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Pharmacokinetics of rocuronium bromide in obese female patients

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Summary

Following administration of 0.6 mg kg^{-1} rocuronium, the pharmacokinetics and the pharmacodynamics were studied in six obese and six control (normal weight) patients receiving balanced anaesthesia. Twelve gynaecological patients were allocated into two groups, according to body mass index (normal weight: body mass index: 20–24, obese weight: body mass index > 28). Venous plasma concentrations were determined by high-pressure liquid chromatography before administration of rocuronium, at 1, 2, 4, 6, 8, 10, 15, 20, 25, 30, 35, 40, 48, 60, 75, 120, 180, 240, 300, 360 and 420 min after administration of rocuronium and at recovery of single twitch to 25% and 75% of control twitch height. Onset time was shorter (NS) in the obese compared with normal weight (obese weight: 65 $\pm$ 16, normal weight: 100 $\pm$ 39 s, mean $\pm$ SD). Duration 25% (obese weight: 29.5 $\pm$ 5.3, normal weight: 28.4 $\pm$ 5.3 min) and spontaneous recovery time (obese weight: 12.6 $\pm$ 2.7, normal weight: 12.5 $\pm$ 2.3 min) did not show any differences between the two groups. The pharmacokinetics of rocuronium were comparable in the two groups. The volume of distribution at steady state Vss (mL kg^{-1}) was 208 $\pm$ 56 in normal weight and 169 $\pm$ 37 in obese weight. Distribution ($T_{\frac{1}{2}}\alpha$) and elimination half-life ($T_{\frac{1}{2}}\beta$) as well as mean residence time were 15.6 $\pm$ 3.7, 70.3 $\pm$ 23.9 and 53.2 $\pm$ 9.8 min in normal weight and 16.9 $\pm$ 3.8, 75.5 $\pm$ 25.5 and 51.1 $\pm$ 18.9 min in obese weight, respectively. Also, no differences were observed in plasma clearance (3.89 $\pm$ 0.58 in normal weight and 3.62 $\pm$ 1.42 mL kg^{-1} min^{-1} obese weight). This study indicates that the pharmoacodynamics and pharmacokinetics of rocuronium are in female patients not altered by obesity.

Keywords: NEUROMUSCULAR RELAXANTS, rocuronium; PHARMACOKINETICS, obesity; COMPLICATIONS, obesity; POTENCY, obesity.

Introduction

Obesity is associated with many changes in body composition and function that may alter the pharamcodynamics and pharmacokinetics of various drugs.

Previous studies have shown prolonged duration of action and a slower recovery from vecuronium-induced neuromuscular blockade in obese surgical patients when compared with controls [1,2]. In a pharmacodynamic study using a single bolus of 0.6 mg kg^{-1} rocuronium, the duration 25% was slightly prolonged (approximately 5 min, NS) with a large individual variability, but spontaneous and induced recovery times were similar in the obese (OB) and in normal weight (NW) patients [3].

The aim of this study was to investigate the pharmacokinetic and pharmacodynamic responses in OB and NW patients after administration of 0.6 mg kg^{-1} rocuronium.

Methods

After approval by the Medical Ethics Committee of Innsbruck University, 12 ASA physical status I, II or III consenting patients scheduled for elective gynaecological surgery with an expected duration of approximately 60 minutes, were enrolled in this study. Patients known to take medication to alter neuromuscular transmission, or to have impaired liver or renal function, as well as those addicted to drugs or

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alcohol were excluded from this study. Patients were divided in two groups (six patients per group) according to their body mass index (formula: BMI = weight (kg) height^2 (m^2)). Women with a BMI between 20 and 24 were scored NW, and with a BMI of more than 28 OB. All patients were premedicated with pethidine 1 mg kg^{-1} and atropine 0.01 mg kg^{-1} intramuscularly (i.m.) approximately 1 h before the anticipated start of surgery. Anaesthesia was induced using fentanyl 3 mg kg^{-1} and propofol 2–3 mg kg^{-1} intravenously (i.v.) and maintained by controlled ventilation with 66% nitrous oxide in oxygen and a continuous infusion of propopol (4–6 mg kg^{-1} h^{-1}). The end-tidal concentration of carbon dioxide was controlled and kept between 4.7 and 5.3.

