HEPATIC AND EXTRAHEPATIC DISPOSITION OF PROPOFOL IN PATIENTS UNDERGOING CORONARY BYPASS SURGERY†

H. LANGE, H. STEPHAN, H. RIEKE, M. KELLERMANN, H. SONNTAG AND J. BIRCHER

SUMMARY

In order to clarify the relative contribution of the liver to the short term disposition of propofol, hepatic blood flow was measured during induction of anaesthesia with an i.v. bolus dose of propofol 2 mg kg⁻¹. Total clearance of the drug was 2390 (SD 340) ml min⁻¹, hepatic extraction 82% and hepatic clearance 1060 (260) ml min⁻¹. During the 60-min period of observation, hepatic extraction of propofol increased from 79% to 92%. It is concluded that, within 1 h, only 44% of the administered dose is removed by the liver. Consequently, drug accumulation may occur with repeated dosing or infusion of propofol. The increase in extraction results presumably from slow release of propofol from the soy-bean emulsion.

KEY WORDS
Anaesthetics intravenous: propofol. Pharmacokinetics: disposition, hepatic blood flow.

In 1977 propofol (2,6 di-isopropyl phenol) was described by Kay and Rolly as a short acting induction anaesthetic [1]. Complications with the solvent Cremophor EL led to the formulation of a soy-bean oil emulsion [2]. Clinical studies with both preparations suggested that propofol should serve as a short acting hypnotic drug, ideally suited for day-case anaesthesia [3, 4] or other routine operations [5]. Comparison of the two formulations in the literature suggest that, for induction of anaesthesia, the dose requirement of the emulsion form seemed to be higher than that of the Cremophor EL preparation [6, 7]. The short duration of action of propofol was explained by the very high total body clearance [2, 8, 9]. Calculated total body clearance, however, exceeded hepatic plasma or blood flow estimated from physiological values in normal man and the relative contribution of the liver to the overall disposition was not known.

In order to examine some of these questions, a study was designed in patients undergoing cardiac surgery, and who were therefore subjected to extensive cardiovascular monitoring. This permitted measurement of hepatic blood flow and simultaneous assessment of systemic and hepatic venous concentrations of propofol.

SUBJECTS AND METHODS

Subjects

The study was approved by the local Ethics Committee and all patients gave informed written consent. The investigation was performed in 11 male patients (table I) who were referred for elective coronary artery bypass surgery. All had involvement of one to three coronary vessels, but compensated ventricular function. Clinical history, physical findings and serum concentrations of transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, bilirubin and prothrombin time were within normal limits and revealed no evidence of liver disease.

Current medication was continued until the day...
TABLE I. Patient data. A = Acetylsalicylic acid; B = benzafibrate; Bi = bisoprolol; D = diltiazem; Di = digoxin; Dz = diazepam; E = enalapril; F = fenofibrate; H = hydrochlorothiazide; M • = mohidomine; Me = metoprolol; N = nifedipine; P = propranolol; S = ritosterine; SN = sorbi nitrate; T = triamterene

<table>
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<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Serum creatinine (μmol litre⁻¹)</th>
<th>Hb (g dl⁻¹)</th>
<th>PCV (%)</th>
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<td>14.2</td>
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<td>G.N.</td>
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<td>Bi, D, F, H, T, P</td>
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<td>80</td>
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<td>B, D, E, H, SN, T, N</td>
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<td>97</td>
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<td>97.1</td>
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<td>46.0</td>
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<td>4.6</td>
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before operation. Premedication consisted of flunitrazepam 2 mg orally at 06:00 and piritramide 15 mg combined with promethazine 50 mg i.m. 1.5 h before induction of anaesthesia.

Procedures

Measurement in patients. In the anaesthetic room, a blank plasma sample was taken and an indocyanine green (ICG) infusion was started through an indwelling 14-gauge cannula in a forearm vein. After cannulation of a radial artery, a 7-French gauge catheter was inserted through the right internal jugular vein and positioned under fluoroscopic control into a right hepatic vein; hepatic venous oxygen saturation was measured to verify its position. A 7-French gauge triple lumen pulmonary arterial thermodilution catheter was inserted via a brachial vein and the wedge position was verified by the pressure curve. After measurement of cardiovascular variables at rest, anaesthesia was induced with fentanyl 0.5 mg, pancuronium 8 mg and propofol 2 mg kg⁻¹ i.v. The lungs were ventilated mechanically to maintain normocapnia as verified by arterial blood-gas analysis and determination of carbon dioxide concentration in end expired gas. Anaesthesia was maintained by an infusion of fentanyl 20 μg min⁻¹ and 50% nitrous oxide in oxygen. Immediately after injection of propofol, hepatic plasma flow and cardiovascular variables were measured again for 15 min and arterial, pulmonary arterial and hepatic venous samples were collected for measurement of plasma propofol concentrations. The same procedures of measurement and sampling were performed during sternotomy.

