Urinary, biliary and faecal excretion of rocuronium in humans

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The excretion of rocuronium and its potential metabolites was studied in 38 anaesthetized patients, ASA I–III and 21–69 yr old. Rocuronium bromide was administered as an i.v. bolus dose of 0.3 or 0.9 mg kg^{-1}. In Part A of the study, the excretion into urine and bile, and the liver content were studied. Plasma kinetics (n=19) were similar to those reported previously. Urinary recovery within 48 h after administration was 26 (8)% (mean (SD)) (n=8) of the dose. In bile obtained from T-drains, the recovery within 48 h was 7 (6)% (n=11). The rocuronium concentration in bile declined bi-exponentially, with half-lives of 2.3 (0.7) and 16 (11) h respectively (n=6). In three patients from whom stoma fluid was collected, the amount of rocuronium recovered ranged from 0.04 to 12.0% of the dose. In liver tissue obtained from four patients undergoing hemihepatectomy, the estimated amount of rocuronium at 2–5 h after administration ranged between 6.3 and 13.2% (n=4). In the second part of the study (Part B), urine and faeces were collected over 4–8 days and the recovery was 27 (13)% and 31 (23)% of the dose respectively (n=10). In most samples, irrespective of the type of biological material, only small amounts of the metabolite 17-desacetyl-rocuronium was found. The results demonstrate that rocuronium is taken up by the liver and excreted into bile in high concentrations. The faecal and urinary excretion of unchanged rocuronium are the major routes of rocuronium elimination.

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Rocuronium, the 2-morpholino, 3-desacetyl, 16-*N*-allyl-pyrrolidino derivative of vecuronium, is a non-depolarizing neuromuscular blocking agent with a rapid onset of action, and a duration similar to that of vecuronium. The pharmacokinetics of rocuronium have been studied extensively during the last decade, both in animals[1 2 33] and in man.[3–18] Until the present time, knowledge of the routes of elimination of rocuronium has been limited to animal data and to urinary excretion data in man.

In animals, 9–25% of radiolabelled rocuronium was found in urine, and 65–75% in faeces (unpublished observations, Organon Teknika). Rocuronium was rapidly taken up by isolated perfused rat liver with a high extraction ratio and was also rapidly excreted into the bile.[2] In addition, *in vitro* experiments with human liver tissue have shown that rocuronium and vecuronium are rapidly taken up by hepatocytes by a carrier mediated process.[19 20] In man, the mean amounts excreted into urine were 12–22% of an 0.6 mg kg^{-1} dose and 31% of a 1 mg kg^{-1} dose of rocuronium within the first 12 h after administration, the major part being excreted within the first 2 h.[3 7 8]

On the basis of its chemical structure, rocuronium is expected to be metabolized into its 17-desacetyl derivative and possibly into its *N*-desallyl derivative. In man, the rat and the dog, 17-desacetyl-rocuronium has been found in negligible amounts. To date, *N*-desallyl-rocuronium has not been detected in any experimental or clinical *in vivo* studies.

In clinical studies with vecuronium, bile samples were collected from patients where a T-drain was placed in the common bile duct in the course of surgery.[21] However, during the last decade the surgical techniques for cholecystectomy and choledocholithiasis have changed significantly and choledochostomy with placement of a T-drain is seldom performed. In addition to bile sampling from a T-drain, it

was therefore, necessary to employ other techniques to study the hepatic elimination of rocuronium and its potential metabolites such as: (i) direct sampling of bile by puncturing the common bile duct during laparoscopic surgery; (ii) collection of stoma fluid during and after surgery; (iii) taking liver tissue biopsies from patients undergoing partial hepatectomy; and (iv) collection and analysis of faeces over a postoperative period of 7 days.

On the basis of the above considerations the present study was designed in order to ascertain the fate of rocuronium in man with particular emphasis on the hepatic uptake and biliary excretion of the parent compound and its potential metabolites.

Patients and methods

The study was divided into two parts with different aims (Table 1).

Patients

Each study protocol had been approved by the Ethical Committee of the centre participating in the corresponding part of the study. In total, 38 patients (14 male, 24 female), ASA I–III and aged 21–69 (median 45) yr, weighing 51–105 (median 71) kg participated in the study after written informed consent had been obtained. Patients in Part A were scheduled for upper abdominal (including laparoscopic) or low ileostomy surgery under general anaesthesia, with either insertion of a T-drain in the common bile duct or formation of a small bowel stoma located at least 60 cm proximal to the ileocaecal valve, or patients where such a stoma was already present. Patients in Part B were scheduled for peripheral surgery and expected to remain in hospital for 7 days. Patients who were pregnant or breast-feeding, patients with a history of cardiovascular, renal, hepatic, metabolic or neuromuscular disorders, patients with a body weight more than 20% below or 35% over their ideal body weight (height in cm minus 100 equals weight in kg) and those receiving any medication interfering with neuromuscular function or with the HPLC analysis were excluded.

