DOI:10.1111/j.1365-2125.2005.02393.x

Kidneys contribute to the extrahepatic clearance of propofol in humans, but not lungs and brain

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Keywords
Propofol, kidneys, metabolism, lungs, brain

Received
7 October 2004
Accepted
15 December 2004

Aims
The principal site for the metabolism of propofol is the liver. However, the total body clearance of propofol is greater than the generally accepted hepatic blood flow. In this study, we determined the elimination of propofol in the liver, lungs, brain and kidneys by measuring the arterial-venous blood concentration at steady state in patients undergoing cardiac surgery.

Methods
After induction of anaesthesia, propofol was infused continuously during surgery. For measurement of propofol concentration, blood samples were collected from the radial and pulmonary artery at predetermined intervals. In addition, blood samples from hepatic and internal jugular vein were collected at the same times in 19 patients in whom a hepatic venous catheter was fitted and the other six in whom an internal jugular venous catheter was fitted, respectively. In six out of 19 patients fitted with a hepatic venous catheter, blood samples from the radial artery and the renal vein were also collected at the same time, when the catheter was inserted into the right renal vein before insertion into the hepatic vein.

Results
Hepatic clearance of propofol was approximately 60% of total body clearance. The hepatic extraction ratio of propofol was 0.87 ± 0.09. There was no significant difference in the concentration of propofol between the radial, pulmonary arteries and internal jugular vein. However, a high level of propofol extraction in the kidneys was observed – the renal extraction ratio being 0.70 ± 0.13.

Conclusions
We have demonstrated substantial renal extraction of propofol in human. Metabolic clearance of propofol by the kidneys accounts for almost one-third of total body clearance and may be the major contributor to the extrahepatic elimination of this drug.

Introduction

Propofol is a widely used agent for induction and maintenance of anaesthesia and sedation in critically ill patients. Since only 0.3% of administered dose of propofol is excreted in unchanged form in urine [1], the primarily elimination pathway is likely to be metabolism. Recently, we have reported that total body clearance of propofol was unaffected by changes in plasma

protein binding because the hepatic extraction ratio of propofol was very high indicating that hepatic clearance was blood flow-limited [2]. However, it has been shown that the total body clearance of propofol is about 30 ml kg^{-1} min^{-1} [2–6] and is larger than the generally accepted hepatic blood flow (21 ml kg^{-1} min^{-1}) [7]. Furthermore, extrahepatic elimination of propofol has been demonstrated in patients during the anhepatic phase of liver transplantation [8–10].

Lungs, kidneys and brain have been suspected as possible extrahepatic sites of propofol metabolism. Extensive first pass elimination of propofol at lungs has been reported in sheep, cats and rats [11–14]. However, the role of lungs in the metabolism of propofol in human is controversial [15, 16]. Dawidowicz *et al.* [15] reported higher propofol concentration in blood from right atrium than from radial artery (6.17 ± 2.15 and 3.49 ± 1.38 μg ml^{-1}) and oxidative pulmonary metabolism of propofol during propofol infusion. The calculated pulmonary extraction ratio was approximately 0.3–0.4. By contrast, He *et al.* [16] reported no pulmonary extraction at pseudo-steady state.

Glucuronidation is the major metabolic pathway of propofol [17] and uridine diphosphate glucuronosyltransferase (UGT) isoforms are expressed in the kidney and brain [18–22]. Recent *in vitro* studies demonstrate a significantly higher rate of propofol glucuronidation in human kidney than in human liver [20–22]. However, the contribution of kidney to the total body clearance of propofol *in vivo* remains unclear.

It is important to determine the contribution of each organ to total propofol clearance in order to adjust the dosage for certain disease states or specific surgical procedures. In this study, we directly evaluated the elimination of propofol in the lungs, brain and kidneys by measurement of arterial-venous blood concentration at steady state. The contribution of these tissues to the total body clearance of propofol was determined.

Methods

The study was approved by the Committee on Medical Ethics at the Saitama Cardio-Respiratory Center. Twenty-five patients (17 males and 8 females, age 40–77 years, weight 45–80 kg, height 149–177 cm) participated in this study after giving written, informed consent. All subjects were selected according to the criteria of the New York Heart Association (NYHA) functional classes I–III (class I, $n = 6$; class II, $n = 16$; class III, $n = 3$); each had a left ventricular ejection fraction (EF) of 40% or more and was scheduled for cardiac surgery with cardiopulmonary bypass (CPB) (Table 1). Routine clinical laboratory tests indicated normal renal and hepatic function in all patients. None were receiving premedications and all medication was discontinued 12 h before surgery.