Measurement of hepatic plasma flow (Q_H)
Hepatic plasma flow was determined by the steady state infusion and extraction technique according to Bradley [10] using ICG as indicator. The infusion rate was 0.5 mg min⁻¹ throughout the period of investigation and the ICG infusion was started at least 45 min before the first measurements in order to allow time for achievement of steady state conditions.

Three arterial and three hepatic venous blood samples were collected alternately at intervals of 3 min. If plasma concentrations changed less than 6% within 12 min, steady state conditions were assumed and hepatic plasma flow was calculated according to Bradley [10].

Cardiovascular variables. Cardiac output (CO) was determined by the thermodilution method using an automatic device (Fischer HZV, Mod. BN 7260, Göttingen, FRG). Systemic and pulmonary arterial pressures were recorded using Statham transducers.

Analytical procedures

Plasma concentrations of ICG. Three millilitre of heparinized blood was centrifuged immediately after sampling and extinction was read photometrically at 800 nm. The calibration curve consisted of concentrations of 50, 250, 750 and
1250 mg litre\(^{-1}\) with a within-day coefficient of variation of 4.5\% \((n = 12)\) at 50 mg litre\(^{-1}\) and 3.9\% \((n = 12)\) at 1250 mg litre\(^{-1}\), respectively.

**Plasma concentrations of propofol.** Plasma concentrations of propofol were determined by HPLC. The equipment consisted of a Merck Hitachi 655 A-12 solvent pump, 655 A-40 autosampler, F-1000 fluorescence spectrophotometer, D-2000 chromato-integrator and a 25-cm Merck 100 RP-18 endcapped 5-µm column (all E. Merck, Darmstadt, FRG). Excitation wavelength was 276 nm and emission wavelength 310 nm. The mobile phase was acetonitrile:water:85 % orthophosphoric acid (60:40:0.2) and the flow rate 1.5 ml min\(^{-1}\); thymol served as internal standard. Each assay was calibrated at concentrations of 25, 50, 100, 500, 1000, 2000 and 5000 ng ml\(^{-1}\). The limit of detection was 10 ng ml\(^{-1}\). Standards of 50, 500 and 1000 ng ml\(^{-1}\) were measured after every 25th sample for quality control. Interserial coefficients of variation ranged from 6.5 \%(n = 11)\) to 3.9\% \((n = 11)\). No difference was detected between whole blood and plasma concentrations of propofol when measured at a known concentration of 1000 ng ml\(^{-1}\), 10 times in whole blood and in plasma, which was prepared from propofol-spiked whole blood.

**Calculations**

*Splanchnic consumption of oxygen.* Oxygen consumption \(\left(V_{H_{O}}\right)\) was calculated as the product of hepatic blood flow \((\text{hepatic plasma flow}/1 - \text{PCV})\) and arterial–hepatic venous difference in oxygen content \((\text{Lex-O}_{2} \text{ Con, IL})\).

**Hepatic extraction of propofol.** This was calculated by two methods.

1. The overall extraction \((E)\) was calculated as:

\[
E = \frac{\text{AUC}_{\text{art}} - \text{AUC}_{\text{hv}}}{\text{AUC}_{\text{art}}}
\]

where \(\text{AUC}_{\text{art}}\) = area under the arterial, \(\text{AUC}_{\text{hv}}\) = area under the hepatic venous plasma concentration–time curve. These AUC were calculated by the iteration method with the Gauss–Newton algorithm using the PCNONLIN computer program (Statistical Consultants Inc., Lexington/Kentucky, U.S.A.). Weighting was \(1/y\).

2. The instantaneous extraction \((E_{i})\) was calculated as:

\[
(E_{i}) = \frac{C_{\text{art}} - C_{\text{hv}}}{(1 - \text{PCV})E}
\]

with concentrations found simultaneously by interpolation on the plasma concentration–time curves.

**Clearances.** Hepatic clearance of ICG at steady state was calculated as ratio of the infusion rate to \(C_{\text{art}}\), the arterial plasma concentration. For the calculation of the intrinsic clearance \((C_{l}\)) of ICG and propofol, the formula of the sinusoidal model \([11, 12]\) was applied:

\[
C_{l} = Q_{h} \times \ln \left(\frac{C_{\text{art}}}{C_{\text{hv}}}\right)
\]

where \(Q_{h}\) is hepatic plasma flow and \(C_{hv}\) the hepatic venous plasma concentration.

Total clearance of propofol \((Cl_{p})\) was calculated as the ratio of the dose to the AUC of propofol and hepatic blood clearance \((Cl_{h})\) as follows:

\[
Cl_{p} = \left(\frac{Q_{h}}{1 - \text{PCV}}\right)E
\]

where \(Q_{h}\) = hepatic plasma flow and \(E\) = hepatic extraction of propofol.