Anaesthesia

Following pre-oxygenation for 2 min, patients underwent either a rapid sequence induction or a routine induction of anaesthesia with sodium thiopental 3–5 mg kg^{-1} and fentanyl 2–3 μg kg^{-1} i.v. Intubation was facilitated with succinylcholine 1 mg kg^{-1}, pancuronium 80–100 μg kg^{-1} or rocuronium 0.9 mg kg^{-1}. Following intubation the patients were ventilated mechanically with 66% nitrous oxide in oxygen, supplemented with isoflurane (inspired concentration 0.5–0.8 vol% in Part A; 0.4–1.7 vol% in Part B). Adequate anaesthesia was maintained by fentanyl supplements as required. Ventilation was adjusted to maintain a normal end-tidal carbon dioxide and anaesthesia was adjusted to the requirements of the patient. In patients who had not received rocuronium on induction, rocuronium 0.3 mg kg^{-1} was administered after obtaining control (blank) samples of various body fluids. In all patients, rocuronium bromide (0.3 or 0.9 mg kg^{-1}) was administered over 10 s as a single bolus in a rapidly running i.v. infusion. Pancuronium or succinylcholine were administered for further muscle relaxation if required. ECG, blood pressure, heart rate, body temperature, fluid balance, electrolyte balance, and acid–base balance were monitored as part of the routine clinical management and were not evaluated further in this study.

Sampling

The type of samples taken depended on the type of surgery performed. A blank sample of all types of fluids was taken prior to rocuronium adminstration. Bile was collected from a T-drain which was inserted either during surgery or had been in place previously. Samples were taken at intervals for 48 h after the administration of rocuronium, thoroughly mixed, and the volume of bile was measured. Bile samples (2–3 ml) were also taken from the common bile duct during laparoscopic surgery while this duct was accessible to the surgeon. If possible, three samples at least 5 min apart, were collected. Stoma fluid was collected at intervals for 48 h after the administration of rocuronium. Samples were mixed thoroughly and the volume measured. In cases of partial liver resection, the surgeon was asked to provide a section of normal liver tissue. The liver tissue samples were carefully blotted dry and weighed. They were cut into small pieces and homogenized for 10 min with 1 M NaH_2PO_4 (1:9). The surgeon was asked to estimate the liver weight. Urine was collected at intervals for 48 h (Part A) or for 7 days (Part B) after the administration of rocuronium, mixed thoroughly, and the volume measured (each protocol). Blood samples (4 ml) were taken from a dedicated i.v. cannula at 1, 3, 5, 10, 15, 20, 30, 60, 120, 180, 240, 360 and 480 min after rocuronium administration (Part A). Faeces were collected for 7 days. After weighing and homogenization, samples were mixed with 1 M NaH_2PO_4 (Part B). All samples were acidified to prevent spontaneous hydrolysis of rocuronium with 0.2 ml of 1 M NaH_2PO_4 for every millilitre of sample taken, unless stated otherwise. Samples were frozen and stored at –18°C until analysis.

Rocuronium assay

Concentrations of rocuronium and its potential metabolites 17-desacetyl-rocuronium and *N*-desallyl-rocuronium in plasma, urine, bile, faeces, stoma fluid and liver homogenate were analysed by HPLC as described previously.[22] The assay accuracy, expressed as the percentage of the added amount recovered, varied from –14 to +14% (depending on concentration, matrix and compound) over the range of 25–1000 ng. The mean precision, as indicated by the within-

Table 1 Study design

	Part A	Part B
Special aims	Liver and bile collection	Prolonged (7 day) faeces and urine collection
Study centres	Belfast (n=7), Groningen (n=11), Linköping (n=10)	Stockholm (n=10)
Surgery	Upper abdominal, ileostomy, biliary, hepatectomy	Peripheral
Rocuronium dose	0.3 mg kg^{-1} (n=11) 0.9 mg kg^{-1} (n=17)	0.9 mg kg^{-1}
Plasma kinetics	Yes (n=19)	No

