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Pharmacokinetics and Pharmacodynamics of Vecuronium (ORG NC 45) in Patients with Cirrhosis

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To evaluate the effect of liver cirrhosis on the pharmacokinetics and the pharmacodynamics of vecuronium, 12 patients with cirrhosis, aged (mean ± SD) 52 ± 12 yr, and 14 control patients, 42 ± 15 yr, undergoing elective surgery under general anesthesia were studied. The simultaneous time courses of the plasma concentration of vecuronium and of the neuromuscular blockade were studied after the administration of a bolus dose of 0.2 $mg \cdot kg^{-1}$. Vecuronium plasma concentration declined biexponentially in both groups. Vecuronium plasma clearance was reduced significantly ($P < 0.01$) from 4.26 ± 1.38 $ml \cdot min^{-1} \cdot kg^{-1}$ in the controls to 2.73 ± 1.19 $ml \cdot min^{-1} \cdot kg^{-1}$ in the patients with cirrhosis. The elimination half-life was 58 ± 19 min in the controls and was prolonged significantly to 84 ± 23 min ($P < 0.01$) in the patients with cirrhosis. The total apparent volume of distribution was unchanged in patients with cirrhosis (0.253 ± 0.086 $l \cdot kg^{-1}$ *vs.* 0.246 ± 0.092 $l \cdot kg^{-1}$ in the controls). Cirrhosis caused a prolongation of the neuromuscular blockade induced by vecuronium: the duration of effect from injection to 50% recovery of the twitch height was prolonged by 100% ($P < 0.01$) from 62 ± 16 min in the controls to 130 ± 52 min in patients with cirrhosis. The recovery rate (TH 25–75) also was prolonged ($P < 0.05$) from 21 ± 7 min in the controls to 44 ± 18 min in patients with cirrhosis. Vecuronium plasma concentration measured during recovery from paralysis indicates that cirrhosis did not alter the sensitivity to the relaxant, the plasma concentration corresponding to 50% of recovery (Cp 50) being unchanged between the two groups: 247 ± 60 $ng \cdot ml^{-1}$ in the controls *versus* 281 ± 129 $ng \cdot ml^{-1}$ in the cirrhotic patients. Thus, vecuronium seems to exert a prolonged neuromuscular blockade in patients with cirrhosis, and this change is mediated through its delayed elimination. (Key words: Liver: cirrhosis. Neuromuscular relaxants: vecuronium. Pharmacodynamics: vecuronium. Pharmacokinetics: vecuronium.)

VECURONIUM is a monoquaternary ammonium analog of pancuronium that produces a neuromuscular blockade of shorter duration than pancuronium. The short duration of the neuromuscular blockade induced by vecuronium is explained by the more rapid clearance and shorter elimination half-life as compared with pancuronium.[1] The lack of a significant alteration in vecuronium pharmacokinetics in the absence of renal function in animals[2] and humans[3] suggests that nonrenal clearance perhaps via hepatic mechanisms may play an important role in the elimination of vecuronium. In accordance with this concept, neuromuscular blockade induced by vecuronium has been found to be prolonged by liver exclusion in cats.[4] Furthermore, in rats, more than 40% of the dose of vecuronium was recovered in the bile as compared with 8% in the urine.[5] Therefore, in humans vecuronium might be eliminated primarily by the liver, and its effect might be prolonged in patients with liver disease. To evaluate this possibility, we compared the pharmacokinetics and the pharmacodynamics of vecuronium in patients with normal hepatic function and in patients with liver cirrhosis.

