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Influence of acute normovolaemic haemodilution on the relation between the dose and response of rocuronium bromide

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Summary

The influence of acute moderate haemodilution on the relation between dose and response for rocuronium was evaluated in 60 adult patients, ASA grade I, undergoing elective plastic surgery. The patients were randomly allocated to either the control or the haemodilution group. Following the induction of general anaesthesia, the status of acute moderate haemodilution in the haemodilution group was achieved by draining venous blood, and intravenous infusion of lactated Ringer's solution, 6% dextran or gelofusine, during which the levels of haemoatocrit and haemoglobin dropped from 44% to 27.5% and from 148.3 to 91.3 g L^{-1}, respectively. Neuromuscular function was assessed mechanomyographically with train-of-four stimulation at the wrist every 12 s and the percentage depression of T_1 response was used as the study parameter. The relation between dose and response for rocuronium in the two groups was determined by the cumulative dose–response technique. The results showed that the dose–response curve for rocuronium during acute moderate haemodilution was shifted in a parallel fashion to the left and the potency of rocuronium was increased. There were significant differences in ED_{50}, ED_{90} and ED_{95} between the two groups. The ED_{50}, ED_{90} and ED_{95} of rocuronium in the haemodilution group was decreased by 28.2%, 35.4% and 38.8%, respectively, compared with the control group.

Keywords: NEUROMUSCULAR RELAXANTS, rocuronium; DOSE–RESPONSE RELATION, haemodilution, humans.

Introduction

Rocuronium bromide is a new non-depolarizing muscle relaxant that has a monoquaternary aminosteroid molecular structure similar to that of vecuronium bromide. Its main advantage compared with other currently available relaxants is its shorter time of onset. Other time course characteristics are similar to vecuronium. Further advantages are the lack of side-effects, such as histamine release, and its low interaction with cardiac muscarinic receptors [1,2]. Factors possibly influencing the pharmacokinetics and pharmacodynamics of rocuronium, such as age, inhalational anaesthetic agents [3], hepatic [4], and renal [5] insufficency, hypothermia [6], and obesity [7], have been studied extensively. Pre-operative normovolaemic haemodilution is an effective method for reducing homologous blood transfusion during surgery, and is often associated with changes in haemodynamics and blood chemistry. Attention has been drawn to the possibility that haemodilution might affect the action of drugs administered during anaesthesia [8]. Previous studies had shown that the potency of suxamethonium, pancuronium and tubocurarine was increased, and the duration of action was prolonged following pre-operative normovolaemic haemodilution [9,10]. However, there is no reference dealing with the relation between dose and response for rocuronium during acute haemodilution in adult patients. It was the purpose of this study to determine the effect of acute normovolaemic haemodilution on the relation between dose and response for rocuronium in healthy adult patients under N_2O-O_2-opioid anaesthesia.

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Material and methods

After institutional ethics committee approval and written informed consent, 60 adult patients, ASA grade I, of both sexes (17–52 years of age and 46–86 kg body weight) who were scheduled for elective plastic surgery were included in this study. The function of heart, lungs, liver and kidney was normal in all patients. Patients with neuromuscular disease and with recent exposure to medications known to interfere with neuromuscular transmission were excluded. Those with anaemia (i.e. haemoglobin concentration <120 g L^{-1}) were also excluded.

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} intramuscularly 1 h prior to anaesthesia. On arrival in the operating room, an intravenous (i.v.) catheter was inserted, and general anaesthesia was induced with i.v. thiopentone 4–6 mg kg^{-1} and fentanyl 2–4 μg kg^{-1}. After topical anaesthesia with 2% lignocaine, the trachea was intubated without the aid of a muscle relaxant, and general anaesthesia was maintained with N_2O:O_2 3:2 (total flow of 5 L min^{-1}), and further increments of thiopentone 2 mg kg^{-1} or fentanyl 2 μg kg^{-1}, as required. No volatile anaesthetic agents were used. The lungs were ventilated (V_T = 8–10 mL kg^{-1}, RR = 8–10 min^{-1}) during surgery and $P_{ET}CO_2$ was kept in the 4–5 kPa range.

After stable anaesthesia was achieved, patients were randomly allocated, via a computer-generated random numbers list, to either the control or the haemodilution group. In the haemodilution group, 12–15 mL kg^{-1} blood was withdrawn from the cubital vein and stored in a reservoir bag containing ACD solution before the start of surgery. At the same time, Ringer's lactate solution, gelofusine (molecular mass 30000 kDa) and 6% medium molecular dextran (molecular mass 70000 kDa) were rapidly infused through a separate venous catheter until the haematocrit (Hct) had dropped to 25–30%. The patients in the control group received only Ringer's lactate solution (10–12 mL kg^{-1} h^{-1}). Haemodynamic variables remained stable throughout surgery in all patients.

