EXTRAHEPATIC METABOLISM OF PROPOFOL IN MAN DURING THE ANHEPATIC PHASE OF ORTHOTOPIC LIVER TRANSPLANTATION†

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SUMMARY

We have investigated extrahepatic metabolism of propofol in 10 patients undergoing orthotopic liver transplantation (group 1) (mean age 38 yr, mean weight 60 (SD 7) kg) and compared it with that in 10 patients without liver dysfunction undergoing extrahepatic abdominal surgery (group 2) (mean age 56 yr, mean weight 68 (11) kg). A single i.v. bolus dose of propofol 0.5 mg kg⁻¹ was injected into a peripheral vein 5 min after the beginning of the anhepatic phase in group 1 and 60 min after the induction of anaesthesia in group 2. Arterial blood samples were obtained at 5, 10, 15, 20, 30, 40, 50 and 60 min after injection and urine samples were collected every 15 min. Propofol concentrations in whole blood and urine were measured by high performance liquid chromatography with fluorescence detection. Propofol glucuronide was measured in urine by incubation with a specific β-glucuronidase. The area under the time-blood concentration curve from 0 to 60 min was found to be significantly greater in group 1 (13743 (2830) ng litre⁻¹ h⁻¹) than in group 2 (7992 (4895) ng litre⁻¹ h⁻¹) (P < 0.05). Unchanged propofol was not detected in the urine of either group. No significant difference was found in the amount of propofol glucuronide excreted by patients in group 1 (457 (269) µg) and in group 2 (921 (672) µg). The presence of a propofol metabolite in urine when the liver was excluded from the circulation suggests that extrahepatic metabolism occurred.

KEY WORDS

Propofol (2,6-diisopropylphenol), a substituted phenol, is the most recent i.v. anaesthetic agent available for clinical practice. It is a short-acting drug with a large volume of distribution and a high total body clearance [1]. The metabolism is mainly hepatic and is rapid [2]. However, the total body clearance suggests the existence of other routes of elimination. It has been suggested that the lung of the ewe [3] and of the rat [4] could metabolize propofol. In man, the anhepatic phase of orthotopic liver transplantation provides a unique opportunity to study the extrahepatic metabolism of this drug.

PATIENTS AND METHODS

After Institutional approval, informed consent was obtained from 20 patients who formed two groups. Ten patients undergoing orthotopic liver transplantation (OLT) for cirrhosis (group 1) (mean age 38 yr (range 29–49 yr), mean weight 60 (SD 7) kg) were compared with a control group which consisted of 10 patients without liver dysfunction, undergoing extrahepatic abdominal surgery (group 2) (mean age 56 yr (range 43–64 yr), mean weight 68 (SD 11) kg).

All patients were premedicated with hydroxyzine 2 mg kg⁻¹ 60 min before induction of anaesthesia. In both groups, anaesthesia was induced with thio- pentone 5 mg kg⁻¹ and maintained with a continuous infusion of fentanyl 10 µg kg⁻¹ h⁻¹ and midazolam 50 µg kg⁻¹ h⁻¹. Vecuronium was given to provide neuromuscular block. The lungs were ventilated mechanically with a warmed humidified air–oxygen mixture in order to maintain the end-tidal carbon dioxide concentration in the range 4–4.7 kPa (Capnomac, Datex). No volatile anaesthetic was used.

A single i.v. bolus dose of propofol 0.5 mg kg⁻¹ was injected into a peripheral vein and flushed with 0.9% sodium chloride 10 ml. In group 1 (OLT) the injection was given 5 min after the beginning of the anhepatic phase, after acute haemodynamic changes had resolved. In group 2 (control) the injection was given 60 min after induction of anaesthesia. Arterial blood samples (5 ml) were obtained from a cannula inserted in the radial artery and collected in plastic
tubes containing ammonium oxalate anticoagulant at 5, 10, 15, 20, 30, 40, 50 and 60 min after injection [5]. Samples were mixed thoroughly and stored immediately at +4 °C until subsequent analysis (within 2 weeks). During the same 1 h, urine samples were collected every 15 min through a urinary catheter and frozen at −20 °C before analysis.

