

Vecuronium in Alcoholic Liver Disease: A Pharmacokinetic and Pharmacodynamic Analysis

James R. Arden, M.D.,* Daniel P. Lynam, M.D.,* Kay P. Castagnoli, B.A.,† P. Claver Canfell, M.S.,†
John C. Cannon, M.D.,‡ Ronald D. Miller, M.D.§

To determine the effect of alcoholic liver disease on the pharmacokinetics and pharmacodynamics of vecuronium, the authors administered vecuronium $0.1 \text{ mg} \cdot \text{kg}^{-1}$ iv to ten surgical patients with alcoholic liver disease and ten healthy surgical patients. All patients were anesthetized with nitrous oxide and isoflurane. We recorded and quantitated the force of thumb adduction in response to supra-maximal ulnar nerve stimulation. Plasma concentrations of vecuronium and its 3-desacetyl metabolite were determined by a capillary gas chromatography assay. Only the time to attain 100% twitch depression (onset time) was prolonged in liver disease patients (2.8 ± 0.7 min; mean \pm SD) as compared to control patients (1.9 ± 0.4 min). The time from vecuronium administration to recovery of twitch tension was unaffected by alcoholic liver disease. The time to the reappearance of twitch response was 32.7 ± 9.7 min in patients with liver disease and 36.8 ± 15.5 min in controls. Plasma concentration-time data were fit to a two-compartment model. Vecuronium clearance, steady-state volume of distribution, and elimination half-time were unchanged by alcoholic liver disease. The authors conclude that alcoholic liver disease does not affect the pharmacokinetics or duration of action of vecuronium when an intravenous bolus dose of $0.1 \text{ mg} \cdot \text{kg}^{-1}$ is administered. (Key words: Liver. Neuromuscular relaxants: vecuronium. Pharmacodynamics: vecuronium. Pharmacokinetics: vecuronium.)

HEPATIC UPTAKE LOWERS the blood concentration of vecuronium and is partly responsible for terminating its neuromuscular blocking actions.¹ Vecuronium is probably degraded by deacetylation, and its disposition could, therefore, be abnormal in patients with significant hepatocellular dysfunction.

In experiments which combined both pharmacokinetic and pharmacodynamic analysis of vecuronium, Lebrault *et al.*² demonstrated a prolonged duration of

action and a decrease in plasma clearance when a relatively large dose of vecuronium ($0.2 \text{ mg} \cdot \text{kg}^{-1}$) was administered to patients with hepatic cirrhosis. In two other studies^{3,4} of patients with hepatic cirrhosis, the duration of action of vecuronium, $0.1 \text{ mg} \cdot \text{kg}^{-1}$, was shorter than control, and the duration of action of vecuronium, $0.15 \text{ mg} \cdot \text{kg}^{-1}$, a dose intermediate in size to the above doses, was unchanged from control. No pharmacokinetic data were collected in either of these studies.

We designed this study to test the hypothesis that alcoholic liver disease does not alter the response to a dose of vecuronium commonly used to facilitate tracheal intubation.^{5,6} Specifically, we analyzed the pharmacokinetics and pharmacodynamics of vecuronium $0.1 \text{ mg} \cdot \text{kg}^{-1}$ iv in anesthetized, surgical patients who had either acute or chronic alcohol-induced hepatocellular disease, and compared these results with those obtained in healthy surgical patients.

Materials and Methods

With approval by the Human Studies Review Board and after obtaining informed consent, we selected ten ASA physical status I and ten ASA physical status II-III patients with alcohol-related hepatocellular disease, all of whom were scheduled for elective surgery. These patients did not differ significantly in age or weight. Mean age was 41 ± 9 yr, and mean weight was 70 ± 13 kg. We included patients in the alcoholic liver disease group if they had a history of alcohol abuse and they met one of the following criteria: 1) biopsy-proven hepatic cirrhosis or 2) alcohol-related elevation of serum transaminase values (aspartate transaminase, alanine transaminase) to a level greater than five times the upper limits of normal within the previous 36 h.