Following induction of anaesthesia, a skin patch, for measurement of skin temperature, was placed on the hand and assessment of neuromuscular transmission commenced. Recordings of the single twitch contractions of the adductor pollicis muscle were obtained by stimulating the ulnar nerve at the wrist through surface electrodes with a supramaximal square wave stimuli of 0.2 m sec duration at a frequency of 0.1 Hz. The resultant force of thumb adduction was quantified via a force displacement transducer after applying a resting tension of 200–400 g and recorded. Once a stable twitch response was obtained, after approximately 5 min, all patients were given rocuronium 0.6 mg kg^{-1} as a rapid single i.v. bolus. The time from end of injection of the neuromuscular blocking drug to maximum block (onset time) was measured. Two minutes after administration of the muscle relaxant the patients trachea was intubated. The block of all patients was allowed to recover spontaneously. The times to 25% recovery of control of twitch height (duration 25%) and between 25% and 75% recovery of control of twitch height (recovery time) were recorded. Venous blood samples (4 mL) were obtained from a dedicated cannula on the contralateral arm before administration of rocuronium, at 1, 2, 4, 6, 8, 10, 15, 20, 25, 30, 35, 40, 48, 60, 75, 120, 180, 240, 300, 360 and 420 min after administration of rocuronium. Samples were also obtained at recovery of T1 to 25% and 75%. Samples were collected in lithium-heparinized tubes and centrifugated within 4 h. Plasma was acidified with sodium dihydrogen phosphate solution 1 mol litre^{-1} (0.2 mL to every 1.0 mL plasma) and stored at –18C until analysis. Analysis of rocuronium and its putative metabolites, 17-desacetyl rocuronium and 16-N desallyl rocuronium was performed using high-pressure liquid chromatography (HPLC), with 3,17-didesacetyl vecuronium (Org 7402) as the internal standard [4]. The precision (reproducibility) of the method was 8% over the range 10–100000 ng mL^{-1} rocuronium, 7% over 10–25000 ng mL^{-1} for 17-desacetyl rocuronium and 12% over 10–25 000 ng mL^{-1} for 16-N desallyl rocuronium. The lower limits of detection were 3, 5 and 15 ng mL^{-1} rocuronium, 17-desacetyl rocuronium and 16-N desallyl rocuronium, respectively.

Table 1. Values of age, weight, height, body mass index (formula: BMI = weight (kg)·height^{-2} (m^2)), onset, duration 25% and spontaneous recovery are given as mean ± SD

	Normal weight	Obese
Age (years)	40 ± 11	47 ± 12
Weight (kg)	57 ± 2	87 ± 10
Height (cm)	161 ± 4	159 ± 5
Body Mass Index	21.92 ± 0.76	34.30 ± 4.57
Onset (s)	100 ± 39	65 ± 16
Duration 25% (min)	28.4 ± 5.3	29.5 ± 5.3
Spontaneous recovery (min)	12.8 ± 2.3	12.6 ± 2

Plasma concentration time data were analysed with the programme Multifit (JH Proost, University Centre for Pharmacy, Groningen, The Netherlands), which uses standard procedures and pharmacokinetic formulae derived from the literature [5]. The method has been used previously both for single dose and continuous infusion of neuromuscular blocking agents [6,7].

The Student's *t*-test was performed to compare pharmacodynamic and pharmacokinetic data. Results were considered significant when $P < 0.05$.

Results

Body mass index, patients weight, height and age of the two different groups are shown in Table 1. Onset time (time from end of injection to maximum effect) in the OB group was shorter when compared with the

Table 2. Main pharmacokinetic variables are presented as mean ± SD (range). Vc (mL kg^{-1}) = volume of the central compartment; Vss (mL kg^{-1}) = volume of distribution at steady state; $T_{\frac{1}{2}}\alpha$ and $T_{\frac{1}{2}}\beta$ (min): distribution and elimination half-lives; Cl (mL kg^{-1} min^{-1}) = clearance; MRT (min) = mean residence time; EC 25% and EC 75% (mg mL^{-1}) plasma concentration at T1 of 25% and 75%

	Normal weight	Obese
Vc	62.8 ± 19.7	66.1 ± 20.0
	(33.9–84.6)	(38.3–87.9)
Vss	208 ± 56	169 ± 37
	(149–271)	(100–199)
$T_{\frac{1}{2}}\alpha$	15.6 ± 3.7	16.9 ± 3.8
	(10.6–20.0)	(12.6–23.0)
$T_{\frac{1}{2}}\beta$	70.3 ± 23.9	75.5 ± 25.5
	(40.8–93.6)	(51.8–113.4)
Cl	3.89 ± 0.58	3.62 ± 1.42
	(3.02–4.56)	(1.96–5.61)
MRT	53.2 ± 9.S	51.1 ± 18.9
	(43.8–67.2)	(33.5–87.5)
EC 25%	1.73 ± 0.50	1.81 ± 0.77
	(1.37–2.46)	(0.96–2.61)
EC 75%	1.12 ± 0.39	1.20 ± 0.50
	(0.78–1.79)	(0.67–1.98)

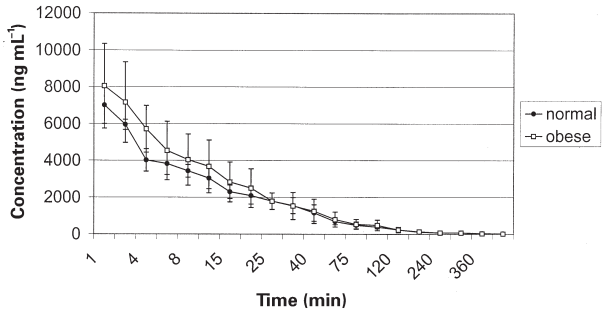

Fig. 1. Plasma concentrations of rocuronium in obese and normal weight patients.

controls (as shown in Table 2), but did not reach a level of statistical significance. All 12 patients developed 100% block. Onset, duration 25% and spontaneous recovery (Table 1) were similar in both groups. Figure 1 shows the plasma concentrations of rocuronium in the two groups. Pharmacokinetic characteristics are given in Table 2. The values did not show any statistically significant differences between the two groups. No metabolites were detected in any of the patients.

