

Anesthesiology
80:1241-1247, 1994
© 1994 American Society of Anesthesiologists, Inc.
J. B. Lippincott Company, Philadelphia

Pharmacokinetics and Pharmacodynamics of Rocuronium in Patients with Cirrhosis

M. Khalil, M.D.,* G. D'Honneur, M.D.,† P. Duvaldestin, M.D.,‡ V. Slavov, M.D.,* C. De Hys, M.D.,†
R. Gomeni, Ph.D.§

Background: Rocuronium, like other steroidal nondepolarizing muscle relaxants, may in part be eliminated by the liver. To determine the influence of liver disease on its neuromuscular blocking effect, we studied the pharmacokinetics and pharmacodynamics of rocuronium in patients with cirrhosis.

Methods: Eighteen patients undergoing elective surgery, 10 with cirrhosis and 8 with normal liver function, were studied. Anesthesia was induced with intravenous thiopental 5–7 mg · kg⁻¹ and maintained with 60% nitrous oxide in oxygen and repeated doses of fentanyl 2 µg · kg⁻¹. The force of thumb adduction in response to supramaximal ulnar nerve stimulation was monitored and recorded. An intravenous bolus of rocuronium 0.6 mg · kg⁻¹ was administered and venous blood sampled at frequent intervals for 6 h. Plasma concentrations of rocuronium was measured by high-pressure liquid chromatography. Data were fitted to both a pharmacokinetic and a pharmacodynamic model by using a two-compartment open model and an effect compartment model. Data were analyzed by least-squares regression.

Results: The onset of neuromuscular blockade was longer ($P < 0.01$) in patients with cirrhosis (158 ± 56 s) than in normal patients (108 ± 33 s). Recovery of the thumb twitch to 75 and 90% of its control value was 77 ± 25 and 88 ± 29 min in cirrhotic patients versus 57 ± 11 and 64 ± 13 min, respectively, in normal patients ($P < 0.05$). The central volume of distribution of rocuronium was 104 ± 21 in cirrhotic patients and 78 ± 24 ml · kg⁻¹ in normal patients ($P < 0.05$). No significant difference in elimination kinetics was observed between the two groups. The elimination half-life was 87.5 ± 17.5 min in normal patients and 96.0 ± 36.8 min in cirrhotic patients (difference not significant). This increased onset time was linearly correlated to the increased central volume of distribution of rocuronium in cirrhosis.

Conclusion: Rocuronium onset time is longer in cirrhotic patients than in those with normal liver function; this can be

explained by an increase in the volume in which rocuronium initially distributes. Although elimination kinetics are unchanged in patients with cirrhosis, rocuronium recovery time is prolonged in cirrhotic patients. (Key words: Complications: cirrhosis. Liver: failure. Neuromuscular relaxants: rocuronium. Pharmacodynamics: rocuronium. Pharmacokinetics: rocuronium.)

ROCURONIUM is a new aminosteroid muscle relaxant of rapid onset and of intermediate duration of neuromuscular blocking effect.¹ The elimination of this muscle relaxant appears to be dependent on biliary excretion. In animals, rocuronium is eliminated unchanged, principally in bile, with urinary elimination as a minor pathway.² In humans, one third of an administered dose appears unchanged in the urine within 24 h.³ Indirect evidence in favor of the predominant hepatic elimination of rocuronium was provided by the investigation of the pharmacokinetics of rocuronium in patients undergoing renal transplantation.⁴ Elimination kinetics were unchanged in patients with renal failure, suggesting that in humans nonrenal pathways of elimination may be important.⁴ In addition, in patients with liver parenchymal failure, altered pharmacokinetics of two other steroidal muscle relaxants, pancuronium and vecuronium, have been observed.^{5,6}

The aim of this study was to examine the influence of decreased liver parenchymal function on the pharmacokinetics and pharmacodynamics of rocuronium in humans. We compared the pharmacokinetics and pharmacodynamics in patients with normal hepatic and renal function to those in patients with histologically proven cirrhosis undergoing elective surgery under general anesthesia.

Material and Methods

After approval from the local ethical committee on human research and written informed consent had been obtained, we studied 18 male patients. Eight patients had no history or biologic evidence of hepatic or renal

* Resident in Anesthesiology.

† Assistant Professor in Anesthesiology.

‡ Professor in Anesthesiology.

§ Director of Research.

Received from the Department of Anesthesiology, Henri Mondor Hospital, and from SIMED, Creteil, France. Accepted for publication February 7, 1994.