Table 2 Total recovery of rocuronium and 17-desacetyl-rocuronium as percentage of the administered dose in urine and bile (Part A) and in urine and faeces (Part B). Mean values (SD) [range] (number of patients). [a]Ranging from 4–8 days after administration. [b]Patients with evaluable recovery of both urine and bile (Part A) or urine and faeces (Part B)

	Part A		Part B
	Within 24 h	Within 48 h	Within 7 days[a]
Part A			
Urine	22 (7) [9–36] (n=14)	26 (8) [12–37] (n=8)	27 (13) [14–60] (n=10)
Bile	6 (6) [0.2–21] (n=11)	7 (6) [0.5–22] (n=11)	
Faeces			31 (23) [2–67] (n=10)
Total [b]	32 (5) [23–36] (n=7)	34 (6) [25–42] (n=6)	58 (28) [16–101] (n=10)

day coefficients of variation, was 6.8, 6.8 and 5.9% for rocuronium, 17-desacetyl-rocuronium and *N*-desallyl-rocuronium respectively. The lower limit of quantification (LOQ) for rocuronium, 17-desacetyl-rocuronium and *N*-desallyl-rocuronium were 10, 20, and 20 ng ml^{-1} in plasma, 25, 25, and 50 ng ml^{-1} in urine, 10, 25, and 25 ng ml^{-1} in bile, 50 and 50 ng ml^{-1} in faeces, 20 and 20 ng ml^{-1} in stoma fluid and 250 ng ml^{-1} in liver homogenate for all three compounds. (*N*-desallyl-rocuronium could not be quantified in faeces and stoma fluid due to interference by endogenous substances with similar retention times.)

Pharmacokinetic analysis

Plasma concentration–time data were analysed by Iterative Two-Stage Bayesian analysis using the program MultiFit (written by J. H. Proost). The mean values and variance-covariance matrix of the pharmacokinetic population parameters of a two-compartment model (CL, V_1, CL_{12}, V_2) and of a three-compartment model (CL, V_1, CL_{12}, V_2, CL_{13}, V_3)[23] and the residual variance were estimated by an iterative Bayesian procedure as described in the literature[24 25] using the plasma concentration–time data of each patient participating in this part of the study. A log-normal distribution for both the pharmacokinetic population parameters and the plasma concentration measurement errors was assumed. The correctness of the latter assumption was tested by visual inspection of the graphs of the residuals plotted against time and against concentration. Moreover, the relative error of the bioanalysis is known to be almost independent of concentration over the entire concentration range.[22] Goodness-of-fit was evaluated from visual inspection of the measured and calculated data points and of the residuals plotted against time and against concentration. The choice between the two- and three-compartment models was based on Akaike's Information Criterion.[26]

Mean values (SD) of the steady-state volume of distribution (V_{ss}), mean residence time (MRT) and elimination half-life ($t_{1/2}$) were calculated from the individual parameter estimates by a procedure similar to that used for the model parameters.[24 25]

Bile concentration–time (midpoint of sampling interval) data obtained from the T-drain were analysed using the same technique. Since the aforementioned pharmacokinetic model does not apply to bile concentration and we were primarily interested in the terminal half-life of rocuronium in bile, the model was defined as a (multi) exponential equation.

Statistical analysis

Data were summarized as mean (SD) (range). When concomitant medication interfered with the assay, the relevant data generated after the administration of the interfering drug were eliminated from the data analysis. For patients participating in Part A, the bile, stoma, urine and total recovery data were summarized for up to 24 and 48 h wherever possible. Because of the descriptive aims of the study, no further statistical analysis was performed.

Results

The data for the total recovery of rocuronium and 17-desacetyl-rocuronium in urine, bile and faeces are summarized in Table 2.

Part A

Excretion into urine

The mean urinary recovery within 48 h after administration was 26% of the dose (Table 2). The recovery in patients receiving rocuronium 0.3 mg kg^{-1} was comparable to that in patients receiving 0.9 mg kg^{-1}.

Excretion into bile collected from T-drain

In 11 patients from whom bile was collected from the T-drain, the indications for surgery were cholelithiasis (n=2), ductus choledochus lesions (n=3), liver tumours (n=4), choledochal cyst (n=1) or hepatic cyst (n=1). The amounts of bile collected from the T-drains ranged from 149–822 ml (mean 493 ml). The mean recovery within 48 h after administration was 7% of the dose (Table 2).

Total excretion into urine and bile

Total excretion was calculated in those patients from whom evaluable urine and T-drain bile samples were available. The total percentage recovered was 34% of the dose (Table 2), of which up to 0.4% was 17-desacetyl-rocuronium. The amounts of 17-desacetyl-rocuronium recovered were of the same order of magnitude in all sample types tested.

