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Pharmacokinetics and Protein Binding of Propofol in Patients with Cirrhosis

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The pharmacokinetics and protein binding of propofol were studied in ten patients with cirrhosis and in ten control patients undergoing elective surgery. All patients received 2.5 mg · kg^{-1} propofol as an intravenous bolus injection for the induction of anesthesia. Whole blood propofol concentrations were measured at intervals up to 12 h, using a high-performance liquid chromatography (HPLC) technique. Propofol protein binding was estimated by equilibrium dialysis 10 min after injection of propofol. Individual propofol profiles for all patients were best described by a three-compartment open mammillary model. Rapid and slow propofol distribution half-times were observed, followed by an elimination phase with a half-time of 4–5 h. Propofol total body clearance was reduced (1.99 ± 0.68 l · min^{-1}) in the patients with cirrhosis but did not differ significantly from that in the control patients (2.30 ± 0.61 l · min^{-1}). The apparent volume of distribution at steady state (Vdss) was similar in the two groups. No significant difference in elimination half-life was observed between the two groups. Propofol was extensively bound (mean: 97–98%) to the plasma protein of both cirrhotic and control groups. This study shows that propofol pharmacokinetics and protein binding of propofol following a single intravenous bolus dose were not markedly affected by uncomplicated cirrhosis of the liver. (Key words: Anesthetics, intravenous: propofol. Liver: cirrhosis. Pharmacokinetics: propofol. Protein binding: propofol.)

PROPOFOL (2,6-DIISOPROPYLPHENOL), a substituted phenol, is currently under study as a new intravenous anesthetic agent. Owing to the general concern with Cremophor-containing preparations, propofol has been formulated at a concentration of 1% w/v in an emulsion containing 10% w/v soya bean oil, 1.2% egg phosphatide, and 2.25% glycerol. This new formulation displays some loss of potency compared to the Cremophor formulation.[1] Pharmacokinetic data generated using the present formulation have shown that propofol is extensively distributed from blood into tissues and has a high total body clearance.[2] A study in which ^{14}C propofol was administered to male volunteers showed 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.[3] Therefore, the liver is the main eliminating organ for propofol, and, consequently, propofol clearance might be decreased in patients with cirrhosis. This study was designed to investigate the pharmacokinetics and protein binding of propofol after a single intravenous bolus dose in patients with cirrhosis, and to compare these results with those from patients with normal hepatic function.

Materials and Methods

The pharmacokinetics of propofol were investigated in ten patients with cirrhosis and ten patients without hepatic or renal dysfunction undergoing surgical procedures after giving their informed consent. The age and weight of the cirrhotic patients was 54.4 ± 8.6 yr (mean ± SD) and 66.4 ± 12.3 kg, respectively, while that for the normal patients was 41.6 ± 14.8 yr and 65.9 ± 12.4 kg, respectively. Cirrhosis of the liver had previously been established in all cases by a liver biopsy and all cirrhotic patients had previously suffered from clinical decompensation of their disease. None of the patients with cirrhosis had ascites or encephalopathy at the time of the study and none had ingested alcohol for at least 2 weeks prior to the study. Table 1 gives the laboratory data from the cirrhotic patients, as well as the nature of the surgical procedure. In all patients with cirrhosis, liver dysfunction, as estimated from the liver function tests, was moderate and compatible with elective surgery. All patients were premedicated orally with diazepam, 10 mg, and atropine, 1 mg, 1 h before anesthesia. An indwelling intravenous cannula was placed in a large forearm vein for the injection of propofol. Following lidocaine infiltration, an arterial cannula was inserted in the contralateral arm for collection of blood samples for pharmacokinetic analysis.