During surgery, ECG, blood pressure, heart rate, temperature and SpO_2 were monitored continuously with a patient monitor (Cardiocap, Datex Instrumentarium, Helsinki, Finland). Inspired and end-tidal concentrations of oxygen, carbon dioxide, and nitrous oxide were measured and displayed digitally with an anaesthetic gas monitor (Anaesthesia Gas Monitor Type 1304, Bruel & Kjaer, Gentofte, Denmark). A cannula was placed in the radial or femoral artery for sampling. Arterial pH, PaO_2, $PaCO_2$, Hct, haemoglobin, K^+, Na^+, Cl^- and ionized calcium which were determined with a Model-5 blood-gas-electrolyte analyser (Nova Biomedical Company, Hoboken, New Jersey, USA) before and during surgery (when rocuronium was administered). Total plasma protein (TPP) and albumin (Alb) were also measured with an automatic biochemical analyser Type-550 (Corning Medical Company, Oberlin, Ohio, USA). Skin temperature over the thenar muscles was maintained above 32°C throughout the study period by wrapping the arm in cotton.

Neuromuscular function was assessed 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 MK, 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 immobilized in supination and abduction on a splint, and the fingers were strapped in extension. Evoked muscle contraction of the *adductor pollicis brevis* was quantified isometrically by a force displacement transducer, and amplified and recorded continuously on a polygraph (Gould brush recorder 220, Cleveland, OH, USA). The first response (T_1) of the TOF stimulus was used as the parameter for pharmacodynamic measurements. The relation between dose and response for rocuronium in the two groups was evaluated using a cumulative dose-response technique according to Donlon and colleagues [11]. A total dose of 250 μg kg^{-1} of rocuronium was given in four doses (an initial dose of 100 μg kg^{-1} and three increments of 50 μg kg^{-1} each) and administered cumulatively. Each dose of rocuronium was injected as an i.v. bolus over <5 s into a rapidly running infusion. Ten minutes were allowed for stabilization of the response to TOF stimulation before administration of the first dose of rocuronium. The mean of 10 T_1 responses immediately preceding the first administration of rocuronium was accepted as the control with which all subsequent T_1 responses were compared. Each dose increment was given (at times T_1, T_2 and T_3, respectively) only after the effect

Table 1. Patient demographic data [means ± SD (range)]

	Control group	Haemodilution group
Gender (M/F)	16:14	15:15
Age (years)	29.23 ± 10.07 (17–52)	31.70 ± 10.82 (19–50)
Weight (kg)	59.57 ± 11.8 (46–86)	58.71 ± 9.85 (48–74)
Height (cm)	166.30 ± 9.28 (158–186)	165.91 ± 11.42 (155–179)
Duration of operation (h)	3.40 ± 1.11 (2.0–6.9)	3.61 ± 1.27 (2.6–5.9)
Temperature (°C)	36.5 ± 0.37 (36.2–37)	36.4 ± 0.38 (36.2–37)

of the previous dose had reached a stable response, defined as three equal (± 1%) consecutive T_1 responses, or when 5 min had passed with no decrease in T_1 from control. If 90% or more of twitch depression was achieved following the second incremental dose, the third incremental dose was not given.

The individual dose–response relation was examined by least squares linear regression of the logarithm of each dose against a probit transformation of the depression of T_1 response, from which the doses required for 50%, 90% and 95% T_1 depression (ED_{50}, ED_{90} and ED_{95}, respectively) were calculated. The regression lines were tested to determine if they deviated from parallelism [12]. If they did not, ED_{50}, ED_{90} and ED_{95} values were compared between the groups.

All data were stored on disk and analysed with POMS statistical software Version 2.00 (Shanghai Scientific and Technical Publishers, Shanghai, People's Republic of China). A χ^2 test was used to compare male:female distribution between the two groups. An 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 means ± SD. A value of $P < 0.05$ was considered to be significant.

Results

The two groups of patients were comparable with respect to demographic details (Table 1). All patients had stable haemodynamic performance and were normothermic throughout observation. In the haemodilution group, the levels of Hct and haemoglobin dropped from 44.04% to 27.5% and from 148.25 to 91.3 g L^{-1}, respectively. There were no significant differences between the two groups in arterial blood gas data, and in the control group with respect to Hct, haemoglobin concentration, electrolytes, TPP and Alb between, before and during surgery. However, there were significant differences with regard to Hct, haemoglobin concentration, electrolytes (except for Na^+), TPP and Alb between, before and during surgery in the haemodilution group, and between the two groups at administration of rocuronium (Table 2).