Address reprint requests to Dr. Duvaldestin: Service d'Anesthésie Réanimation, Hôpital Henri Mondor, 51, avenue du Maréchal de Lattre de Tassigny, 94010 Creteil, Cedex, France.

disease (53 ± 13 yr of age; mean \pm standard deviation). Ten patients had liver cirrhosis (56 ± 12 yr of age) and were undergoing abdominal surgery. The diagnosis of cirrhosis had been established by liver biopsy, and the cause was alcoholic in all cases. All patients' disease was Child's class B, with mild ascites or encephalopathy and with hypoalbuminemia and prolonged prothrombin time.⁷ Exclusion criteria included known neuromuscular disorders, obesity (defined as weight 30% in excess of ideal body weight), and treatment with drugs, such as aminoglycosides, known to interfere with neuromuscular blocking agents.

Patients received lorazepam 1 mg orally 1–2 h before induction of anesthesia, which was induced with thiopental $5\text{--}7$ mg \cdot kg⁻¹ and fentanyl $1\text{--}2$ μ g \cdot kg⁻¹. Rocuronium was given as an intravenous bolus dose of 0.6 mg \cdot kg⁻¹ 3 min after induction of anesthesia. Tracheal intubation was performed 2–3 min after the administration of rocuronium. Anesthesia was maintained with nitrous oxide 60–70% in oxygen and repeated doses of fentanyl of 2 μ g \cdot kg⁻¹. Ventilation was controlled to obtain end-tidal carbon dioxide of 4–5%. Central body temperature (esophageal or tympanic) was kept between 35 and 37°C.

The ulnar nerve was stimulated supramaximally at the wrist with surface electrodes by applying train-of-four stimuli every 12 s. Stimuli of 0.2-ms duration were delivered *via* skin surface electrodes from the nerve stimulator (S 88, Grass instruments, Quincy, MA), and twitch tension of the adductor pollicis (TH) was measured with a force transducer (UTC 3, Gould, Cleveland, OH) and recorded on a polygraph. Supramaximal ulnar nerve stimulation was performed when stable anesthesia had been obtained. Rocuronium was administered only when a stable twitch response was recorded. The following variables were obtained from the monitoring of TH: maximal depression of the first twitch; time delay between the injection of rocuronium and the achievement of TH maximum depression (onset time); times between rocuronium administration and recovery of the twitch height to 10, 25, 50, 75, and 90% of control (TH₁₀, TH₂₅, TH₅₀, TH₇₅, and TH₉₀); the time for the train-of-four ratio to recover to 70%; and the time for the twitch to recover from 25 to 75% of control.

Venous samples (5 ml each) were drawn in sodium heparin tubes from the contralateral arm or the external jugular vein before and at 2, 5, 10, 15, 30, 45, 60, 75, 90, 120, 150, 180, 210, 240, 300, and 360 min after rocuronium administration. Tubes were centrifuged

within 10 min of collection. Plasma was decanted, acidified by the addition of 0.1 ml NaH₂PO₄ 1 M to 1 ml plasma, and stored at -20°C until analysis. The concentration of rocuronium in plasma was measured by high-pressure liquid chromatography with postcolumn derivatization and fluorometric detection.⁸ This method has been described for measurement of vecuronium concentration and may be applied to rocuronium.³ In our study, this method was sensitive to 20 ng \cdot ml⁻¹ with a coefficient of variation $< 5.6\%$ at 200 ng \cdot ml⁻¹.

A biexponential equation was fitted to the concentration *versus* time data for each patient by using the SIPHAR program⁹ with a weighting function of $1/y^2$. The best fit for the data was determined using the F ratio test. The following parameters were derived: fast distribution half-life, elimination half-life, mean residence time (MRT), apparent volume of distribution at steady state, volume of distribution based on the area under the curve, apparent volume of the central compartment (V₁), apparent total body clearance, and area under the concentration–time curve.

The paralysis data were fitted to the estimates of the pharmacokinetic parameters by using the effect compartment model developed by Sheiner *et al.*¹⁰ The equilibrium rate constant, which characterizes the temporal aspects of equilibration between the concentration in the central and the effect compartments, was determined by use of a nonparametric model.¹¹ For each patient, the effect compartment concentration–time profile was derived from the previously estimated pharmacokinetic parameters and the equilibrium rate constant. The observed neuromuscular blocking effect was fitted with the concentration in the effect compartment by use of the maximum effect pharmacodynamic model.¹² The SIPHAR program was also used to fit these data. Effect data were not weighted. The slope factor γ , which represents the exponent of the Hill equation, also was derived. The concentration in the effect compartment corresponding to 50% of the maximum neuromuscular blocking effect was used to assess sensitivity.

Comparison between the values obtained in normal patients and in cirrhotic patients were performed with the Mann–Whitney *U* test. A *P* value < 0.05 was considered to indicate a statistically significant difference.