Propofol concentrations in whole blood and in urine were measured using high performance liquid chromatography (HPLC) with fluorescence detection [6]. The limit of sensitivity of the assay was 10 ng ml⁻¹ and the coefficient of variation over the concentration range measured was < 8%. The area under the curve from 0 to 60 min (AUC₀₋₆₀) was determined by the trapezoidal rule. In urine, glucuron conjugated propofol metabolites were hydrolysed to the free form by incubation with a specific β-glucoconidase (E. coli—2000 IU ml⁻¹) according to Vree, Baars and de Grood [7]. The initial conditions were modified as follows: 1 ml of phosphate buffer 0.1 mol litre⁻¹, pH 5, and β-glucuronidase solution 100 μl were added to 1 ml of urine. The mixture was incubated at 25 °C for 48 h and 50 μl of the solution extracted as for blood measurements. A calibration curve was established in the 2–40 μg ml⁻¹ range. Because of chromatographic interferences in the urine blank sample, the composition of the mobile phase was modified to: acetonitrile–water–phosphoric acid 40:60:0.2 vol/vol. Under these conditions, propofol and 2,6-diisopropyl-1,4-quinol separate. The ability of the chromatographic system to differentiate between propofol and 2,6-diisopropyl-1,4-quinol was not evaluated. The selectivity of the extraction step of the analytical method allowed the measurement of the propofol that appeared after hydrolysis with β-glucuronidase.

All results are expressed as mean (SD). Comparisons between groups were performed using the Student t test and the Mann-Whitney U test. P < 0.05 was considered statistically significant.

RESULTS

In group 1 (OLT), the duration of the anhepatic phase was 84 (24) min. During the study, the patients were transfused with packed cells (2.5 (2.7) u.) and fresh frozen plasma (4.0 (3.9) u.) to maintain haemodynamic stability and PCV at 30%. Cardiac index was 4.8 (1.8) litre min⁻¹ m⁻² and mean arterial pressure 94.1 (8.6) mm Hg. Body temperature was 35.5 (0.6) °C. Patients in group 2 (control) received Ringer lactate solution 10 ml kg⁻¹ h⁻¹. As patients in group 2 did not require a pulmonary artery catheter for the procedure, no measurement of cardiac index was made in this group and haemodynamic stability was maintained throughout.

Blood concentration of propofol decreased rapidly in the two groups during the study period (fig. 1). AUC₀₋₆₀ was significantly greater in group 1 (13743 (2830) μg litre⁻¹ h⁻¹) than in group 2 (7992 (4895) μg litre⁻¹ h⁻¹) (P < 0.01).

With regard to urinary clearance, only six patients could be studied in each group. The urinary volume was similar in the two groups (table I). Unchanged propofol was not detected in the urine of either group. No significant difference was found in the amount of propofol glucuronide excreted by each group during the sampling period (table I).

DISCUSSION

After a bolus injection of propofol 0.5 mg kg⁻¹, the blood concentration of propofol decreased rapidly in both groups. However, AUC₀₋₆₀ was significantly greater in group 1 (OLT) than in group 2 (control). The appearance of a propofol metabolite in the urine of anhepatic patients suggests the existence of extrahaepatic metabolism for this drug.

The rapid initial decline in blood concentration of propofol observed during the 60 min of the sampling period in the two groups is consistent with the large initial distribution phase after i.v. injection [2]. Propofol is a highly lipophilic drug and distributes rapidly from blood into tissues with a large central compartment and a large apparent volume of distribution at steady state [2]. During the first 60 min after injection of the bolus of propofol, the difference observed between the two groups in the AUC was caused probably by a difference in distribution to body tissues rather than by a difference in metabolism or elimination. A difference in distribution could be induced by cross-clamping.

<table>
<thead>
<tr>
<th>Urinary volume (ml)</th>
<th>Urinary propofol glucuronide (μg)</th>
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<tbody>
<tr>
<td>Group 1 (OLT)</td>
<td>130 (45)</td>
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<tr>
<td>Group 2 (control)</td>
<td>129 (47)</td>
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of the hepatic vessels and the inferior vena cava with subsequent diminution in cardiac index [8] after a reduced venous return and tissue hypoperfusion.

