

# Rocuronium potency and recovery characteristics during steady-state desflurane, sevoflurane, isoflurane or propofol anaesthesia†

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We have studied the potency and recovery characteristics of rocuronium during 1.25 MAC of isoflurane, desflurane, sevoflurane or propofol anaesthesia in 84 patients using electromyography. Potency was determined by a cumulative bolus technique. The mean ED<sub>50</sub> of rocuronium was 169 (SD 41), 126 (32), 121 (28) and 136 (25) µg kg<sup>-1</sup> during propofol, isoflurane, sevoflurane and desflurane anaesthesia, respectively (ns), and ED<sub>90</sub> values were 358 (62), 288 (29), 289 (28) and 250 (28) µg kg<sup>-1</sup>, respectively. The reduction in ED<sub>90</sub> was statistically significant for all three inhalation anaesthetics ( $P < 0.05$ ) compared with propofol. After 120 min, the cumulative infusion rate of rocuronium to obtain twitch depression of 90–95% was 9.0 (1.9), 6.3 (1.6), 6.1 (2.0) and 6.1 (1.1) µg kg<sup>-1</sup> min<sup>-1</sup> during propofol, isoflurane, sevoflurane and desflurane anaesthesia, respectively ( $P < 0.01$ ). Recovery index was 22 (13), 27 (10), 28 (13) and 26 (14) min under propofol, isoflurane, sevoflurane and desflurane anaesthesia, respectively (ns). There were no significant differences between the three potent inhalation anaesthetics in relation to potency, infusion requirements or recovery characteristics of rocuronium.

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Potent inhalation anaesthetics are known to potentiate the neuromuscular blocking effects of benzylisoquinoline<sup>1–3</sup> and aminosteroid<sup>4–11</sup> neuromuscular blocking agents. Halothane,<sup>6</sup> enflurane<sup>5 6</sup> and isoflurane<sup>5 7 8</sup> and the new agents desflurane<sup>8 11</sup> and sevoflurane<sup>9–11</sup> have been shown to enhance the neuromuscular blocking potency of rocuronium, a newer aminosteroid neuromuscular blocking drug. To our knowledge, only one study has compared the interactions of isoflurane, desflurane and sevoflurane with a single dose of rocuronium.<sup>11</sup> A comparative study of the interactions of the new inhalation anaesthetics and rocuronium after continuous infusion or repeated doses of the neuromuscular blocking drug is lacking. Thus the influence of various anaesthetics on the neuromuscular effects of rocuronium during and after prolonged anaesthesia is not clear. Furthermore, to quantify the enhancement of the neuromuscular block produced by potent inhalation anaesthetics, it is important to start the investigation after adequate time has elapsed for inhalation anaesthetics to diffuse into the muscular compartment.<sup>12</sup>

Hence we have compared the influence of propofol, isoflurane, desflurane and sevoflurane on the potency of rocuronium during steady-state conditions after a 40-min

equilibration period of the inhalation anaesthetic. In addition, the infusion rate of neuromuscular blocking drug required to maintain constant block and recovery characteristics were analysed.

## Patients and methods

After obtaining approval from the Local Ethics Committee and written informed consent, we studied 84 patients undergoing major surgery (Table 1). This prospective, randomized study was performed in close accordance to the recommendations of 'good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents'.<sup>13</sup> Exclusion criteria were: body weight more or less than 20% of ideal; patients younger than 18 yr; expected difficult intubation; pre-existing hepatic, renal or neuromuscular disease; allergic diathesis; pregnancy or breastfeeding; and preoperative medications known to

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**Table 1** Patient characteristics (mean (range) or number). No significant differences between groups

	Propofol	Isoflurane	Desflurane	Sevoflurane
<i>n</i>	21	21	21	21
Age (yr)	49.8 (21–78)	60.3 (23–81)	59.6 (37–74)	50.8 (23–77)
Sex (M/F)	7/14	11/10	11/10	9/12
Height (cm)	170 (154–181)	170 (153–199)	168 (156–181)	167 (153–181)
Weight (kg)	73.8 (49–100)	74.4 (47–105)	69.9 (42–97)	68.2 (40–100)
Duration of operation (min)	261 (160–400)	287 (200–420)	292 (135–450)	267 (170–450)
Age-adjusted 1.25 MAC of inhalation anaesthetic in N <sub>2</sub> O (%)		0.6 (0.3–0.9)	2.8 (2.2–4.0)	1.0 (0.6–1.5)
Surgical procedure				
Major colonic resection	15	16	19	16
Upper abdominal surgery	1	0	0	1
Major urological surgery	5	5	1	3
Peripheral surgery	1	0	0	1

interact with non-depolarizing neuromuscular blocking drugs.