Stoma fluid

The three patients from whom stoma fluid was collected underwent bowel surgery. The volume of stoma fluid amounted to 60, 455 and 313 ml respectively. The percentage of the rocuronium dose (0.3 mg kg^{-1}) recovered in stoma fluid was 0.04, 0.02 and 2.5% after 24 h and 0.04, 4.1 and 12.0% after 48 h in these three patients respectively. The amounts of 17-desacetyl-rocuronium in stoma fluid were very small, ranging from 0 to 0.13% of the dose.

Liver content

Liver tissue was obtained from four patients who underwent hemihepatectomy because of a liver tumour, between 2.3 and 5.1 h after administration of rocuronium 0.9 mg kg^{-1}. Assuming an even distribution of rocuronium, the livers were estimated to contain between 6.3 and 13.2% (mean 9.3%) of the injected dose as rocuronium and up to 0.11% as 17-desacetyl-rocuronium.

Concentration in bile sampled from common bile duct

In 10 patients who underwent laparoscopic surgery for cholelithiasis, two to four bile samples were taken between 27 and 70 min after administration of rocuronium 0.9 mg kg^{-1}. The rocuronium concentrations ranged between 2 and 1217 mg l^{-1} (median value 377 mg l^{-1}), and the ratio of simultaneous concentrations in bile and plasma ranged from 130 to 2800 (median ratio 400). The concentrations of metabolites were much lower, and amounted to between 0 and 2.1% (median value 1.2%) for 17-desacetyl-rocuronium, and between 0 and 0.24% (median value 0.06%) for *N*-desallyl-rocuronium, expressed as a percentage of the rocuronium concentration.

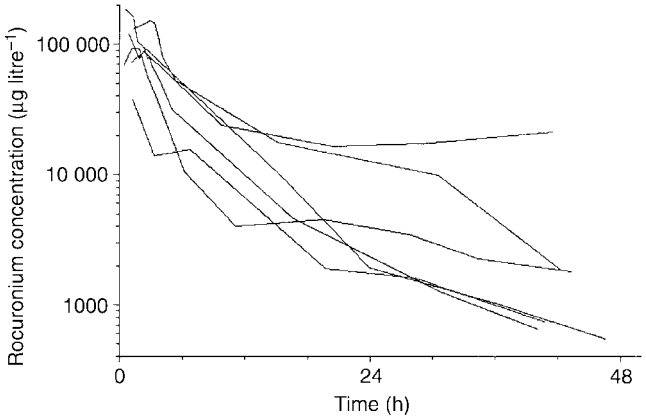

Fig 1 Semi-log plot of bile concentration profiles obtained from T-drain for each individual patient who received rocuronium 0.9 mg kg^{-1} (n=6).

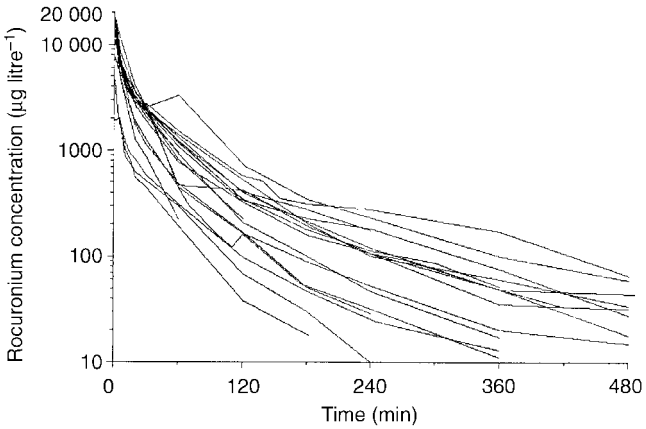

Fig 2 Semi-log plot of measured plasma concentration profiles for each individual patient (n=19). The two lower lines refer to the two patients who received rocuronium 0.3 mg kg^{-1}; the remaining lines refer to a 0.9 mg kg^{-1} dose.

Pharmacokinetic analysis of bile concentration data

A total of 51 bile samples from the T-drains were obtained from six patients receiving rocuronium 0.9 mg kg^{-1}. The measured bile concentration profiles for each individual patient are shown in Figure 1. Using the Iterative Two-Stage Bayesian analysis, a bi-exponential equation fitted the data significantly better than a mono-exponential equation. The mean (SD) (range) values for the two half-lives were 2.3 (0.7) h (1.6–2.8 h) and 16 (11) h (10–44 h) respectively.