Patients were pre-medicated with diazepam 2-10 mg po; one patient was encephalopathic, and was not pre-medicated. After monitors were applied, anesthesia was induced with thiopental ($3-4 \text{ mg} \cdot \text{kg}^{-1}$ iv). Ventilation was controlled and anesthesia continued with end-tidal concentrations of isoflurane, 1-3% in 60% N_2O , as determined by mass spectrometry. A second intravenous catheter was inserted into the contralateral arm for

* Assistant Professor of Anesthesia.

† Associate Specialist.

‡ Research Fellow.

§ Professor and Chairman, Anesthesia, Professor of Pharmacology.

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Address reprint requests to Dr. Arden: Department of Anesthesia, 3S-50 San Francisco General Hospital, 1001 Potrero Avenue, San Francisco, California 94110.

TABLE 1. Vecuronium Pharmacokinetics

Age (Yr)	Diagnosis (Child's Class)	Initial Distribution Volume ($l \cdot kg^{-1}$)	Clearance ($ml \cdot kg^{-1} \cdot min^{-1}$)	Volume of Distribution (Steady-state) ($l \cdot kg^{-1}$)	Terminal Elimination Half-time (Min)
31	EtOH Hepatitis	.09	4.1	.20	63.0
44	Cirrhosis (C)	.11	4.1	.20	63.0
43	Cirrhosis (C)	.09	5.6	.26	43.0
40	Cirrhosis (A)	.19	5.4	.30	57.8
51	Cirrhosis (B)	.07	2.7	.18	57.8
53	Cirrhosis (A)	.11	3.6	.24	63.0
62	Cirrhosis (C)	.11	4.8	.30	57.8
44	Cirrhosis (C)	.07	4.9	.21	40.8
31	EtOH Hepatitis	.10	4.1	.14	38.5
45	Cirrhosis (C)	.12	5.1	.17	28.9
Mean 44.4 (SD) (9.5)		.11 (.03)	4.4 (0.9)	.22 (.05)	51.4 (12.4)
27	Healthy	.09	3.6	.18	63.0
35	Healthy	.11	4.0	.22	77.0
33	Healthy	.07	4.7	.13	40.8
52	Healthy	.05	2.1	.08	63.0
43	Healthy	.08	3.0	.20	63.0
36	Healthy	.12	8.8	.27	53.3
39	Healthy	.09	6.3	.15	31.5
38	Healthy	.06	2.2	.17	77.0
26	Healthy	.09	5.2	.17	31.5
44	Healthy	.11	5.3	.25	77.0
Mean 37.3 (SD) (7.9)		.08 (.02)	4.5 (2.0)	.18 (.06)	57.7 (17.9)

blood sampling. We recorded the force of thumb adduction in response to supramaximal ulnar nerve stimulation at 0.15 Hz using a Grass S44 (Grass Instruments, Quincy, MA) stimulator and a Medar transducer (Medar Inc., Scarsdale, NY). Recording of twitch tension was continuous throughout the study period. The trachea was then intubated without the use of a muscle relaxant. Mechanical ventilation was instituted, and inspired isoflurane concentration was reduced until a stable end-tidal concentration of isoflurane, 1–1.5% in N_2O/O_2 , was attained. End-tidal P_{CO_2} was maintained at 35–40 mmHg. Temperature was maintained at 35–37° C.

After baseline recording, we administered vecuronium 0.1 $mg \cdot kg^{-1}$ as an intravenous bolus. Venous blood was collected into heparinized tubes at 2, 4, 6, 8, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150, and 180 min and at 4, 5, 6, 7, and 8 h after vecuronium was administered. Blood samples were briefly stored on ice, centrifuged, and separated into the plasma fraction that was acidified with phosphoric acid and frozen at $-20^\circ C$ until further analysis.

Plasma vecuronium concentration and the concentration of its metabolite, 3-desacetylvecuronium,^{7,8}

were determined by capillary gas chromatography using a nitrogen-sensitive detector.⁹ The assay was sensitive to 5 $ng \cdot ml^{-1}$ with a coefficient of variation of 9.7% at 10.3 $ng \cdot ml^{-1}$, and was linear to 5000 $ng \cdot ml^{-1}$. Plasma protein binding was not measured.