### Study design

After oral premedication with midazolam 7.5 mg, anaesthesia was induced with fentanyl 3–7 µg kg<sup>-1</sup> and propofol 2–3 mg kg<sup>-1</sup>. Tracheal intubation was performed under local anaesthesia without the aid of neuromuscular blocking agents and anaesthesia was maintained according to a computer-generated randomization scheme with propofol 4–6 mg kg<sup>-1</sup> h<sup>-1</sup>, isoflurane, desflurane or sevoflurane (1.25 MAC of end-tidal concentration in each instance, age-adjusted) supplemented with 60% nitrous oxide in oxygen. After tracheal intubation, mechanical ventilation of the lungs was started and a neuromuscular monitor (Relaxograph; Datex, Helsinki, Finland) attached to the patient's right arm.

### Neuromuscular monitoring

The arm used for neuromuscular monitoring was fixed to an arm board. The ulnar nerve was stimulated transcutaneously at the wrist via reference electrodes. Supramaximal stimuli of 0.2 ms duration in a single twitch mode at 0.1 Hz were used for potency estimation and thereafter in a TOF mode at 2 Hz every 15 s until the end of the study. The resultant force of contraction of the adductor pollicis muscle was quantified using electromyography (Relaxograph). Recovery variables were calculated using TOF ratios given on the Relaxograph readout. (This prevented discrepancies arising if the Relaxograph trace did not recover to control.)

After calibration of the Relaxograph, end-tidal  $P_{CO_2}$  was adjusted to 4.3–4.7 kPa (measured by Cicero, Draegerwerke, Lubeck, Germany). Core temperature and skin temperature over the thenar muscle were monitored and maintained at greater than 36.0°C and 32.0°C, respectively, by forced-air warming. Arterial pressure was recorded on the arm that was not used for evaluation of neuromuscular transmission. Fluids were given via a central venous line or an i.v. cannula inserted proximal to the area of nerve stimulation. Hypotension was treated with lactated Ringer's solution

and small doses of vasopressor agents. During operation, fentanyl or propofol was given to maintain an adequate level of anaesthesia. Forty minutes after a 1.25 MAC end-tidal concentration of inhalation anaesthetic was reached, the Relaxograph was re-calibrated and rocuronium 0.1, 0.15 or 0.2 mg kg<sup>-1</sup> was administered via the central venous line, which was not used for other medications to avoid precipitation. Maximal depression of the twitch response was recorded to calculate the dose–response curve for rocuronium. Having recorded maximal depression under stable conditions, a supplementary bolus dose of rocuronium was given so that all patients received a cumulative dose of rocuronium 0.3 mg kg<sup>-1</sup>. After spontaneous recovery of the first response to 5%, a continuous infusion of rocuronium was started to maintain 90–95% neuromuscular block. The infusion rate of rocuronium needed to produce 90% continuous twitch depression was noted after 30, 60, 90 and 120 min. After cessation of the infusion, the time interval to spontaneous recovery to a TOF ratio of 0.7 was recorded.

