Do the pharmacokinetics of vecuronium change during prolonged administration in critically ill patients?

V. Segredo, J. E. Caldwell, P. M. C. Wright, M. L. Sharma, L. D. Gruenke and R. D. Miller

Summary
Neuromuscular blocking drugs may be administered over several days to patients in the intensive care unit (ICU), but their pharmacokinetics have been studied at only one point in time, or assumed to be constant throughout the period of administration. We sought to determine if, in individual patients, the pharmacokinetics of vecuronium changed over the course of its administration in the ICU. In six critically ill patients, we measured plasma vecuronium concentrations during two periods: first, during initial administration of vecuronium and second, after its administration continuously for 3–6 days. A pharmacokinetic model was fitted to these plasma concentration data, and its parameters permitted to vary between the periods to determine if they had altered. Individual clearance values during the study ranged from 1.4 to 4.4 ml kg\(^{-1}\) min\(^{-1}\). During prolonged administration, vecuronium clearance increased in three and decreased in two patients. This change ranged from a 61% decrease to a 58% increase, and was not linked to any clinical factor. The steady-state volume of distribution (range 368–1765 ml kg\(^{-1}\); median 494 ml kg\(^{-1}\)) did not change in any patient during the study. The change in clearance of vecuronium during its prolonged administration in critically ill patients suggests that future studies of neuromuscular blocking drugs in the ICU should take account of their changing pharmacokinetics over the course of administration. (Br. J. Anaesth. 1998; 80: 715–719)

Keywords: intensive care vecuronium; neuromuscular block vecuronium; pharmacokinetics vecuronium

The administration of neuromuscular blocking drugs is a common practice in the intensive care unit (ICU), where these drugs may be given for days or weeks.\(^1\) Studies of the pharmacokinetics of neuromuscular blocking drugs in the ICU have been performed at only a single time during drug administration\(^4\) or, if the study was conducted over several days, it was assumed that the pharmacokinetics were constant during the period of study.\(^5\) Because neuromuscular blocking drugs are often given for several days, during which time the physiological status of the patients may alter, the pharmacokinetics of the drugs may also change, and an estimate of pharmacokinetics at one point in time may not be accurate at a later time. Vecuronium has been used commonly, and for prolonged periods, in the ICU.\(^4\) In the present study we determined the pharmacokinetics of vecuronium in patients in the ICU, and investigated whether the pharmacokinetics in individual patients changed during prolonged administration of the drug. If the pharmacokinetics of vecuronium change during prolonged administration, the potential for changing pharmacokinetics should be taken into account in future studies of other neuromuscular blocking drugs in the ICU.

Patients and methods
The study was approved by the Committee of Human Research of the University of California at San Francisco. After obtaining written informed consent from each patient’s next of kin and primary ICU physician, we consecutively studied six critically ill patients (three males, three females) aged 22–86 yr. Patients receiving assisted ventilation for adult respiratory distress syndrome (ARDS) were screened for possible enrolment in the study if the attending ICU physician decided that neuromuscular block was clinically indicated. Patients with a history of neuromuscular disease, renal failure requiring haemodialysis, or administration of a neuromuscular blocking drug in the 24 h before the start of the study were excluded.

PHARMACOKINETIC STUDY
In all patients vecuronium was administered i.v. at a rate of 6 \(\mu g\) kg\(^{-1}\) min\(^{-1}\) until complete neuromuscular block was induced (approximately 10 min). Arterial blood was sampled before and at 2, 4, 6, 8, 10, 15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300 and 360 min after the beginning of the infusion.

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Patient 1 2 3 4 5 6 function of 9.2 denotes a significant improvement over a simpler model (\(P < 0.01\)). Bold type: values for the optimal model reached a steady state before discontinuation of the final infusion. Basic parameters of the models were clearance (\(C_l\)), intercompartmental clearances (\(Q_1\) and \(Q_2\)), and volumes of distribution \(V_1\), \(V_2\) and \(V_3\). Volume of distribution at steady state (\(V_p\)) was equal to \(V_1 + V_2 + V_3\). First two- and three-compartment mamillary models were fitted to the data from each subject. The three-compartment model was used subsequently only if it could be statistically justified. Next, additional (change) parameters were introduced, each permitting one basic parameter (\(C_l\), \(V_p\) etc.) to vary from the first to the second infusion. These change parameters were accepted into the model only if they statistically and visually improved the fit of the model to the data. When all justified parameters had been introduced, the necessity for each one was tested by removing it and obtaining fresh parameter estimates. The necessity for a change parameter was used to evaluate whether or not a basic parameter had altered, and the magnitude of the change in the basic parameter was determined from the value of the change parameter.