**Statistics**

Data were analysed using the \(t\) test for paired and unpaired samples and correlations were tested using linear regression analysis.

**RESULTS**

All patients tolerated the investigation without complications, and were discharged from hospital clinically improved.

Before induction of anaesthesia, mean heart rate \((HR)\) was 59 (SD 7.7) beat min\(^{-1}\) and this did not change significantly during the period of investigation (table II). Mean arterial pressure \((MAP)\) decreased from 94 (15.5) mm Hg by 18 \%(P < 0.05) after induction and this returned to initial values at sternotomy. CO was initially 5.30 (0.95) litre min\(^{-1}\), decreased by 17 \%(P < 0.02) after induction, and increased slightly at sternotomy.

Estimated hepatic plasma flow \((Q_{h})\) initially was 0.74 (0.19) litre min\(^{-1}\). After induction it decreased by 14 \%(P < 0.01) and approached baseline values at sternotomy (ns). \(Q_{h}\) was constant at about 15 \% of CO. Hepatic oxygen consumption did not change significantly during the procedure. Absolute values were within the normal physiological range. The intrinsic clearance of ICG \(1.06 \text{ litre min}^{-1}\) was similar to published values \([11]\) although, compared with predrug values, there was a significant decrease after induction \((by\ 54\%)\) and at sternotomy \((by\ 38\%)\).

The mean area under the plasma propofol concentration–time curve \((\text{AUC})\) of the arterial
samples was 68.0 (12.1)μg ml⁻¹ h⁻¹ and of the hepatic venous samples 9.8 (4.4)μg ml⁻¹ h⁻¹, resulting in a mean hepatic extraction ratio of 0.83 (0.10). The AUC of pulmonary arterial samples for eight patients was 53.0 (22.4)μg ml⁻¹ h⁻¹. Compared with the corresponding arterial AUC (65.5 (7.6)μg ml⁻¹ h⁻¹) there was no significant difference. For the plasma concentration–time curves (fig. 1), the difference between arterial and hepatic venous plasma concentrations increased with time. Consequently, mean hepatic extraction ratio of propofol after 6 min was 0.79 (0.15) and 0.92 (0.07) after 60 min (P < 0.03 compared with the extraction after 6 min) (table III).

Total clearance of propofol (the ratio of the dose to the systemic arterial AUC) was 2.39 (0.34) litre min⁻¹ and the hepatic blood clearance 1.06 (0.26) litre min⁻¹ (table III). Consequently,
the extrahepatic clearance of propofol was 1.33 (0.36) litre min⁻¹—about 1.3 times greater than hepatic clearance.

There was a strong correlation between hepatic ICG and propofol clearance (y = 1.36x + 455; r = 0.81; P < 0.01) (fig. 2). No significant correlation was found between intrinsic clearances of ICG and propofol (r = 0.01), ICG clearance and total propofol clearance (r = 0.30) and hepatic extractions of ICG and propofol (r = 0.64).

**DISCUSSION**

This study has confirmed that propofol is subject to a very high hepatic extraction. Consequently, its hepatic elimination is dependent heavily on hepatic blood flow. However, distribution into deep compartments is relatively more important for the overall disposition of propofol than is

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**TABLE III. Pharmacokinetics of propofol.**

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<tr>
<th>Propofol dose (mg)</th>
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**DISCUSSION**

This study has confirmed that propofol is subject to a very high hepatic extraction. Consequently, its hepatic elimination is dependent heavily on hepatic blood flow. However, distribution into deep compartments is relatively more important for the overall disposition of propofol than is
clearance by the liver. As a result, the potential for drug accumulation after repeated or continuous dosing cannot be disregarded. Nevertheless, these conclusions must be tempered by the limitations of the study.

For accurate measurements of hepatic plasma flow, a steady state must be achieved: infusion rate of the indicator and removal by the liver should be equal. In our study, intrinsic clearance of ICG decreased significantly in the presence of propofol compared with baseline values, and plasma concentrations of ICG increased disproportionately after injection of propofol, indicating that removal of ICG was reduced. Although plasma concentrations remained relatively stable (±6%) during measurement of hepatic plasma flow, steady state conditions cannot be assumed. Thus hepatic removal of ICG was presumably less than calculated from the infusion rate and, as a consequence, hepatic plasma flow after induction was overestimated. ICG is removed from the plasma by uptake into the hepatocyte and eliminated unchanged by canalicular excretion with the bile. Therefore, it is reasonable to exclude metabolic interactions between ICG and propofol. The reduced intrinsic clearance of ICG is more likely to result from an interaction of propofol with hepatic uptake of ICG. Despite this methodological limitation, interpretation of the relative changes in hepatic plasma flow remain the same. Only the differences between the values before anaesthesia and after induction are underestimated and may be somewhat more marked than described in our data. As hepatic elimination of ICG has been influenced by propofol, it is possible that elimination of propofol was modified by ICG. However, hepatic extraction of propofol was 0.92 after 60 min. On the assumption that ICG may have reduced hepatic uptake of propofol, the maximum error has to be less than 8%, because hepatic extraction cannot exceed 1.0. Also, the lack of a statistical relation between hepatic extractions of ICG and propofol argues against an important interaction. Interactions between propofol and fentanyl as described by Cockshott and colleagues [8] would lead to the same conclusions and would not alter the interpretation of the results obtained.

