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Repeated Doses of Rocuronium Bromide Administered to Cirrhotic and Control Patients Receiving Isoflurane

A Clinical and Pharmacokinetic Study

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Background: **Steroid muscle relaxants often display pharmacodynamic changes in patients with cirrhosis because of alterations in elimination processes. Rocuronium is a new steroid muscle relaxant possibly eliminated through the liver. This study was designed to compare rocuronium pharmacodynamics and pharmacokinetics in cirrhotic and healthy patients.**

Methods: **Rocuronium was administered to 26 cirrhotic patients and 24 control subjects anesthetized with isoflurane for an elective procedure. Patients were randomly allocated to receive an initial dose of rocuronium: 120, 180, 250, or 300 $\mu g \cdot kg^{-1}$. Dose-response curves were established, and ED_{50} was calculated. Preselected maintenance doses (75, 150, or 225 $\mu g \cdot kg^{-1}$) were administered at 25% recovery of twitch height to compare clinical duration of action. At the end of the procedure, relaxation was reversed in half of the patients, and the time course of recovery was compared in the two groups. Blood samples drawn during the procedure and after the last maintenance dose allowed pharmacokinetic analysis in six cirrhotic patients and six control subjects.**

Results: **ED_{50} of the initial dose was 144 $\mu g \cdot kg^{-1}$ in cirrhotic patients and 60 $\mu g \cdot kg^{-1}$ in control subjects, related to a higher initial volume of distribution (cirrhotic 78.5 ± 31.7 $ml \cdot kg^{-1}$, control 29.8 ± 17.3 $ml \cdot kg^{-1}$). Time from complementary dose to 25% recovery was longer in cirrhotic patients (41.0 ± 20.7 min *vs.* 30.2 ± 9.7 min), but time course of action during maintenance was not statistically different in the two groups. In cirrhotic patients receiving five maintenance doses or more, prolongation of the duration of action with successive maintenance doses could be statistically demonstrated. Spontaneous recovery was delayed in cirrhotic patients, because of impaired elimination processes: greater volume of distribution at steady-state (264 ± 92 *vs.* 151 ± 59 $ml \cdot kg^{-1}$); trend toward a lower clearance (189 ± 60 *vs.* 296 ± 169 $ml \cdot min^{-1}$).**

Conclusions: **Rocuronium pharmacodynamics are moderately altered by cirrhosis, possibly because of pharmacokinetic alterations. Individual variability in response to rocuronium is great, and dosage should be carefully titrated to that required. (Key words: Liver cirrhosis. Neuromuscular relaxants: rocuronium. Pharmacodynamics. Pharmacokinetics.)**

ROCURONIUM is a short-acting, nondepolarizing muscle relaxant with an intermediate duration of action and a steroid structure derived from that of pancuronium and vecuronium.

Its elimination pathways remain uncertain in humans because only one-third of the dose is recovered in urine,[1] with thus far no evidence of metabolism. Animal studies have shown biliary excretion, specifically in cats,[2] but the importance of this pathway in humans remains unknown. Human hepatocytes in culture seem to take up rocuronium swiftly,[3] and thus some hepatic elimination of the compound in humans might be expected.

Muscle relaxants often display pharmacodynamic and pharmacokinetic changes in cirrhotic patients because alterations in elimination processes.[4,5] We therefore compared pharmacodynamic effects and pharmacokinetic parameters after repeated doses of rocuronium in cirrhotic and healthy patients.

Methods and Materials

Written informed consent to participate to this prospective, randomized, institutionally approved study was obtained from 50 ASA physical status 1 or 2 patients (26 cirrhotic patients and 24 normal patients), aged

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18–65 yr, scheduled for elective surgery, mostly otolaryngologic, with an anticipated duration of 1–3 h. For all cirrhotic patients, the diagnosis of cirrhosis had been established by liver biopsy or by a clinical and biologic history of cirrhosis, with at least one previous episode of clinically significant hepatic decompensation. Patients who during the last 7 days had received medications known to interfere with neuromuscular function were not studied, but corticosteroids and β-adrenergic blockers were allowed in cirrhotic patients. Body weight limits were imposed, calculated on the basis of [height (cm) − 100] kg + 25% or − 15%. Additional exclusion criteria included pregnancy, presence of encephalopathy or ascites, history of malignant hyperthermia, neuromuscular disorders, metabolic disease, or impaired kidney or (in the noncirrhotic group) liver function.