Statistical justification for the use of a three-compartment rather than a two-compartment model and for inclusion of a new parameter in the model was a decrease of 9.2 in the NONMEM objective function \((P < 0.01)\).10

Table 1  Patient characteristics, plasma creatinine, total bilirubin, and liver function grade during initial administration of vecuronium (I) and after stopping its administration (II) in critically ill patients. *Liver function was graded in four classes: 0 = normal liver function tests; 1 = increased plasma aspartate aminotransferase (AST) and alkaline phosphatase (ALK-P) levels without increased bilirubin concentration or prothrombin time; 2 = increased plasma AST, ALK-P and bilirubin concentration without increased prothrombin time; 3 = increased prothrombin time caused by altered liver function

<table>
<thead>
<tr>
<th>Patient</th>
<th>Primary pathology</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Creatinine ((\mumol\ l^{-1}))</th>
<th>Bilirubin ((\mumol\ l^{-1}))</th>
<th>Liver function*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sepsis F</td>
<td>61</td>
<td>65</td>
<td>106</td>
<td>124</td>
<td>10.4</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Liver failure F</td>
<td>27</td>
<td>67</td>
<td>80</td>
<td>71</td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Unknown M</td>
<td>22</td>
<td>64</td>
<td>80</td>
<td>71</td>
<td>20</td>
<td>18.1</td>
</tr>
<tr>
<td>4</td>
<td>Sepsis M</td>
<td>32</td>
<td>60</td>
<td>150</td>
<td>168</td>
<td>41</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>Pneumonia M</td>
<td>86</td>
<td>64</td>
<td>159</td>
<td>248</td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Sepsis F</td>
<td>39</td>
<td>65</td>
<td>80</td>
<td>71</td>
<td>20</td>
<td>18.1</td>
</tr>
</tbody>
</table>

Table 2  Reasons for mechanical ventilation and sedative drugs used

<table>
<thead>
<tr>
<th>Patient</th>
<th>Primary pathology</th>
<th>Aetiology of respiratory failure</th>
<th>Sedation and analgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>Pneumocystis pneumonia; systemic candidiasis</td>
<td>Midazolam, lorazepam, morphine</td>
</tr>
<tr>
<td>2</td>
<td>Alcoholic cirrhosis and encéphalopathy</td>
<td>Aspiration pneumonia</td>
<td>Lorazepam, morphine</td>
</tr>
<tr>
<td>3</td>
<td>Postoperative urinary tract infection</td>
<td>Enterococcal sepsis</td>
<td>Midazolam, morphine</td>
</tr>
<tr>
<td>4</td>
<td>Repair of abdominal aortic aneurysm</td>
<td>Aspiration pneumonia</td>
<td>Lorazepam, morphine</td>
</tr>
<tr>
<td>5</td>
<td>Testicular cancer and pancytopenia</td>
<td>Sepsis of unknown aetiology</td>
<td>Midazolam, morphine</td>
</tr>
<tr>
<td>6</td>
<td>Malignant histiocytosis and pancytopenia</td>
<td>Staphylococcal sepsis</td>
<td>Midazolam, pethidine</td>
</tr>
</tbody>
</table>

Table 3  Details of NONMEM pharmacokinetic analysis. *In the basic model, volumes of distribution and clearance are assumed to be the same throughout the administration of vecuronium. In the other models, volumes of distribution, or clearance or both are allowed to vary between the time of initial administration and the end of administration of vecuronium, several days later. A decrease in the objective function of 9.2 denotes a significant improvement over a simpler model \((P < 0.01)\). Bold type: values for the optimal model