Iterative calculations of the area under the plasma concentration–time curves may be inaccurate as a result of analytical errors, sampling times and relatively small differences in exponential functions. For instance, late onset of sampling may lead to high exponential errors in the α-phase, and early termination to substantial errors in extrapolation to infinity. In this study, arterial and hepatic venous sampling was started 3 min after injection of propofol; this represents a reasonable compromise and an acceptable definition of the α-phase with more than three definite measurements.

Pulmonary arterial sampling started 3 min later, leading to a higher potential error in definition of the α-phase. As a consequence of the cardiothoracic surgery, sampling could be extended only until onset of extracorporeal circulation, that is about 120 min after injection of propofol. Therefore, iteration involves some inaccuracy in extrapolation to infinity. Presumably, this error is acceptable because, on average, the extrapolated area was 23.2 ± 12.7% of the AUC₀–∞ in arterial samples and was comparable quantitatively in all cases. Calculations of propofol clearances were based on plasma concentrations and interpreted as blood clearances because of the equal distribution of propofol in plasma and erythrocytes. Haemodynamic changes may also have been changed by other factors after induction of anaesthesia. Preoperative stress was probably unimportant because of the heavy premedication. All patients tolerated preoperative manipulations, including catheterizations under local anaesthesia, without significant cardiovascular changes. Interference caused by ICG may also be excluded as there is no evidence for any direct cardiovascular effects of ICG, which is used widely for de-
termination of cardiac output and hepatic plasma flow [10, 11].

The high total clearance of propofol agrees well with the findings of other investigators [2, 8, 13], who measured blood concentrations of propofol [14]. A priori, the mean value of 2.4 litre min$^{-1}$ implies extrahepatic disposition of propofol, because it exceeds hepatic blood flow. However, to our knowledge the relative contributions of the liver and of extrahepatic organs have not yet been reported. Based on our findings, the difference between total and hepatic blood clearance suggests an extrahepatic clearance of 1.3 litre min$^{-1}$. We therefore looked for other organs which might be responsible, and calculated the AUC of pulmonary arterial samples. The tendency to lower AUC of the latter compared with systemic arterial AUC does not suggest pulmonary removal of propofol. This insignificant difference is explained easily by an error in estimation of the $\alpha$-phase as a result of the sampling procedure. We conclude, therefore, that the high extrahepatic clearance of propofol is presumably an error related to the terminal portion of the concentration–time curve. It may result either from inaccuracies of the $\beta$-phase or from inability to investigate a third $\gamma$-phase with an extremely long half-life which might reduce the total propofol clearance, possibly to the level of hepatic clearance. In the latter case, extrahepatic elimination of propofol would have to be considered as distribution into deep compartments. Therefore, drug accumulation after repeated administration or during infusion remains a possibility. These findings are compatible with the results of Campbell and colleagues [15] who demonstrated a significant correlation between sampling period and the systemic blood clearance of propofol, indicating possible errors in the definition of the terminal slope of the plasma concentration–time curve. They found a systemic blood clearance of 1020 ml min$^{-1}$, equal to normal physiological values for hepatic blood flow in healthy man.

The cardiovascular effects of propofol in this study are similar to the results of other investigators [5, 16–18]: notably, a significant decrease in cardiac output combined with a corresponding reduction in mean arterial pressure and in hepatic plasma flow. However, compared with predrug values, splanchnic oxygen consumption and hepatic venous oxygen content remained unchanged. The lack of change in hepatic venous oxygen content resulted from an increase in arterial oxygen content after induction of anaesthesia, caused by mechanical ventilation, and an increase in $F_{1/2}$ from 0.21 to 0.5.

There was a continuous increase in hepatic extraction of propofol with time to a maximum value of 0.92 after 60 min (fig. 1, table III). As ICG is unlikely to affect hepatic propofol uptake into hepatocytes, this may result from slow release of propofol from the soy-bean oil emulsion. This hypothesis is compatible with the finding that the early Cremophor preparation was associated with smaller dose requirements than the soy-bean oil emulsion used in this study [1, 7, 19].

ACKNOWLEDGEMENTS

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REFERENCES