Patients received 10 mg diazepam orally, approximately 1 h before induction of anesthesia. On arrival in the operating room, baseline values of heart rate and blood pressure were recorded. In all patients, the electrocardiogram, heart rate, end-tidal p_{CO_2} and hemoglobin oxygen saturation (pulse oximetry), and inspiratory and end-tidal concentrations of isoflurane were monitored continuously. Arterial blood pressure was measured every 5 min, and always just before and every minute for 3 min after administration of rocuronium. Anesthesia was induced with 4 $mg \cdot kg^{-1}$ intravenous thiopental and by the inhalation of increasing concentrations of isoflurane in oxygen. Tracheal intubation was performed without the use of neuromuscular blocking agents. Anesthesia was maintained with isoflurane and incremental doses of fentanyl as needed. Patients' lungs were ventilated to normocapnia with a mixture of 60% N_2O and 40% O_2. To obtain a steady-state concentration of isoflurane, the patients' lungs were ventilated with 3 MAC isoflurane for 3 min and 1 MAC for the succeeding 7 min. End-tidal isoflurane concentrations were measured throughout the study to ensure a steady-state of 0.9–1.1%. After this period of equilibration, control values of heart rate and blood pressure were recorded. Esophageal temperature was maintained between 35°C and 36.5°C by surface warming.

The ulnar nerve was stimulated at the wrist *via* surface electrodes with supramaximal pulses of 0.2 ms duration at a rate of 0.1 (twitch response) or 2.0 Hz (train-of-four (TOF)), when appropriate, and the evoked responses of the adductor pollicis were transduced and recorded by a force transducer (Bioindustry, Boulogne, France). Monitoring of the neuromuscular response was continued until full recovery of the twitch height and a percentage TOF above 70% had been accomplished. The supramaximal stimulation current was determined after equilibration of isoflurane concentration and stabilization of twitch height. Next, one of four selected initial doses of rocuronium (120, 180, 250, or 300 $\mu g \cdot kg^{-1}$) was administered in a randomized fashion. With each selected initial dose, six cirrhotic patients and six control subjects were studied. Once the maximum effect of the initial dose was reached, *i.e.,* when no further decrease in evoked twitch height occurred during three consecutive stimuli, a second dose of rocuronium (330, 270, 200, or 150 $\mu g \cdot kg^{-1}$) was administered to reach a total dose of 450 $\mu g \cdot kg^{-1}$ in all patients. Onset time, maximal blockade before and after the second dose and time from complementary dose to 25% recovery of the twitch height were recorded, allowing construction of the dose-response curve by means of a log(dose)/probit linear regression analysis. At 25% recovery of the twitch height, one of three selected maintenance doses of rocuronium (75, 150, or 225 $\mu g \cdot kg^{-1}$) was randomly administered. With each selected maintenance dose, eight cirrhotic patients and eight control subjects were studied. Each time 25% recovery of the twitch height was obtained, an identical maintenance dose of the same amount was given until the end of the procedure. After each maintenance dose, maximal blockade and clinical duration were recorded. At the end of the procedure after a new randomization, in half of the patients (12 cirrhotic patients and 12 control subjects), the neuromuscular block was allowed to recover spontaneously, and the times of recovery of 25%, 75%, and 90% of the twitch height (T1/T0) were determined, as well as the TOF percentage (T4/T1) at those times. The remaining patients were given 30 $\mu g \cdot kg^{-1}$ intravenous neostigmine when the residual block reached 25% of the initial twitch height. Atropine (10 $\mu g \cdot kg^{-1}$) was administered simultaneously. Five minutes after neostigmine administration, T1/T0 and T4/T1 were determined. Times to T1/T0 of 90% and T4/T1 of 70% were recorded. The recovery index, defined as the time between 25% and 75% recovery of the twitch height, was calculated in patients who were allowed to recover spontaneously.

