PHARMACOKINETICS OF PROPOFOL AND HAEMODYNAMIC CHANGES DURING INDUCTION OF ANAESTHESIA IN URAEMIC PATIENTS

M. KIRVELÄ, K. T. OLKKOLA, P. H. ROSENBERG, A. YLI-HANKALA, K. SALMELA AND L. LINDGREN

SUMMARY

The pharmacokinetics of an i.v. bolus of propofol 2 mg kg\(^{-1}\) were studied in 10 uraemic patients undergoing renal transplantation and in seven healthy controls matched for age, weight and duration of anaesthesia. Haemodynamic changes during induction of anaesthesia were recorded in the uraemic and in 10 healthy control patients. Pharmacokinetic variables were similar in uraemic and control patients; mean elimination half-lives were 1638 (SD 340) min and 1714 (842) min, respectively. Induction of anaesthesia with propofol was preceded by fentanyl 3 \(\mu\)g kg\(^{-1}\). After administration of propofol over 60 s, systolic arterial pressure decreased by 19 (12) %, and by 24 (11) % in the adequately volume loaded uraemic and healthy patients, respectively. Propofol caused a marked peripheral vasodilatation in all patients. A moderate increase in systolic arterial pressure after intubation was statistically significant only in the control patients (P < 0.01). We conclude that, in terms of pharmacokinetics and haemodynamic changes, propofol may be used safely for the induction of general anaesthesia in uraemic patients.

KEY WORDS


The main steps in the elimination of propofol are hepatic metabolism and urinary excretion of glucuronidated metabolites [1, 2]. Preliminary results from four uraemic patients studied by Morcos and Payne [3] suggested that the pharmacokinetics of propofol are similar to those in non-uraemic subjects. In their study, about 40% decreases in arterial pressures were noticed after a 2.5-mg kg\(^{-1}\) bolus of propofol for induction of anaesthesia in the uraemic patients.

Arterial hypotension occurs commonly during induction of anaesthesia with a rapid injection of propofol [4-7]. The decrease is probably caused by decreased systemic vascular resistance and not reduction in cardiac output [7]. Therefore, propofol may not be suitable for uraemic patients, who are susceptible to significant cardiovascular instability during anaesthesia [8]. Cardiovascular problems during anaesthesia nowadays are less likely to occur [9] because of prevention of anaemia and hypovolaemia and of complications caused by renal hypertension.

We have undertaken a controlled clinical study to evaluate the pharmacokinetics of a slow induction bolus dose of propofol and its haemodynamic consequences in patients undergoing renal transplantation.

PATIENTS AND METHODS

We studied 10 uraemic patients undergoing renal transplantation (table I). Ten ASA I patients undergoing elective minor surgery of approximately the same duration served as controls. Pharmacokinetics of propofol were studied in all the uraemic and in seven control patients and the haemodynamic changes during induction of anaesthesia were studied in all patients. The study was approved by the Hospital Ethics Committee, and all patients gave informed consent.

The uraemic patients had been dialysed within the previous 12 h (table I). Nine were receiving antihypertensive therapy (table II). Three had cardiac enlargement in the preoperative chest x-ray. The plasma protein concentrations in the uraemic patients were normal. Liver function was normal in all patients in the study. The control patients underwent extraperitoneal surgery, mostly on the breast. All patients were premedicated with oral diazepam 0.2 mg kg\(^{-1}\) about 1 h before anaesthesia. After arrival of the patient in the operating theatre, a forearm vein was cannulated. In the uraemic patients, a central venous catheter was inserted via the internal jugular vein. Thereafter, potassium-free Ringer’s acetate and 4% human albumin solution were administered until the central venous pressure...
was at least 4 mm Hg. The control patients were given approximately 700 ml of Ringer's acetate solution into a forearm or cubital vein as pre-anaesthetic volume loading. After i.v. glycopyronium 3 μg kg⁻¹, fentanyl 3 μg kg⁻¹ and droperidol 1.25 mg had been given, anaesthesia was induced with propofol 2 mg kg⁻¹ administered over 60 s into the forearm vein. Immediately thereafter, vecuronium 0.1 mg kg⁻¹ was given and the lungs were ventilated via a face mask with 50% nitrous oxide in oxygen and fentanyl 3 μg kg⁻¹ and droperidol 1.25 mg had been given, anaesthesia was maintained with isoflurane (end-tidal concentration 0.5-0.7%) and 70% nitrous oxide in oxygen for 2 min before tracheal intubation.