Pharmacokinetic analysis of plasma concentration data

Plasma samples were obtained from 17 patients receiving rocuronium 0.9 mg kg^{-1} and from two patients receiving 0.3 mg kg^{-1} (a total of 218 samples). The measured plasma concentration profiles for each individual patient are shown in Figure 2. Using the Iterative Two-Stage Bayesian analysis, a three-compartment model fitted the data significantly better than a two-compartment model. Since the parameters of the two patients receiving the 0.3-mg kg^{-1} dose were within the range of values in the group receiving

0.9 mg kg^{-1}, the data of both dose groups were analysed together. The following values (mean (SD); n=19) were obtained: CL 3.7 (1.2) ml kg^{-1} min^{-1}, V_1 58 (15) ml kg^{-1}, CL_{12} 7.0 (1.5) ml kg^{-1} min^{-1}, V_2 58 (20) ml kg^{-1}, CL_{13} 0.79 (0.30) ml kg^{-1} min^{-1}, V_2 102 (36) ml kg^{-1}, V_{ss} 223 (43) ml kg^{-1}, MRT 60 (20) min, and elimination $t_{1/2}$ 115 (27) min. The residual coefficient of variation was 14%.

In six patients, low levels of 17-desacetyl-rocuronium were detected immediately following administration of rocuronium, rapidly decreasing to levels below the detection limit.

Part B

Excretion into urine

In Part B, urine was collected from 10 patients for up to 4–8 days after surgery. After 3 days the urinary excretion rates of rocuronium and metabolites were very low. The mean percentage of rocuronium recovered from urine was 27% of the administered dose (Table 2). The amounts of 17-desacetyl-rocuronium recovered in urine were small, ranging from 0 to 0.5% of the dose of rocuronium.

Excretion into faeces

The number of stools during the study period varied between patients from one to six, collected up to 7 days after surgery. In three patients the scheduled collection period of 7 days could not be completed since they left hospital earlier than anticipated. In these three patients the faecal recovery of rocuronium was not lower than in the remaining seven patients. These patients were therefore included in the analysis. The mean percentage of rocuronium recovered from faeces was 31% of the dose (Table 2). The amounts of 17-desacetyl-rocuronium recovered in faeces were small, ranging from 0 to 2.4% of the administered dose of rocuronium.

Total excretion into urine and faeces

The mean total excretion into urine and faeces was 58% of the dose (Table 2). In four out of 10 patients, the total recovery exceeded 80% of the administered dose of rocuronium.

Discussion

This study was performed in order to evaluate the relative contributions of the various excretion pathways of rocuronium and its potential metabolites in man. In Part A, all feasible techniques for bile collection in routine practice were employed: collection from T-drains, sampling by direct puncture of the common bile duct and collection of stoma fluid. In addition, the urinary excretion and the concentration in plasma and liver tissue were measured. This necessitated performing the study in various types of patients and at several locations. In Part B, the recovery of rocuronium and its metabolites in urine and faeces was determined.

The pharmacokinetic parameters of a three-compartment model obtained from plasma data were in good agreement with those reported previously,[3–18] indicating that the population of patients participating in this study was representative of those usually enrolled in pharmacokinetic studies of rocuronium and other neuromuscular blocking agents.

The recovery of rocuronium from bile collected from the T-drain ranged from 0.5 to 21.5% of the dose, with a mean value of 6.9%. In a similar study, Bencini and colleagues reported a recovery of 11% (range 2–18%) for vecuronium.[21] The biliary recovery may be underestimated in this study for the several reasons. First, the mean amount of bile collected in 48 h was 493 ml. This is about 50% of the normal bile production of 500–600 ml day^{-1}.[27,28] This small quantity of bile obtained from T-drains could be related to the fact that four out of the six patients receiving rocuronium 0.9 mg kg^{-1}, and with evaluable T-drain samples, underwent hemihepatectomy for a hepatic tumour. Immediately after liver resection, drug clearance by the liver may be reduced and bile production and the biliary excretion of rocuronium may be decreased. Second, an unknown fraction of bile may have reached the bowel instead of leaving the body via the T-drain during the surgical procedure. Third, bile could be collected for only 2 days in patients who were fed parenterally and little was produced. It is, therefore, likely that the biliary excretion of rocuronium was underestimated in this study.