Anaesthesia was induced by propofol (4 mg kg^{-1} h^{-1}), midazolam (0.1 mg kg^{-1}), fentanyl (10 μg kg^{-1}) and vecuronium (0.15 mg kg^{-1}) after the insertion of peripheral intravenous and radial arterial cannulae, and maintained with propofol (4 mg kg^{-1} h^{-1}) and fentanyl as required according to clinical criteria. The infusion rate of propofol was kept constant until the end of surgery. For 19 out of 25 patients fitted with a pulmonary artery catheter (Vigilance, Swan-Ganz CCO Thermodilution Catheter, Baxter, Co., Irvine, CA, USA), a hepatic venous catheter (Harmac Medical Products, Buffalo, NY, USA) was also inserted into the right hepatic vein via the right femoral vein after induction of anaesthesia. The other six patients were fitted with a jugular venous catheter (Harmac Medical Products, USA) inserted into the right internal jugular venous bulb under fluoroscopic guidance before the start of surgical preparations.

Non-pulsatile normothermic CPB was performed with a pump flow of 2.2 l min^{-1} m^{-2}. A mean arterial pressure of 50–90 mmHg and a haematocrit greater than 20% were maintained by phenylephrine infusion and transfusion of packed red blood cells, respectively. After the CPB was discontinued, the cardiac index was maintained above 2.5 l min^{-1} m^{-2} by the infusion of dopamine, dobutamine or both.

Blood samples for the measurement of propofol concentrations were collected from the radial and pulmonary artery and hepatic or internal jugular vein at various time points (T1–T6 as defined below). T1: mean 48 min (range: 40–55 min) after the start of infusion of propofol; T2: mean 130 min (range: 90–185 min) after the start of infusion of propofol, before administration of heparin; T3 and T4 correspond to 30 and 60 min after the start of CPB; T5: 30 min after the end of CPB; T6: 60 min after the end of CPB or the end of surgery. The blood samples from the pulmonary artery could not be collected during CPB. In six out of 19 patients fitted with a hepatic venous catheter, blood samples from the renal vein were also collected when the catheter was inserted into the right renal vein under fluoroscopic and ultrasonic echo guidance before insertion into the hepatic vein. Blood samples from the radial artery were collected at the same time. The blood samples were obtained in heparinized polyethylene tubes and stored at −20°C. All samples were analysed within 2 days of collection. The propofol concentrations in whole blood were measured using high performance liquid chromatography (HPLC) as described previously [2].

Table 1
Characteristics of the patients

Patient	Age (years)	Sex	Height (cm)	Weight (kg)	Surgical procedure	EF (%)	NYHA
1	73	Male	168	60	MVR	42	III
2	40	Male	177	77	MVR	61	II
3	77	Male	155	60	AVR	40	III
4	64	Male	176	73	AVR	54	II
5	74	Female	149	45	MVR	67	II
6	62	Male	159	59	AVR	50	II
7	72	Male	172	69	AVR	55	II
8	69	Male	150	48	AVR	58	II
9	59	Male	163	67	CABG	72	I
10	76	Female	154	60	AVR	67	II
11	72	Male	154	57	CABG	57	II
12	48	Male	163	65	CABG	65	I
13	44	Male	167	72	AVR	60	II
14	74	Female	151	48	CABG	49	II
15	54	Male	164	55	CABG	63	I
16	63	Male	162	69	MVR	40	II
17	58	Male	170	57	CABG	52	II
18	40	Male	170	80	CABG	40	III
19	75	Female	149	51	AVR	43	II
20	52	Male	165	66	CABG	65	I
21	66	Female	157	62	CABG	55	II
22	60	Male	172	69	CABG	54	II
23	66	Female	159	63	CABG	58	I
24	52	Female	156	58	CABG	65	I
25	71	Female	154	48	CABG	50	II

CABG, coronary artery bypass grafting; MVR, mitral valve replacement; MVP, mitral valve plasty; AVR, aortic valve replacement; EF, left ventricular ejection fraction; NYHA, New York Heart Association functional classes I to III.

In the six patients fitted with a hepatic venous catheter, hepatic blood flow was determined using the previously reported indocyanine green (ICG) method at time T2 [23, 24]. ICG was administrated by a bolus intravenous injection of 6 mg, followed by continuous infusion (1 mg min^{-1}) into a central vein. Heparinized blood samples (3 ml) from the radial artery and hepatic vein were collected 20, 25 and 30 min after bolus administration and centrifuged immediately. Haematocrit (Ht) was also measured at the same time. ICG concentration in plasma was measured spectrophotometrically at 805 nm. ICG concentrations were in steady-state at sampling. Hepatic plasma flow ($Q_{H,P}$) was calculated as follows: $Q_{H,P}$ = infusion rate/($C_{A,ICG} - C_{HV,ICG}$), where $C_{A,ICG}$ and $C_{HV,ICG}$ represent the plasma ICG concentration in the radial artery and hepatic vein, respectively. Hepatic blood flow (Q_H) was calculated as follows: $Q_H = Q_{H,P}/(1 - Ht/100)$.

