PIPECURONIUM AND PANCURONIUM: COMPARISON OF PHARMACOKINETICS AND DURATION OF ACTION†


Pipecuronium bromide is a long-acting, non-depolarizing neuromuscular blocking drug which is devoid of cardiovascular effects [1]. These properties have been confirmed in both healthy patients and those with significant cardiac disease [2]. The pharmacokinetics of pipecuronium in humans were determined by Tassonyi, Szabo and Vereczkey [3], using a relatively insensitive colorimetric assay [4]. Plasma concentrations were measured for only 60 min after the injection of pipecuronium, a short sampling time that precluded accurate determination of the elimination phase. We have developed a sensitive and specific capillary gas chromatographic assay for the quaternary ammonium steroidal neuromuscular blocking agents that can measure plasma concentrations of pipecuronium for 6 h after administration of usual clinical doses [5]. We used this assay to determine the pharmacokinetics of pipecuronium in humans and, for purposes of comparison, those of its analogue, pancuronium. To compare the duration of action of these two agents, we have measured the duration of neuromuscular blockade which each produced.

METHODS AND MATERIALS

With approval from the local Committee for Human Research and written informed consent, we studied 39 patients (ASA class I or II) undergoing various surgical procedures. Patients were premedicated with diazepam 10 mg by mouth or midazolam 0.02–0.05 mg kg⁻¹ i.v., as appropriate. Anaesthesia was induced with thio-pentone 1–5 mg kg⁻¹ i.v. and maintained with halothane 0.7–0.8% and 60–70% nitrous oxide (end-tidal concentrations) in oxygen, as determined by mass spectrometry. Oesophageal temperature was maintained at 35–37 °C and venti-

SUMMARY

The pharmacokinetics of pipecuronium 0.07 mg kg⁻¹ and pancuronium 0.1 mg kg⁻¹ were compared in 39 ASA class I or II patients. Plasma concentrations of these agents were measured for 6 h following administration, using a sensitive and specific capillary gas chromatographic assay. Concentration vs. time data were analysed by non-linear regression and fitted to a two- or three-compartment model as appropriate. Neuromuscular blockade was assessed by measuring the mechanical evoked response of the adductor pollicis muscle to train-of-four stimulation of the ulnar nerve. Pipecuronium had a larger steady-state volume of distribution (Vss) (309 (SD 103) ml kg⁻¹) and greater plasma clearance (Cl) (2.4 (0.6) ml kg⁻¹ min⁻¹) than pancuronium (199 (54) ml kg⁻¹ and 1.5 (0.4) ml kg⁻¹ min⁻¹, respectively). The volumes of the central compartment, distribution and elimination half-lives and mean residence times were similar for both agents and within the range expected for drugs of this type. The durations of action (injection to 25% recovery of twitch tension) of pipecuronium and pancuronium were similar: 98.0 (36.1) min and 117.2 (35.8) min, respectively. We conclude that the time courses of neuromuscular blockade following pipecuronium and pancuronium are similar, despite the differences in Vss and Cl.
lation was controlled to maintain end-tidal \( PCO_2 \) at 4–5.3 kPa.

Subcutaneous needle electrodes were placed adjacent to the ulnar nerve at the wrist; through them, a Grass S88 nerve stimulator delivered supramaximal impulses in a train-of-four (TOF) pattern at 2 Hz at intervals of 15 s. The evoked twitch tension of the adductor pollicis muscle was measured using a Gould Statham UTC3 force transducer attached to the thumb. Twitch responses were recorded on a polygraph and, following analog-to-digital conversion, on microcomputer floppy disc [6]. Measurements of the twitch responses were taken from the computer printout generated at the completion of the study. When a stable level of twitch tension was attained, the twitch response to the first stimulus in the train (T1) was taken as the control response with which all subsequent T1 responses were compared. The interval from the end of the injection of neuromuscular blocking drug until the return of T1 response to 25% of control T1 was recorded as the duration of action (Dur25).

Patients were allocated randomly to receive either pipecuronium 0.07 mg kg\(^{-1}\) or pancuronium 0.1 mg kg\(^{-1}\) as a rapid i.v. bolus. Venous blood samples were drawn before and at 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330 and 360 min after injection. Samples were heparinized, placed in ice, and centrifuged and acidified within 1 h. Plasma concentration (C) was calculated following single organic ion-pair extraction of the drug from acidified plasma and quantification using a sensitive and specific capillary gas chromatographic assay with nitrogen-sensitive detection [5]. This assay is specific for the pipecuronium and pancuronium parent compounds. It has a coefficient of variation 4–15% and is linear over the range 2–5000 ng ml\(^{-1}\).

