and pharmacodynamic profile of rocuronium are significantly altered during sevoflurane anaesthesia. There is a decrease in the effective dose required to produce comparable neuromuscular block, a prolongation in the duration of action and an increase in the recovery time.

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