The last six cirrhotic patients and the last six control subjects were included in the pharmacokinetic study. Blood samples were withdrawn on lithium-heparinized tubes before any rocuronium administration every time 25% recovery of the twitch height was obtained and 2,

4, 6, 8, 10, 15, 30, 45, 60, 90, 120, 180, 240, 360, and 480 min after the last maintenance dose. Plasma was separated and deep-frozen until subsequent analysis. Plasma rocuronium concentrations were measured by the Laboratory of Pharmacology of the University of Gröningen, Gröningen, The Netherlands, by a high-pressure liquid chromatography assay derived from that previously described for vecuronium, followed by postcolumn ion-pair extraction and fluorimetric detection.[6] The mean precision of the assay, almost independent of the concentration, was 8% over a range of 10–20,000 $ng \cdot ml^{-1}$ rocuronium. The accuracy of the assay, expressed as percentage found of the added amount, was 86.0%, 102.7%, 107.1%, and 98.1% at concentrations of 10, 1,000, 5,000, and 10,000 $ng \cdot ml^{-1}$ rocuronium, respectively. The lowest limit of quantification, defined as the lowest concentration that can be determined with a precision and accuracy better than 15%, was 10 $ng \cdot ml^{-1}$. The specificity of the assay was demonstrated, and the retention times of rocuronium and its putative metabolites ORG9943 and ORG 20860 were different enough for the peaks to be well separated on the chromatograms. Pharmacokinetic modeling was performed using SIPHAR program[7] for the fitting of the curves, using extended least squares to weight the data. The data obtained from the decay curve after the last dose were fitted to the whole plasma concentration *versus* time curve, taking into account the dosing scheme. The quality of the fit of the two exponential models was assessed by the presence of a random scatter of the data around the calculated value[8] and by visual assessment of the residuals of the observed values from the fitted curve. The following parameters were derived from the fitted model[9]: distribution and elimination half-lives, volume of the central compartment, total body clearance, volume of distribution at steady-state, and mean resident time.

The physiologic measured parameters were compared using unpaired *t* test. A chi-square test was used to compare sex ratio between the two groups. The dose-response data were analyzed with log(dose)/probit regression analysis. Any patient for which maximal block equaled 0% was assigned two probits, as long as one patient in the same group had maximum block not equal to 0%. Similarly, any patient for which maximal block was equal to 100% was assigned eight probits as long as one patient in the same group had maximal block not equal to 100%. Regression curves were compared by means of analysis of covariance. Repeated-measures analysis of variance was used to compare clinical duration of maintenance doses. Mann-Whitney U test was used to compare cirrhotic patients and control subjects for all other parameters. Statistical significance was inferred if $P < 0.05$.

Results

All data are presented as mean ± SD unless otherwise stated. Clinical characteristics of all patients are presented in table 1, along with those of the subgroup of patients in which kinetic data were obtained. There were no statistical differences between cirrhotic patients and control subjects with respect to sex ratio and weight. Control subjects were statistically younger (43.3 *vs.* 54.0 yr), but all the patients were considered middle-aged adults. In the cirrhotic group, 17 patients were Pugh class A[10] and 9 were Pugh class B, with a mean plasma creatinin concentration of 77 ± 18 $\mu mol \cdot l^{-1}$ (range 55–124 $\mu mol \cdot l^{-1}$), a mean plasma bilirubin concentration of 22 ± 28 $\mu mol \cdot l^{-1}$ (range 6–146 $\mu mol \cdot l^{-1}$), a mean plasma albumin concentration of 35 ± 6 $g \cdot l^{-1}$ (range 25–43 $g \cdot l^{-1}$), a mean prothrombin ratio of 80 ± 19% (range 42–100%), and a mean plasma alanine transaminase activity of 54 ± 81 $IU \cdot l^{-1}$ (range 10–421 $IU \cdot l^{-1}$).

The degree of neuromuscular block was statistically less in the cirrhotic group for the smallest initial dose of 120 $\mu g \cdot kg^{-1}$ rocuronium (table 2). The dose-response curves are displayed in figures 1 and 2, with the 95% confidence intervals. Analysis of covariance displayed a statistically significant difference between the two groups of patients. The ED_{50}, ED_{90}, and ED_{95} derived from these equations are displayed in table 3, with the 95% confidence limits. In the control group, the accuracy of the estimation of the ED_{50} was reduced

Table 1. Clinical Characteristics of the Patients

	Age (yr)	Gender Ratio	Weight (kg)
All patients			
Cirrhotics	54.0 ± 9.4	7F/18M	65.3 ± 13.4
Controls	43.3 ± 7.4	10F/14M	67.6 ± 12.9
P	<0.05	NS	NS
Patients who underwent kinetic analysis			
Cirrhotics	55.0 ± 10.1	2F/4M	63.2 ± 14.1
Controls	45.0 ± 8.9	2F/4M	66.3 ± 14.3
P	NS	NS	NS

NS = not significant.