Materials and Methods

SUBJECT

The pharmacokinetics and pharmacodynamics of vecuronium were investigated in 12 patients with alcoholic cirrhosis who were between the ages of 33 and 66 yr (52 ± 12 yr, mean ± SD) and weighing 40–80 kg (62 ± 14 kg) and 14 patients without hepatic or renal dysfunction between the ages of 21 and 68 yr (42 ± 15 yr) and weighing 57–107 kg (70 ± 13 kg) undergoing

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TABLE 1. Characteristics, Liver Function Tests, and Serum Creatinin Concentration of Cirrhotic Patients

Patient No.	Sex	Age (yr)	Body Weight (kg)	Surgical Procedure	SGPT* ($U \cdot ml^{-1}$)	Serum Bilirubin ($mg \cdot dl^{-1}$)	Prothrombin (percent of normal)	Serum Creatinine ($mg \cdot dl^{-1}$)
1	M	60	60	Gastrectomy	19	1.4	55	1.25
2	M	33	66	Pancreatectomy	85	6.1	40	1.05
3	F	65	46	Surgical hepatic biopsy	90	0.8	56	0.85
4	M	59	40	Jejunostomy	37	0.8	60	1.00
5	M	62	71	Cholecystectomy	100	8.5	45	0.95
6	M	34	51	Total hip arthroplasty	40	0.6	80	0.75
7	M	45	75	Colectomy	45	0.9	29	1.00
8	M	59	40	Colectomy	19	0.7	62	0.85
9	M	48	67	Abdominal herniae	17	1.0	75	0.70
10	M	44	70	Surgical hepatic biopsy	18	1.3	63	0.90
11	M	46	75	Gastric ulcer	36	4.9	36	1.15
12	M	66	80	Abdominal herniae	17	1.8	60	1.60

* Serum glutamic pyruvic transaminase, normal value < 30 $U \cdot ml^{-1}$.

surgery. Informed consent was given by all the patients, and the study protocol was approved by the Research Committee of our institution. The diagnosis of liver cirrhosis previously had been established by a liver biopsy. At the time of the study no patient had ascites, encephalopathy, or renal failure. The laboratory data from these patients are given in table 1. All the patients studied were scheduled for elective abdominal or orthopedic surgery. None of the patients received drugs preoperatively that might interfere with the neuromuscular blocking effect of vecuronium. Premedication consisted of atropine 0.5 mg intramuscularly and diazepam 10 mg or lorazepam, 2.5 mg orally given 45 min before induction of anesthesia. For induction of general anesthesia, a dose of thiopental of 6 to 8 $mg \cdot kg^{-1}$ iv was administered. Vecuronium 0.2 $mg \cdot kg^{-1}$ was administered by bolus (10 s) intravenous injection within 5 min after the induction dose of thiopental. General anesthesia was maintained with nitrous oxide (60% in oxygen) delivered by mechanical ventilation and repeated doses of fentanyl (total dose: 0.3–1.3 mg) and thiopental (total dose: 350–650 mg). The duration of general anesthesia was of 137 ± 26 min in the controls and 188 ± 65 min in the patients with cirrhosis.

Clinical Protocol

The pharmacodynamics of vecuronium were compared between the two groups. A Grass S-48® stimulator was used to administer supramaximal single stimuli of 0.2 ms duration at a rate of 0.1 pulses/s to the ulnar nerve at the wrist through thin-wall electrodes. The evoked response of the adductor pollicis, *i.e.*, the twitch height (TH), was quantitated continuously with a Statham UC3® force transducer and recorded on a polygraph. Prior to induction of anesthesia, an indwelling venous catheter was inserted into a forearm vein, and a blank blood sample was collected. Further 5-ml blood samples were collected in heparinized plastic tubes at 5, 10, 15, 30, 45, 60, 75, 90, 120, 150, 180, and 210 min after vecuronium administration. A blood sample also was withdrawn when the twitch height had recovered to 50% of its control value, and the concentration of vecuronium present in this sample was defined as Cp 50.