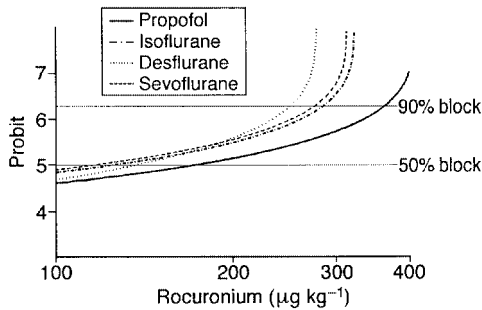
### Calculations and statistical analysis

The following variables were calculated: maximum block after the initial and supplementary dose of rocuronium (defined as maximal depression of the twitch response); time from the end of infusion to spontaneous recovery to a TOF ratio of 0.25; and time from the end of infusion to spontaneous recovery to a TOF ratio of 0.7. Recovery index was defined as the time to spontaneous recovery from a TOF ratio of 0.25 to a TOF ratio of 0.7. This was done according to clinical practice in our institution instead of TOF=0.8.<sup>13</sup> The dose–response relationship (mg kg<sup>-1</sup>) was determined by least squares linear regression of the logarithm of each dose against a probit transformation of the initial dose and response of each patient. The effective doses to obtain 50% and 90% neuromuscular block (ED<sub>50</sub> and ED<sub>90</sub>, respectively) were calculated from individual dose–response curves.

Fisher's exact test, one-way ANOVA, two-tailed *t* test with Bonferroni's correction, chi-square test and two-way ANOVA were used, where appropriate, to perform statistical

**Table 2** ED<sub>50</sub>, ED<sub>90</sub>, cumulative infusion rate of rocuronium to maintain 90–95% block and recovery index (from TOF ratio 0.25 to 0.7) during various anaesthetic regimens. \* $P < 0.05$ , \*\* $P < 0.01$  between propofol and inhalation anaesthesia groups

	Propofol	Isoflurane	Desflurane	Sevoflurane
ED <sub>50</sub> ( $\mu\text{g kg}^{-1}$ )	169 (41)	126 (32)	136 (25)	121 (28)
ED <sub>90</sub> ( $\mu\text{g kg}^{-1}$ )	358 (62)*	288 (29)	250 (28)	289 (28)
Infusion rate at 120 min ( $\mu\text{g kg}^{-1} \text{min}^{-1}$ )	9.0 (1.9)**	6.3 (1.6)	6.1 (1.1)	6.1 (2.0)
Recovery index (min)	22 (13)	27 (10)	26 (14)	28 (13)

**Fig 1** Dose–response curves for rocuronium during propofol, isoflurane, desflurane, sevoflurane and propofol anaesthesia. During inhalation anaesthesia, the dose–response relationship was shifted to the left compared with propofol.

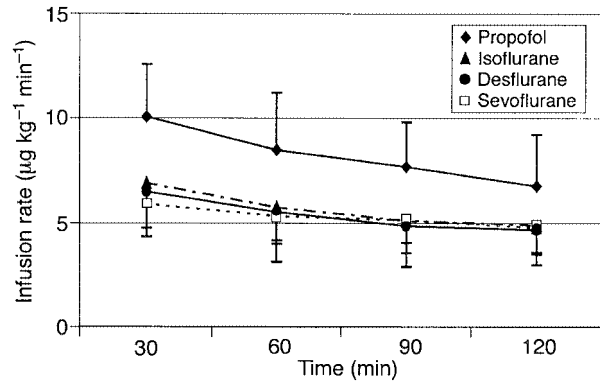
analyses of physical characteristics and pharmacodynamic data. Data are given as mean (SD or range).

## Results

Patient characteristics, type and duration of surgery, and end-tidal concentrations of the inhalation anaesthetic are given in Table 1. There were no significant differences between groups. During the study, an end-tidal concentration of 1.25 MAC of the inhalation anaesthetic was maintained in all patients.

The mean ED<sub>50</sub> of rocuronium was 169 (SD 41)  $\mu\text{g kg}^{-1}$  during propofol, 126 (32)  $\mu\text{g kg}^{-1}$  during isoflurane, 121 (28)  $\mu\text{g kg}^{-1}$  during sevoflurane and 136 (25)  $\mu\text{g kg}^{-1}$  during desflurane anaesthesia (Table 2). The reduction in ED<sub>50</sub> of rocuronium by the inhalation anaesthetics was not statistically significant. In contrast, the ED<sub>90</sub> of rocuronium was 358 (62)  $\mu\text{g kg}^{-1}$  under propofol, 288 (29)  $\mu\text{g kg}^{-1}$  under isoflurane, 289 (28)  $\mu\text{g kg}^{-1}$  under sevoflurane and 250 (28)  $\mu\text{g kg}^{-1}$  under desflurane anaesthesia (Table 2). This reduction was statistically significant for all inhalation anaesthetics compared with propofol anaesthesia ( $P < 0.05$ ). There were no significant differences between the potency of the inhalation anaesthetics. The groups receiving potent inhalation anaesthetics showed comparable slopes of the dose–response curves, and the curves were shifted to the left (Fig. 1).

