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CRITICAL CARE

Changes in apparent systemic clearance of propofol during transplantation of living related donor liver

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Background. Propofol is used during living-related donor liver transplantation because its metabolism is not greatly affected by liver failure. However, the pharmacokinetics of propofol during liver transplantation have not been fully defined. The purpose of this study was to evaluate the apparent systemic clearance of propofol during the dissection, anhepatic and reperfusion phases of living-related donor liver transplantation, and to estimate the role of the small intestine and lung as extrahepatic sites for propofol disposition.

Methods. Ten patients scheduled for living-related donor liver transplantation were enrolled in the study. Anaesthesia was induced with vecuronium 0.1 mg kg^{-1} and propofol 2 mg kg^{-1}, and then maintained by 60% air, 0.5–1.5% isoflurane in oxygen and a constant infusion of propofol at 2 mg kg^{-1} h^{-1}. Apparent systemic clearance during the dissection, anhepatic and reperfusion phases was calculated from the pseudo-steady-state concentration for each phase. Disposition in the small intestine was determined by measuring arteriovenous blood concentration in 10 liver transplantation donors. Pulmonary disposition was determined by measuring the arteriovenous blood concentration in 10 recipients during the anhepatic phase. The data are expressed as mean (SD).

Results. Apparent systemic clearances in the dissection, anhepatic and reperfusion phases were 1.89 (SD 0.48) litre min^{-1}, 1.08 (0.25) litre min^{-1} and 1.53 (0.51) litre min^{-1}, respectively. The concentration of propofol in the portal vein was lower than in the radial artery. The intestinal extraction ratio calculated from the concentration in the radial artery and portal vein was 0.24 (0.12). There were no significant differences in propofol concentrations between the radial and pulmonary arteries.

Conclusion. Apparent systemic clearance was decreased by ∼42 (10)% during the anhepatic phase compared with the dissection phase. After reperfusion, liver allografts rapidly began to metabolize propofol. The small intestine also participates in the metabolism of propofol.

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The number of patients needing liver transplantation greatly exceeds the number of cadaveric donors available in Japan. Therefore living-related donor liver transplantation has been performed for patients with endstage liver disease more frequently than for patients with orthotopic liver transplantation.

Living-related donor liver transplantation procedure was performed in three phases: the dissection phase, the anhepatic phase and the reperfusion phase. Propofol is used during liver transplantation because its metabolism is not greatly affected by liver failure.[1] However, the pharmacokinetics of propofol during each phase of liver transplantation have not been fully defined. Recently, we reported that a pseudo-steady state was established during the anhepatic phase of living-related donor liver transplantation.[2] Furthermore, we found in a previous study that human kidneys played an important role in the elimination of propofol.[3] It has been reported that the small

intestine[4] and the lung[5] participate in the elimination of propofol. The purpose of this study was to estimate the total body clearance of propofol during living-related donor liver transplantation and to examine the role of the small intestine and lung as extrahepatic sites of propofol disposition *in vivo*.

Materials and methods

With ethics committee approval and informed consent, 10 patients with liver cirrhosis (six men and four women of mean age 54.8 (43–62) yr, height 159 (SD 10) cm and weight 57.6 (11) kg) undergoing liver transplantation were recruited. Individuals were excluded from the study if they had severe renal insufficiency, were chronic alcoholics and/or had a known allergy to eggs or propofol. Individuals who had significant haemodynamic instability during surgery were also excluded from the study.

Routine monitoring included electrocardiography, pulse oximetry, invasive arterial pressure (radial artery), central venous and pulmonary arterial pressure via the right jugular vein and continuous cardiac output (Vigilance Monitor; Baxter, CA, USA). Anaesthesia was induced with vecuronium 0.1 mg kg^{-1} and propofol 2 mg kg^{-1} and was maintained with 60% air, 0.5–1.5% isoflurane in oxygen, fentanyl 30 μg kg^{-1} and an infusion of propofol at 2 mg kg^{-1} h^{-1}. After injection of propofol, samples were collected from a cannula inserted in the radial artery for measurement of blood propofol concentration at 5, 10, 15, 30, 45, 60, 90, 120 min, and every 60 min in the dissection and reperfusion phases. During the anhepatic phase, radial arterial samples were collected at 5, 10, 15, 20, 30, 45 and 60 min, and at 30-min intervals thereafter until completion of the anhepatic phase. Pulmonary arterial samples were collected from a cannula inserted in the pulmonary artery at 120 min after hepatic blood flow was stopped at the anhepatic phase.