Anaesthesia was maintained with isoflurane (end-tidal concentration 0.5-0.7%) and 70% nitrous oxide in oxygen and fentanyl 3 μg kg⁻¹ i.v. Heart rate (HR), arterial pressures (non-invasive, oscillotonometeric method; Cardiocap, Datex Ltd, Finland), central venous pressure (CVP) and peripheral skin temperature at the fingertip contralateral to the arm with the arteriovenous fistula were recorded before and after the volume expansion, 1 and 2 min after injection of propofol, immediately and 5 min after tracheal intubation and before the connection of the transplanted graft circulation (in the control patients about 90 min after the induction of anaesthesia). Blood samples were taken into heparinized vials before and 2, 5, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 720 and 1440 min after the bolus of propofol, from the central catheter or via a cannula inserted into a contralateral arm vein in 10 uraemic and seven control patients, respectively.

After centrifugation, the plasma was stored at −70°C. Propofol concentrations in plasma were measured by high-pressure liquid chromatography [10] (lower limit of sensitivity of approximately 5 ng ml⁻¹; intra-assay coefficient of variation about 5%).

To describe the decay of plasma propofol concentrations after the bolus administration of propofol 2 mg kg⁻¹, we used non-linear curve-fitting to fit the following formula to the curve representing the plasma concentration of propofol [11]:

$$C(t) = \sum_{i=1}^{n} A_i \cdot e^{-a_i \cdot t}$$

where $C(t)$ = plasma concentration of propofol at time $t$; $A_i$ = zero-time intercept; $a_i$ = a disposition rate constant. The measured concentration values were weighted with equal weights and with the factor $1/c_i^2$. The goodness of the fit was determined by Akaike's information criterion [12] and by assessment of randomness of "scatter" of actual data points about the fitted function. The initial estimates were obtained using an iterative curve stripping technique [13]. The compartmental pharmacokinetic parameters, volume of the central compartment ($V_C$), steady-state volume of distribution ($V_{ss}$), volume during elimination phase ($V_e$), clearance ($Cl$) and elimination half-life ($T_{1/2}$) were calculated according to standard formulae [14]. The non-compartmental pharmacokinetic parameters, volume of distribution at steady state ($V_{ss(eq)}$) and clearance ($Cl_{(eq)}$) were calculated according to standard methods using statistical moment theory [15].

Parametric data were analysed with Student's $t$ test and the two-way analysis of variance (ANOVA) for repeated measurements. The results are expressed as mean (SD).

### RESULTS

The uraemic and control patients were comparable in age and weight (table I). The duration of anaesthesia was 202 (54) min and 184 (57) min in the uraemic and control groups, respectively. Plasma kinetics of propofol were described by a tri-
TABLE III. Pharmacokinetic data. Volume of the central compartment ($V_C$), steady-state volume of distribution ($V^\infty$), volume during elimination phase ($V'$), clearance ($Cl$) and elimination half-life ($T^\frac{1}{2}$) (mean (SD) [range]).

<table>
<thead>
<tr>
<th></th>
<th>Uraemic group ($n = 10$)</th>
<th>Control group ($n = 7$)</th>
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<tbody>
<tr>
<td>$V_C$ (litre)</td>
<td>50.0 (21.4) [4.2–75.6]</td>
<td>34.7 (12.7) [11.0–45.4]</td>
</tr>
<tr>
<td>$V^\infty$ (litre)</td>
<td>1607 (494) [701–2463]</td>
<td>1487 (606) [816–2367]</td>
</tr>
<tr>
<td>$V'$ (litre)</td>
<td>2150 (630) [1328–3290]</td>
<td>2046 (891) [1071–3198]</td>
</tr>
<tr>
<td>$Cl$ (litre min$^{-1}$)</td>
<td>0.919 (0.234) [0.641–1.425]</td>
<td>0.888 (0.231) [0.570–1.200]</td>
</tr>
<tr>
<td>$T^\frac{1}{2}$ (min)</td>
<td>1638 (340) [1101–2154]</td>
<td>1714 (842) [700–2700]</td>
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</table>

Fig. 1. Mean plasma concentrations of propofol in 10 uraemic (○) and seven control (●) patients (mean (SEM)).

exponential function in all patients. The calculated pharmacokinetic parameters (compartmental and non-compartmental) in the uraemic and in the control patients were similar (table III). Figure 1 shows that the mean plasma concentration of propofol followed the same pattern in both groups.

The eyelash reflex disappeared and apnoea occurred in all patients after injection of propofol. None of the patients complained of pain on injection.