Analytic Techniques

Each blood sample was centrifuged 5 min after withdrawal, and 1 ml of plasma was acidified by adding 150 μl of 1 M NaH_2PO_4 in order to prevent hydrolysis of vecuronium. Spontaneous hydrolysis of vecuronium in plasma occurs at neutral *p*H and room temperature at a rate 0.3% as determined in our laboratory. The samples then were frozen until subsequent analysis. The plasma concentration of vecuronium was measured using a minor modification of the Rose Bengale fluorimetric method for pancuronium assay.[6] Among the drugs eventually used during anesthesia, Althesin® is the only one that may interfere with the assay of vecuronium and therefore was excluded from the anesthetic protocol. The lower limit of sensitivity of this method was 25 $ng \cdot ml^{-1}$, and the coefficient of variation was of 5% for eight samples at a concentration of 250 $ng \cdot ml^{-1}$. Since this method is not specific and measures vecuronium and its metabolites, it was compared with the specific method of Paanakker and Laar,[7] which measures unchanged vecuronium using high-pressure liquid chromatography (HPLC). After the administration of a large intravenous dose of 0.3 $mg \cdot kg^{-1}$ of vecuronium to three anesthetized patients, the plasma concentration of vecuronium was determined in serial blood samples by fluorimetry and by HPLC. The plasma concentration estimated by HPLC was 15% lower than by fluorimetry

over a range of concentration of 200 ng·ml^{-1} to 1,000 ng·ml^{-1}. After 90 min the plasma concentration of vecuronium decreased below the detection limit of 200 ng·ml^{-1} of the HPLC method. No peak corresponding to the 3–17- or 3,17-hydroxydeacetyl metabolites could be detected by HPLC. When fluorimetry was coupled with thin-layer chromatography, as previously described for the assay of pancuronium metabolites,[6] the 3-hydroxy metabolite was the only metabolite of vecuronium detectable in plasma. The relative proportion of this metabolite over the total plasma concentration accounted for only 5% after 5–75 min and 10% after 75–120 min. Data were fitted by both two- and three-compartment open pharmacokinetic models using a nonlinear, least-squares regression. A two-compartment model was selected using the technique of Gomeni and Gomeni.[8] The following parameters were calculated: the half-lives of distribution ($t_{1/2}$ α) and of elimination ($t_{1/2}$ β), the volume of the central compartment (V_1), the total apparent volume of distribution measured during the steady state (Vd_{ss}) or according to the method of the area under the curve (Vd β) and the plasma clearance (Cl). Statistical differences between the control group and the group of patients with cirrhosis were analyzed by the two-tailed nonparametric Mann-Whitney U-test.

Results

The clinical characteristics and the liver function tests of the patients with cirrhosis are shown in table 1. The plasma concentration decay curve of vecuronium is shown in the two groups of patients in figure 1. The initial plasma concentrations were not significantly different between the two groups, whereas the concentration remained at a much higher level during the elimination phase in patients with cirrhosis. The plasma clearance was decreased significantly ($P < 0.01$) in patients with cirrhosis to 2.73 ± 1.19 ml·min^{-1}·kg^{-1} as compared with 4.26 ± 1.38 ml·min^{-1}·kg^{-1} in the controls. The volume of the central compartment and the total apparent volume of distribution were not significantly different between the two groups: the elimination half-life was prolonged by 60% from 58 ± 19 min to 84 ± 23 min in patients with cirrhosis (table 2). The time interval from injection to recovery from neuromuscular blockade (at 50% of the control value) was prolonged significantly in patients with cirrhosis (table 3). The recovery index, which is the time interval from the recovery of 25–75% of the twitch height, also was prolonged significantly ($P < 0.05$) in patients with cirrhosis. The plasma concentrations that correlated with recovery to 50% of paralysis did not differ between the two groups (table 3).