Intraoperative haemodynamics were recorded at the following time points: ∼30 min after induction of anesthesia (base line), 5 min pre-anhepatic, 20 min post-anhepatic, 5 min pre-reperfusion, 20 min post-reperfusion and 1 h post-reperfusion.

Measurement of propofol elimination in liver transplantation donors

Ten patients (six men and four women aged 32.2 (25–40) yr, height 164 (6.3) cm and weight 54 (7.2) kg) who donated a segment of their liver were enrolled in this study. Anaesthesia was induced with vecuronium 0.1 mg kg^{-1} and propofol 2 mg kg^{-1}, and maintained with 60% nitrous oxide, 1.0–1.5% isoflurane in oxygen and propofol infusion at 2 mg kg^{-1} h^{-1}. When steady state was established (at least 2 h after the start of continuous infusion), a radial arterial sample was collected before hepatectomy from a cannula inserted in the radial artery for measurement of blood propofol concentration. At the same time, a portal venous sample and a hepatic venous sample were obtained by

the surgeons directly using a syringe under ultrasonigraphic guidance. Since the concentration of propofol is >85% of the steady-state value,[6] the level of propofol 2 h after the start of constant infusion was regarded as steady state.

Analytical procedure

Propofol concentrations in whole blood were measured within 48 h by high-performance liquid chromatography (HPLC), as reported previously.[7] Briefly, each sample [0.5 ml (0.1 ml whole blood plus 0.4 ml distilled water)] with internal standard (thymol in methanol: 20 μl, 5 μg ml^{-1}) was buffered with 1 ml of 0.1 M phosphate buffer (pH 7.4) and extracted with 5 ml of n-hexane. After centrifuging, 30 μl of tetra-n-butyl-ammonium hydroxide (TBAH) solution (0.5 M TBAH: methanol:2-propanol=0.75:2.27:37.0) was added to 4 ml of the organic phase and the solution was evaporated to dryness. The residue was resolved in methanol (200 μl) and an aliquot (10 μl) was injected into an HPLC system (Waters 2690, Waters Corp., Milford, MA, USA). The column (WAT054275, 5 μm ODS, 4.6×250 mm ID, Waters Corp., Milford, MA, USA) was maintained at 30°C. The mobile phase, composed of methanol–water (84:16 v/v), was pumped at a flow rate of 1.0 ml min^{-1}. Propofol and thymol were detected with a fluorescence detector (Waters 474, Waters Corp., Milford, MA, USA) (excitation, 276 nm; emission, 297 nm). The limit of detection was 4 ng ml^{-1} and the reproducibility of the measurement was confirmed by coefficients of variation of 3.3%, 2.1% and 0.6% at 10 ng ml^{-1}, 20 ng ml^{-1} and 50 ng ml^{-1}, respectively.

Calculating the hepatic clearance of propofol

The apparent systemic clearances in the dissection phase (CL$_d$), the anhepatic phase (CL$_a$) and the reperfusion phase (CL$_r$) were calculated from the pseudo-steady-state concentration at each phase.

$$\text{CL}_d = R_0 / C_{\text{ss-d}}$$
$$\text{CL}_a = R_0 / C_{\text{ss-a}}$$
$$\text{CL}_r = R_0 / C_{\text{ss-r}}$$

where R_0 is the infusion rate (mg min^{-1}) and $C_{\text{ss-d}}$, $C_{\text{ss-a}}$ and $C_{\text{ss-r}}$ are the final whole-blood concentrations (μg ml^{-1}) (pseudo-steady-state concentrations) at the dissection phase, anhepatic phase and reperfusion phase, respectively.

Calculating the hepatic and small intestinal extraction ratio of propofol

The hepatic extraction ratio (E_H) and the small intestinal extraction ratio (E_I) were calculated as follows:

$$E_H = (C_{\text{ss-a}} - C_{\text{ss-v}}) / C_{\text{ss-a}}$$
$$E_I = (C_{\text{ss-a}} - C_{\text{ss-i}}) / C_{\text{ss-a}}$$

where $C_{\text{ss-a}}$, $C_{\text{ss-i}}$, $C_{\text{ss-v}}$ were the steady-state concentrations (μg ml^{-1}) in donor samples of the radial artery, portal vein

and hepatic vein, respectively. Therefore, the estimated hepatic extraction ratio is, in fact, the extraction ratio of both the liver and the small intestine.

Statistical analysis

Statistical analysis was performed using Statview-J 5.0 for Macintosh (SAS Institute, Cary, NC). Differences in propofol concentrations between the radial artery and the pulmonary artery were analysed using the paired *t*-test. The differences in propofol clearance between the recipients and the donors were analysed using the unpaired *t*-test. Analysis of variance for repeated measurements was used to detect significant changes in propofol concentrations in the radial artery. When significance was found, Scheffe's test was used for post hoc comparison. A *P*-value <0.05 was considered statistically significant. Data are expressed as mean (SD).