The times of administration of the first (T_1), second (T_2) and third dose (T_3) increments were 2.5 ± 0.5 min, 4.6 ± 1.3 min and 8.2 ± 2.8 min, respectively, in the control group, and 2.3 ± 0.4 min, 4.7 ± 1.4 min and 8.5 ± 3.0 min in haemodilution group. These did not differ significantly between the two groups ($P > 0.05$). During acute normovolaemic haemodilution, the cumulative dose-response curve for rocuronium was shifted to the left (Fig. 1), indicating an enhancement of rocuronium 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 for rocuronium in the haemodilution group was not significantly different from the control (Table 3).

Discussion

The incremental cumulative dose technique was used to evaluate the dose–response relation for 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 [13–16]. However, administration of rocuronium was consistent throughout the study and the patients were chosen at random; 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 the use to three cumulative doses. Additionally, the aim of this study was to determine the acute normovolaemic haemodilution-related effect on neuromuscular block with rocuronium and not to provide an absolute potency estimate.

The measured potency of rocuronium (ED_{50} and

Table 2. Arterial blood gas data, and the concentrations of haemoglobin (Hb), haematocrit (Hct), electrolytes (K^+,Na^+, $C1^-$ and ionized calcium), total plasma protein (TPP) and albumin (Alb) before and during surgery in the two groups. Values are means ± SD

	Control group		Haemodilution group	
	Before surgery	During surgery	Before surgery	During surgery
pH	7.41 ± 0.03	7.44 ± 0.04	7.41 ± 0.02	7.45 ± 0.04
$PaCO_2$ (kPa)	5.3 ± 0.2	4.5 ± 0.25*	5.2 ± 0.2*	4.5 ± 0.2
PO_2 (kPa)	12.4 ± 1.2	18.5 ± 1.3*	12.4 ± 1.3	18.8 ± 1.8*
Hb (g L^{-1})	147.2 ± 14.59	146.82 ± 13.71	148.25 ± 15.74	91.30 ± 7.28**
Hct (%)	45.21 ± 5.21	43.82 ± 6.37	44.04 ± 4.63	27.5 ± 2.28**
K^+ (mmol L^{-1})	4.01 ± 0.28	3.86 ± 0.25	3.98 ± 0.31	3.21 ± 0.29**
Na^+ (mmol L^{-1})	144.16 ± 2.57	145.29 ± 1.86	143.96 ± 2.83	144.04 ± 1.15
Cl^- (mmol L^{-1})	106.43 ± 1.83	108.32 ± 1.27	106.65 ± 2.60	115.07 ± 2.57**
Calcium† (mmol L^{-1})	1.08 ± 0.02	1.02 ± 1.27	1.07 ± 0.03	0.97 ± 0.05**
TPP (g L^{-1})	62.58 ± 9.85	61.69 ± 10.95	61.68 ± 11.04	42.18 ± 7.83**
Alb (g L^{-1})	39.15 ± 3.92	37.72 ± 4.14	38.96 ± 2.85	27.27 ± 3.61**

*P<0.01, compared with pre-operative value.
**P<0.01, compared with control group.
†Calcium = ionized calcium.

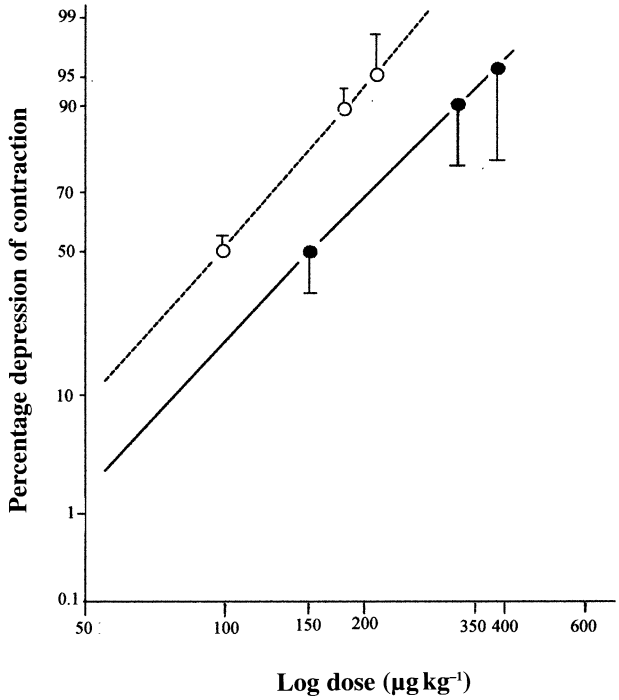

Fig. 1. Dose-response curves of rocuronium: (●—●) control group; and (○---○) haemodilution group.