Results

There were no differences between the groups with respect to age or weight (table 1). Patients with cir-

ROCURONIUM IN CIRRHOSIS

Table 1. Demographic Data, Hematocrit, Plasma Creatinine, Bilirubin, Albumin Concentration, and Prothrombin Time of Patients

	Normal Hepatic Function	Cirrhosis
Age (yr)	53 ± 13	56 ± 12
Body weight (kg)	72 ± 8	71 ± 14
Hematocrit (%)	45 ± 4	35 ± 6*
Creatinine (μM)	90 ± 20	86 ± 28
Bilirubin (μM)	13 ± 5	31 ± 15*
Plasma albumin (g/L)	43 ± 2	32 ± 8*
Prothrombin time (s)	13 ± 2	19 ± 5*

Values for age and weight are mean ± SD.

* $P < 0.05$ versus normal hepatic function.

rhosis had higher plasma bilirubin concentrations, lower plasma albumin concentrations, and prolonged prothrombin times. So that the neuromuscular blocking effect of rocuronium could be measured in all patients, no patient received additional doses of muscle relaxants.

The plasma concentration decay curves of rocuronium for the two groups of patients are shown in figure

Table 2. Pharmacokinetic Parameters

	Normal Hepatic Function	Cirrhosis
$T_{1/2\alpha}$ (min)	12.0 ± 4.9	11.8 ± 5.6
$T_{1/2\beta}$ (min)	87.5 ± 17.5	96.0 ± 36.8
V_1 (ml/kg)	78 ± 24	104 ± 21*
$V_{d_{ss}}$ (ml/kg)	184 ± 41	234 ± 50
$V_{d\beta}$ (ml/kg)	306 ± 54	333 ± 88
Cl (ml · min · kg ⁻¹)	2.79 ± 0.62	2.41 ± 0.57
AUC (μg · ml ⁻¹ · min)	231 ± 46	274 ± 68
MRT (min)	65 ± 15	105 ± 48*

$T_{1/2\alpha}$ = half-life of distribution; $T_{1/2\beta}$ = half-life of elimination; V_1 = volume of the central compartment; $V_{d_{ss}}$ = total apparent volume of distribution at steady-state; $V_{d\beta}$ = volume of distribution based on AUC; Cl = plasma clearance; AUC = area under the curve; MRT = mean residence time.

* $P < 0.05$ versus normal hepatic function.

1. At 2, 5, and 10 min, mean concentrations of rocuronium in plasma were significantly ($P < 0.05$) lower in patients with cirrhosis than in normal patients. The distribution half-life was 12.0 ± 4.0 min in patients with normal hepatic function and was similar in those with cirrhosis, at 11.8 ± 5.6 min (table 2). A significant