Concentration–time data were fitted to both a two-compartment \( (C = Ae^{-t/T1} + Be^{-t/T2}) \), and a three-compartment \( (C = Pe^{-t/Tf} + Ae^{-t/Vc} + Be^{-t/Va}) \) model by derivative-free, non-linear regression [7]. All plasma samples were assayed at the same dilution, and variance was broadly in proportion to the concentration, therefore a weighting factor of \( 1 \times C^{-2} \) was used. The more appropriate model in each case was determined by \( F \) test [8]. The pharmacokinetic parameters of distribution half-life \( T_1 \), elimination half-life \( T_2 \), volume of central compartment \( V_c \), volume of distribution at steady state \( V_a \), plasma clearance \( Cl \) and the derived variable, mean residence time in the body \( T_{res} \), were calculated for each patient according to standard formulae [9,10]. For both groups mean plasma decay curves were obtained by calculating the mean concentration at each time point and fitting these points to a three-compartment model (fig. 1).

Statistical comparisons were made using Student's \( t \) test for unpaired data. Differences were considered significant at \( P < 0.05 \).

**RESULTS**

Mean age and weight of the patients in the pipecuronium group (46 (SD 15) yr, 71 (13) kg) did not differ from those in the pancuronium group (41 (15) yr and 75 (15) kg, respectively).

A three-compartment model best described the pharmacokinetic data in 15 patients in the pipecuronium group and 10 patients in the pancuronium group. A two-compartment model was used in the remainder. In one patient given pancuronium, it was not possible to measure plasma concentrations beyond 240 min because of high background noise in the assay. The drug elimination phase could not be accurately determined, therefore, and the data for this patient were not included in the pharmacokinetic analysis. Compared with pancuronium, pipecuronium had a larger \( V_a \) and a greater \( Cl \). The values for \( T_1 \), \( T_2 \), \( V_c \) and \( T_{res} \) were not different (table I). The durations of action (Dur25) of pipecuronium (98.0 (36.1) min) and pancuronium (117.2 (35.8) min) were not significantly different (fig. 2). Five patients in each group required antagonism of neuromuscular blockade before recovery of T1 to 25% of control.

TABLE I. Pharmacokinetic parameters (mean (SD)) for pipecuronium and pancuronium: distribution half-life (\( T_1 \)), elimination half-life (\( T_2 \)), volume of the central compartment \( (V_c) \), volume of distribution at steady state \( (V_a) \), plasma clearance \( (Cl) \) and mean residence time in the body \( (T_{res}) \)

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>Pipecuronium ( n = 20 )</th>
<th>Pancuronium ( n = 18 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( T_1 ) (min)</td>
<td>16.3 (10.1)</td>
<td>15.6 (16.4)</td>
<td>ns</td>
</tr>
<tr>
<td>( T_2 ) (min)</td>
<td>137 (68)</td>
<td>115 (40)</td>
<td>ns</td>
</tr>
<tr>
<td>( V_c ) (ml kg(^{-1}))</td>
<td>67.1 (30.2)</td>
<td>59.6 (18.5)</td>
<td>ns</td>
</tr>
<tr>
<td>( V_a ) (ml kg(^{-1}))</td>
<td>309 (103)</td>
<td>199 (54)</td>
<td>( &lt; 0.005 )</td>
</tr>
<tr>
<td>( Cl ) (ml kg(^{-1}) min(^{-1}))</td>
<td>2.4 (0.6)</td>
<td>1.5 (0.4)</td>
<td>( &lt; 0.0005 )</td>
</tr>
<tr>
<td>( T_{res} ) (min)</td>
<td>140 (63)</td>
<td>134 (26)</td>
<td>ns</td>
</tr>
</tbody>
</table>
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Fig. 1. Mean plasma concentration v. time curves for pipecuronium and pancuronium. The lines represent the fit of a three-compartment model to each set of data and are described by the equations 

\[ C = 879e^{-0.31t} + 242e^{-0.035t} + 117e^{-0.0053t} \] (pipecuronium) and 

\[ C = 948e^{-0.32t} + 356e^{-0.042t} + 340e^{-0.0064t} \] (pancuronium), where \( C \) is the plasma concentration (ng ml\(^{-1}\)) at time \( t \).

