PHARMACOKINETICS OF PANCURONIUM IN PATIENTS WITH NORMAL AND IMPAIRED RENAL FUNCTION

K. McLord, M. J. Watson and M. D. Rawlins

SUMMARY
Plasma concentrations of pancuronium were measured using a fluorimetric method in six patients with normal renal function and seven patients in chronic renal failure. A two-compartment open model was used in the pharmacokinetic analysis of the data. With this model, the clearance of pancuronium was found to be reduced significantly in the patients with renal failure, and in these individuals the volume of the central (distribution) compartment was increased significantly. The clinical implications of these findings are discussed.

The bisquaternary ammonium steroid pancuronium bromide (Pavulon, Organon) has gained widespread acceptance as a useful non-depolarizing muscle relaxant in anaesthetic and intensive-care practice. Studies on the pharmacokinetics of this agent in man indicate that renal excretion represents a major route of elimination (Agoston et al., 1973; Buzello, 1975). These investigations have revealed that 40–50% of an injected dose of pancuronium appears unchanged in the urine. Therefore we have compared the pharmacokinetic behaviour of this drug in patients with normal and impaired renal function.

METHODS

Patients
Thirteen patients undergoing general anaesthesia for a variety of surgical procedures (table I) were investigated. Six patients, classified as the “normal” group, had no clinical evidence of renal damage. The remaining seven patients were in end-stage chronic renal failure necessitating regular haemodialysis, and they constituted the “renal failure” group. All the patients in this group had undergone haemodialysis during the 36 h before operation, and three were anephric. Table I summarizes the clinical details in both groups. The renal failure patients were anemic with low haematocrit values and had increased plasma urea and creatinine concentrations.

A standard anaesthetic technique was employed for all patients. Thiopentone (175–300 mg) and fentanyl (100 µg) were given i.v. to induce anaesthesia.

Suxamethonium 50 mg i.v. was given to facilitate endotracheal intubation and anaesthesia was maintained with 70% nitrous oxide in oxygen and halothane 0.25–0.5%, together with regular i.v. injections of fentanyl 25 µg. Ventilation was controlled throughout the surgical procedure and all patients received atropine 1.2 mg and neostigmine 2.5 mg at the end of the operation. No patient showed clinical evidence of residual neuromuscular blockade. The operative blood loss in the normal and renal failure groups was 132 ± 30 ml and 167 ± 35 ml respectively (P > 0.1).

Fifteen minutes after the administration of suxamethonium a single dose of pancuronium bromide 4 mg was given i.v. to both groups of patients. Venous blood was withdrawn at 5, 10, 20, 30, 60, 90, 120, 180, 240 and 300 min following the administration of the pancuronium. The heparinized plasma was separated by centrifugation and stored at −20 °C until subsequent analysis.

Analytical technique
Plasma concentrations of pancuronium were estimated fluorimetrically (Kersten, Meijer and Agoston, 1973). Standard curves relating plasma concentrations of pancuronium to fluorescence were obtained by adding known quantities of pancuronium bromide to blank plasma samples. Using this technique, the lower limit of sensitivity was found to be 20 ng/ml. The coefficient of variation of repeated estimations of known concentrations (100–1000 ng/ml) was 0.02.

Calculations
The plasma concentration–time data were analysed according to a two-compartment open model (Riggs, 1963). This model considers the body to be composed of two compartments—a central compartment...
comprising highly perfused tissues (with a volume \( V_1 \)), and a peripheral compartment of poorly perfused tissues (with a volume \( V_2 \)). The drug is administered into the central compartment and the exchange of drug between the two compartments is regarded as a first-order process. The rate constant for the transfer of drug from the central to the peripheral compartment is denoted by \( k_{12} \), and the rate constant for transfer of drug from the peripheral compartment to the central compartment is denoted by \( k_{21} \). Elimination is also assumed to occur solely from the central compartment by a first-order process with the rate constant indicated by \( k_{13} \). This model is summarized in figure 1.

The general equation describing the plasma concentration (\( c \)) at any time (\( t \)) after the instantaneous (i.v.) administration of a drug into a two-compartment open system is given by:

\[
c = Ae^{-\alpha t} + Be^{-\beta t},
\]

where \( A \) and \( B \) are hybrid terms with units of concentration (ng/ml), and \( \alpha \) and \( \beta \) are hybrid rate constants with units of reciprocal time (h\(^{-1}\)). The hybrid rate constant \( \beta \) is the slope of the terminal monoexponential decline of the log plasma concentration–time curve. Back-extrapolation of this line to zero time yields \( B \) on the intercept of the plasma concentration axis. The initial exponential decay curve with slope \( \alpha \) and zero-time intercept \( A \) was determined by the method of residues. Both \( \alpha \) and \( \beta \) were determined by least-squares regression analysis on a minimum of four points, and in all instances the correlation coefficient was greater than 0.95. The volumes and rate constants were calculated thus:

\[
V_1 = \frac{\text{dose}}{A \times B},
\]

\[
k_{21} = \frac{A \cdot \beta + B \cdot \alpha}{A + B},
\]
PANCURONIUM KINETICS

\[ k_{12} = \frac{\alpha \cdot \beta}{k_{21}} \quad \text{(iv)} \]

\[ k_{12} = \alpha + \beta - k_{21} - k_{13} \quad \text{(v)} \]

\[ V_e = V_1 \cdot \frac{k_{12}}{k_{21}} \quad \text{(vi)} \]

Plasma drug clearance \((\dot{V}_p)\) was calculated from the area under the plasma concentration time curve \((\text{AUC})\) as determined by the trapezoidal rule (with extrapolation to infinity):

\[ \dot{V}_p = \frac{\text{dose}}{\text{AUC}} \quad \text{(vii)} \]

The distribution volume during the \(\beta\) phase \((V_\beta)\) was determined thus:

\[ V_\beta = \frac{V_p}{\beta} \quad \text{(viii)} \]

RESULTS

Plasma concentrations of pancuronium 5 min after injection were 600 ± 50 ng/ml in the normal group and 460 ± 36 ng/ml in the renal failure group \((P<0.01)\). The plasma concentrations in both groups thereafter showed an initial rapid decline followed by a more gradual reduction (fig. 2). Four hours after injection, plasma pancuronium concentrations were 67 ± 2 ng/ml in the normal group and 180 ± 10 ng/ml in the renal failure group \((P<0.01)\). A semi-logarithmic plot of the plasma concentration–time data for both groups is shown in figure 3. From this, it appears that the decline of plasma pancuronium concentrations is monoexponential with respect to time.

**TABLE II. Pharmacokinetic variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal group (± SEM)</th>
<th>Renal failure group (± SEM)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) (ng/ml)</td>
<td>383 ± 58</td>
<td>191 ± 29</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>(\alpha) (h(^{-1}))</td>
<td>5.12 ± 1.09</td>
<td>2.26 ± 0.46</td>
<td>&lt; 0.05</td>
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<tr>
<td>(B) (ng/ml)</td>
<td>352 ± 35</td>
<td>275 ± 28</td>
<td>n.s.</td>
</tr>
<tr>
<td>(\beta) (h(^{-1}))</td>
<td>0.414 ± 0.014</td>
<td>0.085 ± 0.013</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>(V_1) (litre/kg)</td>
<td>0.079 ± 0.009</td>
<td>0.135 ± 0.005</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>(V_3) (litre/kg)</td>
<td>0.053 ± 0.010</td>
<td>0.089 ± 0.020</td>
<td>n.s.</td>
</tr>
<tr>
<td>(\dot{V}_p) (litre/kg)</td>
<td>0.148 ± 0.014</td>
<td>0.236 ± 0.025</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>(k_{14}) (h(^{-1}))</td>
<td>2.02 ± 0.57</td>
<td>0.84 ± 0.18</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>(k_{14}) (h(^{-1}))</td>
<td>2.63 ± 0.42</td>
<td>1.37 ± 0.30</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>(k_{15}) (h(^{-1}))</td>
<td>0.809 ± 0.080</td>
<td>0.136 ± 0.010</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>(\dot{V}_p) (ml/min)</td>
<td>74 ± 8</td>
<td>20 ± 2</td>
<td>&lt; 0.005</td>
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* Student's \(t\) test; n.s. = not significant.

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**FIG. 2.** The mean plasma concentration (± SEM) in both groups following i.v. injection of pancuronium bromide 4 mg.

**FIG. 3.** Semi-logarithmic plot of plasma concentration (± SEM) in both groups following i.v. injection of pancuronium bromide 4 mg.
time, in both groups, 60–90 min after drug administration. The pharmacokinetic variables are shown in table II. It is apparent that there are significant differences in the hybrid constants $A$ and $\alpha$, and in $V_1$, $V_\beta$, $k_{12}$ and $k_{21}$ between the two groups. Moreover, plasma clearance of pancuronium ($V_p$) and the elimination rate constant ($k_{1a}$) are both diminished markedly in the renal failure group.

**DISCUSSION**

In this study we have interpreted our data according to a two-compartment open model. Whilst our findings are compatible with this pharmacokinetic model, we cannot exclude the possibility that other, more complex, models could fit our data. In particular, we studied only the decline in plasma pancuronium concentrations for 240–300 min after i.v. administration. If sampling had been continued beyond this time, an even slower elimination phase might have occurred.