Anesthesia was induced with a single intravenous injection of propofol, 2.5 mg · kg^{-1} over a period of about 20 s. Succinylcholine was given to facilitate endotracheal intubation and neuromuscular paralysis was achieved with pancuronium. Anesthesia was maintained with nitrous oxide and oxygen (2:1) supplemented with intermittent bolus injections of fentanyl. Ventilation was controlled to maintain normal values of end-tidal carbon dioxide tension. When required, morphine hydrochloride was administered postoperatively. The doses and times of ad-

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TABLE 1. Characteristics and Liver Function Tests of Patients with Cirrhosis

Patient	Sex	Age (Yr)	Surgical Procedure	SGPT* (IU · ml^{-1})	Serum Alkaline Phosphatase† (IU · ml^{-1})	Serum Bilirubin‡ (μmol · l^{-1})	Prothrombin Time (% of Normal)	Plasma Albumin (g · l^{-1})
1	M	52	Laparotomy	25	195	11	71	38
2	M	47	Orchidectomy	32	176	37	59	31
3	F	57	Hip replacement	91	151	237	66	37
4	M	56	Urethrotomy	26	315	5	75	40
5	F	35	Sclerosis of esophageal varices	62	329	29	90	37
6	M	60	Sclerosis of esophageal varices	52	145	45	63	32
7	M	62	Sclerosis of esophageal varices	15	65	14	82	34
8	M	60	Sclerosis of esophageal varices	37	170	20	58	33
9	M	64	Colectomy	23	120	12	71	36
10	M	51	Sclerosis of esophageal varices	20	97	29	66	38

* Serum glutamic pyruvic transaminase, normal value: <30 UI · ml^{-1}.
† Normal value: <180 UI · ml^{-1}.
‡ Normal value: <20 μmol · l^{-1}.

ministration were recorded. No other drugs were administered.

For pharmacokinetic assessments, 5 ml arterial blood samples were collected in tubes containing potassium oxalate prior to propofol administration and at 2, 4, 6, 8, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150, 180, 240, 300, 360, 420, 480, 600, and 720 min after the end of the injection of propofol. Samples were immediately cooled to +4° C and stored at +4° C until subsequent analysis (within 2 weeks). Additional 10-ml samples of blood were collected 20 min after propofol administration to obtain plasma for plasma protein binding estimation. Whole blood propofol concentrations were measured using a high-performance liquid chromatography method. Blood samples (1 ml) to which internal standard (thymol) had been added were buffered with 0.1 M potassium dihydrogen orthophosphate (1 ml) and extracted on a rotary mixer for 15 min with cyclohexane (spectroscopic grade). The phases were separated by centrifugation and to an aliquot (4.5 ml) of the cyclohexane, 0.1 M potassium hydroxide in ethanol (30 μl) was added. The residue was reconstituted in HPLC eluent (250 μl) and an aliquot (50–100 μl) was injected into a 25 cm × 4.6 mm ID 5 *u* ultrasphere ODS (Altech) column. The mobile phase was composed of acetonitrile-water-orthophosphoric acid (85%): 60-40-0.2 at a flow rate of 1.5 ml · min^{-1}. Propofol and thymol were detected by spectrofluorimetry (λ excitation: λ276 nm, emission: 310 nm) with a Shimatzu RF-5230 detector. The sensitivity of the assay was 3 ng · ml^{-1} with a coefficient of variation of 6.4% at 25 ng · ml^{-1} and 3.6% at 250 ng · ml^{-1}. Stability of propofol in whole blood cooled down to 4° C both in glass and in plastic tubes was studied. Maximum concentration loss was inferior to 5 *p* 100 over a period of 3 weeks, whatever the concentration up to 100 mg · l^{-1}.

