Vecuronium in Alcoholic Liver Disease: A Pharmacokinetic and Pharmacodynamic Analysis

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To determine the effect of alcoholic liver disease on the pharmacokinetics and pharmacodynamics of vecuronium, the authors administered vecuronium 0.1 mg·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 supramaximal 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 ± 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 36.3 ± 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 mg·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 mg·kg⁻¹) was administered to patients with hepatic cirrhosis. In two other studies³,⁴ of patients with hepatic cirrhosis, the duration of action of vecuronium, 0.1 mg·kg⁻¹, was shorter than control, and the duration of action of vecuronium, 0.15 mg·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 mg·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 mg·kg⁻¹ iv). Ventilation was controlled and anesthesia continued with end-tidal concentrations of isoflurane, 1–3% in 60% N₂O, as determined by mass spectrometry. A second intravenous catheter was inserted into the contralateral arm for
TABLE I. Vecuronium Pharmacokinetics

<table>
<thead>
<tr>
<th>Age (Yr)</th>
<th>Diagnosis (Child's Class)</th>
<th>Initial Distribution</th>
<th>Volume of Distribution</th>
<th>Terminal Elimination Halftime (Min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>EtOH: Hepatitis</td>
<td>0.09</td>
<td>4.1</td>
<td>0.20</td>
</tr>
<tr>
<td>44</td>
<td>Cirrhosis (C)</td>
<td>0.11</td>
<td>4.1</td>
<td>0.20</td>
</tr>
<tr>
<td>43</td>
<td>Cirrhosis (C)</td>
<td>0.09</td>
<td>5.6</td>
<td>0.24</td>
</tr>
<tr>
<td>40</td>
<td>Cirrhosis (A)</td>
<td>0.19</td>
<td>5.4</td>
<td>0.30</td>
</tr>
<tr>
<td>51</td>
<td>Cirrhosis (B)</td>
<td>0.07</td>
<td>7.7</td>
<td>0.18</td>
</tr>
<tr>
<td>53</td>
<td>Cirrhosis (C)</td>
<td>0.11</td>
<td>3.6</td>
<td>0.24</td>
</tr>
<tr>
<td>62</td>
<td>Cirrhosis (C)</td>
<td>0.11</td>
<td>4.8</td>
<td>0.30</td>
</tr>
<tr>
<td>44</td>
<td>Cirrhosis (C)</td>
<td>0.07</td>
<td>4.9</td>
<td>0.21</td>
</tr>
<tr>
<td>31</td>
<td>EtOH: Hepatitis</td>
<td>0.10</td>
<td>4.1</td>
<td>0.14</td>
</tr>
<tr>
<td>45</td>
<td>Cirrhosis (C)</td>
<td>0.12</td>
<td>5.1</td>
<td>0.17</td>
</tr>
<tr>
<td>Mean 44.4</td>
<td>(SD 9.5)</td>
<td>0.11</td>
<td>4.4</td>
<td>0.22</td>
</tr>
</tbody>
</table>

were determined by capillary gas chromatography using a nitrogen-sensitive detector.9 The assay was sensitive to 5 ng·ml⁻¹ with a coefficient of variation of 9.7% at 10.3 ng·ml⁻¹, and was linear to 5000 ng·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 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 0-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.

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 N₂O/O₂, was attained. End-tidal P CO₂ was maintained at 35–40 mmHg. Temperature was maintained at 35–37°C.

After baseline recording, we administered vecuronium 0.1 mg·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°C until further analysis.

Plasma vecuronium concentration and the concentration of its metabolite, 3-desacetylvecuronium,7,8
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 ± 0.9 ml·kg⁻¹·min⁻¹ (mean ± SD), and control clearance was 4.5 ± 2.0 ml·kg⁻¹·min⁻¹. Combining these values, mean clearance for both groups was 4.4 ± 1.5 ml·kg⁻¹·min⁻¹. The volume of distribution at steady-state was 0.21 ± 0.07 l·kg⁻¹ in liver disease patients and 0.18 ± 0.06 l·kg⁻¹ in controls. This resulted in a mean steady-state volume of distribution of 0.20 ± 0.06 l·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 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...
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 mg·kg⁻¹ is administered. Clearance, steady-state volume of distribution, and elimination halftime were all unaffected by alcoholic liver disease.

Lebrault et al. found that the duration of action of vecuronium was increased by 100% over control when a dose of 0.2 mg·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 ± 1.2 ml·kg⁻¹·min⁻¹ (control, 4.3 ± 1.4 ml·kg⁻¹·min⁻¹) after a dose of 0.2 mg·kg⁻¹. In the patients with liver disease in our study, clearance was 4.2 ± 0.9 ml·kg⁻¹·min⁻¹ (control, 4.5 ± 2.0 ml·kg⁻¹·min⁻¹) after a dose of 0.1 mg·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. 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, since animal data suggest that a relatively small fraction of a dose of vecuronium is metabolized. 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, in the 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. 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 ± 1.4 ml·kg⁻¹·min⁻¹ and 4.5 ± 2.0 ml·kg⁻¹·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, 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 con-
taining 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 dis-
ease has been proposed as a possible explanation of
the relative resistance of these patients to nondepolarizing
neuromuscular blocking drugs. 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 vecuro-
nium has shown that the protein binding of vecuronium
is unaffected by liver disease. 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 phar-
macodynamic change in liver disease, we would expect
different concentrations to have the same neuromuscu-
lar 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 ear-
lier recovery in patients with liver disease. Thus, a phar-
macodynamic 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 mg·kg⁻¹ of
vecuronium. Bell et al. showed that vecuronium, 0.1
mg·kg⁻¹, resulted in a shorter time to the reappearance
of twitch response in liver disease patients (18.3 ± 6
min) than in controls (23 ± 5 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 ± 15.5 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 ef-
effect of vecuronium in our patients, who were anesthe-
tized with isoflurane instead of the combination of
N₂O-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 han-
dle 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 un-
derstanding that they should have a similar type of im-
pairment 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 hepato-
tomized patient. Instead, we studied patients who were
not severely debilitated by their alcohol-induced liver
disease to illustrate clinically relevant effects in a popu-
lation that the anesthesiologist would be likely to en-
counter.

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 em-
ployed a more complex mass spectrometry assay that
had a sensitivity (2 ng·kg⁻¹) and coefficient of variation
(10%) similar to that in our assay. Using a gas chro-
matography technique, we were able to document the
presence of the 3-desacetyl metabolite of vecuronium in
human plasma. Analysis of the metabolism of vecuro-
nium 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
mg·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 dem-
strate a pharmacokinetic explanation for this obser-
vation.

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