Extraction ratio (E) of each organ was calculated as follows: $E = (C_{IN} - C_{OUT})/C_{IN}$, where C_{IN} and C_{OUT} represent the propofol concentration of the in-flow blood and out-flow blood, respectively. Hepatic clearance of propofol (CL_H) was calculated as follows: $CL_H = Q_H \times E_H$, where E_H represents the hepatic extraction ratio of propofol. Total body clearance (CL_{TOT}) of propofol was calculated as follows: CL_{TOT} = Infusion rate/C_{SS}, where C_{SS} represents the concentration at steady state. The concentration at T2 was regarded as the steady state concentration. True steady-state was not reached during surgery because the terminal elimination half-life of propofol is rather long (4–6 h). Since the rapid distribution half-life is rather short (1–3 min) and the distribution clearance is large [3, 4], the concentration of propofol reaches pseudo steady-state at 20 min after a constant infusion, and then it increases slowly until true steady-state is reached [16]. Contribution of rapid distribution, slow distribution (30–50 min) and terminal elimination half life (4–6 h) to the changes in concentration are 94.6%, 4.9%, 0.57%, respectively

Table 2
Renal and hepatic extraction of propofol or hepatic and total body clearance of propofol

Patient no.	E_H	E_R	HBF	CL_H	CL_{TOT}	CL_H/CL_{TOT}
1	0.96	–	15.5	14.9	28.6	0.52
2	0.82	–	21.0	17.2	25.8	0.67
3	0.96	–	14.3	13.7	26.1	0.53
4	0.76	–	25.7	19.5	26.1	0.75
5	0.88	–	21.1	18.5	26.3	0.71
6	0.88	–	17.7	15.6	29.8	0.52
7	0.93	0.78	–	–	26.8	–
8	0.94	0.51	–	–	30.4	–
9	0.83	0.61	–	–	28.5	–
10	0.98	0.74	–	–	31.4	–
11	0.94	0.87	–	–	32.7	–
12	0.97	0.69	–	–	36.8	–
Mean ± SD	0.89 ± 0.07	0.70 ± 0.13	19.2 ± 4.2	16.6 ± 2.2	29.1 ± 3.3	0.62 ± 0.10

CL_{TOT}, HBF and CL_H represent total body clearance of propofol, hepatic blood flow and hepatic clearance of propofol (ml/kg min^{-1}), respectively. E_H, E_R and CL_H/CL_{TOT} represent hepatic extraction ratio of propofol, renal extraction of propofol and ratio of CL_H to CL_{TOT}, respectively. E_R was measured just before insertion into hepatic vein. Other parameters were measured at the time T2.

[25]. There is a slight contribution of terminal half-life to the increase in concentration of propofol, but this is probably clinically irrelevant. Thus, we have estimated total clearance in the pseudo steady-state (about 1 h after starting the propofol infusion), which is almost equal to the true steady-state [2].

The data are expressed as mean ± SD. A paired *t*-test was used to detect differences in propofol concentration between the radial and pulmonary arteries and between the radial artery and internal jugular vein. Values of $P < 0.05$ were considered to be significant.

Results

The total arterial propofol concentration was constant throughout the surgery (T1: 2.43 ± 0.63, T2: 2.35 ± 0.33, T3: 2.49 ± 0.35, T4: 2.59 ± 0.48, T5: 2.64 ± 0.80 and T6: 2.52 ± 0.66 μg ml^{-1}, respectively). Total body clearance of propofol measured at T2 was 29.3 ± 6.4 ml kg^{-1} min^{-1} ($n = 25$). In the six patients whose hepatic blood flow was measured, hepatic and extrahepatic clearance of propofol was approximately 60% and 40% of total body clearance, respectively (Table 1). The hepatic extraction ratio of propofol was 0.87 ± 0.09 ($n = 114$). In the six patients where blood samples were taken from the renal vein, the higher propofol concentration in blood from the radial artery than from the renal vein was observed (1.97 ± 0.29 and 0.61 ± 0.31 μg ml^{-1}, $n = 6$, $P < 0.0001$, respectively). The renal extraction ratio of propofol was 0.70 ± 0.13 (Table 2). However, there was no significant difference in propofol concentration between the radial and pulmonary arteries at time points T1, T2, T5 and T6 in 25 patients (2.53 ± 0.46 and 2.54 ± 0.59 μg ml^{-1}, respectively, $n = 100$, $P = 0.81$), indicating no extraction in the lungs. There was also no significant difference in propofol concentration between the radial artery and internal jugular vein at time points from T1 to T6 in six patients (2.33 ± 0.27 and 2.33 ± 0.35 μg ml^{-1}, respectively, $n = 36$, $P = 0.88$), suggesting no extraction in the brain.