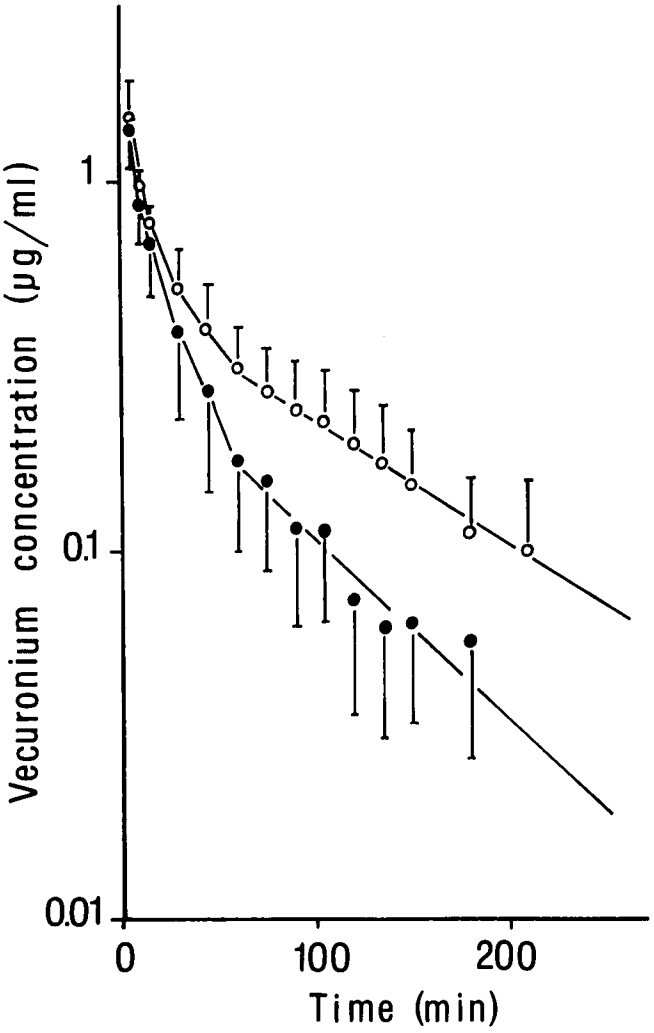

FIG. 1. Disappearance of vecuronium from the plasma following a single bolus dose of 0.2 mg·kg^{-1}. Semilogarithmic plot of the plasma concentration *versus* time for control patients (black circles) and cirrhotic patients (open circles).

Discussion

The present study clearly demonstrates that the plasma clearance of vecuronium is decreased markedly in patients with cirrhosis, since it was approximately half that found for normal patients. This change resulted in an increase in the elimination half-life and a prolonged vecuronium-induced neuromuscular blockade. In comparison, the plasma clearance of vecuronium remained unchanged in patients with complete renal failure.[3]

In the present study, the plasma concentration of vecuronium may be overestimated, since the fluorimetric assay[6] measures vecuronium as well as its hydroxydeacetyl metabolites. The comparison between the fluorimetric method and the more specific high-liquid pressure chromatographic method[7] suggests that metabolites may