The extent of the binding of propofol to plasma protein was estimated using equilibrium dialysis at 37° C. A Dianorm dialyser as described by Weder *et al.* was used.¶ The buffer system was 0.067 M phosphate buffer (*p*H 7.4) made isotonic with sodium chloride.[4] This buffer is of adequate molarity to maintain the *p*H of plasma at the physiologically relevant value. The membrane was Spectrapor® 2 with a molecular weight cut off 12.000–14.000 as described by Meuldermans *et al.*[5] Previous studies had shown no significant binding of propofol either to the membrane or the cell during dialysis. After equilibrium had been reached, the drug concentration in the buffer compartment was equal to the concentration of unbound drug Cu, whereas the drug concentration in the protein compartment was equal to the sum of the concentrations of both unbound and bound drug Cu + Cb = C. Then the percent unbound (Fu) drug was Cu/C × 100 = Fu × 100.

The blood concentration curves obtained for individual patients were fitted to the sum of two or three exponential functions interpreted as two- or three-compartment open mammillary models. Pharmacokinetic modeling was performed using ELSFIT® version 3.1 program for the fitting of the curves, with an error variance model: variance = $A^2 \times B^c$ where B is the propofol concentration, and A and C are variables estimated during the fitting procedure. In all cases but one (control patient 2), the three-compartment model was preferred by reference to the

¶ Weder HC, Schildknecht J, Kesselring P: A new equilibrium dialysing system. American Laboratory 10:15–21, 1971

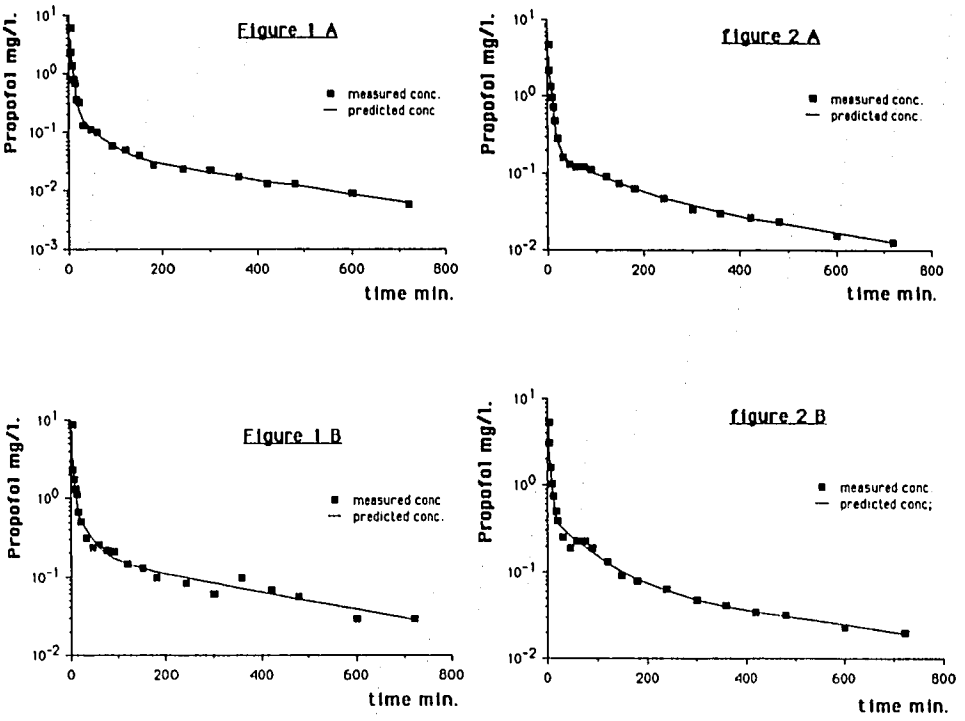

FIG. 1. Whole blood propofol concentration decay curves for two representative normal patients. Equations of the models are: *A:* $C(t) = 5.73e^{-0.25t} + 0.0262e^{-0.0261t} + 0.047e^{-0.00285t}$; *B:* $C(t) = 14{,}4e^{-0.407t} + 0.71e^{-0.0377t} + 0.189e^{-0.00265t}$. ■ = measured propofol concentrations; —— = predicted concentrations from the fitted functions. FIG. 2. Whole blood propofol concentration decay curves for two representative patients with cirrhosis. Equations of the models are: *A:* $C(t) = 4{,}61e^{-0.191t} + 0.136e^{-0.00984t} + 0.057e^{-0.00209t}$; *B:* $C(t) = 7{,}92e^{-0.305t} + 0.363e^{-0.0156t} + 0.0728e^{-0.00185t}$. ■ = measured propofol concentrations; —— = predicted concentrations from the fitted functions.

