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Propofol Infusion for Maintenance of Anesthesia in Morbidly Obese Patients Receiving Nitrous Oxide

A Clinical and Pharmacokinetic Study

Frédérique Servin, M.D.,* Robert Farinotti, Ph.D.,† Jean-Pierre Haberer, M.D.,‡ Jean-Marie Desmonts, M.D.§

Background: The pharmacokinetic and pharmacodynamic properties of propofol indicate that this may be an appropriate agent for induction and maintenance of anesthesia in obese patients. This study was designed to assess the rates of recovery and the pharmacokinetics of propofol infusions in morbidly obese patients.

Methods: Anesthesia was induced and maintained using a stepwise infusion regimen of propofol in eight morbidly obese patients. The patients' lungs were ventilated with nitrous oxide:oxygen (66:34%). Pharmacokinetic parameters were calculated from iterative blood sampling during the propofol infusion and during 8 h after its completion.

Results: Results were compared with those from a concurrent study of propofol pharmacokinetics in nonobese adults. The initial volume of distribution of propofol was not modified in obese patients. Total body clearance increase was correlated to body weight ($R = 0.76$, $25.4 \pm 6.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, mean \pm SD). Volume of distribution at steady state was also correlated to body weight ($R = 0.61$, $1.63 \pm 0.54 \text{ l} \cdot \text{kg}^{-1}$, mean \pm SD). Propofol concentration at the time of eye opening in response to verbal command was $0.94 \pm 0.26 \text{ mg} \cdot \text{l}^{-1}$.

Conclusions: Results from this study confirm the absence of propofol accumulation in morbidly obese patients when the current dosing scheme is used. Dosing schemes expressed in $\text{mg} \cdot \text{kg}^{-1}$ are the same as those in normal patients. (Key words:

Anesthetics, intravenous: propofol. Pharmacokinetics, obesity.)

THE choice of anesthetic for maintenance of general anesthesia in morbidly obese patients remains controversial. Rapid recovery is desirable to ensure early efficient coughing and to minimize postoperative respiratory complications, which frequently occur.¹ The use of propofol in morbidly obese patients has been reported in a few clinical studies.²⁻⁴ No delayed recovery was recorded. However, no pharmacokinetic data regarding propofol infusions are currently available to confirm the absence of propofol accumulation in this population. This study was designed to simultaneously investigate the quality of early recovery and pharmacokinetics of propofol infusions used for the maintenance of general anesthesia in morbidly obese patients. The parameters calculated in obese patients were compared with those calculated in a group of healthy patients concurrently studied in our institution.⁵

Materials and Methods

Pharmacokinetics of propofol were studied in eight morbidly obese patients aged $47.1 \pm 15.6 \text{ yr}$ (mean \pm SD, range 25-66 yr) and weighing $115.5 \pm 20.8 \text{ kg}$ (mean \pm SD, range 97-160 kg). All patients were undergoing nonhemorrhagic elective surgical procedures requiring general anesthesia for a minimum period of 2 h and gave informed consent to participate in the study. Patients with evidence of renal, hepatic, or cardiac dysfunction were excluded from the study. All patients received diazepam 10 mg and atropine 1 mg orally 1 h before anesthesia. An intravenous cannula was inserted in a forearm vein for injection of propofol. Following infiltration with lidocaine, a cannula was inserted in the contralateral radial artery for monitoring arterial pressure and for collection of blood samples for pharmacokinetic analysis.

* Staff Anesthesiologist, Département d'Anesthésie-Réanimation, Chu Bichat-Claude Bernard.

† Professor of Clinical Pharmacy, Laboratoire de Toxicologie, Chu Bichat-Claude Bernard.

‡ Professor of Anesthesia, Département d'Anesthésie-Réanimation, Hopitaux de Brabois.

§ Professor of Anesthesia, Département d'Anesthésie-Réanimation, CHU Bichat-Claude Bernard.

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Address reprint requests to Dr. Servin: Département d'Anesthésie-Réanimation, CHU Bichat-Claude Bernard, 46, rue Henri Huchard, 75878 Paris, Cedex 18, France.