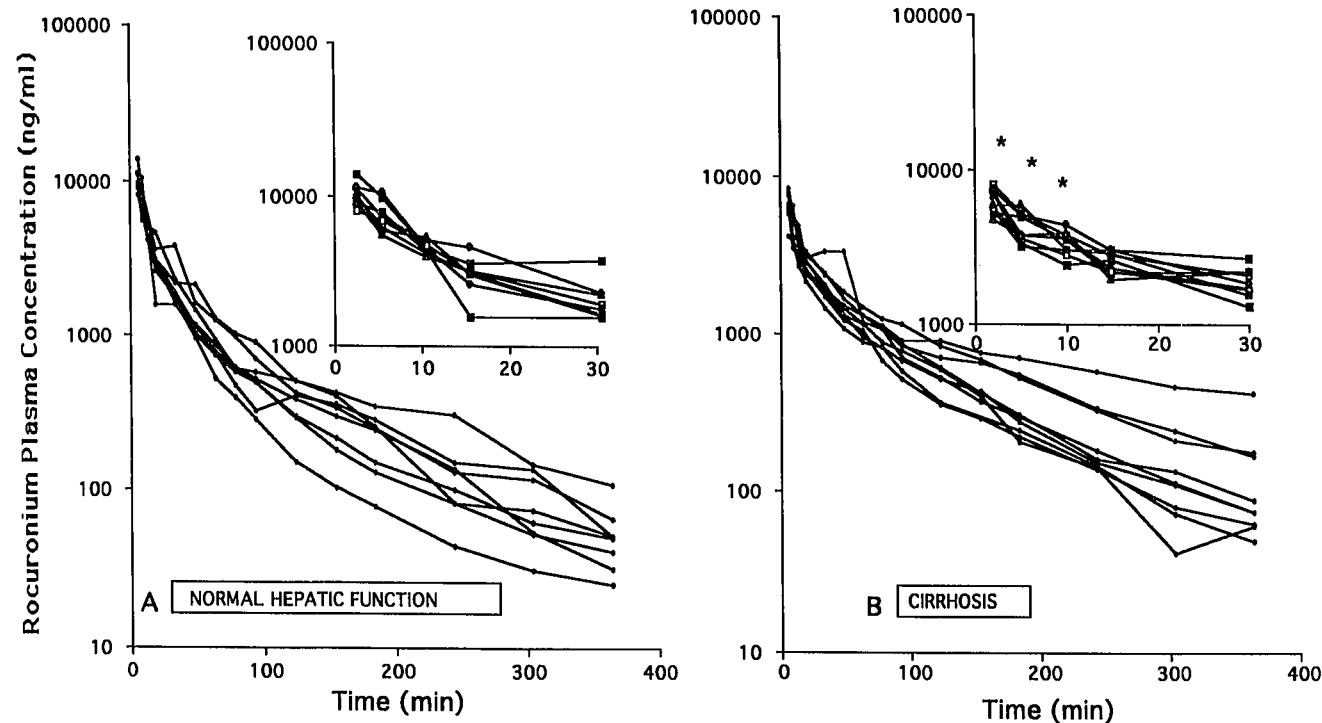


Fig. 1. Mean rocuronium plasma concentration versus time in (A) patients with normal liver function and in (B) patients with cirrhosis. At top, the data between 0 and 30 min are represented on an expanded time scale. * $P < 0.05$ versus concentration in patients with normal hepatic function.

increase ($P < 0.05$) in V_1 was observed with cirrhosis: V_1 was $104 \pm 21 \text{ ml} \cdot \text{kg}^{-1}$ compared to $78 \pm 24 \text{ ml} \cdot \text{kg}^{-1}$ in normal patients. The volume of distribution at steady state was $234 \pm 50 \text{ ml} \cdot \text{kg}^{-1}$ with in cirrhotic patients and $184 \pm 41 \text{ ml} \cdot \text{kg}^{-1}$ in normal patients. The volume of distribution based on the area under the curve did not differ between the two groups. The half-life of elimination and the plasma clearance were not different between the two groups. MRT was significantly increased ($P < 0.05$) in patients with cirrhosis, at 105 ± 48 compared to 65 ± 15 in normal patients; the area under the concentration–time curve did not differ between the two groups.

The onset time of maximal neuromuscular blockade was significantly ($P < 0.01$) prolonged in patients with cirrhosis (table 3). Maximal depression of TH was 100% in all control subjects (fig. 2); in cirrhotic patients, however, a 100% depression of TH was observed in only five of ten patients. In the remaining five patients, the maximum block varied between 75 and 95%. Recovery from the neuromuscular blocking effect is shown in figure 3. TH_{10} , TH_{25} , and TH_{50} were not different between the two groups (table 3), but a significant ($P < 0.05$) increase in TH_{75} and TH_{90} was observed in patients with cirrhosis. The time for the train-of-four ratio to recover to 70% did not differ between the two groups. The recovery index was also signifi-

Table 3. Neuromuscular Effects of a Bolus Dose of 600 $\mu\text{g}/\text{kg}$ Rocuronium in Patients with Normal Hepatic Function and Patients with Cirrhosis

	Normal Hepatic Function	Cirrhosis
Onset time (s)	108 ± 33	$158 \pm 56^*$
Maximum block (%)	100	95 ± 8
TH_{10} (min)	34 ± 6	34 ± 14
TH_{25} (min)	41 ± 7	42 ± 16
TH_{50} (min)	50 ± 10	58 ± 21
TH_{75} (min)	57 ± 11	$77 \pm 25^\dagger$
TH_{90} (min)	64 ± 13	$88 \pm 29^\dagger$
TH_{25-75} (min)	17 ± 5	$35 \pm 14^*$
T4 0.7 (min)	69 ± 15	93 ± 30

TH_{10} , TH_{25} , TH_{50} , TH_{75} , TH_{90} = times between injection of rocuronium and recovery of the twitch height to 10%, 25%, 50%, 75%, and 90% of the control value, respectively; TH_{25-75} = time between recovery from 25% to 75% of the twitch height; T4 0.7 = time between injection of rocuronium and recovery of the fourth response to 70% of the first response to train-of-four stimulation.

* $P < 0.01$ versus normal hepatic function.

† $P < 0.05$ versus normal hepatic function.

cantly ($P < 0.01$) prolonged in cirrhosis. Figure 4 is a representative tracing of the fitting of simultaneous plasma concentration and effect data.