TABLE 2. Pharmacokinetics of Vecuronium in Cirrhotic and Normal Patients

Patients Number	$t_{1/2}\ \alpha$* (min)	$t_{1/2}\ \beta$† (min)	V_1‡ ($l \cdot kg^{-1}$)	Vd_{ss}§ ($l \cdot kg^{-1}$)	$Vd\ \beta$¶ ($l \cdot kg^{-1}$)	Cl** ($ml \cdot min^{-1} \cdot kg^{-1}$)
Controls						
1	4.3	56	0.098	0.329	0.443	5.54
2	5.7	47	0.087	0.220	0.305	4.51
3	3.1	62	0.095	0.503	0.708	7.81
4	13.0	70	0.135	0.246	0.329	3.28
5	3.2	28	0.062	0.129	0.144	3.61
6	7.3	86	0.111	0.384	0.649	5.22
7	10.1	77	0.091	0.221	0.331	2.99
8	7.0	27	0.111	0.171	0.270	6.84
9	3.8	64	0.051	0.192	0.236	2.57
10	17.0	87	0.172	0.309	0.438	3.48
11	11.2	85	0.092	0.217	0.319	2.61
12	3.9	41	0.208	0.159	0.208	3.51
13	6.0	24	0.074	0.107	0.135	3.96
14	7.8	60	0.113	0.264	0.366	4.20
Mean ± SD	7.4 ± 3.6	58 ± 19	0.107 ± 0.036	0.246 ± 0.092	0.349 ± 0.148	4.26 ± 1.38
Cirrhosis						
1	5.8	61	0.170	0.394	0.451	5.10
2	7.8	90	0.081	0.206	0.245	1.87
3	9.1	92	0.138	0.385	0.543	4.14
4	4.7	94	0.065	0.183	0.201	1.47
5	2.6	70	0.066	0.303	0.350	3.50
6	1.7	39	0.034	0.139	0.164	3.40
7	11.7	100	0.065	0.143	0.173	1.20
8	4.9	89	0.099	0.281	0.309	2.40
9	6.1	88	0.111	0.342	0.419	3.31
10	2.2	59	0.036	0.205	0.257	3.03
11	10.6	90	0.150	0.271	0.311	2.39
12	8.7	134	0.080	0.168	0.179	0.93
Mean ± SD	6.3 ± 3.1	84 ± 23††	0.091 ± 0.042	0.253 ± 0.086	0.304 ± 0.112	2.73 ± 1.19††

* Distribution (alpha) half-life.
† Elimination (beta) half-life.
‡ Initial volume of distribution.
§ Total apparent volume of distribution at steady state.
¶ Total apparent volume of distribution measured by the method of the area under the curve.
** Plasma clearance.
†† $P < 0.01$.

account for 15% of the total concentration. Thus, there is a possibility that the presence of vecuronium metabolites slightly may alter the pharmacokinetic data. However, there is no reason to suggest that metabolites may be present in greater proportion in patients with cirrhosis than in controls. Thus, the comparison of the pharmacokinetic data between the two groups remains valid.

TABLE 3. Pharmacodynamics of Vecuronium in Cirrhotic and Normal Patients

	Duration (TH 0–50) (min)	Recovery Rate (TH 25–75) (min)	C_p 50 $\mu g \cdot ml^{-1}$
Controls (n = 14)	62 ± 16	21 ± 7	0.247 ± 0.060
Cirrhosic patients (n = 12)	130 ± 52*	44† ± 18	0.281 ± 0.129

* $P < 0.01$ *versus* controls.
† $P < 0.05$ *versus* controls.

Furthermore, the pharmacokinetic variables presently obtained in controls are very similar to those previously reported by Cronelly *et al.*[1] using a specific mass spectrometric method of assay of vecuronium.

These findings strongly support the hypothesis of a predominant hepatic elimination of vecuronium. It has been suggested that vecuronium may be relatively lipophilic as compared with pancuronium because it contains only one quaternary ammonium function. The additional although weak lipophilicity of vecuronium may favor its entry into the hepatocyte.[5] However, only 10–30% of the dose of vecuronium has been estimated to be eliminated in the bile in humans.[9] On the other hand, the biliary excretion of vecuronium may be underestimated in humans for technical reasons, mainly because of the difficulties in recovering the total bile flow immediately after the injection of the drug. Another possible mechanism could be an extensive uptake of vecuronium in special organelles, in the same manner as *d*-tubocurarine is stored in the lysosomes of hepatocytes.[10] Hepatic

uptake might be the main step influencing the rapid elimination of vecuronium, while biliary excretion would occur secondarily at a slower rate.

In previous pharmacokinetic studies of pancuronium and fazadinium in patients with cirrhosis we observed a marked increase in the total apparent volume of distribution and a decrease in the clearance of these two muscle relaxants.[11,12] In the present study, the volume of distribution of vecuronium was not enlarged in patients with cirrhosis, although their clinical profile did not differ from that of the patients in the previous studies. The degree of hepatic failure was moderate, corresponding to a 50% decrease in the prothrombin factors, and did not prevent elective surgery. A more likely explanation would be that the liver represents an important fraction of the total volume of distribution of vecuronium in healthy subjects. Consequently, a decrease in the accumulation of vecuronium in the cirrhotic liver would offset the increased distribution of this drug in other body tissues, so that the overall volume of distribution would not be altered.