Anesthesia was induced and maintained using a stepwise infusion regimen of propofol $21 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for 5 min, $12 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for 10 min, and $6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for the remainder of the procedure. The weight used for the calculation of the infusion rate was established using an empirical formula (corrected weight = ideal weight + $[0.4 \times \text{excess weight}]$) because, in these patients, the dosages calculated on an actual weight basis were so high that the absence of deleterious hemodynamic effects could not be assured. Following the onset of unconsciousness, succinylcholine was given to facilitate tracheal intubation and vecuronium to maintain muscle relaxation. Small incremental doses of fentanyl ($50 \mu\text{g}$) were given intravenously as required throughout the procedure. The patients' lungs were ventilated to normocapnia with a mixture of 66% nitrous oxide in oxygen. At the end of the procedure, the propofol infusion and nitrous oxide administration were simultaneously stopped. The time from the beginning of infusion to the loss of consciousness, the time to opening eyes on verbal command after stopping the infusion, the duration of the infusion, and the total amount of propofol infused were recorded.

For pharmacokinetic analysis, 2.5-ml blood samples were collected before infusion of propofol and at 2, 5, 10, 15, 20, 25, 30, 45, 60, 75, 90, 105, and 120 min thereafter. For infusions continuing beyond 120 min, additional samples were obtained every 15 min. A sample was collected as the infusion was stopped, and further 5-ml samples were collected 2, 4, 6, 8, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150, 180, 240, 300, 360, 420, and 480 min after the end of the infusion. An additional sample was drawn when the patient opened his or her eyes on verbal command. After thorough mixing, the samples were cooled immediately to 4°C and stored at that temperature until subsequent analysis. Whole blood concentrations of propofol were measured by high-pressure liquid chromatography⁶ with a coefficient of variation of 8% and a lower limit of detection of 4 ng/ml.

The blood concentration curves obtained for individual patients were fitted to the sum of exponential functions derived from Colburn⁷ and interpreted as three-compartment open mammillary models. Pharmacokinetic modeling was performed using SIPHAR program⁸ for the fitting of the curves, with a weighing function

of $1/y^2$. The quality of the fit of the three exponential models was assessed by the presence of a random scatter of the data around a calculated value,⁸ and by visual assessment of the residuals of the observed values from the fitted curve.

The following parameters were derived from the fitted model:⁹ distribution and elimination half lives ($T_{1/2\alpha}$, $T_{1/2\beta}$, $T_{1/2\gamma}$), volume of the central compartment (V); total body clearance (Cl_T); distribution clearance ($\Sigma Cl_i = V \cdot k_{12} + V \cdot k_{13}$); and volume of distribution at steady state (V_{ss}).

Propofol pharmacokinetics in ten healthy patients within the normal weight range,¹⁰ aged 42.0 ± 11.7 yr (24–56) and weighing 65.6 ± 14.9 kg (50–96), were determined in a concurrent study in our institution.⁵ The study design was identical as far as clinical protocol data recording and blood propofol analysis were concerned. In that concurrent study, pharmacokinetic modelling had been performed using the ELSFIT program¹¹ for the fitting of the curves. For the purpose of the current study, the raw data of the control patients underwent a new pharmacokinetic analysis using the SIPHAR program for the fitting of the curves, with a weighing function of $1/y^2$, the same as in obese patients.

Statistical analysis was performed by Wilcoxon Rank Sum test for between-group comparisons of pharmacokinetic data and unpaired t test for between-group comparisons of measured data; ANOVA for repeated measures was used to compare the measured blood propofol concentrations. A P value ≤ 0.05 was considered significant. Values are expressed as mean \pm SD.

Results

Table 1 shows the clinical characteristics of the patients and displays a significant difference in weight between the two groups. The percentage of female patients was greater in the obese group. Infusion data in both groups of patients are displayed in table 2. Induction was achieved in 3–4 min in both groups. Because of the dosage scheme used, the amount of propofol infused (mg/kg) was significantly less in the obese group and led to a significantly shorter time to opening eyes on verbal command at the end of the infusion. The propofol concentration when opening eyes was similar in both groups. Changes in mean blood concentrations of propofol with time, both during and after the infusion, followed a similar pattern in both groups of patients (figs. 1, 2).