Because of the specificity of the gas chromatography assay, the pharmacokinetic analysis of vecuronium was based on concentrations of the parent compound alone, and did not include any contribution by the deacetylated analogs. Plasma vecuronium concentration-time data were fit to both two- and three-compartment mammillary pharmacokinetic models using non-linear regression. Models were compared statistically to determine the simplest model which accounted for the data.¹⁰ Pharmacokinetic parameters were calculated using standard formulas.

We determined the time at which complete depression of twitch tension (*i.e.*, <5% control) was achieved and the times at which twitch tension recovered to 5, 10, 25, 50, 75, and 95% of baseline values. Recovery index, the time between 25 and 75% recovery of twitch tension, was calculated. To define the time course of the onset of vecuronium blockade more precisely, we determined the percent of control twitch tension at 6-s intervals. We used these data to construct each patient's onset curve, a plot of the twitch height as a percent of control versus time. The onset curve was linear between 20 and 80% of control twitch tension. Using linear regression, we calculated the slope and the x-intercept (minutes) of this portion of the onset curve for each patient, and pooled these data for group comparisons.

Pharmacokinetic and pharmacodynamic data from both groups were compared by the Mann-Whitney rank-sum test or by Student's *t* test where appropriate. Correlations between pharmacokinetic and pharmacodynamic values were described by linear regression. A BMDP statistical package (1983) was used for all statistical analyses. A value of $P < .05$ was considered significant.

Results

Pharmacokinetic data were collected for ten normal patients and ten patients with alcoholic liver disease. Eight of the ten liver disease patients had biopsy-proven cirrhosis, and six of these patients had 0.5–1.5 liters of ascites by the surgeon's intraoperative estimate. Two patients had acute alcoholic hepatitis by history and preoperative transaminase elevation. Patients had general, orthopedic, gynecologic, or plastic surgery with a mean anesthesia time of 2.5 h (range 0.7–4.1 h). Isoflurane concentrations were similar for both groups of patients throughout the study period.

The total dose of vecuronium administered was similar for both liver disease patients and control patients (6.8 ± 1.1 and 7.3 ± 1.5 mg, respectively). A two-compartment pharmacokinetic model was statistically preferred to a three-compartment model. Pharmacokinetic data for liver disease patients and controls are shown in table 1. There were no significant pharmacokinetic differences between groups. Clearance and steady-state volume of distribution were similar for all patients. The clearance in alcoholic liver disease patients was $4.2 \pm 0.9 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (mean \pm SD), and control clearance was $4.5 \pm 2.0 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Combining these values, mean clearance for both groups was $4.4 \pm 1.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. The volume of distribution at steady-state was $0.21 \pm .07 \text{ l} \cdot \text{kg}^{-1}$ in liver disease patients and $0.18 \pm .06 \text{ l} \cdot \text{kg}^{-1}$ in controls. This resulted in a mean steady-state volume of distribution of $0.20 \pm .06 \text{ l} \cdot \text{kg}^{-1}$ for both groups. The elimination half-times in liver disease patients and controls were 51.4 ± 12.4 and 57.7 ± 17.9 min, respectively. The mean elimination half-time for all patients was 54.5 ± 15.3 min. There was no significant difference in rate constants, initial distribution volume, or mean residence time between groups.

The 3-desacetyl metabolite of vecuronium was detectable in plasma samples from both groups of patients throughout the period of sample collection.

The onset time of neuromuscular blockade was determined for ten patients with liver disease and ten controls. The time required to achieve 100% twitch depression was significantly different between the two groups ($P < .005$). Complete twitch depression was observed at 2.8 ± 0.7 min in liver disease patients and at 1.9 ± 0.4 min in controls.

The onset curve (twitch height vs. time curve, figs. 1, 2) was defined for nine patients from each group. Onset curves were displaced to the right in alcoholic liver disease patients. The x-intercepts of the linear portion of the onset curves were significantly greater in patients with liver disease than in normal patients ($P < .005$). The slopes of the linear portion of the onset curves were similar for both groups.