After 120 min, the cumulative infusion rate of rocuronium to obtain twitch depression of 90–95% was 9.0 (1.9)  $\mu\text{g kg}^{-1} \text{min}^{-1}$  during propofol, 6.3 (1.6)  $\mu\text{g kg}^{-1} \text{min}^{-1}$  during isoflurane, 6.1 (1.1)  $\mu\text{g kg}^{-1} \text{min}^{-1}$  during desflurane and 6.1 (2.0)  $\mu\text{g kg}^{-1} \text{min}^{-1}$  during sevoflurane anaesthesia (see Table 2). During propofol anaesthesia, the cumulative

**Fig 2** Mean (SD) infusion rate of rocuronium required to maintain 90–95% neuromuscular block. Significant difference ( $P < 0.01$ ) between propofol anaesthesia compared with each inhalation anaesthetic.

infusion rate was significantly greater compared with the inhalation anaesthetics ( $P < 0.01$ ). There were no significant differences between the potent inhalation anaesthetics. Figure 2 shows the infusion rates of rocuronium required to maintain 90–95% block at 30, 60, 90 and 120 min. Patients receiving potent inhalation anaesthetics had lower requirements for rocuronium compared with those receiving propofol ( $P < 0.01$ ). There were no significant differences between the inhalation anaesthetics. In all groups, the infusion rates were reduced to avoid accumulation of the neuromuscular blocking agent. Recovery index was 22 (13) min under propofol, 27 (10) min under isoflurane, 28 (13) min under sevoflurane and 26 (14) min under desflurane anaesthesia (Table 2). There were no significant differences between groups. Inter-individual variability of the neuromuscular response was lowest among patients receiving isoflurane anaesthesia.

## Discussion

During steady state conditions, we found that there was a marked interaction between the neuromuscular blocking effects of rocuronium and isoflurane, desflurane and sevoflurane, resulting in a leftward shift of the dose–response curve (Fig. 1). To maintain 90–95% neuromuscular block, the infusion rate of rocuronium was reduced by 30–40% during isoflurane, desflurane and sevoflurane anaesthesia compared with propofol.

After the age-adjusted end-tidal concentration of the inhalation anaesthetic was reached, another period of 40 min was allowed to elapse before the first dose of rocuronium was given. As tracheal intubation is usually performed after

only a short period of anaesthesia, it may be of theoretical importance to wait for equilibration of the muscular compartment with the inhalation agent before estimating the dose–response relationship. However, the duration of action of a neuromuscular blocking drug and the amount needed for maintenance during long operations are affected by the type and duration of anaesthesia. Particularly for determination of infusion rate, it is important to study the interactions between neuromuscular blocking drugs and anaesthetics at pre-set stable concentrations of inhalation agent.<sup>12</sup> It is generally accepted that 40 min is sufficient for equilibration of the muscular compartment with volatile anaesthetics which have a high blood-gas coefficient.<sup>12</sup> In clinical practice, intermediate-acting neuromuscular blocking agents are often given repeatedly and not as a single bolus. In our opinion, it is also important to estimate the recovery variables of these drugs after complete equilibration of the muscular compartment with the potent inhalation anaesthetic has been allowed to occur. This opinion has been confirmed by two reports on recovery from aminosteroid neuromuscular blocking drugs: in one, time to 25% recovery after a single dose of vecuronium was prolonged when the dose was given 60 or 120 min after the beginning of anaesthesia with sevoflurane.<sup>14</sup> In contrast, a 30-min period of stabilization did not prolong the time to 25% recovery. In the second study, after rocuronium 0.6 mg kg<sup>-1</sup>, recovery indices were prolonged when 0.8 MAC of isoflurane, desflurane or sevoflurane was administered compared with 0.4 MAC.<sup>15</sup>