Systolic arterial pressures (SAP) in the uraemic patients were significantly greater before ($P < 0.05$) and after ($P < 0.001$) the preanaesthetic volume loading, 2 min after propofol ($P < 0.01$) and about 90 min after anaesthetic induction ($P < 0.05$) than in the control patients (fig. 2). SAP decreased 1 min after administration of propofol in both groups ($P < 0.001$). Mean decrease from the baseline to 2 min after propofol was $19$ ($12$) % in the uraemic and $24$ ($11$) % in the control patients. In the control patients, laryngoscopy and intubation caused a significant increase in SAP ($P < 0.001$), but the mean pressure did not exceed the baseline value. This increase was not significant in the uraemic patients.

Diastolic arterial pressures (DAP) in the uraemic patients were greater after volume loading ($P < 0.05$), 1 min ($P < 0.05$) and 2 min ($P < 0.01$) after propofol than in the control patients. DAP decreased only in the control patients 1 min after propofol ($P < 0.01$) and increased in response to laryngoscopy and intubation ($P < 0.01$). DAP decreased 5 min after intubation in the uraemic patients ($P < 0.05$) (fig. 2).

Heart rate increased moderately in both groups as a response to intubation ($P < 0.05$), followed by a decrease 5 min later ($P < 0.05$) (fig. 3). Central venous pressures in the uraemic patients were 3 (2), 5 (2) ($P < 0.01$), 4 (2), 4 (2), 4 (2), 4 (2) and 7 (2) ($P < 0.01$) mm Hg before and after volume loading, 1 and 2 min after propofol, immediately and 5 min after intubation and at connection of the graft circulation, respectively. There were no significant differences in the haemodynamic responses between groups (two-way ANOVA).

Peripheral skin temperature increased steadily during induction of anaesthesia and was significantly greater than the preanaesthetic value 5 min after intubation and thereafter throughout anaesthesia in both groups (fig. 4).

DISCUSSION

Our results show that the pharmacokinetics of a bolus dose of propofol were similar in both uraemic and control patients. This is in agreement with the results of Morcos and Payne [3]. Theoretically, the sampling of blood from a central venous catheter in
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The volume of the central compartment appeared to be somewhat larger in uraemic patients than in the non-uraemic controls, but the difference was not statistically significant. The elimination half-life of propofol was longer than that observed previously following bolus administration of propofol [10, 16]. It is assumed that too short a sampling period after the administration of propofol used in some previous studies did not allow identification of the true elimination phase [17]. Although we used a blood collection period which was longer than that of most previous studies, it might not have been long enough to estimate reliably the long elimination half-lives observed in the present study. However, our results are in agreement with those of Campbell and others [17] and Albanese and others [18], who used an extended period of blood collection to define the distribution and elimination kinetics of propofol. These authors, and others [3, 10, 16, 19–21], reported somewhat greater clearance values for propofol. This discrepancy probably results because we measured the concentration of propofol in plasma and not in whole blood, as did the other workers. The ratio of the concentration of propofol in blood to that in plasma is approximately 0.64:1 [22]. Because blood clearance = plasma concentration/blood concentration × plasma clearance [23], there appear to be no major differences between the clearance values in the present study and those in previous publications. Our values for the volume of distribution are similar to those reported in studies using an extended period of blood collection.

The haemodynamic changes in our patients were modest after induction of anaesthesia with fentanyl and propofol. This may be because of adequate cardiac filling achieved by preanaesthetic volume loading. Adequate antihypertensive therapy in uraemic patients may have contributed also to the surprisingly stable circulatory conditions [9]. Furthermore, Peacock and others [24] have shown recently that the slower the infusion of propofol the smaller were the decreases in arterial pressure in elderly patients. Our dose and injection times of propofol were comparable to their median dose and...
were followed by similar haemodynamic changes. Peripheral skin temperature reflects directly the change in peripheral vascular resistance [25]. It increased significantly after induction with propofol in both groups. Our results indicate that propofol caused marked peripheral vasodilatation, which also has been demonstrated in earlier studies [4–7].

In conclusion, we have found that the pharmacokinetics of propofol were not altered in uraemic patients. Propofol was tolerated well by uraemic patients and, we suggest, may be used for anaesthesia in patients undergoing renal transplantation. Total i.v. anaesthesia with a combination of propofol and, for example, alfentanil [26, 27] could be useful, therefore, as an anaesthetic technique for patients undergoing renal transplantation.

REFERENCES
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