Schwarz goodness of fit criterion. It was used to derive the following pharmacokinetic parameters:[6] the half-lives T ½ alpha, T ½ beta, and T ½ gamma; initial dilution volume (Vi); distribution volume at steady state (Vdss); and total body clearance (Cl). Pharmacokinetic parameters based upon unbound propofol were not calculated as total blood clearance clearly appeared to be nonrestrictive. The microconstants $K_{1\text{-}2}$, $K_{2\text{-}1}$, $K_{1\text{-}3}$, and $K_{3\text{-}1}$ were apparent first-order intercompartmental transfer rate constants for the three compartment model, and Kel was the rate constant of elimination from the central compartment.

Statistical analysis was performed using the Mann and Whitney U test for between-group comparisons of pharmacokinetic data.

Results

Table 1 shows the clinical characteristics and the liver function tests of the patients with cirrhosis. While all cirrhotic patients in this study had histologically confirmed evidence of cirrhosis, the liver function test data for these individuals suggest that the degree of hepatic function impairment was mild. Profiles of propofol blood concentration decay as a function of time were similar for both patient groups. Figures 1 and 2 show representative curves from two normal patients and two patients with cirrhosis. Individual and mean values for pharmacokinetic parameters are recorded in tables 2 and 3. There were no significant differences between the control and cirrhotic groups for any of the pharmacokinetic parameters estimated with $P < 0.05$ taken as the minimum level of statistical significance. Values of central compartment volume were appreciably higher than blood volume (mean range: 20–40 l). Rapid and slow distribution half-times were observed (half-lives, respectively, 2 and 30 min) followed by an elimination phase with a half-life of 4–5 h. Values of $K_{3\text{-}1}$ ($2\text{–}10 \cdot 10^{-3} \cdot \text{min}^{-1}$) were only a small proportion of values of Kel ($45\text{–}250 \cdot 10^{-3} \cdot \text{min}^{-1}$). This confirms that the slow rate of return of propofol from the third compartment to the central compartment constrains the rate of drug elimination during the final exponential phase. Clearance values for the majority of individuals of both groups approached the generally accepted upper limit estimate of total hepatic blood supply in humans,[7] suggesting involvement of extrahepatic mechanisms in the metabolic clearance of propofol. Propofol was shown to be extensively bound (mean: 97–98%) to the plasma proteins of both the cirrhotic and control groups (table 4). As plasma protein binding of propofol and albumin concentrations were similar in both patient groups, the consistency of the estimates of apparent volume of distribution between patient groups was predictable. The plasma/whole blood propofol concentration ratios were similar (0.8–0.9) in both groups (table 4).

Discussion

In patients with cirrhosis, propofol pharmacokinetics were not significantly modified, despite its mainly hepatic route of elimination. Although total body clearance in

TABLE 2. Body Weight and Pharmacokinetics of Propofol in Cirrhotic and Normal Patients