The results of the pharmacodynamic analysis are shown in table 4. Cirrhosis did not alter the values of the pharmacodynamic parameters. The concentration in the effect compartment corresponding to 50% of the

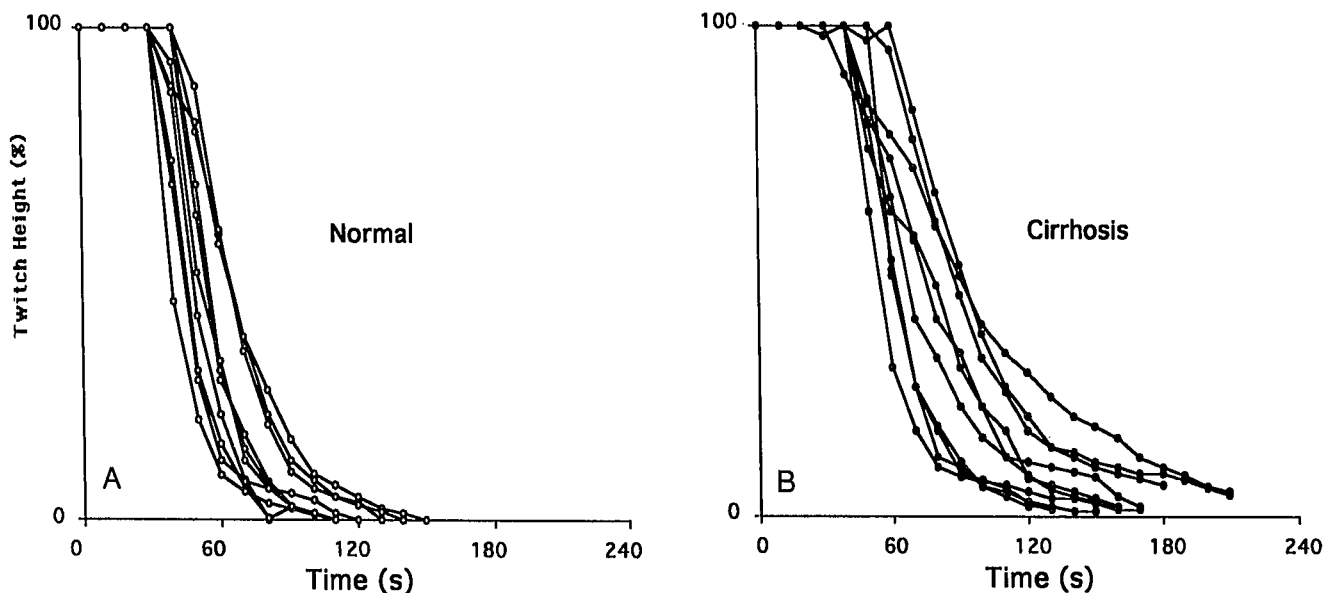


Fig. 2. Onset curves showing twitch height (as a percentage of control twitch height) versus time for the period between rocuronium administration and the achievement of maximum effect, in eight patients with normal liver function and ten patients with cirrhosis. Comparison of these data reveals that onset curves are displaced to the right in patients with cirrhosis.

ROCURONIUM IN CIRRHOSIS

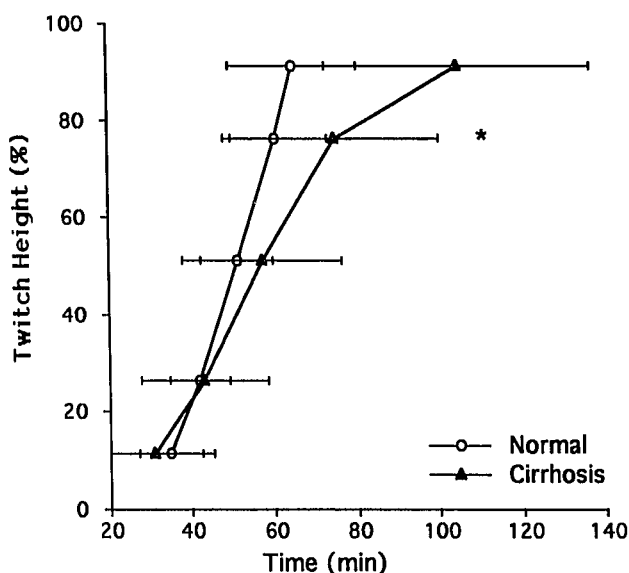


Fig. 3. Evolution of the twitch height (mean \pm standard deviation) for the eight patients with normal liver function (filled circles) and ten patients with cirrhosis (open circles) after intravenous administration of $0.6 \text{ mg} \cdot \text{kg}^{-1}$ rocuronium. * $P < 0.05$ versus twitch height in normal subjects.

maximum neuromuscular blocking effect was $1,220 \pm 255 \text{ ng} \cdot \text{ml}^{-1}$ in control subjects and $1,190 \pm 445 \text{ ng} \cdot \text{ml}^{-1}$ in cirrhotic patients. A linear correlation was observed between onset time and V_1 in all patients (fig. 5). No correlation was found between the duration of neuromuscular blockade and the pharmacokinetic parameters of rocuronium.