DISCUSSION

We have used both two- and three-compartment models to describe the concentration v. time data. This approach was adopted because the two-compartment model did not represent the data adequately in several patients, but there were some for whom the three-compartment model did not provide a significantly better fit than the two-compartment model [8] and, therefore, the latter was used. Mean values for the fast-distribution \( \pi \) half-life are not reported because this phase was not defined in cases where the two-compartment model was used. Figure 1 shows the plasma decay curves for the mean pipecuronium or pancuronium concentration at each time point and gives the tri-exponential equations which describe the models fitted to the data.

The assay we used in this study was specific for the parent compound and did not measure the metabolites of either pipecuronium or pancuronium. Previous studies of pancuronium pharmacokinetics using both specific [11] and non-specific assay techniques [12–14] have reported pharmacokinetic values similar to those which we obtained. Our findings, therefore, appear to support the contention of Cronnelly and colleagues [11], that metabolites do not contribute to the plasma concentrations of pancuronium regardless of the method of measurement.

Tassonyi, Szabo and Vereczkey [3] studied pipecuronium pharmacokinetics in humans and reported a \( T_F^0 \) of only 44 min and \( Cl \) of 320 ml min\(^{-1}\). These results differ significantly from the values of 137 min and 2.4 ml kg\(^{-1}\) min\(^{-1}\), respectively, which we derived. However, in that study [3], an insensitive colorimetric assay was used which allowed measurement of plasma concentrations of pipecuronium for only 60 min after administration. Such a short sampling time prevents accurate characterization of the elimination phase of the drug, resulting in an overestimation of the true \( \beta \) decay slope and an underestimation of the area under the plasma concentration v. time curve. We consider the values derived in our study to be more accurate estimates of the true \( T_F^0 \) and \( Cl \) of pipecuronium.

Our findings demonstrate that pipecuronium has a greater \( Cl \) and a larger \( V^{ss} \) in humans than pancuronium. In the rat, there is only minimal

Fig. 2. Individual data points for the time from injection of pipecuronium or pancuronium until twitch tension recovery to 25 % of control (Dur25). Error bars represent the mean and standard deviation.
biliary elimination of both pipecuronium [15] and pancuronium [16]. If this pattern is the same in humans, hepatic mechanisms cannot account for the rapid clearance of pipecuronium. Because the two charged quaternary nitrogen groups are located more peripherally on the pipecuronium than on the pancuronium molecule, it is likely that there are differences in the hydrophilic and protein-binding characteristics of these two drugs. The structural differences suggest that pipecuronium is the more polar and hence the more hydrophilic molecule. This characteristic might enhance the renal elimination of pipecuronium and account for its greater clearance.

In addition, if pipecuronium were bound less to plasma protein than to pancuronium, this would explain the greater $V_{ss}^{\text{as}}$ of pipecuronium. Pipecuronium is 32% bound to plasma protein in the rat [17], while estimates for pancuronium protein binding range from 7% to 87% [18-20]. With the evidence available, the differences in $V_{ss}^{\text{as}}$ cannot be attributed to differences in the protein binding characteristics of the drugs.

The end result of the differences in $V_{ss}^{\text{as}}$ and $Cl$ is that the elimination phases for pipecuronium and pancuronium are similar. As can be seen from the mean plasma decay curves (fig. 1) the slopes during the elimination phase are similar.

The difference in the duration of action (Dur25) of pipecuronium 0.07 mg kg$^{-1}$ and pancuronium 0.1 mg kg$^{-1}$ failed to reach statistical significance. The impression from inspection of the results, however (fig. 2), is that the duration of action would be matched more closely if we had used a larger dose of pipecuronium. Earlier studies [21, 22] have shown that pipecuronium and pancuronium have similar duration of action when the dose ratio of pipecuronium to pancuronium is approximately 80%. Our results are compatible with these findings. One patient in each group had prolonged neuromuscular blockade. Neither the clinical profile nor the treatment of each patient could account for this. The patient with prolonged blockade following pipecuronium had a low $Cl$ (1.5 ml kg$^{-1}$ min$^{-1}$), a large $V_{ss}^{\text{as}}$ (505 ml kg$^{-1}$) and a long $T_1^0$ (332 min). Unfortunately, the patient with prolonged blockade following pancuronium was also the patient for whom we were unable to calculate the elimination phase. Overall, however, there was not a good correlation between the duration of neuromuscular blockade and any pharmacokinetic parameter.

From these comparisons we conclude that the clinical time course of action of pipecuronium and pancuronium in normal, healthy patients is similar, despite significant differences in $V_{ss}^{\text{as}}$ and $Cl$.

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REFERENCES

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