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veburonium administration Days of administration</td>
<td>5</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Total dose (mg)</td>
<td>331</td>
<td>115</td>
<td>342</td>
<td>180</td>
<td>135</td>
<td>212</td>
</tr>
<tr>
<td>Value of objective function*</td>
<td>(347.7)</td>
<td>(277.5)</td>
<td>(161.0)</td>
<td>(216.1)</td>
<td>(261.6)</td>
<td>(219.8)</td>
</tr>
<tr>
<td>Basic model Volume allowed to vary</td>
<td>(339.0)</td>
<td>(263.3)</td>
<td>(161.0)</td>
<td>(211.0)</td>
<td>(261.2)</td>
<td>(219.7)</td>
</tr>
<tr>
<td>Clearance allowed to vary</td>
<td>(302.2)</td>
<td>(231.8)</td>
<td>(151.7)</td>
<td>(195.8)</td>
<td>(246.3)</td>
<td>(218.6)</td>
</tr>
<tr>
<td>Volume and clearance allowed to vary</td>
<td>(299.6)</td>
<td>(231.8)</td>
<td>(151.2)</td>
<td>(191.1)</td>
<td>N/A</td>
<td>(245.9)</td>
</tr>
</tbody>
</table>
Renal and liver function tests were performed for all patients on the first and final days of the study. Renal function was assessed using plasma creatinine concentrations. Plasma concentrations of total bilirubin, aspartate aminotransferase (AST) and alkaline phosphatase (ALK-P) were measured. If the results suggested an abnormality, prothrombin time was also measured. Liver function was graded in four classes: 0 = normal liver function tests; 1 = increased plasma AST and ALK-P levels without increased bilirubin concentration or prothrombin time; 2 = increased plasma AST, ALK-P and bilirubin concentrations without increased prothrombin time; and 3 = increased prothrombin time because of altered liver function. The administration of vasoactive drugs, and of any drugs that might alter the pharmacology of vecuronium, was recorded.

**Results**

**CLINICAL DATA**

Patient characteristics, renal and hepatic function are detailed in table 1. For all but one patient (patient 4), plasma creatinine concentration changed less than 30 μmol l⁻¹ during the study period; in patient 4, the plasma creatinine concentration increased from 159 to 248 μmol l⁻¹. Liver function changed little in any patient during the study, and only for patient 5 did the grade change. In this patient, prothrombin time increased from a normal value of 13.1 s to a marginally elevated value of 14.2 s, resulting in his score changing from 2 to 3.

In all patients, mechanical ventilation was instituted for respiratory failure. Vecuronium was administered to enable the patients to tolerate mechanical ventilation, after appropriate sedation had been given. The patients’ lungs were ventilated to achieve normocapnia. The patients’ underlying pathology and the aetiology of their respiratory failure are shown in table 2.

Only one patient (patient 2) required inotropic support, and this was during the late phase only, using dopamine at an average rate of 6 μg kg⁻¹ min⁻¹; patients 4 and 6 received dopamine in renal doses of 1.6–3.2 μg kg⁻¹ min⁻¹. All patients except patient 2 received an aminoglycoside antibiotic during the course of vecuronium administration. Patients 1, 4 and 5 received frusemide during the early, but not the late, phase of the study. Patients 1, 5 and 6 received hydrocortisone throughout the study. Patient 6 received phenytoin throughout the study.
PHARMACOKINETIC STUDY

For all patients, the three-compartment model was superior. Allowing the $V_{\text{ss}}$ to vary between early and late phases did not improve the fit in any patient (table 3, figure 1). In contrast, for five of the six patients, there was a significant improvement in fit when $Cl$ was allowed to change from early to late phases (table 3, figure 1). Allowing the intercompartmental clearances to vary from early to late phases did not improve the fit in any patient.

The values of the pharmacokinetic variables are given in table 4. $V_{\text{ss}}$ was calculated by summing the volumes of each of the three compartments, and mean residence time was calculated as $V_{\text{ss}}/Cl$. $V_{\text{ss}}$ (range 368–1765 ml kg$^{-1}$; median 494 ml kg$^{-1}$) did not change in any patient during the course of vecuronium administration. In contrast, the clearance of vecuronium (range 1.4–4.4 ml kg$^{-1}$ min$^{-1}$) increased in three and decreased in two patients.

Only one patient (patient 4) had a significant deterioration in renal function, and this was accompanied by a small decrease in clearance from 2.5 to 2.1 ml kg$^{-1}$ min$^{-1}$. In patient 5 liver function deteriorated slightly, but clearance increased from 1.8 to 2.2 ml kg$^{-1}$ min$^{-1}$.