Discussion

The current study demonstrates that in cirrhotic patients rocuronium exerts a slightly prolonged effect and that the onset of the neuromuscular blockade is slower than in control subjects. The pharmacokinetics of rocuronium were almost identical in control subjects and cirrhotic patients except for V_1 and MRT. The pharmacokinetics of rocuronium were determined by measuring venous plasma concentration which may overestimate of V_1 compared to values obtained from arterial concentration.¹³ However, as the same method of measurement was used in both groups, the differences in V_1 between the two groups remain valid. The pharmacokinetic data from patients with normal hepatic function are similar to those reported from patients with normal liver and renal function.^{3,4} The pa-

tients with liver disease in this study had a similar degree of hepatocellular dysfunction, all corresponding to Child's B class, indicating that they had a marked degree of hepatic insufficiency. If rocuronium is principally eliminated by the liver, then a major alteration in rocuronium pharmacokinetics would be expected in patients with cirrhosis. We have found no change in plasma clearance in cirrhotic patients suggesting that rocuronium is not principally eliminated by the liver in humans. However, the MRT was longer in patients with cirrhosis, this is explained by the fact that MRT depends on both the total apparent volume of distribution at steady state and the plasma clearance. Although the change in plasma clearance and volume of distribution at steady state were not significant, the combination of these two factors explains the increase in MRT in cirrhotic patients. The implication of this finding is that rocuronium will be present at an effective concentration for a longer period in patients with cirrhosis than in normal patients.

There is no documented data about the elimination pathway of rocuronium in humans. Wierda *et al.*³ found that about 33% of the dose of rocuronium is recovered in the urine over 24 h with no metabolites detected. In the cat however, hepatic uptake and biliary excretion are the dominant mechanisms of rocuronium clearance.² The major finding in this study is an increase in the central volume of distribution in cirrhotic patients, this is not surprising as most of them had an increase in extracellular fluids in the form of ascites found at the time of surgery. Rocuronium, like other muscle relaxants, distributes in extracellular fluids because of its high water solubility. This has been previously shown with pancuronium whose volume of distribution was shown to be increased by 50% in cirrhotic patients.⁵ However, the total apparent volume of distribution was not significantly increased in patients with cirrhosis. One may speculate that as in the cat,² rocuronium is taken up to a significant extent by the liver in humans and that this hepatic uptake is diminished in cirrhosis. Thus, the increased extracellular fluid volume and reduced hepatic uptake counterbalance each other.

In the current study we observed that the onset time of rocuronium was longer in patients with cirrhosis with large variation. The observation that the same dose of rocuronium $0.6 \text{ mg} \cdot \text{kg}^{-1}$ did not produce the same degree of initial neuromuscular blockade may suggest that rocuronium is less potent in cirrhotic patients than in normal patients. However, the pharmacokinetic-

pharmacodynamic modeling for each subject showed that patients with cirrhosis require the same plasma concentration of rocuronium to obtain a comparable degree of neuromuscular blockade as normal patients. The rate constant for transfer of rocuronium from V_1 into the effect compartment was similar in the two groups. Therefore, we suggest that the longer onset time of neuromuscular blockade is only caused by the increased V_1 in patients with cirrhosis. In cirrhotic patients, rocuronium initially distributes in a larger volume, therefore its concentration rises slower than in normal patients. Arden *et al.*,¹⁴ studying the pharmacokinetics and pharmacodynamics of vecuronium in patients with alcoholic liver disease did not observe any alteration in the elimination kinetics of vecuronium; however, they observed the same initial phenomenon that we have found. The onset of the maximum

Table 4. Pharmacodynamic Values for Rocuronium in Patients with Normal Hepatic Function and Patients with Cirrhosis

	Normal Hepatic Function	Cirrhosis
Cp SS 50 (ng/ml)	1220 ± 255	1190 ± 445
γ	6.75 ± 1.65	7.45 ± 2.55
k_{e0} (min)	0.182 ± 0.058	0.228 ± 0.108

Cp SS 50 = concentration in the effect compartment corresponding to 50% of maximum neuromuscular blocking effect; γ = slope factor representing the exponent of the Hill equation; k_{e0} = equilibration rate constant between the central and the effect compartment.

neuromuscular blocking effect of 0.15 mg · kg⁻¹ vecuronium was delayed in patients with liver disease.¹⁴ This finding has been previously proposed as an explanation for the so-called resistance of patients with cir-