⁸ Gomeni R: PHARM—an interactive graphic program for individual and population pharmacokinetic parameter estimation. *Comput Biol Med* 14: 25–34, 1984.

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Table 1. Clinical Characteristics of the Patients

Patients	Surgical Procedure	Age (yr)	Sex	Weight (kg)	Ideal Body Weight (kg)	Plasma Albumin Concentration (g/L)	Plasma Creatinine Concentration (μM)	Hemoglobin Concentration (g/100 ml)
Obese								
1	Hip replacement	55	F	108	55.5	40	81	15
2	Cholecystectomy	37	F	160	62.0	37	90	14
3	Cholecystectomy	30	F	97	52.5	38	93	13.5
4	Cholecystectomy	66	M	130	72.5	38	100	16.2
5	Wound dehiscence	66	F	105	55.0	37	91	13.4
6	Wound dehiscence	53	M	107	62.7	38	119	13.7
7	Lipoma resection	25	F	100	55.0	47	57	14
8	Wound dehiscence	45	F	117	53.5	44	71	14.3
Mean \pm SD		47.1 \pm 15.6	6F/2M	115.5 \pm 20.8	58.6 \pm 6.8	39.9 \pm 3.7	87.8 \pm 18.7	14.3 \pm 0.93
Control*								
1	Femoral pseudarthrosis repair	24	M	60	66.5	40	75	11.9
2	Femoral pseudarthrosis repair	34	M	55	63.5	42	74	14.1
3	Pulmonary resection	42	M	54	65.0	33	93	16.3
4	Pleurectomy	54	F	55	56.5	40	65	12.7
5	Colectomy	55	M	70	66.5	46	107	16.6
6	Hysterectomy	52	F	85	61.0	38	57	14.9
7	Wound dehiscence	56	M	70	65.0	36	48	13.8
8	Selective vagotomy	33	M	61	66.5	31	81	14.4
9	Cholecystectomy	39	M	96	75.5	38	85	15.2
10	Ileal resection	30	F	50	55.0	36	55	12
Mean \pm SD		41.9 \pm 11.7	3F/7M	65.6 \pm 14.9†	64.1 \pm 5.8	38.0 \pm 4.3	74.0 \pm 18.3	14.2 \pm 1.6

* Patients included in the concurrent study.⁵

† $P \leq 0.001$.

Pharmacokinetic parameters are displayed in tables 3, 4, and 5. The evolution of blood propofol concentrations over time could be best described by a three-compartment open mammillary model in nine control patients and in all obese patients, whereas the fit was better with a two-compartment model in one control patient. The volume of the central compartment was similar in both groups. It could not be defined accurately in one patient of the obese group (patient 2). Total body clearance of propofol was significantly correlated to body weight (fig. 3), and, as a result, clearance normalized by body weight was not statistically different in obese and control patients. The same phenomenon was observed with V_{ss} (fig. 4). By contrast, ΣCl_i was not correlated to body weight (fig. 5), and its value was not statistically significantly different in control and obese patients. The amount of extrapolated AUC was $3.16 \pm 1.51\%$ in the obese group and $3.16 \pm 1.13\%$ in the control group. The order of magnitude in the elimination half lives did not differ between the two groups. The coefficients A, B, and C reported in table 5 represent the amount that each half life con-

tributes to the decrease in propofol blood concentration, and can be expressed as a percent of the sum of all coefficients,¹² thus figuring the relative importance of the different half lives in the decrease of blood propofol concentration. Those coefficients are displayed in table 6.