Data on recovery from the vecuronium neuromuscular blockades are shown in figure 3. One patient from each group of ten patients showed no evidence of recovery after more than 60 min. Both patients had prompt recovery of muscle strength after reversal of neuromuscular blockade with edrophonium. Recovery data were not recorded for one patient with liver disease. The time to the beginning of recovery of twitch tension is reported for eight patients with liver disease and nine controls. There was no difference between the groups in the time required to begin recovery of control twitch

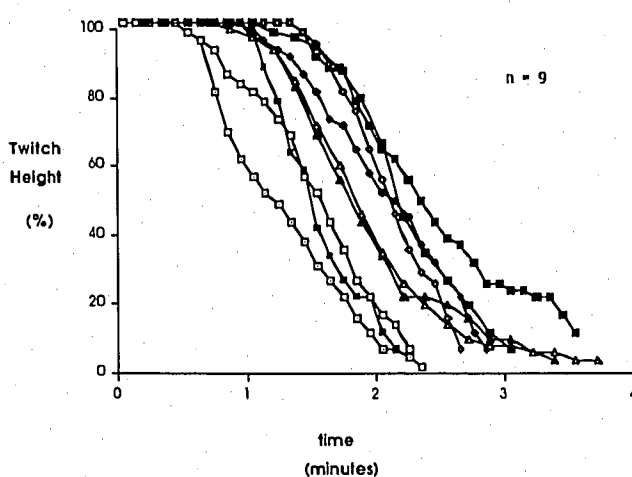


FIG. 1. Onset curves for nine patients with liver disease showing twitch height (as a percent of control twitch height) versus time for the period between vecuronium administration and the time at which complete twitch depression (<5% control twitch height) was observed.

tension, which was 32.7 ± 9.7 min in liver disease patients and 36.8 ± 15.5 min in controls. Other recovery times were not different between groups. The time to 50% recovery was 59.8 ± 26.5 min for liver disease patients and 66.1 ± 28.7 min for controls (NS).

Correlation of pharmacokinetic and pharmacodynamic data revealed only a weak correlation between clearance and the time to the beginning of recovery from the block ($r = -.63$). Steady-state volume of distribution did not correlate with recovery time. We found no pharmacokinetic correlation with the longer

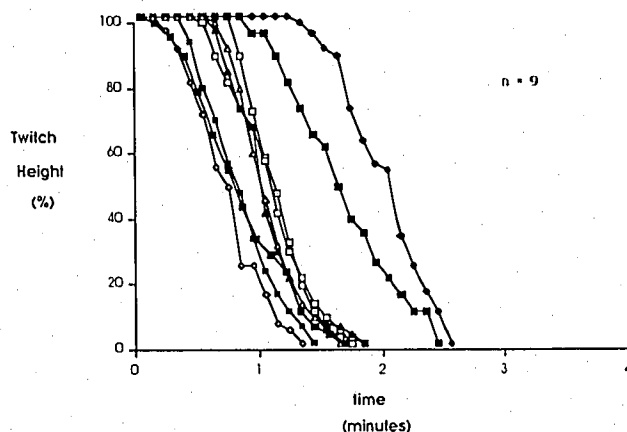


FIG. 2. Onset curves for vecuronium neuromuscular blockade in nine healthy patients. Comparison of these data with those of figure 1 reveals that the onset curves are displaced to the right in patients with liver disease.

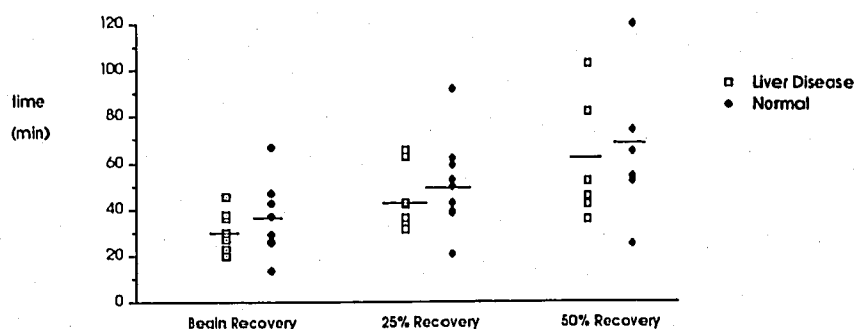


FIG. 3. Recovery times for patients with liver disease and for healthy patients after vecuronium $0.1 \text{ mg} \cdot \text{kg}^{-1}$. The time to the beginning of recovery of twitch tension is reported for eight liver disease and nine healthy patients, the time to 25% recovery is reported for seven liver disease and nine healthy patients, and the time to 50% recovery is reported for six liver disease and seven healthy patients. The end of surgery precluded further recording of spontaneous recovery in the remaining patients. There was no difference in recovery times between patients with liver disease and healthy patients.

time required to achieve 100% blockade in patients with liver disease.