Table 2. Onset Time and Magnitude of Block after Different Initial Doses in Cirrhotic and Control Patients

Initial Dose (μg/kg)	Onset Time (min)	Magnitude of Block (%)
120		
Cirrhotics (n = 7)	3.0 ± 0.6 (n = 5)	25 ± 22 (n = 7)* [0]
Controls	2.3 ± 0.6	73 ± 23 [1]
180		
Cirrhotics (n = 7)	3.2 ± 1.1 (n = 7)	77 ± 26 (n = 7) [3]
Controls	1.7 ± 0.8	96 ± 9 [5]
250		
Cirrhotics	1.5 ± 0.7	99 ± 2 [4]
Controls	1.6 ± 1.1	99 ± 2 [4]
300		
Cirrhotics	1.7 ± 0.6	99 ± 2 [5]
Controls	1.5 ± 0.8	98 ± 5 [5]

n = 6 unless otherwise stated. Values in brackets represent the number of patients with 100% maximum block. Two patients in the cirrhotic group did not display any reduction in twitch height after administration of an initial dose of 120 $\mu g \cdot kg^{-1}$.

* $P < 0.05$, cirrhotics *versus* controls.

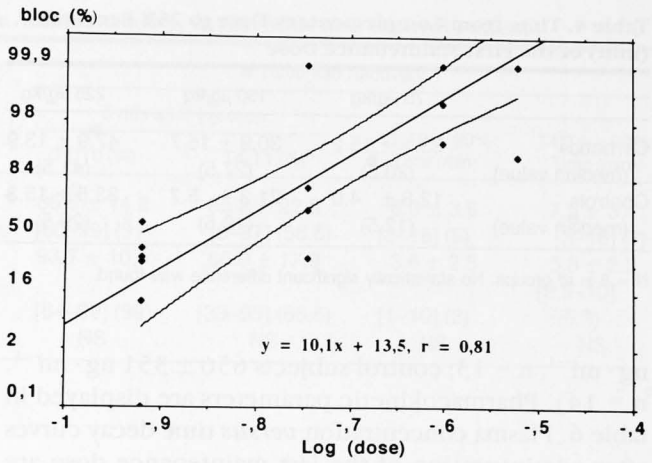

Fig. 2. Dose-response curve obtained by log(dose)/probit linear regression in cirrhotic patients; 95% confidence intervals are displayed.

by the fact that the neuromuscular block was already greater than 50% in most patients with the lowest administered dose.

The mean interval between the first dose and the complementary dose was 3.8 ± 1.8 min in cirrhotic patients and 2.8 ± 1.8 min in control subjects. Time from complementary dose to 25% recovery was 41.0 ± 20.7 min (range 10–86 min) in cirrhotic patients and 30.2 ± 9.7 min (16–51 min) in control subjects ($P < 0.05$). Time from complementary dose to 25% recovery was more than 50 min in seven patients with cirrhosis. Three of those had intraabdominal surgery, and three were Pugh class B patients.

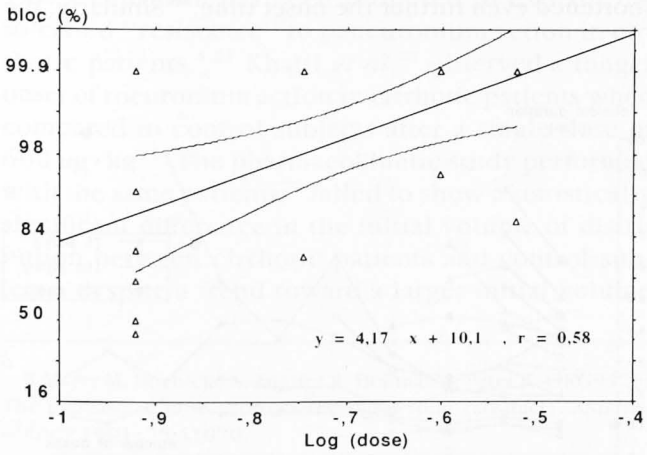

Fig. 1. Dose-response curve obtained by log(dose)/probit linear regression in control subjects; 95% confidence intervals are displayed.