Discussion

Few data are currently available concerning propofol dosages for induction and maintenance of general anesthesia in morbidly obese patients. Kirby *et al.*² advised the use of reduced body-related dosages in these cases. Redfern *et al.*¹³ found that the total propofol dose required to induce anesthesia did not correlate with the weight of the patient. Considering the moderately increased steady-state concentration in heavier patients during propofol constant rate infusions at 3, 6, and 9 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, Gepts *et al.*¹⁴ suggested that a combination of a fixed dose and a body weight-related dose may be preferable. On the other hand, propofol has marked hemodynamic effects and an excessive dos-

Table 2. Infusion Details in Obese and Control Patients

Patients	Loss of Consciousness (min)	Duration of Infusion (min)	Propofol Infused (mg/kg)	Propofol Concentration When Opening Eyes (mg/L)	Time to Opening Eyes (min)	Time to Orientation (min)
Obese						
1	1.5	156	15.3	0.745	20	48
2	5	120	9.4	0.604	10	12
3	3.25	165	13.9	0.733	8	15
4	3	140	12.5	1.200	9	15
5	2	250	23.2	0.848	19	40
6	6	183	16.5	1.069	2	6
7	5	55	6.4	0.964	5	7
8	2	150	13	1.380	10	20
Mean ± SD	3.8 ± 1.7	153.4 ± 55.2	13.8 ± 5.0	0.943 ± 0.262	10.38 ± 6.26	20.38 ± 15.41
Control						
1	2.5	142	16.5	0.907	24	28
2	4.5	226	24.9	1.106	16	19
3	3	170	19.3	0.696	13	25
4	2	296	31.8	0.903	18	36
5	4	287	31.0	1.134	25	40
6	3	173	19.6	1.360	11	18
7	4	151	15.7	1.229	25	30
8	3	133	15.6	0.792	10	30
9	3	162	18.5	1.979	20	38
10	3.5	208	23.1	1.555	22	43
Mean ± SD	3.3 ± 0.8	194.8 ± 58.3	21.6 ± 6.0	1.166 ± 0.388	18.4 ± 5.7	30.7 ± 8.6
<i>P</i>	NS	NS	≤0.02	NS	≤0.02	NS

age for induction might lead to severe cardiovascular depression in those patients who are often hemodynamically unstable. These are the reasons why, in this study, obese patients received comparatively less propofol per kg of body weight than lean patients in the concurrent study.⁵ This might explain why the time to opening eyes on verbal command was significantly less in the obese group, although propofol blood concentrations when opening eyes were similar in the two groups. The differences in the dosage used in the two groups could make questionable the comparison of the pharmacokinetic data between them. However, Gepts *et al.* showed that propofol pharmacokinetics were linear in the usual therapeutic range.¹⁴ This allows the comparison of calculated pharmacokinetic parameters in obese or lean patients despite different dosages. Propofol elimination half life is known to be dependent on the sampling time.^{15,16} Thus, when the sampling period exceeds 42 h, apparent elimination half life and volume of distribution are much greater than those previously reported in the literature. In addition, systemic blood clearance is within the range of usually accepted values of hepatic blood flow.¹⁵ The relatively short sampling time after the end of infusion in our

study (8 h) could lead to an overestimation of clearance. Nevertheless, the last elimination slopes in our studies were not different in obese or in lean patients, and nothing suggests that a fourth slope might be steeper in lean patients, leading to differences in elimination half lives when compared to those observed in the obese patients. Similarly, after such infusion schemes, the amount of extrapolated area is comparatively low and reduces the imprecision on the clearance values. Thus, even if some inaccuracy regarding the actual value of elimination half lives in obese patients may not be eliminated, the influence of this phenomenon on the estimation of clearance remains marginal, and its clinical implication appears minor. However, if elimination half life is an important parameter to define the pharmacokinetic model and to extrapolate the area under the concentration curve to infinity, it is of little clinical interest in estimating the recovery time when using a drug such as propofol, when the first "distribution" half lives account for more than 99% of blood concentration decrease.¹² This sustained influence of distribution processes in governing propofol disposition was clearly demonstrated by Hughes *et al.*,¹⁷ who emphasized the difference between the