Results

All patients tolerated surgery without complications. The mean (SD) duration of the anhepatic phase was 151 (36) min. The mean blood loss was 3998 (2533) ml. The transfused blood volume of mannitol adenine phosphate (MAP) and fresh frozen plasma (FFP) was 2020 (1740) ml and 584 (640) ml, respectively. The intraoperative haemodynamics are shown in Table 1. There were no significant differences in haemodynamic values with time. Propofol concentrations from the radial artery of patients undergoing living-related donor liver transplantation are shown in Figure 1. There were no significant differences in the last three samples from each phase. Pseudo-steady state was established within 2 h at every phase. The pseudo-steady-state propofol concentration in the anhepatic phase was significantly higher than that in the dissection phase (*P*<0.001). The pseudo-steady-state propofol concentration in the reperfusion phase was significantly lower than in the anhepatic phase (*P*<0.001). Apparent systemic clearances in the dissection, anhepatic and reperfusion phases were 1.89 (0.48) litre min^{-1}, 1.08 (0.25) litre min^{-1} and 1.53 (0.51) litre min^{-1}, respectively. Apparent systemic clearance decreased significantly (by 42 (10)%) in the anhepatic phase compared with the dissection phase (*P*=0.0008) (Table 2). Apparent systemic clearance was significantly higher in the reperfusion phase than in the anhepatic phase (*P*=0.0209). The apparent systemic clearance of the donors was 1.76 (0.29) litre min^{-1}. There was no significant difference in apparent systemic clearance between the recipients (1.89 (0.48) litre min^{-1}) and the donors (1.76 (0.29) litre min^{-1}). Propofol concentrations in the radial artery, the portal vein and the hepatic vein in the donors are shown in Figure 2. Propofol concentration in blood from the radial artery was greater than that in blood from the portal vein at pseudo-steady state (*P*=0.0036). The propofol concentration in blood from the radial artery was greater than that in blood from the hepatic vein at pseudo-steady state (*P*<0.0001). The propofol concentration in blood from the portal vein was greater than that in blood from the hepatic vein at pseudo-steady state (*P*<0.0001). The hepatic

Table 1 Changes in haemodynamics of recipients during liver transplantation. HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; CO, cardiac output. Data are mean (SD)

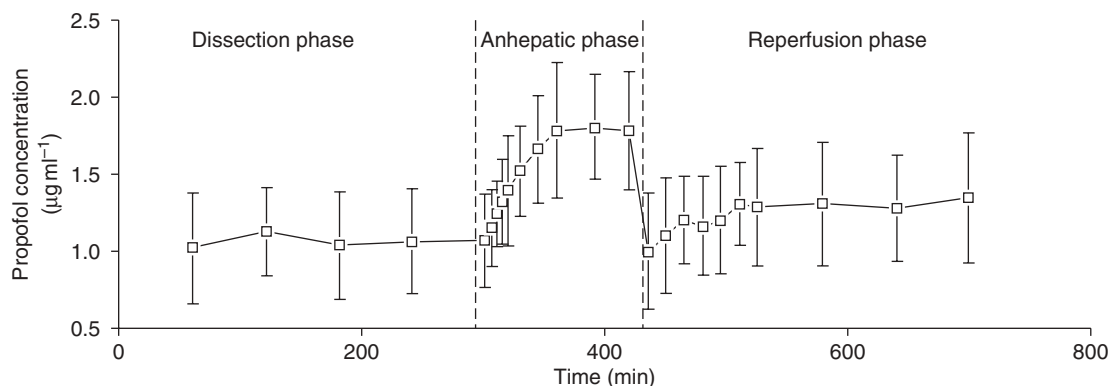|	Baseline	5 min pre-anhepatic	20 min post-anhepatic	5 min pre-reperfusion	20 min post-reperfusion	1 h post-reperfusion
HR (beats min^{-1})	77 (13)	85 (21)	78 (25)	76 (29)	83 (35)	81 (27)
MAP (mm Hg)	76 (14)	84 (18)	82 (21)	75 (25)	69 (31)	73 (26)
CVP (mm Hg)	11 (2.7)	12 (3.1)	11 (2.6)	10 (2.5)	11 (3.2)	9 (2.1)
CO (litre min^{-1})	6.7 (1.0)	6.5 (1.4)	7.2 (2.2)	6.8 (2.6)	7.1 (2.3)	7.3 (3.2)

Fig 1 Propofol concentrations in the radial artery during the dissection, anhepatic and reperfusion phases. Data are expressed as mean (SD). Propofol concentrations were increased significantly compared with the last sample of the dissection phase (*P*<0.001). The propofol concentration at pseudo-steady state during the reperfusion phase was decreased significantly compared with the anhepatic phase (*P*<0.001). There were no significant differences in the last three samples of each phase. Pseudo-steady state was established within 2 h at every phase.