The pharmacokinetic changes presently observed are relatively modest and may not reflect the importance of the hepatic disposal of vecuronium in humans. Since the patients we studied had only a moderate degree of hepatic failure, a substantial hepatic elimination of vecuronium probably occurred in the remaining functional hepatocytes. More pronounced pharmacokinetic alterations might be expected in patients with more severe liver failure or with complete biliary obstruction.

Delayed elimination of vecuronium caused a prolonged duration of paralysis in patients with cirrhosis. The enhanced duration of vecuronium-induced neuromuscular blockade in patients with cirrhosis was demonstrated in this study using a relatively large single dose of 0.2 $mg \cdot kg^{-1}$. It is likely that the rate of recovery from paralysis after a large dose of vecuronium is related directly to the elimination half-life. In the present study, a 44% increase in the elimination half-life was associated with a 100% increase in the duration of the recovery rate. The Cp 50 was measured during the elimination phase when a state of equilibrium is almost achieved between the concentration in the plasma and in the space surrounding the motor end-plate. The absence of significant change of the Cp 50 between the two groups of patients therefore suggests that the sensitivity of the neuromuscular junction to vecuronium is unchanged in patients with cirrhosis.

References

1. Cronnelly R, Fisher DM, Miller RD, Gencarelli P, Nguyen-Gruenke L, Castagnoli N: Pharmacokinetics and pharmacodynamics of vecuronium (Org NC 45) and pancuronium in anesthetized humans. ANESTHESIOLOGY 58:405–408, 1983
2. Durant NN, Houwertjes MC, Agoston S: Renal elimination of ORG-NC45 and pancuronium. ANESTHESIOLOGY 51:S266, 1979
3. Fahey MR, Morris RB, Miller RD, Nguyen TL, Upton RA: Pharmacokinetics of ORG NC 45 (norcuron) in patients with and without renal failure. Br J Anaesth 53: 1049–1052, 1981
4. Durant NN, Houwertjes MC, Agoston S: Hepatic elimination of ORG-NC 45 and pancuronium. ANESTHESIOLOGY 51:S267, 1979
5. Upton RA, Nguyen TL, Miller RD, Castagnoli N: Renal and biliary elimination of vecuronium ORG NC 45 and pancuronium in rats. Anesth Analg 61:313–316, 1982
6. Kersten UW, Meijer DKF, Agoston S: Fluorimetric and chromatographic determination of pancuronium bromide and its metabolites in biological materials. Clin Chim Acta 44:59–66, 1973
7. Paanakker JE, Van de Laar GLM: Determination of Org NC 45 (A myoneural blocking agent) in human plasma using high-performance normal-phase liquid chromatography. J Chromatogr 183:459–466, 1980
8. Gomeni C, Gomeni R IGPHARM: Interactive graphic package for pharmacokinetic analysis. Comp Biomed Res 11:345–361, 1978
9. Sohn YJ, Bencini A, Scaf AHJ, Kersten UW, Gregoretti S, Agoston S: Pharmacokinetics of vecuronium in man. ANESTHESIOLOGY 57:A256, 1982
10. Blom A, Scaf AHJ, Meijer DKF: Hepatic drug transport in the rat. A comparison between isolated hepatocytes, the isolated perfused liver and the liver in vivo. Biochem Pharmacol 31: 1553–1565, 1982
11. Duvaldestin P, Agoston S, Henzel D, Kersten UW, Desmonts JM: Pancuronium pharmacokinetics in patients with cirrhosis. Br J Anaesth 50:1131–1136, 1978
12. Duvaldestin P, Saada J, Henzel D, Saumon G: Fazadinium pharmacokinetics in patients with liver disease. Br J Anaesth 52:789–794, 1980