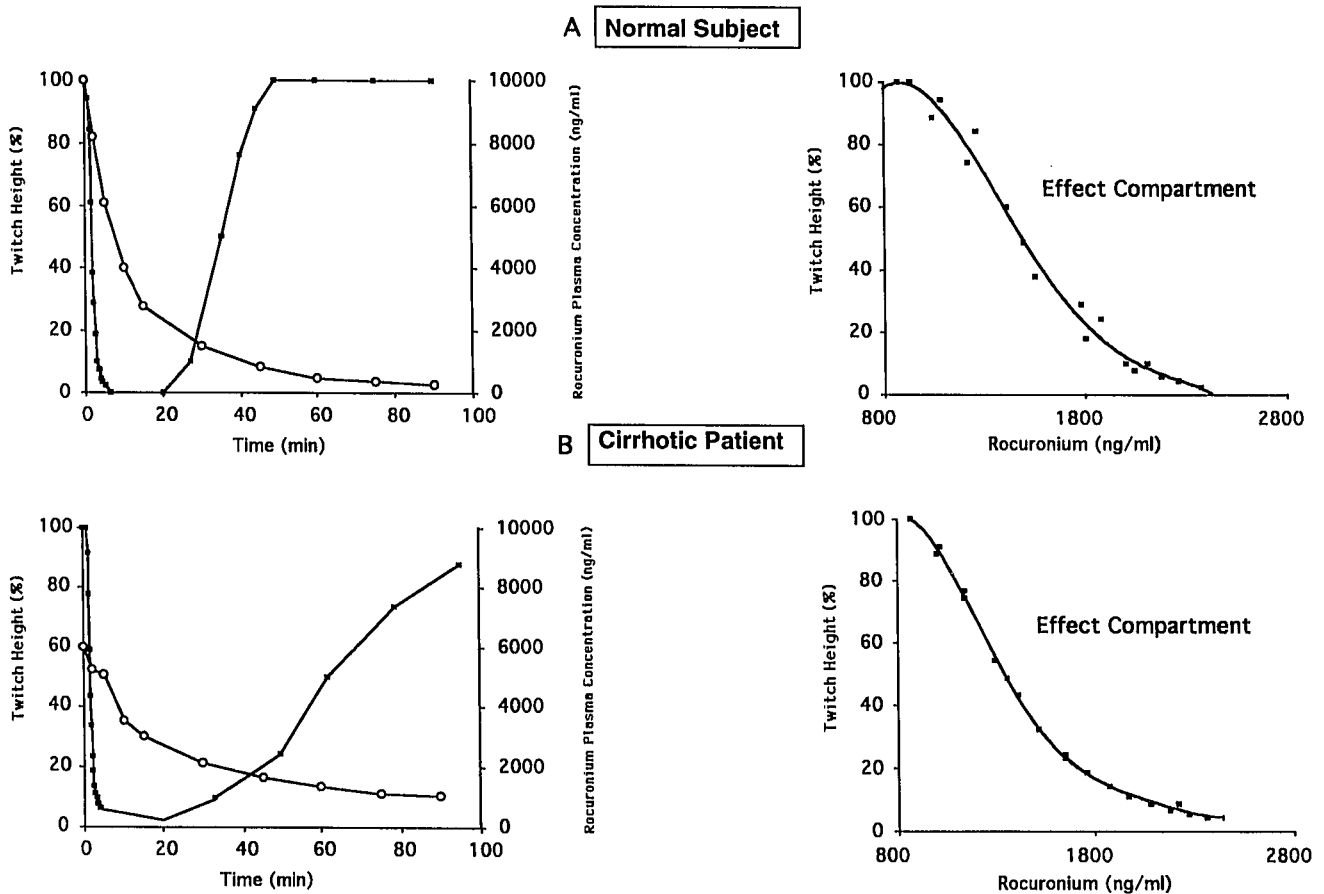


Fig. 4. Relationship between plasma rocuronium concentration and neuromuscular blocking effect for (A) a patient with normal hepatic function and (B) a patient with cirrhosis. (Left) Open circles = measured plasma concentration; squares = degree of muscle paralysis. (Right) The plasma concentration–response data were fitted to Sheiner *et al.*'s effect model.¹⁰

ROCURONIUM IN CIRRHOSIS

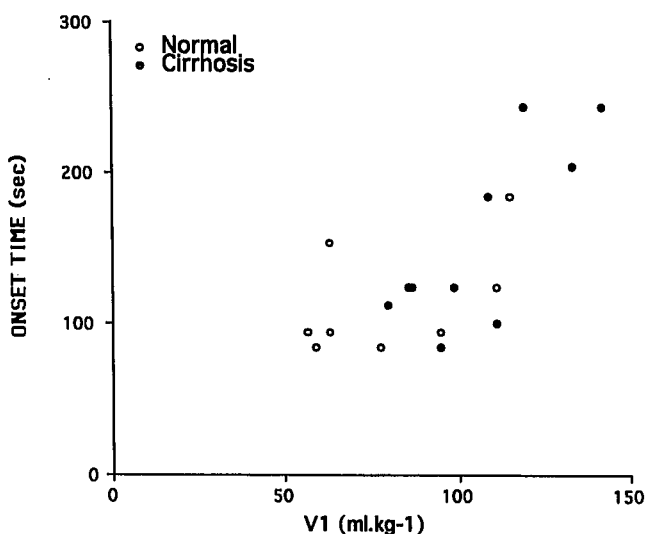


Fig. 5. Onset of maximum neuromuscular blocking effect as a function of central volume of distribution of rocuronium in patients with normal liver function and in those with cirrhosis. The linear correlation existed for all patients ($y = -0.89 + 2.3x$; $R^2 = 0.64$) and for patients with cirrhosis ($y = -1.6 + 1.4x$; $R^2 = 0.45$). No correlation existed for normal patients when studied alone.