As the duration of the anhepatic period was necessarily short, the blood sampling period was far too brief to allow any reliable estimate of pharmacokinetic variables. No extrapolation of the area under the curve was relevant and clearance could not be evaluated. The clearance estimates of propofol in patient and volunteer studies [2, 9, 10] always exceed the capacity of the liver in respect of its total blood flow (1.5 litre min\(^{-1}\)). This observation could be explained by inaccurate estimate of the terminal elimination phase related to the sensitivity of the method of analysis and by the occurrence of extrahepatic metabolism. In order to study the relative contribution of the liver to the short-term disposition of propofol, Lange and colleagues [11] administered a single i.v. bolus dose of propofol 2 mg kg\(^{-1}\) for induction of anaesthesia in patients undergoing coronary bypass surgery. Measuring hepatic blood flow with indocyanine green as an indicator, the authors showed that, during the 60 min after injection of propofol, the extrahepatic clearance was 1.33 litre min\(^{-1}\)—about 1.3 times greater than hepatic clearance. To explain this phenomenon, we, in common with others [4, 10] suggest the presence of extrahepatic metabolism, a hypothesis that we confirm in this trial, and distribution to a deep compartment. Although it remains uncertain which organs are making a contribution to extrahepatic clearance of propofol from blood, it is likely that they are limited to organs receiving a significant proportion of the total cardiac output—for example, lungs, kidneys or bowel. Among these organs, Servin and colleagues [4] showed that isolated, ventilated and perfused rat lungs were able to trap and conjugate propofol with a low extraction coefficient (E = 0.1). Mather and colleagues [3] studied regional kinetics and mass balance of propofol administered i.v. as a bolus and as an infusion in sheep. Substantial regional blood concentration gradients were observed across the lungs and the liver (but not across the splanchic bed drained by the portal vein), indicating high clearance by or extensive uptake of propofol into the lungs and hepatosplanchnic system.

The fact that the pulmonary uptake was caused more by clearance than by distribution was supported by their failure to detect propofol in lung tissue. Lungs are known to be able to conjugate phenol over a wider dose range than liver [12, 13]. However, the existence of this particular extrahepatic route in man remains to be determined, as a smaller AUC determined by pulmonary arterial samples compared with the AUC from systemic arterial samples did not suggest pulmonary removal of propofol in man [11]. Renal excretory conjugation might also be important for the metabolism and excretion of phenolic compounds in humans, as conjugation of phenol occurs in the isolated perfused human kidney [14]. However, in one study, renal venous concentrations of propofol exceeded aortic concentrations [3]. Although haemoconcentration in the renal vein occurs because of free water removal by the kidney, the gradients were greater than expected, and it was suggested that a propofol metabolite was being metabolized back to propofol in the kidney.

In both groups in the present study, concentrations of unchanged propofol in urine were less than the lower limit of detection of the assay. This result is consistent with a previous study which indicated that 88% of the dose was recovered in urine as hydroxylated and conjugated metabolites of propofol, with less than 0.3% of the dose excreted unchanged [2]. The four major urinary metabolites are identified as propofol glucuronide (53%), 1-(2,6-diisopropyl-1,4-quinol) glucuronide (18%), 4-(2,6-diisopropyl-1,4-quinol) glucuronide (13%) and 4-(2,6-diisopropyl-1,4-quinol) sulphate (9%). The metabolite measured by our assay was the propofol glucuronide. No significant difference was observed between the amounts of metabolite excreted in the two groups. The total amount of propofol glucuronide excreted represents approximately 1.6% of the injected dose in group 1 (OLT) and 2.6% of the injected dose in group 2 (control). The presence of this metabolite in the urine from patients given propofol during the anhepatic period is further evidence for extrahepatic metabolism. The existence of an extrahepatic glucuronidation has already been well established for drugs such as midazolam [15] and morphine [16]. The relative contribution of the liver in glucuronidation should be assessed over a longer period of time, which was not feasible in this study.

REFERENCES

11. Lange H, Stephan H, Rieke H, Kellermann M, Sonntag H,