Discussion

The main finding of the present study is that the pharmacokinetics of rocuronium are not altered by obesity when compared with NW patients. Volumes of distribution, distribution and elimination half-lives, plasma clearance, and mean residence times were similar in both groups. Also, the pharmacodynamic data, onset time, duration and 25% recovery time were comparable.

For vecuronium, a chemically related aminosteroidal muscle relaxant, Weinstein *et al.* [1] reported in OB patients a prolonged recovery time (33 min), associated with a large individual variability, and a standard deviation of 15 min for recovery time. In contrast, atracurium was associated with a consistent recovery time (9.7 ± 4.1 min), little variability and a small standard deviation [1]. Schwarz and colleagues [2] observed similar pharmacodynamic data for vecuronium in the obese. They also detected elevated vecuronium plasma concentrations and unaltered pharmacokinetics in the obese, with the exception that when the values for plasma clearance and total volume of distribution of vecuronium were divided by patient body weight (a larger value for the obese) and expressed per kilogram of actual body weight a statistically significant decrease in the obese was recorded. The prolonged recovery was explained for the OB group using Fisher and Rosens pharmacokinetic and pharmacodynamic modelling [8], indicating that with larger total doses of vecuronium recovery occurs in the elimination phase, when plasma concentration decreases more slowly.

In the present study, the mean recovery time following rocuronium in the OB was similar to that in NW persons (12.6 vs. 12.8 min) with an almost identical standard deviation (2.7 vs. 2.3 min). Rocuronium was found to be as consistent in recovery time in the OB as previously only reported for atracurium [1]. In contrast with the finding of Schwarz and colleagues for vecuronium [2], our study revealed no increased plasma concentrations of rocuronium in obese patients. The pharmacokinetic parameter also, when expressed per kilogram of actual body weight, were comparable. It is conceivable that the lower fat solubility of rocuronium (compared with vecuronium) [6] could be responsible for the fact that no elevated plasma levels of rocuronium in the elimination phase

(no redistribution from fat) occurred and therefore the pharmacodynamics of rocuronium in the obese remained unaltered.

The results of the present study favourably correlate with those observed in healthy patients previously published by other investigators. Cooper *et al*. reported in patients with normal renal function during isoflurane anaesthesia [7] values of 207 mL kg^{-1}, 3.7 mL kg^{-1} min^{-1}, 97.2 min and 58.3 min; McCoy and colleagues [9] found in patients under halothane anaesthesia 212 mL kg^{-1}, 3.3 mL kg^{-1} min^{-1}, 85.6 min and 67.2 min, for steady-state volume, clearance, elimination half-life and mean residence time (MRT). In the present study, the mean values in the two different groups ranged between 169 and 208 mL kg^{-1} steady-state volume, 3.62 and 3.89 mL kg^{-1} min^{-1} clearance, 70.3 and 75.5 min elimination half-life and 51.4 and 53.2 min MRT. Also, Szenohradszky *et al*. [10] reported 207 mL kg^{-1}, 2.9 mL kg^{-1} min^{-1} and 76.9 min, respectively, for steady-state volume of distribution, rate of clearance and elimination half-life with 0.6 mL kg^{-1} rocuronium for normal patients under isoflurane anaesthesia.

The rocuronium concentrations in the present sudy were between 1620 and 18 10 ng mL^{-1} at 25% recovery of T1. These plasma concentrations are much higher than those observed by Cooper [7] and McCoy [10] for normal patients. Differences in anaesthetic technique are likely to be responsible for the lower concentrations in their patients. Cooper [7] *et al*. used isoflurane anaesthesia, which is known to potentiate rocuronium relative to opioid-based anaesthesia [11], giving a plasma concentration of only 891 ng mL^{-1} rocuronium at 25% recovery of T1. McCoy and colleagues [9] reported a plasma concentration of 1287 ng mL^{-1} rocuronium at 25% recovery of T1 under halothane anaesthesia.

In the present study, no metabolites were detected in plasma in any patient. Metabolites in plasma or urine in humans have been found to be either absent or below the level of detection after 0.6 or 1.0 mg kg^{-1} bolus dose administration [6,7].

Our results indicate that obesity does not alter the distribution or elimination of rocuronium. The data from the present study do not indicate a prolonged duration of action after a single 0.6 mL kg^{-1} dose of rocuronium in obese female patients.

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