Compared with previous studies,<sup>6–11</sup> we found no clinically important differences between the ED<sub>50</sub> and ED<sub>90</sub> of rocuronium under various inhalation anaesthetics. In all studies, the potency of rocuronium was found to be increased by 25–40% under inhalation anaesthesia compared with propofol. The amount of potentiation of the neuromuscular blocking effect of rocuronium seems to be inversely related to the MAC of each anaesthetic. This effect has been demonstrated for the older inhalation anaesthetics halothane, enflurane and isoflurane.<sup>12</sup> For isoflurane, desflurane and sevoflurane, our results are in accordance with Wulf and co-workers.<sup>11</sup> Other groups, however, found lower values for the ED<sub>50</sub>, but not for the ED<sub>95</sub>, of rocuronium under isoflurane than under desflurane anaesthesia.<sup>8</sup> Thus the amount of potentiation of the neuromuscular blocking effect of rocuronium under desflurane anaesthesia remains somewhat unclear as does the degree of potentiation of vecuronium under desflurane anaesthesia. Desflurane or isoflurane 1 MAC was shown to have similar effects on the potency of vecuronium.<sup>16</sup> In contrast, others observed greater potentiation of the neuromuscular effects of vecuronium under desflurane than under isoflurane anaesthesia.<sup>17</sup> Halothane, enflurane and isoflurane were shown to augment the neuromuscular block of vecuronium, and an inverse relation to their analgesic and hypnotic potency was observed.<sup>4</sup> After a wash-in period of 40 min, the potencies of vecuronium, pancuronium and atracurium were augmented by isoflurane and sevoflurane to the same degree.<sup>18</sup>

In clinical practice, the influence of the potent inhalation anaesthetics on the infusion rate at which complete neuromuscular block is obtained is important. Our results are in agreement with Shanks, Fragen and Ling,<sup>5</sup> who compared the infusion rate of rocuronium under balanced, enflurane and isoflurane anaesthesia. Under inhalation anaesthesia, the infusion rate was reduced by 40%. As in our study, the choice of inhalation anaesthetic had no effect on the total dose of rocuronium required to maintain constant neuromuscular block. In another study, isoflurane reduced the infusion requirements of rocuronium by 35–40% compared with various i.v. anaesthetics.<sup>7</sup> The infusion rates of vecuronium also have to be reduced when inhalation anaesthetics are used for maintenance of anaesthesia.<sup>19</sup>

The time to spontaneous recovery from a TOF ratio of 0.25 to 0.7 was only slightly, but not significantly, affected by the presence of potent inhalation anaesthetics in our study. Provided that the infusion rate of rocuronium is adjusted to produce 90% block, the time to complete recovery during desflurane, sevoflurane and isoflurane anaesthesia is only slightly prolonged. Compared with isoflurane anaesthesia, the recovery variables were also slightly, but not significantly, prolonged during desflurane anaesthesia in another study in which a single dose of rocuronium 0.6 mg kg<sup>-1</sup> was given.<sup>8</sup> In a recent study, the recovery index after a single dose of rocuronium was prolonged during sevoflurane anaesthesia compared with isoflurane or propofol anaesthesia.<sup>10</sup> This may be a result in part of lack of equilibration of the muscle compartment as only 10 min of anaesthesia had been allowed to pass before the neuromuscular blocking agent was given. On the other hand, inter-individual variability was found to be much higher during sevoflurane anaesthesia in that study. In contrast, pancuronium, vecuronium and atracurium showed comparable prolongation of recovery after sevoflurane and isoflurane.<sup>18</sup> After continuous infusion of rocuronium for 120 min, recovery also tended to be prolonged when anaesthesia with enflurane or isoflurane was compared with barbiturate–nitrous oxide–opioid anaesthesia.<sup>5</sup> In another study, the recovery index after neuromuscular block produced by cisatracurium was prolonged during desflurane and sevoflurane anaesthesia compared with propofol or isoflurane anaesthesia.<sup>3</sup> Thus recovery during inhalation anaesthesia may be related inversely to analgesic and hypnotic potency, or to blood solubility. This hypothesis, however, needs to be proved in further studies.

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