Discussion

We found that the clearance of vecuronium changed in five of six patients over the course of vecuronium administration. There was no consistent pattern to this change; clearance increased in three patients and decreased in two. There are several potential reasons why clearance changed; among them are alterations in organ function, and the administration of drugs that might influence the biodisposition of vecuronium.

The largest change in clearance occurred in patient 1, in whom it decreased from 3.6 to 1.4 ml kg$^{-1}$ min$^{-1}$. This was accompanied by an increase in creatinine from 88 to 115 µmol l$^{-1}$ and no change in liver function. Even if renal function had deteriorated to a greater extent than was reflected by the relatively small change in creatinine, we consider it unlikely that the deterioration in renal function produced the decrease in clearance, as even in anephric patients vecuronium clearance may not change.11 The haemodynamic status of this patient actually improved during the study (mean arterial pressure of 86 and 117 mm Hg during early and late phases respectively), without the administration of vasoactive drugs. We could identify no other factors in this patient’s course that would account for the decrease in clearance of vecuronium.

Because vecuronium is eliminated by both kidney and liver we would have expected changes in function of these organs to have been reflected in changes in clearance.12 13 However, in patient 4, who had significant deterioration in renal function, clearance decreased only slightly (2.5 to 2.1 ml kg$^{-1}$ min$^{-1}$), and in patient 5 whose liver function deteriorated slightly, clearance actually increased from 1.8 to 2.2 ml kg$^{-1}$ min$^{-1}$. The reason that we saw little relationship between organ function and clearance may be that the changes in organ function were relatively small and, additionally, other factors were influencing clearance, such as the administration of diuretics. Patients 1, 4 and 5 received frusemide during the early, but not the late, phase of the study and we could speculate that the resultant diuresis may have artificially increased vecuronium clearance in the early phase. The only data on the effect of an induced diuresis on the clearance of a neuromuscular blocking drug relate to mannitol, which had no influence on the clearance of $d$-tubocurarine.14 In the absence of data, we cannot draw any conclusions about the possible interaction between frusemide and vecuronium clearance.

Patient 6 was receiving phenytoin, which significantly alters the neuromuscular response to vecuronium.15 Vecuronium clearance in this patient did not change during the study, however, possibly because she had been receiving long-term phenytoin and any effect of the drug on vecuronium clearance would have been present at the start of the study.

Patients were receiving a variety of other drugs, for example aminoglycoside antibiotics and hydrocortisone, that interact with vecuronium and alter its pharmacodynamics, but have no known effect on its pharmacokinetics. Because patients in the ICU receive many drugs, interactions might occur that affect the pharmacokinetics of vecuronium, but as there are no data available we cannot speculate further on such possible interactions.

During the pharmacokinetic analysis, we assumed linearity, namely that plasma concentrations of vecuronium were proportional to the dose administered and that clearance would not vary with vecuronium concentration. This basic assumption underlies the pharmacokinetic modelling of nondepolarizing neuromuscular blocking drugs, and is supported by experimental evidence.16 In a carefully controlled study, Wright and colleagues demonstrated that the pharmacokinetics of vecuronium were linear over an almost three-fold dose range.10 In our study, the plasma concentrations of vecuronium were within the range of those studied by Wright and colleagues,16 but our experimental conditions were different. Wright and colleagues studied healthy volunteers and vecuronium was administered for only brief periods; our subjects were critically ill and vecuronium was administered over several days. Thus, although we consider it unlikely that non-linearity developed over the course of our study, we cannot rule out the possibility.

As vecuronium clearance could decrease or increase with time in an individual patient, the mean values for the patients as a group would not have differed between the early and late phases of the study. For this reason, we estimated the clearance and its change over time for subjects as individuals, and not as a group. Because patients in the ICU are so heterogeneous with regard to their pathophysiological state, expressing their characteristics as a mean value for a group is potentially misleading; in this study it would have suggested a stability in clearance which did not exist.

We found no change in the $V_{\text{ss}}$ of vecuronium during the study, but the interindividual values (368–1765 ml kg$^{-1}$) varied over a four-fold range; the mean value was 732 and the standard deviation 531 ml kg$^{-1}$, so the coefficient of variation was approximately 70%. These values for mean and coefficient of varia-
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References