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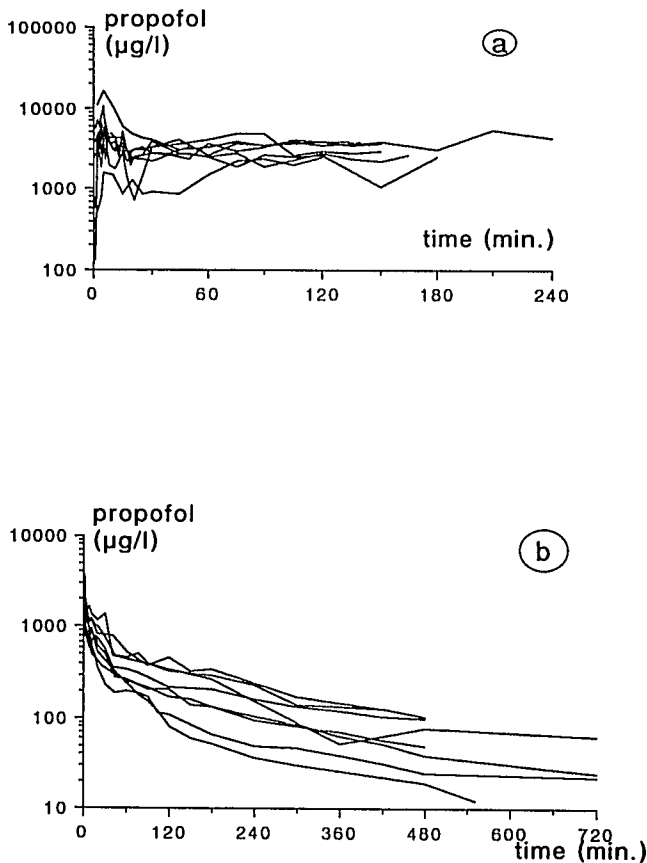


Fig. 1. Individual propofol blood concentration versus time data for each subject during the infusion (a) and after its discontinuation (b) in obese patients.

elimination half life of propofol (order of magnitude 250 min) and the "context sensitive half time" (time required for the central compartment drug concentration at the end of infusion to decrease by 50%) (order of magnitude 10–30 min).

Alterations of propofol disposition in obese patients could be related to several changes, including alterations of the propofol distribution, and of its metabolism in obese patients.

The distribution volume changes related to obesity depend on numerous factors, one of them being the increase of adipose mass. In obese patients, changes in distribution volume correlate with the lipophilicity of the agent.¹⁸ Propofol is highly lipophilic, with an octanol:buffer partition ratio of 15 (Phosphate buffer 10^{-2} M at pH 7.4, measured in our laboratory), similar to that of alprazolam, which is 18.¹⁹ This lipophilicity index is lower than that of midazolam (34),¹⁹ thio-pental (89),²⁰ and diazepam (309).¹⁹ Thiopental,

midazolam, and diazepam display an increase in V_{ss} in obese patients,^{21–23} and this increase in V_{ss} remains significant even after correction for total body weight. However, although alprazolam volume of distribution in obese patients is greater than in control subjects, correction for total body weight results in no difference between the subjects groups.²⁴ Propofol, with a similar octanol:buffer partition ratio, behaves like alprazolam as far as distribution is concerned, although the octanol:buffer partition ratio is perhaps not the more relevant parameter to estimate *in vivo* lipid solubility.¹⁹ The distribution volumes may be affected by numerous factors, including relative tissue affinity; therefore, phar-