The results of this investigation indicate that the elimination of pancuronium is diminished markedly in patients with poor renal function. This might be anticipated in view of the demonstration that renal excretion represents an important route of pancuronium elimination. The fluorescence technique used in our study is not entirely specific for pancuronium and includes a contribution from deacetylated metabolites. The concentrations of these metabolites, which possess neuromuscular blocking activity, appear to be low in relation to unchanged pancuronium (Buzello, 1975), but in end-stage renal disease they may accumulate. For this reason, the clearance value ($V_p$) observed in the renal failure group may be subject to under-estimation.

Renal excretion is an important route of elimination of other muscle relaxants. Thus, tubocurarine (Cohen, Brewer and Smith, 1967), gallamine (Feldman, Cohen and Golling, 1969) and alcuronium (Raaffaub and Frey, 1972) are all excreted more slowly in the presence of renal disease. Redistribution from the central to the peripheral compartment is likely to be the main factor in terminating the activity of pancuronium at the motor end-plate. Metabolic degradation and biliary excretion are considered not to contribute to the duration of neuromuscular block produced by pancuronium (Buzello, 1975). The presence of renal failure has been predicted to increase the duration of activity of tubocurarine only slightly at low doses but significantly after large single or multiple doses (Gibaldi, Levy and Hayton, 1972). Our findings indicate that such a pattern is applicable to our pharmacokinetic analysis of pancuronium in renal failure. Miller, Stevens and Way (1973) have, however, reported an increase in the duration of activity of relatively low doses of pancuronium in renal failure patients.

The likelihood of persisting large plasma concentrations of pancuronium in patients with renal failure in the period following surgery may contribute to recurarization when the patient has received large doses of narcotic analgesics or has developed disturbance of acid–base balance. The absence of adverse cardiovascular effects of pancuronium commend its use in patients with renal failure, but caution must be exercised if adverse neuromuscular blocking effects are to be avoided.

Our investigations indicate also that renal failure is accompanied by disturbance in pancuronium distribution. Thus, the volume of the central compartment ($V_1$), and of $V_\beta$, is increased in patients with renal failure. In addition, the intercompartment rate constants $k_{12}$ and $k_{21}$ were observed to be reduced in these individuals. Because of the possible analytical interference by fluorescent metabolites, the changes we have observed may be greater than we have estimated. The explanation for the changes is unclear, but may be related to retention of water in patients with advanced renal disease, and to the circulatory changes that may accompany this disorder. The rapidity of onset of the neuromuscular blocking effects of pancuronium suggest that this action must be mediated within the drug’s central distribution compartment. The changes in distribution volume which we have observed may explain the difficulties sometimes encountered by anaesthetists in achieving adequate relaxation in patients with renal disease.

**ACKNOWLEDGEMENTS**

We are most grateful to the anaesthetic colleagues who helped in this study, including Dr A. Pridie and Dr P. N. Booth. Organon Laboratories kindly supplied the pancuronium bromide used in the analysis.

**REFERENCES**


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**PHARMACOCINETIQUE DU PANCURONIUM SUR DES PATIENTS AYANT DES FONCTIONS RENALES NORMALES ET ALTEREES**

*RESUME*

Les concentrations de pancuronium dans le plasma ont été mesurées en utilisant une méthode fluorimétrique sur six patients ayant des fonctions rénales normales et sur sept patients ayant une insuffisance rénale chronique. On s'est servi d'un modèle ouvert à deux compartiments pour l'analyse pharmacocinétique des données. Grâce à ce modèle, on a trouvé que le coefficient de pancuronium était réduit d'une manière significative chez les malades ayant une insuffisance rénale et sur ces sujets le volume du compartiment central (distribution) a augmenté d'une manière importante. On traite dans cette communication des implications cliniques de ces découvertes.

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**DIE PHARMAKOKINESE DES PANKURONIUM BEI PATIENTEN MIT NORMALER ODER GESCHÄDIGTER NIERENFUNKTION**

**ZUSAMMENFASSUNG**


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**FARMACOCINETICA DEL PANCURONIO EN PACIENTES CON FUNCIONAMIENTO RENAL NORMAL Y DETERIORADO**

**SUMARIO**

Se midieron las concentraciones de plasma de pancuronio mediante el uso de un método fluorimétrico en seis pacientes con función renal normal y en siete pacientes con insuficiencia renal crónica. Se utilizó un modelo abierto de dos compartimentos en el análisis farmacocinético de los datos. Con este modelo, se encontró que el margen de pancuronio quedaba reducido de forma significante en los pacientes con insuficiencia renal, y en estos individuos el volumen del compartimento central (distribución) había aumentado sensiblemente. Se debaten las implicaciones clínicas de estos descubrimientos.