Table 3. Dose-response data for rocuronium. Values are means ± SD

group	Control group	Haemodilution
ED_{50} (μg kg^{-1})	151.78 ± 47.99	108.97 ± 28.91*
ED_{90} (μg kg^{-1})	297.15 ± 116.01	192.05 ± 50.42†
ED_{95} (μg kg^{-1})	361.23 ± 132.80	221.08 ± 63.8†
Slope (probit log^{-1})	5.07 ± 1.61	6.79 ± 1.78

*P<0.05.
†P<0.01 as compared with control group.

ED_{90}) varies considerably in different studies because of differences in the mode of stimulation employed (single twitch or train-of-four), the method of constructing the dose-response curves (single or cumulative dose), patient selection, and type of anaesthesia during observation among the studies. The average ED_{50} and ED_{90} in previous studies were around 200 μg kg^{-1} (125–220 μg kg^{-1}) and 300 μg kg^{-1} (230–419 μg kg^{-1}), respectively, when combined with a balanced anaesthetic technique (N_2O-opioid), not employing volatile anaesthetic agents [1–5]. The mean ED_{50} and ED_{90} of the control group in the present study were 151.78 μg kg^{-1} and 297.15 μg kg^{-1}, which are within the results of previous studies.

The present results show that the potency of rocuronium increased as a result of haemodilution, as indicated by a parallel shift to the left of the cumulative dose–response curve. The ED_{50}, ED_{90} and ED_{95} of rocuronium in the haemodilution group were decreased

by 28.2%, 35.4% and 38.8%, respectively, when compared with the control group. This is in agreement with the findings of Schuh [9], who found that the potency of suxamethonium, pancuronium and tubocurarine increased following normovolaemic haemodilution. The ratios of $ED_{50}^{Control}$ to $ED_{50}^{Haemodilution}$ of suxamethonium, pancuronium, and tubocurarine were 2.7, 2.5 and 2.1, respectively. The increases in the potencies of suxamethonium, pancuronium and tubocurarine during acute haemodilution are greater than that of rocuronium. The exact reasons for that is unclear, but may be related to differences in the neuromuscular blocking agents with respect to pharmacological characteristics such as potency, protein binding, tissue distribution or other factors.

The increase in the potency of rocuronium following acute normovolaemic haemodilution is considered to be the result of the changes in haemodynamic performance, blood chemistry and blood electrolytes. Haemodilution decreases blood viscosity, and increases cardiac output and blood flow velocity, thus tissue blood flow is increased, particularly to skeletal muscle [8,17,18]. This may result in a more rapid initial uptake of rocuronium into the biophase for receptor interaction [9].

Chaudhry and colleagues reported that the protein-bound fraction of rocuronium was 72% [19]. The present data determined that the concentrations of TPP and Alb were decreased by 32% and 30%, respectively, following haemodilution. A decrease in plasma protein concentration must be followed by a decrease in protein binding capacity. Therefore, following administration of rocuronium, the concentration of unbound drug and the ratio of protein-unbound/bound in plasma were increased in the haemodilution group. This makes more drug available to the tissue and receptor sites during acute haemodilution.

Potassium and calcium ions play an important role in transmission at the neuromuscular junction, so that the changes in plasma concentrations of potassium and calcium ions can significantly alter responses to muscle relaxants, particularly with rapid changes in their plasma concentrations. Hypokalaemia and hypocalaemia may be associated with enhanced effects of nondepolarizing muscle relaxants [20]. In the present study, the plasma concentrations of potassium ions and ionized calcium in the haemodilution group were significantly reduced by 19.4% and 9.4%, respectively, during surgery, values which were lower than those in the control group. The decreases in plasma concentrations of potassium ions and ionized calcium following haemodilution will increase the neuromuscular blocking effect produced by rocuronium. The possible causes of the reduction in plasma potassium and ionized calcium concentrations during acute haemodilution include: potassium ions and calcium ions entering the cell because of acute stress response; the rapid infusion of a large amount of fluid not containing potassium ions and calcium ions, such as medium molecular dextran and gelofusine; and the increase in renal potassium and calcium excretion caused by the increase in urine volume following haemodilution.

In conclusion, during acute normovolaemic haemodilution the dose–response curve for rocuronium was shifted in parallel to the left: the potency of rocuronium was increased and the effective dose required to produce comparable neuromuscular block was decreased. This must be taken into account when rocuronium is used as a relaxant during acute normovolaemic haemodilution. The increase in the potency of rocuronium may be related to changes in haemodynamic responses, blood chemistry including electrolytes following acute normovolaemic haemodilution.

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