Clinical duration of the first maintenance dose is displayed in table 4. The effect of repeated maintenance doses on the clinical duration of those doses is illustrated in figures 3 (control subjects) and 4 (cirrhotic patients). Despite the small number of patients who received five maintenance doses or more, prolongation of the duration of action with successive maintenance doses could be statistically demonstrated in cirrhotic patients.

The recovery parameters are displayed in table 5. In the group of patients who did not receive any reversal agent, recovery index was delayed in cirrhotic patients, who displayed a greater interindividual variability of the response. Neostigmine administration greatly speeded recovery in both groups of patients, and the difference between the two groups was not statistically significant.

Rocuronium concentrations measured at 25% recovery of the twitch height were around 700 $ng \cdot ml^{-1}$ in both groups of patients (cirrhotic patients 711 ± 270

Table 3. ED_{50}, ED_{90}, and ED_{95} Derived from the Log (dose)-Probit Regression Curves in Cirrhotic and Control Patients

	ED_{50} (μg/kg)	ED_{90} (μg/kg)	ED_{95} (μg/kg)
Cirrhotics	114	193	224
(confidence limits)	(116–164)	(172–219)	(188–241)
Controls	60	121	148
(confidence limits)	(6–99)	(43–166)	(76–194)

Table 4. Time from Complementary Dose to 25% Recovery (min) of the First Maintenance Dose

	75 μg/kg	150 μg/kg	225 μg/kg
Cirrhotics	23.1 ± 15.2	30.9 ± 15.7	47.9 ± 13.9
(median value)	(20.5)	(27.5)	(41.5)
Controls	12.8 ± 4.0	21.3 ± 5.7	33.5 ± 15.3
(median value)	(12.5)	(19.5)	(29.5)

N = 8 in all groups. No statistically significant difference was found.

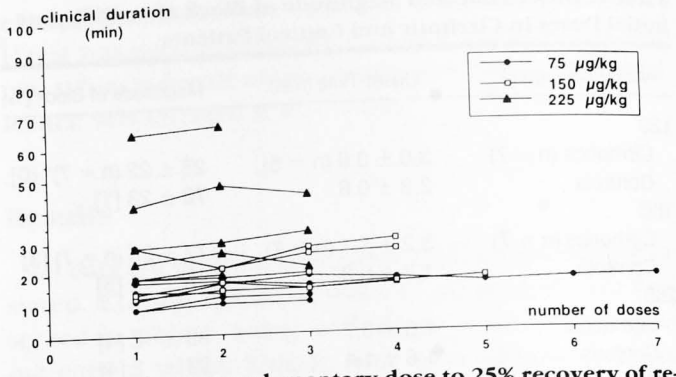

Fig. 3. Time from complementary dose to 25% recovery of repeated doses of rocuronium in control subjects.

ng · ml^{-1}, n = 13; control subjects 656 ± 351 ng · ml^{-1}, n = 14). Pharmacokinetic parameters are displayed in table 6. Plasma concentration *versus* time decay curves after administration of the last maintenance dose are displayed in figures 5 and 6. Rocuronium pharmacokinetics were described by a two-exponential model in all patients. Initial volume of distribution and volume of distribution at steady-state were statistically larger in cirrhotic patients. Clearance was not statistically different in cirrhotic patients and control subjects. Elimination time parameters, mean resident time and k_{10}, were delayed in cirrhotic patients. One cirrhotic patient (n°21) had a volume of distribution at steady-state well above all the other patients. He had suffered previously from an ascites and decompensation of his cirrhosis, although he had no more clinically detectable ascites at the time of surgery (umbilical hernia repair).

No significant changes in heart rate and blood pressure were recorded after maintenance doses under stable anesthetic conditions. No local or general side effects were observed.