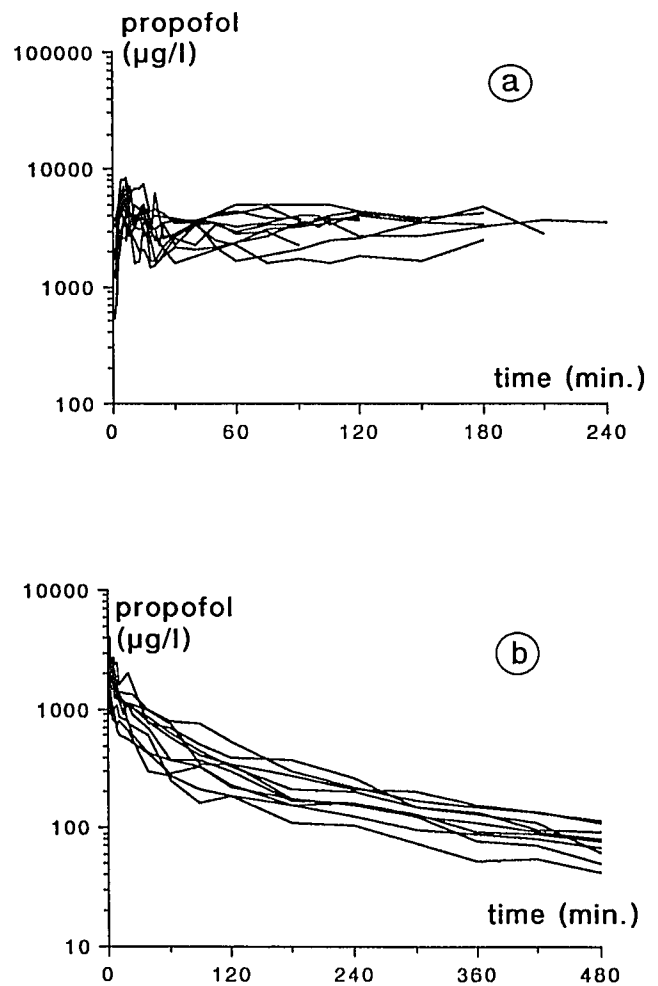


Fig. 2. Individual propofol blood concentration versus time data for each subject during the infusion (a) and after its discontinuation (b) in control patients. This figure used the raw data obtained for the pharmacokinetic study in healthy patients.⁵

Table 3. Pharmacokinetic Parameters

Patients	T _{1/2} α (min)	T _{1/2} β (min)	T _{1/2} γ (min)	V (L)	Cl _E (ml · min ⁻¹ · kg ⁻¹)	V _{ss} (L/kg)	ΣCl _i (L/min)
Obese							
1	0.38	20.1	303	2.80	21.8	2.31	2.68
2	8.36	53.0	285	86.96	34.0	2.65	1.95
3	1.15	18.4	208	7.17	25.6	1.55	1.64
4	1.02	21.6	211	4.17	14.0	0.98	1.01
5	2.16	48.0	247	9.11	20.2	1.52	3.12
6	1.69	23.7	201	10.96	30.4	1.71	1.23
7	0.92	25.3	218	5.9	25.6	1.23	1.69
8	1.57	22.6	273	16.3	22.9	2.72	4.12
Mean ± SD	2.16 ± 2.6	29.1 ± 13.4	243 ± 39	17.9 ± 28.2	24.3 ± 6.2	1.83 ± 0.65	2.18 ± 1.05
Harmonic mean				6.78			
Control*							
1	1.72	20.9	244	25.2	29.8	3.07	5.52
2	2.77	19.1	335	22.8	34.0	3.62	2.55
3	2.04	—	130	4.8	24.3	0.94	0.31
4	0.85	23.7	284	3.6	24.0	1.62	1.5
5	1.53	54.3	526	9.7	25.1	2.31	2.46
6	2.80	30.7	214	18.1	24.9	1.71	1.92
7	1.20	20.6	197	10.0	23.6	1.14	3.53
8	1.73	15.3	184	8.9	34.4	1.66	1.48
9	2.18	19.7	156	17.6	20.7	1.49	2.89
10	1.24	13.5	186	9.8	41.8	3.30	2.93
Mean ± SD	1.81 ± 0.65	24.2 ± 12.3	246 ± 116	13.04 ± 7.4	28.3 ± 6.6	2.09 ± 0.94	2.51 ± 1.40
Harmonic mean				9.10			
P	NS	NS	NS	NS	NS	NS	NS

* SIPHAR.

macologic agents demonstrate inconsistent changes as a result of their relative tissue affinities.