Discussion

Our data indicate that alcoholic liver disease does not alter the pharmacokinetics or duration of action of vecuronium when a dose of $0.1 \text{ mg} \cdot \text{kg}^{-1}$ is administered. Clearance, steady-state volume of distribution, and elimination half-time were all unaffected by alcoholic liver disease.

Lebrault *et al.*² found that the duration of action of vecuronium was increased by 100% over control when a dose of $0.2 \text{ mg} \cdot \text{kg}^{-1}$ was administered to patients with hepatic cirrhosis. The prolonged block in patients with liver disease was explained in part by a decrease in clearance. In that study, the clearance of vecuronium in patients with hepatic cirrhosis was $2.7 \pm 1.2 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (control, $4.3 \pm 1.4 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) after a dose of $0.2 \text{ mg} \cdot \text{kg}^{-1}$.² In the patients with liver disease in our study, clearance was $4.2 \pm 0.9 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (control, $4.5 \pm 2.0 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) after a dose of $0.1 \text{ mg} \cdot \text{kg}^{-1}$. If the results of these two studies are compared, it appears that, in patients with alcoholic liver disease, vecuronium clearance may decrease when the dose is doubled.

Elimination of most drugs at therapeutic concentrations occurs so that a constant fraction of the remaining drug is removed each minute (first-order kinetics). Drugs whose rate of removal from the body is slower at higher drug concentrations (*e.g.*, phenytoin, salicylate) are said to show concentration-dependent or dose-dependent clearance.¹¹ The difference in clearance in alcoholic liver disease patients in this study and in the study by Lebrault *et al.* could be explained if the clearance of vecuronium is dependent on the dose administered. Hepatic uptake may be a major determinant of

vecuronium clearance,¹ since animal data suggest that a relatively small fraction of a dose of vecuronium is metabolized.¹² If higher doses of vecuronium saturate the hepatic uptake capacity of patients with alcoholic liver disease, clearance would decrease. The clinical implication of dose-dependent clearance would be that large, or repeated doses may result in accumulation of vecuronium in the plasma of patients with liver disease.

It is possible that the discrepancy in clearance in patients with liver disease after different doses of vecuronium is the result of analytical differences in these studies. Vecuronium concentration was determined by fluorimetry in the study by Lebrault *et al.*² and by gas chromatography in our study. The fluorimetric assay does not distinguish vecuronium metabolites from the parent compound. It appears that only a small fraction of a dose of vecuronium is metabolized, so the metabolites should contribute little to the calculation of clearance. Control clearance values were similar in both studies ($4.3 \pm 1.4 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and $4.5 \pm 2.0 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), despite the fact that different assays were used and different doses of vecuronium were administered. This suggests that the dose-dependent clearance seen in liver disease patients in these two studies is not due to differences in assay technique.

The time required to achieve 100% twitch depression was longer in patients with liver disease. The linear portion of the onset curve for liver disease patients is displaced to the right, but the rate of decline in twitch height parallels the decline in twitch height seen in normal patients. A delay in the onset of vecuronium blockade in cirrhosis has been reported previously,³ but the pharmacokinetic or pharmacodynamic basis of the delay has not been examined.

If the delay in onset resulted from a pharmacokinetic change, the effective plasma concentration of vecuronium would be the same for liver disease and normal patients. Patients with liver disease would presumably

reach this concentration more slowly, and the initial distribution volume would appear to be larger in liver disease. The results of this study suggest that the initial distribution volume for vecuronium is unchanged by liver disease. Alternately, a prolonged approach to the effective concentration could result from altered inter-compartmental distribution processes in liver disease with slower transfer of drug to the compartment containing the neuromuscular junction. While this might be the case, the two-compartment pharmacokinetic model in our study would not distinguish the multiple compartments which would be altered in liver disease.