Discussion

This study demonstrates some alterations in the pharmacodynamic and pharmacokinetic profile of repeated doses of rocuronium in cirrhotic patients when compared with that observed in healthy patients. The most striking features are a reduction of the clinical efficiency of the initial dose; a trend toward prolongation of action during maintenance, best demonstrated by a delayed spontaneous recovery; and a large interindividual variability. Those alterations are due to pharmacokinetic changes in cirrhotic patients.

The data obtained from control subjects are in good agreement with those already published in the literature. The onset time of rocuronium action was slightly shorter than what usually is considered for those rather low doses. This might be because of the potentiation by isoflurane: In our study, when considering induction time before intubation, equilibration time and time awaited for the twitch height to stabilize, the patients received rocuronium after about 20 min of isoflurane administration. The diffusion of halothane into the muscle compartment requires about 30 min to reach the equilibrium of the concentrations between alveoli, blood, and muscles.[11] The equilibrium between alveoli and blood is more rapid with isoflurane, because of its lower solubility.[12] Thus, the influence of isoflurane, specifically on the initial doses, was probably more important in this study than in reports of rocuronium used earlier in the course of anesthesia.[13] Before desflurane appearance in clinical use,[14] isoflurane appeared to be the volatile agent that potentiated most pharmacodynamic effects of muscle relaxants.[15] The fact that the patients were stimulated until stabilization of the twitch height before rocuronium injection probably shortened even further the onset time.[16] Similarly, the

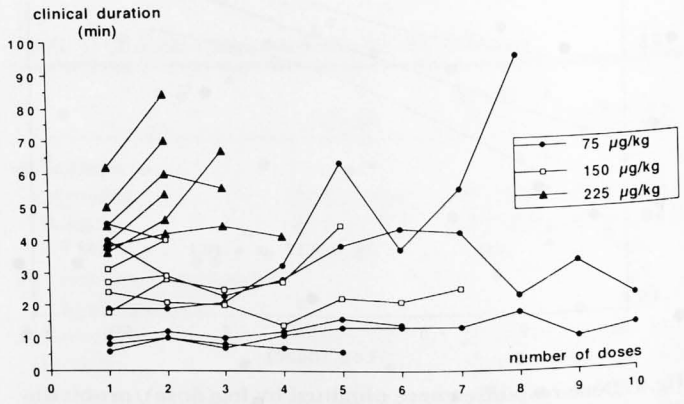

Fig. 4. Time from complementary dose to 25% recovery of repeated doses of rocuronium in cirrhotic patients.

Table 5. Recovery Parameters (Spontaneous or after Neostigmine Administration) in Cirrhotic and Control Patients

	Spontaneous Recovery			Reversed Recovery			
				5 min after Injection			
	Recovery Index (min)	T1/T0 = 90% Time (min)	T4/T1 = 70% Time (min)	T1/T0 (%)	T4/T1 (%)	T1/T0 = 90% Time (min)	T4/T1 = 70% Time (min)
Cirrhotics	19.1 ± 14.6*	26.9 ± 19.3	32.8 ± 14.0	86.5 ± 14.2	55.2 ± 22.8	6.0 ± 3.6	7.5 ± 3.4
[range] (median)	[5–50] (12.5)	[6–62] (22)	[17–60] (27)	[60–99] (91)	[0–87] (58.5)	[3–16] (5)	[3–16] (7)
Controls	9.5 ± 3.0	13.4 ± 4.2	23.2 ± 10.8	93.7 ± 10.4	66.0 ± 17.9	3.6 ± 2.5	5.3 ± 2.2
[range] (median)	[3–14] (10)	[4–18] (13.5)	[7–41] (22)	[84–99] (99)	[33–95] (66.5)	[1–10] (3)	[2.5–10] (5.3)
P	<0.05	NS	NS	NS	NS	NS	NS

NS = not significant.

onset time was shortened in both groups by increasing the dose.§

The ED_{50} obtained from the dose-response curve in healthy patients seems less than what usually is calculated for this agent.[17–19] Oris *et al.*[20] obtained ED_{50} values very close to the current results in patients receiving rocuronium under isoflurane anesthesia. The potentiation of rocuronium action by isoflurane might explain our low ED_{50} value. The large interindividual variability observed in both groups for the lowest doses confirms the results already published by Mellinghoff *et al.*‖