Stoma samples could be collected for only 48 h postoperatively. In the three patients from whom evaluable stoma samples were obtained, a large variability was observed in the volumes produced during this period. This may be explained by the post-operative fasting regime. In the presence of an ileostomy, smaller volumes of stoma fluid will be produced, depending on the duration and type of the fasting regime. Moreover, during that postoperative fasting period, there is no stimulus for bile to be secreted. It is, therefore, likely that the excretion by this route was also underestimated in our study.

Liver tissue was obtained from four patients. For the calculation of the rocuronium content of liver tissue specimens, the individual total liver mass was estimated by the surgeon during the operation. Further, it was assumed that rocuronium was evenly distributed throughout the liver. This assumption may be flawed due to possible uneven or changing blood flow within the liver. Since the liver tissue sections were taken from the tumorous part of the liver, it cannot be excluded that the rocuronium contents in the examined sections underestimated the contents in healthy parts of the liver. In addition, the results may be further underestimated by incomplete extraction of rocuronium during the analytical procedure.

A large variation in total urinary rocuronium excretion was seen between patients, with recovery percentages

ranging from 12 to 60%. In all patients, the highest rocuronium concentration was observed in the first urine samples. After 24 h, rocuronium concentrations in the urine were very low. The urinary recovery of rocuronium was consistent in Parts A and B. These urinary recovery results are also consistent with those reported earlier for rocuronium. Wierda and colleagues reported a mean cumulative urinary excretion of 33% of the administered dose during the first 12 h.[3] Alvarez-Gomez and colleagues and Van den Broek and colleagues observed a mean cumulative urinary excretion of 18%, and of 12–22% of the administered dose within 12 h, respectively.[7 8] As in the present study, the major part of rocuronium was excreted within the first 2 h after administration. The urinary recovery of rocuronium is comparable with that of vecuronium. Bencini and colleagues reported a urinary recovery of 30% of vecuronium, including 10% of the dose as the 3-desacetyl metabolite.[32]

In Part B of the study, a total recovery of more than 80% of the administered dose was observed within 7 days in four out of 10 patients, suggesting that rocuronium may eventually be completely eliminated via the renal and biliary routes. The fact that in six patients a total recovery of less than 60% was observed may be explained in part by the clinical setting in which the study was performed. It is possible that recovery of the compound might have been higher if all patients had stayed in hospital for a prolonged period to allow samples to be collected. As the patients were in bed and sometimes received opioids for pain management, they had irregular stools. Only one or two faecal samples were collected from some patients, which could have resulted in an erroneously low recovery percentage, as at least part of this stool was probably already in the bowel at the time rocuronium was administered. Indeed, in most cases a small percentage of the administered dose was found in the first stool.

The minimal amounts of 17-desacetyl rocuronium detected were mainly excreted in the earlier fractions of bile and urine, which is consistent with findings in the rat and dog (unpublished observations, Organon Teknika). The compound 17-desacetyl rocuronium was present in the ampoules at levels of up to 2% at batch release and at levels of up to 4% at the expiry date. It is, therefore, likely that the amounts of this compound detected were administered rather than the result of *in vivo* biotransformation. *N*-desallyl-rocuronium was found in very small amounts only in bile samples collected from the common bile duct. It is not unlikely that these minute amounts were also present in the ampoules or were formed during analysis, rather than resulting from *in vivo* biotransformation.

Although there are no indications of the presence of unknown derivatives of rocuronium in the present study, it cannot be excluded that rocuronium is excreted into urine and/or bile in the form of as yet unknown metabolites (e.g. conjugated to glucuronic acid or sulphate) which were not detected by the analytic technique used. It is also possible that biotransformation of rocuronium occurs by the faecal flora and/or by the alkaline climate of the intestines, although in the present study there were no indications to substantiate this. This may be the reason for not being able to account for all of the rocuronium.

The pharmacokinetic analysis of the bile concentration data from the T-drains revealed a bi-exponential decay with $t_{1/2}$ of 2.3 and 16 h respectively. The first half-life agrees well with the terminal half-life in plasma; the second half-life is much longer. This may indicate that a similar terminal half-life exists in plasma but is not observed because it occurs either at concentrations below the limit of quantification, or after the last sampling time. However, in the case of prolonged administration of rocuronium, this longer half-life will become apparent. In two studies in intensive care patients, the mean terminal half-life after infusion of rocuronium for 1–2 days was 6–24 h in patients with multi-organ failure.[29 30] The longer terminal half-life observed after prolonged administration demonstrates that the volume of distribution at steady-state is much higher than the value obtained in single-dose studies.[29]

The rocuronium concentrations in bile sampled directly from the common bile duct were much higher than the simultaneous plasma concentration, and in most cases even exceeding the plasma concentration shortly after administration. This finding reflects the efficiency of the biliary excretion of rocuronium in man, as was found earlier in animal experiments,[1 2 33] and suggests that an active carrier-mediated transport process is involved.[31]

In conclusion, the results of this study demonstrate that rocuronium is taken up by the liver and excreted into bile in very high concentrations. The amount of rocuronium excreted within 7 days into urine and faeces was 26 and 30% of the administered dose respectively, including small amounts of 17-desacetyl-rocuronium. The total recovery was on average 58%, and ranged from 16 to 100% of the administered dose.