Alteration of the plasma protein binding in liver disease has been proposed as a possible explanation of the relative resistance of these patients to nondepolarizing neuromuscular blocking drugs.¹³ If protein binding is increased in patients with liver disease, this may result in a smaller active, unbound fraction, and a delay in onset. Measurement of the plasma protein binding of vecuronium has shown that the protein binding of vecuronium is unaffected by liver disease.¹⁴ In addition, vecuronium is not highly protein bound (approximately 30% bound), and alteration of protein binding should have a limited effect on the fraction of the dose which is in the active, unbound form. Alteration in protein binding of vecuronium does not appear to explain the delayed onset in alcoholic liver disease.

If the difference in onset time resulted from a pharmacodynamic change in liver disease, we would expect different concentrations to have the same neuromuscular blocking effect. If patients with liver disease were resistant to vecuronium, more drug would be needed at the site of action to achieve a given degree of blockade. We would expect to see an earlier recovery in liver disease patients as compared to normal patients, since plasma concentrations of vecuronium decline at the same rate for both groups. We did not observe an earlier recovery in patients with liver disease. Thus, a pharmacodynamic mechanism for the delayed onset in liver disease appears unlikely.

The time required to recover from neuromuscular blockade was similar for all patients, regardless of their hepatic function, after a single dose of $0.1 \text{ mg} \cdot \text{kg}^{-1}$ of vecuronium. Bell *et al.*³ showed that vecuronium, $0.1 \text{ mg} \cdot \text{kg}^{-1}$, resulted in a shorter time to the reappearance of twitch response in liver disease patients ($18.3 \pm 6 \text{ min}$) than in controls ($23 \pm 5 \text{ min}$). The times to the reappearance of twitch for both groups of patients in our study were longer (32.7 ± 9.7 and $36.8 \pm 15.5 \text{ min}$) than those reported in that study. The difference in recovery times between these studies may be the result of the potentiation of the neuromuscular blocking effect of vecuronium in our patients, who were anesthe-

tized with isoflurane instead of the combination of N_2O -thiopental-fentanyl, which was used in the Bell *et al.* study.

The alcoholic liver disease patients included in this study had different degrees of hepatic dysfunction. Their response to vecuronium and their ability to handle the drug may reflect these differences. Quantitation of hepatic dysfunction is difficult. Transaminase levels have no quantitative relation to the ability of the liver to handle drugs, and precise descriptions of the liver's drug metabolizing capability (*e.g.*, antipyrine clearance) have limited application. We chose to study patients whose liver disease had the same etiology with the understanding that they should have a similar type of impairment in drug disposition. It is also possible that the liver damage in our patients was not severe enough to affect their response to vecuronium. This study was not designed to develop a model of a functionally hepatectomized patient. Instead, we studied patients who were not severely debilitated by their alcohol-induced liver disease to illustrate clinically relevant effects in a population that the anesthesiologist would be likely to encounter.

This study demonstrates that the recently developed capillary gas chromatography assay for vecuronium is sufficiently specific and sensitive for pharmacokinetic analysis of this drug. Earlier studies of vecuronium employed a more complex mass spectrometry assay¹⁵ that had a sensitivity ($2 \text{ ng} \cdot \text{kg}^{-1}$) and coefficient of variation (10%) similar to that in our assay. Using a gas chromatography technique, we were able to document the presence of the 3-desacetyl metabolite of vecuronium in human plasma. Analysis of the metabolism of vecuronium would require a more complete collection of the eliminated drug than we performed in this study, since the analysis of drug metabolism must account for the entire mass of the dose administered.

In summary, we have demonstrated that alcoholic liver disease does not alter the pharmacokinetics or the duration of action of vecuronium after a dose of $0.1 \text{ mg} \cdot \text{kg}^{-1}$ is administered. The time to attain complete depression of twitch tension is significantly prolonged in patients with alcoholic hepatocellular disease. Although altered sensitivity to vecuronium does not appear to explain this prolongation, this study was unable to demonstrate a pharmacokinetic explanation for this observation.

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