Subjects	Body Weight (kg)	T 1/2 Alpha (Min)	T 1/2 Beta (Min)	T 1/2 Gamma (Min)	Vi (l)	Vdss (l)	Cl ($l \cdot min^{-1}$)
Cirrhotics							
1	72	1.30	10	234	5.7	173	1.43
2	82	2.61	49	282	16.8	323	1.73
3	53	1.91	11	259	11.2	285	1.42
4	70	1.98	50	420	31.4	1195	3.57
5	56	2.03	12	220	20.1	390	2.06
6	55	3.63	70	332	29.2	480	2.14
7	79.5	2.27	51	379	23.9	557	2.16
8	62	2.10	23	327	13.6	311	1.11
9	80	2.18	28	347	24.6	645	2.26
10	54.5	2.11	57	260	25.0	404	2.02
Mean	66.4	2.212	36.10	306	20.2	476	1.99*
±SD	11.7	0.597	21.85	65	8.2	287	0.68
Controls							
1	75	3.15	73	209	66.1	678	2.97
2	65	2.85	—	139	26.4	298	2.19
3	71	1.95	15	164	23.5	319	3.15
4	43	1.79	22	245	10.1	189	1.63
5	75	1.70	41	262	12.4	332	1.51
6	65	0.75	9	134	12.4	304	2.86
7	70	2.09	40	332	16.3	417	2.51
8	70	1.35	33	550	17.6	868	2.45
9	45	2.77	27	243	18.2	283	2.21
10	80	0.70	8	178	3.28	153	1.48
Mean	65.9	1.910	29.78	246	20.6	384	2.30*
±SD	12.4	0.842	20.31	123	17.3	222	0.61

* $U = 30$, $P = 0.10$.

TABLE 3. Pharmacokinetic Microconstants in Cirrhotic and Normal Patients

	$K_{1\text{-}2}$	$K_{2\text{-}1}$	$K_{1\text{-}3}$	$K_{3\text{-}1}$	Kel
Cirrhotics					
1	0.1270	0.0947	0.1250	0.00448	0.2510
2	0.0978	0.0226	0.0557	0.00401	0.1030
3	0.0795	0.0833	0.1300	0.00557	0.1260
4	0.1230	0.0208	0.1040	0.00334	0.1140
5	0.0821	0.0834	0.1280	0.00732	0.1030
6	0.0739	0.0160	0.0363	0.00335	0.0734
7	0.1480	0.0277	0.0513	0.00303	0.0904
8	0.1290	0.0531	0.0931	0.00479	0.0814
9	0.1120	0.0406	0.0965	0.00429	0.0920
10	0.1890	0.0300	0.0390	0.00442	0.0807
Mean	0.1161	0.0472	0.0859	0.00446	0.1115
±SD	0.0354	0.0296	0.0373	0.00126	0.0516
Controls					
1	0.1410	0.0208	0.0188	0.00742	0.0449
3	0.1120	0.0774	0.0758	0.00681	0.1340
4	0.1430	0.0536	0.0593	0.00394	0.1620
5	0.1240	0.0566	0.1390	0.00590	0.1220
6	0.3890	0.1510	0.2250	0.01070	0.2320
7	0.1060	0.0261	0.0615	0.00299	0.1540
8	0.2580	0.0458	0.0915	0.00214	0.1390
9	0.0630	0.0364	0.0538	0.00420	0.1210
10	0.2270	0.1100	0.2770	0.00636	0.4500
Mean	0.1737	0.0642	0.1113	0.0056	0.1732
±SD	0.1009	0.0425	0.0865	0.0026	0.1146
Control 2	0.1500	0.0146			0.0831

TABLE 4. Plasma Protein Concentration and Propofol Protein Binding in Normal Patients and in Patients with Cirrhosis

	Total Prot. Conc. ($g \cdot l^{-1}$)	Plasma Albumin ($g \cdot l^{-1}$)	Plasma Propofol Concentration at 10 Min ($\mu g \cdot ml$) after Injection	Unbound Propofol (%) at 10 Min after Injection	Plasma/Whole Blood Propofol Concentrations (%) at 10 Min after Injection
Cirrhotics					
1	69	38	0.94	1.7	73
2	66	31	0.86	2.6	85
3	68	37	0.73	2.6	89
4	70	40	0.23	3.0	68
5	61	37	0.49	2.0	74
6	70	32	0.54	1.5	86
7	62	34	0.63	1.9	83
8	81	33	1.32	1.5	83
9	68	36	0.50	1.5	116
10	67	38	0.69	2.2	96
Mean	68	36	0.69	1.9	86.5
±SD	5	5	0.30	0.6	13.9
Controls					
1	71	41	0.38	—	84
2	68	39	0.82	1.2	101
3	64	37	0.66	2.6	80
4	59	30	0.62	2.4	74
5	70	42	0.88	2.2	87
6	66	36	0.28	2.9	80
7	70	36	0.50	1.8	79
8	70	36	0.38	1.5	72
9	77	30	0.13	3.1	48
10	69	35	0.70	2.3	71
Mean	68	36	0.59	2.2	77.6
±SD	5	4	0.24	0.6	13.6