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References

1 Khuenl-Brady KS, Castagnoli KP, Canfell PC, Caldwell JE, Agoston S, Miller RD. The neuromuscular blocking effects and

pharmacokinetics of Org 9426 and Org 9616 in the cat. *Anesthesiology* 1990; **72**: 669–74

2 Proost JH, Roggeveld J, Wierda JMKH, Meijer DKF. Relationship between chemical structure and physicochemical properties of series of bulky organic cations and their hepatic uptake and biliary excretion rates. *J Pharmacol Exp Ther* 1997; **282**: 715–26

3 Wierda JMKH, Kleef UW, Lambalk LM, Kloppenburg WD, Agoston S. The pharmacodynamics and pharmacokinetics of Org 9426, a new non-depolarizing neuromuscular blocking agent, in patients anaesthetized with nitrous oxide, halothane and fentanyl. *Can J Anaesth* 1991; **38**: 430–5

4 Szenohradszky J, Fisher DM, Segredo V, Caldwell JE, Bragg P, Sharma ML, Gruenke LD, Miller RD. Pharmacokinetics of rocuronium bromide (ORG 9426) in patients with normal renal function or patients undergoing cadaver renal transplantation. *Anesthesiology* 1992; **77**: 899–904

5 Cooper RA, Maddineni VR, Mirakhur RK, Wierda JMKH, Brady M, Fitzpatrick KTJ. Time course of neuromuscular effects and pharmacokinetics of rocuronium bromide (Org-9426) during isoflurane anaesthesia in patients with and without renal failure. *Br J Anaesth* 1993; **71**: 222–6

6 Khalil M, Dhonneur G, Duvaldestin P, Slavov V, Dehys C, Gomeni R. Pharmacokinetics and pharmacodynamics of rocuronium in patients with cirrhosis. *Anesthesiology* 1994; **80**: 1241–7

7 Alvarez Gomez JA, Estelles ME, Fabregat J, Perez F, Brugger AJ. Pharmacokinetics and pharmacodynamics of rocuronium bromide in adult patients. *Eur J Anaesthesiol* 1994; **11 (**Suppl. 9): 53–6

8 Van den Broek L, Wierda JMKH, Smeulers NJ, Van Santen GJ, Leclercq MGL, Hennis PJ. Clinical pharmacology of rocuronium (Org 9426): study of the time course of action, dose requirement, reversibility, and pharmacokinetics. *J Clin Anesth* 1994; **6**: 288–96

9 Wierda JMKH, Proost JH. The pharmacokinetics and the pharmacokinetic-dynamic relationship of rocuronium bromide. *Anaesth Pharmacol Rev* 1995; **3**: 192–201

10 Magorian T, Wood P, Caldwell J, Fisher D, Segredo V, Szenohradszky J, Sharma M, Gruenke L, Miller R. The pharmacokinetics and neuromuscular effects of rocuronium bromide in patients with liver disease. *Anesth Analg* 1995; **80**: 754–9

11 Larijani GE, Gratz I, Afshar M, McDonald PA, Fisher DM. The effect of isoflurane versus balanced anesthesia on rocuronium's pharmacokinetics and infusion requirement. *Pharmacotherapy* 1995; **15**: 36–41

12 Plaud B, Proost JH, Wierda JMKH, Barre J, Debaene B, Meistelman C. Pharmacokinetics and pharmacodynamics of rocuronium at the vocal cords and the adductor pollicis in humans. *Clin Pharmacol Ther* 1995; **58**: 185–91

13 Servin FS, Lavaut E, Kleef U, Desmonts JM. Repeated doses of rocuronium bromide administered to cirrhotic and control patients receiving isoflurane. A clinical and pharmacokinetic study. *Anesthesiology* 1996; **84**: 1092–100