rhosis to muscle relaxants.⁵ Resistance in cirrhotic patients was explained initially by an increased binding of muscle relaxants to plasma proteins.^{15,16} However plasma protein binding when measured directly has been shown to be negligible in patients with normal liver function as well as in cirrhotic patients.¹⁷ Although the degree of binding of rocuronium to plasma proteins has not been measured in this study, it would be surprising if it behaves differently from other muscle relaxants. Finally, in cirrhosis, we found that the recovery from neuromuscular blockade was slightly prolonged. This finding may also be explained by an increase in the volume of distribution of rocuronium. Although we could not demonstrate a significant increase in the total apparent volume of distribution.

From these data we conclude that rocuronium pharmacodynamics and elimination kinetics are not influenced by liver parenchymal failure. In addition, the prolonged onset of neuromuscular blocking effect of rocuronium observed in cirrhosis is explained by an increased volume in which rocuronium initially distributes.

The authors thank Josiane Petit-Foisy for her technical assistance.

References

1. Wierda JMKH, De Wit APM, Kuizenga K, Agoston S: Clinical observations on the neuromuscular blocking action of ORG 9426, a new steroidal non-depolarizing agent. *Br J Anaesth* 64:521-523, 1990
2. Khuenl-Brady K, 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* 72: 669-674, 1990
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 anesthetized with nitrous oxide, halothane and fentanyl. *Can J Anaesth* 38:430-435, 1991
4. Szenohradszky J, Fischer 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* 77: 899-904, 1992
5. Duvaldestin P, Agoston S, Henzel D, Kersten UW, Desmonts JM: Pancuronium pharmacokinetics in patients with liver cirrhosis. *Br J Anaesth* 50:1131-1136, 1978
6. Lebrault C, Berger JL, D'Hollander A, Gomeni R, Henzel D, Duvaldestin P: Pharmacokinetics and pharmacodynamics of vecuronium (ORG NC 45) in patients with cirrhosis. *ANESTHESIOLOGY* 62: 601-605, 1985
7. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R: Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 60:646-649, 1973
8. Paanakker JE, Thio JMSL, Van Den Wildenberg HM, Kaspersen FM: Assay of vecuronium in plasma using solid-phase extraction, high-performance liquid chromatography and post-column ion-pair extraction with fluorimetric detection. *J Chromatogr* 421:327-335, 1987
9. Gomeni C, Gomeni R: IGP/HARM: Interactive graphic package for pharmacokinetic analysis. *Comp Biomed Res* 11:345-361, 1978
10. Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J: Simultaneous modeling of pharmacokinetics and pharmacodynamics: Application to d-tubocurarine. *Clin Pharmacol Ther* 25:358-371, 1979
11. Fuseau E, Sheiner LB: Simultaneous modeling of pharmacokinetics and pharmacodynamics with a nonparametric pharmacodynamic model. *Clin Pharmacol Ther* 35:733-741, 1984
12. Holford NHG, Sheiner LB: Understanding the dose-effect relationship: Clinical application of pharmacokinetic-pharmacodynamic models. *Clin Pharmacol Ther* 35:733-741, 1984
13. Donati F, Varin F, Ducharme J, Gill SS, Theoret Y, Bevan DR: Pharmacokinetics and pharmacodynamics of atracurium obtained with arterial and venous blood samples. *Clin Pharmacol Ther* 49: 515-522, 1991
14. Arden JR, Lynam DP, Castagnoli KP, Canfell PC, Cannon JC, Miller RD: Vecuronium in alcoholic liver disease: A pharmacokinetic and pharmacodynamic analysis. *ANESTHESIOLOGY* 68:771-776, 1988
15. Baraka A, Gabali F: Correlation between tubocurarine requirements and plasma protein pattern. *Br J Anaesth* 40:89-93, 1968
16. Stovner J, Theodorsen L, Bjelke E: Sensitivity to tubocurarine and alcuronium with special reference to plasma protein pattern. *Br J Anaesth* 43:385-391, 1971
17. Duvaldestin P, Henzel D: Binding of tubocurarine, fazadinium, pancuronium and ORG NC 45, to serum proteins in normal man and in patients with cirrhosis. *Br J Anaesth* 54:513-516, 1982