cirrhotic patients was slightly lower than that in normal patients in our study, this decrease did not reach statistical significance. In addition, total body clearance approached the upper limit of usual hepatic blood flow values,[7] particularly when considering that our patients were anesthetized, a condition frequently leading to a decrease in cardiac output and hepatic blood flow.[8,9] Similar high values of total body clearance of propofol have already been described in other studies.[2,10] Before considering extrahepatic mechanisms to explain those high clearance values, technical problems leading to potential underestimations of the area under the concentration curve (AUC) must be ruled out, because clearance was calculated through the formula Cl = dose/AUC. Samples were immediately cooled down to 4° C, and temperature of storage and the concentration of propofol in samples handled for preliminary studies remained stable in those conditions for up to 3 months, a duration considerably longer than the usual delay before assay. Concentration of propofol in samples stored in glass tubes was not different from that of samples stored in plastic tubes. The clearance was estimated from AUC calculated from the curve fitting; this extrapolated area was very similar to the value obtained using the trapezoidal approximation up to the last sampling time and extrapolating to infinity using the final phase rate constant, obtained from the curve fitting. The extrapolated area in the latter case was only 8.7 ± 5.0 (SD) % of the AUC derived by this model independent method. Consequently, total body clearance of propofol truly seems to exceed the usual values of hepatic blood flow, and extrahepatic mechanisms of clearance appear likely. Despite this, it is very likely that liver is the main, although not the sole, metabolizing organ for propofol. Consequently, its clearance should be dependant on functional blood flow. Functional blood flow is frequently decreased in patients with cirrhosis, even when hepatic functional tests are near normal.[11] This should lead to a decrease in total body clearance of propofol.[12] Although the total body clearance in our cirrhotic patients was slightly lower than that in normal patients, this decrease did not reach statistical significance ($U = 30$, $P = 0.10$).

Propofol was shown to be extensively bound (mean: 97–98%) to the plasma proteins of both the patients with cirrhosis and the control patients. The propofol concentration ratio between plasma and whole blood approached 1. This shows that, although propofol is extensively protein bound, there is appreciable binding of propofol to the formed elements in blood, probably erythrocytes. Within the plasma concentration range studied, patients with cirrhosis did not suffer a significant decrease in protein-binding capacity when compared with control patients. Propofol is weakly acidic and drugs of this type are generally believed to bind to albumin in plasma. Albumin concentrations were similar in both patient groups. On this basis, therefore, the consistency of the observed propofol protein binding between the groups was predictable. Propofol binding to human plasma proteins was linear up to a concentration of at least 20 $mg \cdot l^{-1}$ in a separate *in vitro* study when albumin concentration was 40 $g \cdot l^{-1}$.

Thus, this study shows that the pharmacokinetics and protein binding of propofol following a single induction dose were not markedly affected by uncomplicated cirrhosis of the liver. Further investigations are called for to elucidate extrahepatic metabolism of propofol and to confirm if kinetic parameters are modified or not in patients with more severe hepatic dysfunction. If elimination half-life of propofol is not very different from that of other intravenous anesthetics, the very large Vd_{ss} is rather unusual and explains that, even after infusions lasting several hours, recovery from anesthesia is still partly related to redistribution. The results of this study should not be extrapolated to patients with more severe liver dysfunction.

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