Table 2 Changes in apparent systemic clearance of recipients on removal of the liver. CL_d, apparent systemic clearance of dissection phase; CL_a, apparent systemic clearance of anhepatic phase; ΔCL, CL_a–CL_d

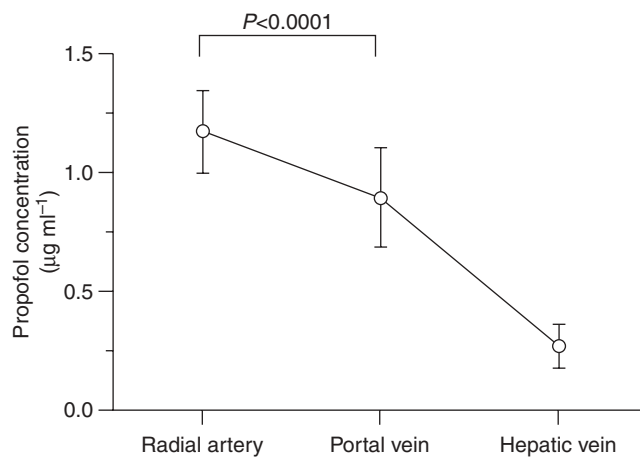| Patient no.	CL_d (litre min^{-1})	CL_{ad} (litre min^{-1})	ΔCL (litre min^{-1})	$\Delta CL/CL_d$ (%)
1	2.25	1.28	0.97	43
2	1.58	1.01	0.57	37
3	1.92	1.15	0.77	40
4	1.47	0.67	0.80	54
5	1.10	0.84	0.26	24
6	1.44	0.92	0.52	36
7	2.44	1.04	1.40	57
8	2.11	1.12	0.99	53
9	2.17	1.17	1.00	46
10	1.56	0.62	0.94	38
Mean	1.89	1.08	0.82	42
SD	0.48	0.25	0.32	10

Fig 2 Propofol concentrations in the radial artery, portal vein and hepatic vein obtained from donors. Data are expressed as mean (SD). The propofol concentration in blood from the radial artery was greater than that in blood from the portal vein at pseudo-steady state (P=0.0036). The propofol concentration in blood from the radial artery was greater than that in blood from the hepatic vein at pseudo-steady state (P<0.0001). Propofol concentration in blood from the portal vein was greater than that in blood from the hepatic vein at pseudo-steady state (P<0.0001).

extraction ratio calculated from the concentration in the radial artery and hepatic vein samples was 0.76 (0.06). The intestinal extraction ratio calculated from the concentration of the radial artery and portal vein was 0.24 (0.12). Propofol concentrations in the radial artery and pulmonary artery are shown in Figure 3. There were no significant differences (P=0.6224).

Discussion

It is important to determine the contribution of each organ to total propofol clearance in order to adjust the dosage in certain disease states or for specific surgical procedures, such as liver transplantation. In this study, we found that apparent systemic clearance decreased by ~42% at the anhepatic phase compared with the dissection phase, and ~0–20% of the administered dose was removed by the small
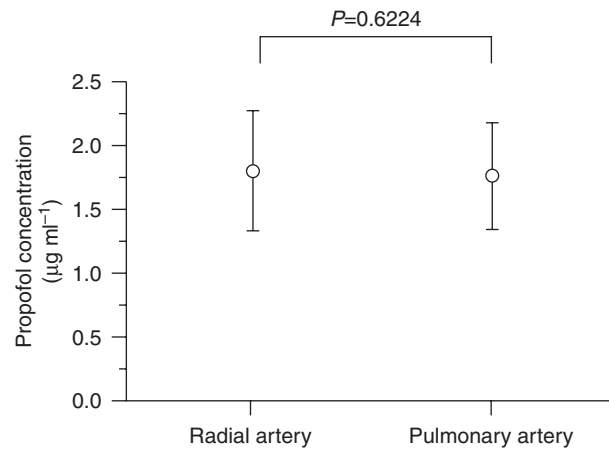

Fig 3 Propofol concentrations in the radial and pulmonary arteries obtained from recipients during the anhepatic phase. Data are expressed as mean (SD). There were no significant differences in propofol concentrations between the radial and pulmonary arteries (P=0.6224).

intestine. After reperfusion, liver allografts rapidly begin to metabolize propofol.