The statistically significantly different dose-response curve in cirrhotic patients associated with an important reduction in the magnitude of block for the lower initial dose and leading to a more than twofold increase in the ED_{50} in those patients can be related to the larger initial volume of distribution. This mechanism has been proposed to explain the so-called "resistance" to pancuronium action in cirrhotic patients.[4,21] Khalil *et al.*[22] observed a longer onset of rocuronium action in cirrhotic patients when compared to control subjects after a single dose of 600 $\mu g \cdot kg^{-1}$. The pharmacokinetic study performed with the same patients[22] failed to show a statistically significant difference in the initial volume of distribution between cirrhotic patients and control subjects, despite a trend toward a larger initial volume of distribution in cirrhotic patients. This might be because of the small number of blood samples in the early phase of rocuronium concentration decay, which might reduce the precision of the analysis of the initial distribution of rocuronium. Similarly, in another study describing the pharmacokinetics of rocuronium after a single bolus injection to patients with liver disease, Magorian *et al.* demonstrated a significant increase in the initial volume of distribution.[23]

Our data show that cirrhosis induces a prolongation of rocuronium action (longer duration of the initial dose, trend toward prolongation of action of maintenance doses), but that this alteration remains moderate (the difference in duration of action of the first maintenance dose did not reach statistical significance), and specifically, that interindividual variability in cirrhotic patients is important (fig. 3 compared to fig. 4). This important interindividual variability among the cirrhotic population is mainly due to the difficulty to define homogeneous groups of patients in liver disease when no clinical or biologic parameter allows so far a precise estimation of the metabolic capacities of the liver. Of the seven cirrhotic patients who had a markedly prolonged duration of action of the initial dose, only three had intraabdominal surgery that might impair liver blood flow, and four were Pugh class A patients, with a mild disease. Those seven patients were not the oldest ones (age might alter rocuronium pharmacodynamics[24,25]), and for six of them, plasma bilirubin concentrations were not the highest even if biliary elimination contributes to rocuronium elimination,[2] as it does to vecuronium elimination.[26–29] The prolongation of rocuronium action in cirrhotic patients is also responsible for the slower spontaneous recovery

§ Mayer M, Doenicke A, Angster R, Hoffman A, Peter K: ORG9426: The increase of dose shortens the onset time (abstract). ANESTHESIOLOGY 1991; 75:A1070.

‖ Mellinghoff H, Diefenbach C, Buzello W: Neuromuscular and cardiovascular proprieties of ORG9426 (abstract). ANESTHESIOLOGY 1991; 75:A807.

Table 6. Pharmacokinetic Parameters Calculated from the Models in Cirrhotic and Control Patients

	$T_{1/2}a$ (min)	$T_{1/2}\beta$ (min)	V (ml/kg)	Cl_E (ml · min^{-1})	V_{ss} (ml · kg^{-1})	MRT (min)	k10 (min^{-1})
Cirrhotics							
19	1.9	62	38	170	267	66	0.1060
21	3.2	84	74	282	438	87	0.0678
22	9.5	95	70	158	206	85	0.0352
23	6.5	79	70	214	214	85	0.0360
24	12.3	159	84	104	270	168	0.0197
26	26	110	135	206	188	60	0.0231
Median values	8	90	72	188	241	85	
Mean ± SD	9.9 ± 8.8	98 ± 34	78.5 ± 31.7	189 ± 60	264 ± 92	92 ± 39	
Controls							
17	1.8	76	12	186	130	61	0.1796
19	4.2	93	59	474	237	30	0.1356
20	1.0	69	19	144	100	56	0.3046
21	2.5	34	33	198	120	33	0.1098
22	1.2	27	18	227	109	25	0.2528
23	1.6	34	38	545	215	26	0.2207
Median values	1.7	52	26	213	125	32	
Mean ± SD	2.1 ± 0.5	56 ± 27	29.8 ± 17.3	296 ± 169	151 ± 59	39 ± 16	
P	<0.02	<0.05	<0.01	NS	=0.05	<0.01	<0.01

in cirrhotic patients, already statistically significant after a single dose.[22]