Discussion

It is crucial to understand the elimination pathway of a drug in order to establish the required dosage adjustment for a specific disease state. When a drug is extensively metabolized, dosage reduction is generally recommended for patients with hepatic dysfunction, since this is the most likely site of metabolism. However, in the case of propofol, total body clearance is much greater than hepatic blood flow, indicating that extrahepatic metabolism contributes substantially to the elimination of the drug from the body [2–6].

In this study the calculated hepatic clearance was approximately 60% of total body clearance, suggesting that about 40% of the propofol dose was extracted by organs other than the liver (Table 2). This observation is similar to that reported by Lange *et al.* [26]. We

found significant extraction of propofol in liver and kidneys – the hepatic and renal extraction ratio being approximately 0.9 and 0.7, respectively (Table 2). The generally accepted estimates for hepatic and renal blood flow are 21 and 18 ml kg^{-1} min^{-1}, respectively [7]. Therefore, the sum of the calculated hepatic and renal clearance is 31 ml kg^{-1} min^{-1}, which is similar to the total body clearance of propofol measured in this study and others [2–6]. Since urinary excretion of the parent drug is less than 0.3% [1], the major elimination pathway of propofol in the kidneys appears to be metabolism, probably by glucuronidation. Many pharmacokinetic studies indicate that total body clearance of propofol is similar in individuals with renal failure or hepatic cirrhosis and healthy subjects [27–32]. It might be considered that renal and hepatic extraction is so high that the total body clearance of propofol depends on renal and hepatic blood flow and is unaffected by moderate impairment of the metabolizing capacity of these organs.

In this study, renal vein samples were taken at time between 25 and 40 min after the infusion of propofol. Renal extraction ratio of propofol was calculated at this time. We can not entirely rule out the possibility that the renal extraction ratio of propofol results from a distribution of the drug into tissues, which would tend to overestimate renal clearance. However, because of the rapid distribution half-life (1–3 min) and the large distribution clearance [3, 4], the concentration of propofol reaches pseudo steady state at 20 min after a constant infusion [16]. Furthermore, the distribution process of propofol into well perfused organ tissue such as lungs reaches equilibrium within a very short time of constant infusion [16]. The kidneys would also reach equilibrium quite rapidly because a significant proportion of the total cardiac output is delivered. Therefore, renal extraction of propofol at the sampling time is likely to result from metabolism rather than distribution. Further investigations are required to describe in detail the role of the kidneys on propofol pharmacokinetics.

Some reports suggest that the lungs of a number of animals are important in the extrahepatic metabolism of propofol [11–14]. The difference between our findings and results of animal studies is probably due to the difference of species. Dawidowicz *et al.* reported that there was oxidative metabolism and extraction of propofol across the lung in humans [15]. However, we could find no significant difference in propofol concentration between the radial and pulmonary arterial blood. The reasons for the discrepancies between our findings and results of Dawidowicz *et al.* remain unknown. Unfortunately, we could not follow the methods of Dawidowicz *et al.* in which they measured both the parent drug and the oxidative metabolite on both sides of the lungs. Allowing for the results of Le Guellec *et al.* in which they found no activity of propofol glucuronidation in human lung microsomes [33], the oxidation of propofol would be the only process of the drug metabolism in the lungs. However, the role of oxidative metabolism of propofol in the organs other than the liver would be expected to be small because the oxidation of propofol accounts for approximately 25–40% of the dose [1, 17, 34] and this reaction would be catalysed mainly in the liver [35, 36]. Furthermore, if propofol is cleared by the lungs, total body clearance should be diminished during CPB, namely, under the condition without lung perfusion. In reality, total body clearance was unchanged during CPB [2], suggesting little contribution of the lung to the extrahepatic clearance of propofol. We therefore conclude that the lungs do not contribute to the extrahepatic clearance of propofol in human. Our findings support the reports of He *et al.* [16] and Gray *et al.* [8].

Expression of UGT isoforms in brain [18, 19] suggested the possibility of glucuronidation of propofol in brain. Zhang *et al.* reported that glucuronidation by UGT1A6 in the brain may be a major pathway of extrahepatic metabolism of propofol [18]. However, in our study, there was no significant difference between the arterial and internal jugular venous bulb blood concentration of propofol. Therefore, we conclude that the brain does not contribute to the extrahepatic clearance of propofol in human.

In conclusion, we have demonstrated a significant extraction of propofol in human kidneys. Indeed, metabolic clearance of propofol by the kidneys accounts for almost one third of total body clearance and is the major site of extrahepatic elimination.

None of the authors have financial or personal relationships that could potentially be perceived as influencing the described research.

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