14 McCoy EP, Mirakhur RK, Maddineni VR, Wierda JMKH, Proost JH. Pharmacokinetics of rocuronium after bolus and continuous infusion during halothane anaesthesia. *Br J Anaesth* 1996; **76**: 29–33

15 Khuenl-Brady KS, Sparr H. Clinical pharmacokinetics of rocuronium bromide. *Clin Pharmacokinetics* 1996; **31**: 174–83

16 Sparr HJ, Wierda JMKH, Proost JH, Keller C, Khuenl-Brady KS. Pharmacodynamics and pharmacokinetics of rocuronium in intensive care patients. *Br J Anaesth* 1997; **78**: 267–73

17 Fisher DM, Ramsay MAE, Hein AT, Marcel RJ, Sharma M, Ramsay KJ, Miller RD. Pharmacokinetics of rocuronium during the three stages of liver transplantation. *Anesthesiology* 1997; **86**: 1306–16

18 VanMiert MM, Eastwood NB, Boyd AH, Parker CJR, Hunter JM. The pharmacokinetics and pharmacodynamics of rocuronium in patients with hepatic cirrhosis. *Br J Clin Pharmacol* 1997; **44**: 139–44

19 Sandker GW, Weert B, Olinga P, Wolters H, Slooff MJ, Meijer DKF, Groothuis GMM. Characterization of transport in isolated human hepatocytes. A study with the bile acid taurocholic acid, the uncharged ouabain and the organic cations vecuronium and rocuronium. *Biochem Pharmacol* 1994; **47**: 2193–200

20 Olinga P, Merema M, Hof IH, Slooff MJ, Proost JH, Meijer DKF, Groothuis GMM. Characterization of the uptake of rocuronium and digoxin in human hepatocytes: carrier specificity and comparison with *in vivo* data. *J Pharmacol Exp Ther* 1998; **285**: 506–10

21 Bencini AF, Scaf AHJ, Sohn YJ, Kersten-Kleef UW, Agoston S. Hepatobiliary disposition of vecuronium bromide in man. *Br J Anaesth* 1986; **58**: 988–95

22 Kleef UW, Proost JH, Roggeveld J, Wierda JMKH. Determination of rocuronium and its putative metabolites in body fluids and tissue homogenates. *J Chromatogr* 1993; **621**: 65–76

23 Hull CJ. *Pharmacokinetics for Anaesthesia*. Oxford: Butterworth-Heinemann, 1991

24 Mentré F, Gomeni R. A two-step iterative algorithm for estimation in nonlinear mixed-effect models with an evaluation in population pharmacokinetics. *J Biopharm Stat* 1995; **5**: 141–58

25 Bennett JE, Wakefield JC. A comparison of a Bayesian population method with two methods as implemented in commercially available software. *J Pharmacokinet Biopharm* 1996; **24**: 403–32

26 Akaike H. An information criterion. *Math Sci* 1976; **14**: 5–9

27 Davenport HW. *Physiology of the Digestive Tract*, 2nd edn. Chicago: Year-book Medical Publishers, 1966; 141

28 Bell GH, Emslie-Smith D, Paterson CR. Hepatic and biliary function. In: *Textbook of Physiology*, 10th edn. Edinburgh, Scotland: Churchill-Livingstone, 1980

29 Sparr HJ, Wierda JMKH, Proost JH, Keller C, Khuenl-Brady KS. Pharmacodynamics and pharmacokinetics of rocuronium in intensive care patients. *Br J Anaesth* 1997; **78**: 267–73

30 Kern H, Daugherty M, Sneyd JR, Proost JH, Spies C, Kox WJ. Pharmacokinetics of the long-term use of rocuronium in ICU patients with multiple organ failure (MOF). *Anaesth Intensivther Notfallmed* 1998; **33** (Suppl. 3): S432

31 Meijer DKF, Smit JW, Müller M. Hepatobiliary elimination of cationic drugs: the role of P-glycoproteins and other ATP-dependent transporters. *Adv Drug Deliv Rev* 1997; **25**: 159–200

32 Bencini AF, Scaf AHJ, Sohn YJ, Meistelman C, Lienhart A, Kersten UW, Schwarz S, Agoston S. Disposition and urinary excretion of vecuronium bromide in anesthetized patients with normal renal function or renal failure. *Anesth Analg* 1986; **65**: 245–51

33 Proost JH, Wierda JMKH, Houwertjes MC, Roggeveld J, Meijer DKF. Structure-pharmacokinetics relationship of series of aminosteroidal neuromuscular blocking agents in the cat. *J Pharmacol Exp Ther* 2000; **292**: 861–9