The alterations in the clinical course of muscle relaxation in cirrhotic patients are related mainly to changes in pharmacokinetics of muscle relaxants.[4,5,21,26,28,30,31] The absence of difference in rocuronium plasma concentrations in this study between cirrhotic patients and control subjects at the time of 25% recovery of the twitch height corroborates this hypothesis. The low rocuronium plasma concentrations observed at 25% recovery of the twitch height when compared to the data obtained during total intravenous anesthesia or halothane anesthesia[1,20] are likely due to the potentiation of rocuronium action by isoflurane. Muscle relaxants are hydrophilic drugs, and their volumes of distribution are highly dependent on extracellular fluid volume, which is frequently enhanced in cirrhotic patients even in the absence of ascitic decompensation of the disease.[4,21] Rocuronium is no exception to this rule.[22,23] This enhancement of both initial and steady-state volumes of distribution cannot be related to the hypoalbuminemia commonly observed in cirrhotic pa-

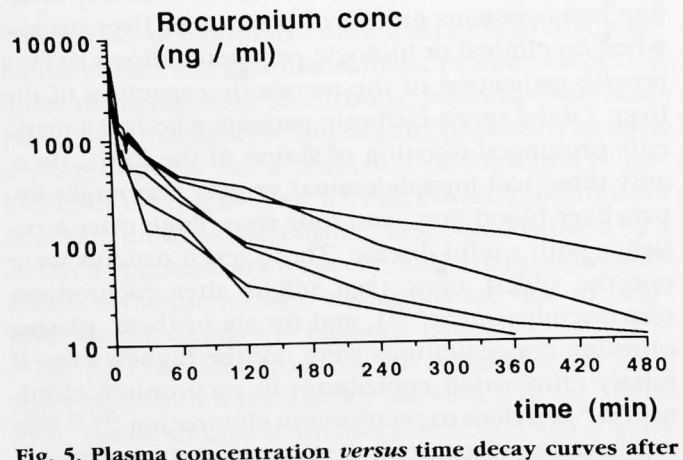

Fig. 5. Plasma concentration *versus* time decay curves after administration of the last maintenance dose in control subjects.

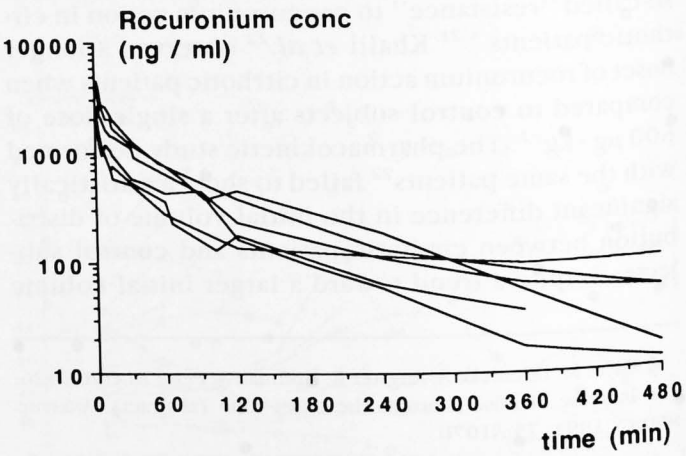

Fig. 6. Plasma concentration *versus* time decay curves after administration of the last maintenance dose in cirrhotic patients.

tients because rocuronium is not very protein-bound (about 25% bound to albumin).# Rocuronium clearance was not significantly altered in our cirrhotic patients, but this might be because of the small number of patients who underwent pharmacokinetic analysis. Nevertheless, more precise data on the role of the liver in rocuronium elimination are warranted to interpret clearance modifications in cirrhotic patients. The association of distribution disturbances and possibly mild elimination impairment led to alterations in time constants, such as a reduction in elimination constant k_{10} and a prolongation of mean resident time, which infer a delayed elimination of rocuronium in cirrhotic patients. In this context and considering the important interindividual variability, it is mandatory in cirrhotic patients to monitor rocuronium action and titrate rocuronium dosage to the patient's needs. The modifications in rocuronium pharmacokinetics are likely responsible for the prolonged recovery index in cirrhotic patients.

Cirrhosis induces moderate changes in rocuronium pharmacodynamics. Those changes, most likely due to pharmacokinetic alterations, are consistent with the data obtained with other muscle relaxants having a steroid structure. The importance of the interindividual variability in the cirrhotic patients suggests the need for a careful titration of the dosage to the patient's needs by monitoring neuromuscular transmission. Reversal of rocuronium action appears useful, specifically in cirrhotic patients.

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