Propofol concentration appeared to exceed 85% of the steady-state concentration within 2 h after initiation of continuous infusion.[6] Similarly, a pseudo-steady state was established within 2 h of the anhepatic phase during liver transplantation after stopping hepatic blood flow. Therefore we examined the apparent systemic clearance at the anhepatic phase based on pseudo-steady-state concentrations. Apparent systemic clearance decreased by 42 (10)% after the removal of the liver. Lange and colleagues[8] examined the contribution of hepatic clearance to total body clearance in patients undergoing coronary bypass surgery, and reported that only 44% of the administered dose was removed by the liver. Furthermore, we have shown in this study that there was no significant difference in apparent systemic clearance between recipients (1.89 (0.48) litre min^{-1}) and donors (1.76 (0.29) litre min^{-1}) in the current study. This similarity of the data indicates that the propofol clearance mechanisms in these patients with severe hepatic illness were not impaired compared with those of patients who did not have severe hepatic insufficiency.

We reported[3] that renal clearance of propofol was 27 (9.9)% of total body clearance and that it depended on renal blood flow. Furthermore, roughly half of the administered dose was removed by the liver in the present study. Raoof and colleagues[4 9] reported glucuronidation of propofol in the gut wall *in vitro*. Gray and colleagues[10] reported that 0.1–0.9% of an administered dose was excreted unchanged in the bile. Therefore we examined propofol concentrations of the radial artery, portal vein and hepatic vein at steady state in liver transplantation donors. The hepatic extraction ratio, calculated from the concentration in the radial artery and the hepatic vein, was 0.76 (0.06) and the small intestinal extraction ratio, calculated from the concentration in the radial artery and portal vein, was 0.24 (0.12). The generally accepted estimate for blood flow in the

portal vein is 75–80% of hepatic blood flow (1.5 litre min^{-1}). Therefore it is believed that ~10–20% of the administered dose is removed by the small intestine. The small intestine undoubtedly participates in the elimination of this drug.

The lungs have been reported as a site of extrahepatic metabolism.[11] He and colleagues[12] found no significant differences in plasma propofol concentrations between the pulmonary and radial artery, and concluded that metabolism was not involved in pulmonary uptake in human lungs. In contrast, Dawidwicz and colleagues[5] reported that the concentration of propofol in the central venous system was greater than in the radial artery, whereas the opposite was observed for the propofol metabolite 2,6-diisopyl-1, 4-quinol. The authors concluded that human lungs take part in the elimination of propofol by transforming the drug into 2,6-diisopyl-1,4-quinol.[5] We compared propofol concentrations in the radial and pulmonary artery in the anhepatic phase, but did not detect significant differences between them. The pulmonary metabolism of propofol remains unclear because we did not measure the propofol metabolite, but we consider the contribution of pulmonary clearance to total body clearance to be small.

A limitation of this study was that the total body clearance at each phase was calculated from pseudo-steady-state concentrations. Therefore it is possible that the apparent systemic clearance at each phase might have been overestimated, and that the apparent elimination in the small intestine results from a distribution of the drug into tissues. True steady state is not established during each phase because the elimination half-life of propofol is long (4–6 h). Since the rapid distribution half-life is short (1–3 min) and the distribution clearance is large,[13 14] the concentration of propofol reaches pseudo-steady state 20 min after a constant infusion and then increases slowly until true steady state is reached.[12] The contribution of rapid distribution, slow distribution (30–50 min) and terminal elimination half-life (4–6 h) to the changes in concentration were 94.6%, 4.9% and 0.57%, respectively.[15] Terminal half-life contributes slightly to the increase in concentration of propofol, but this is probably clinical irrelevant. Thus the pseudo-steady-state propofol concentration is almost equal to the true steady-state concentration. Furthermore, propofol distribution into well-perfused tissues, such as the lungs, reaches equilibrium within a short time during constant infusion.[12] In contrast, less well-perfused tissues, such as fat, approach steady-state conditions quite slowly. Therefore we believe that small intestinal extraction of propofol at pseudo-steady state does not reflect distribution.

In summary, apparent systemic clearance was decreased by ~42% in the anhepatic phase compared with the dissection phase. About 10–20% of the administered dose was removed by the small intestine. Therefore total body clearance of propofol can be accounted for by the liver, small intestine and kidney.[3] After reperfusion, liver allografts rapidly begin to metabolize propofol.

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