In normal-weight patients, propofol clearance is very high, and calculated values usually exceed hepatic blood flow estimated from physiologic values. Although evidence of extrahepatic mechanisms' involvement in

Table 4. Comparison of Pharmacokinetic Data Calculated with SIPHAR and ELSFIT Systems (control patients)

Patients	Cl _E md (SIPHAR) (L/min)	Cl _E md (ELSFIT) (L/min)	V _{ss} (SIPHAR) (L)	V _{ss} (ELSFIT) (L)
1	1.79	1.78	184	144
2	1.87	1.99	199	168
3	1.31	1.37	51	38
4	1.32	1.43	89	93
5	1.76	2.05	162	132
6	2.12	2.17	145	101
7	1.65	1.69	80	84
8	2.10	2.11	101	90
9	1.99	2.19	143	156
10	2.09	2.01	165	203
Mean ± SD	1.80 ± 0.30	1.88 ± 0.30	132 ± 49	121 ± 49

Table 5. Concentration Coefficients and Constant Rates of the Pharmacokinetic Models for Every Patient

	A (ng/L)	α (min ⁻¹)	B (ng/L)	β (min ⁻¹)	C (ng/L)	γ (min ⁻¹)
Obese						
1	352	1.835	4.8	0.0345	0.2	0.0023
2	11	0.083	0.3	0.0131	0.1	0.0024
3	135	0.601	4.0	0.0377	0.2	0.0033
4	237	0.683	2.8	0.0322	0.4	0.0033
5	101	0.627	8.7	0.0444	0.4	0.0037
6	90	0.411	1.0	0.0292	0.2	0.0035
7	166	0.753	3.4	0.0274	0.1	0.0032
8	57	0.441	4.4	0.0306	0.3	0.0025
Control						
1	27	0.404	11.9	0.0331	0.4	0.0028
2	33	0.250	11	0.0363	0.2	0.0021
3	209	0.339			0.8	0.0053
4	270	0.817	8.4	0.0293	0.3	0.0024
5	106	0.400	6.3	0.0454	0.3	0.0038
6	48	0.318	7.8	0.0352	0.6	0.0044
7	92	0.559	9.7	0.0513	0.5	0.0037
8	99	0.454	3.3	0.0128	0.1	0.0013
9	51	0.245	4.3	0.0226	0.2	0.0032
10	89	0.576	10.6	0.0336	0.5	0.0035

The concentration coefficients have been normalized for a 1-μg dose.

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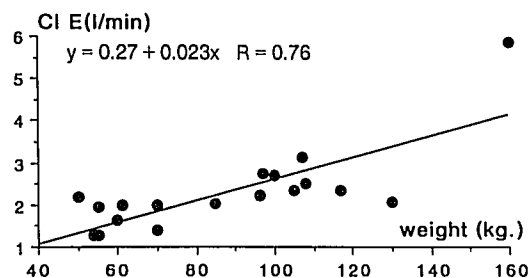


Fig. 3. Correlation between propofol clearance and body weight.

propofol total body clearance is increasing, the very high hepatic extraction of propofol has been confirmed by Lange *et al.*,²⁵ and the liver remains the main site of metabolism for propofol. As a consequence, propofol hepatic clearance is heavily dependent on hepatic blood flow. In obese patients, propofol clearance is correlated to body weight (fig. 3), and may reach very high values. Increases in blood volume, cardiac output, and splanchnic blood flow have been observed as a consequence of obesity.^{**} However, direct evidence of an enhancement of hepatic blood flow is lacking in the obese population. No significant differences were observed in the systemic clearance of lidocaine, a highly extracted drug with a systemic clearance that closely parallels hepatic blood flow, when obese patients were compared to normal-weight patients.²⁶ Similarly, midazolam clearance after either intravenous or oral administration was not modified by obesity, and midazolam systemic availability remained constant.²² These findings indicate that functional hepatic blood flow is not substantially modified in obese subjects. The liver of obese subjects is significantly larger than that of normal-weight subjects because of an increase in the number and size of parenchymal cells.²⁷ Nevertheless, obesity is associated with a number of pathologic conditions, mainly fatty infiltration of the liver, which may compromise hepatic function even when liver function tests are normal.²⁸ Propofol is primarily biotransformed *via* hepatic phase 2 conjugation pathways, its main metabolites being propofol glucuronide, 1 and 4 quinol glucuronides, and 4 quinol sulfate. Oxazepam

^{**} Alexander JK, Dennis EW, Smith WG, Amad KH, Duncan WC: Blood volume, cardiac output and distribution of systemic blood flow in extreme obesity. *Cardiovasc Res Cent Bull* 1: 39-44, 1962-63.

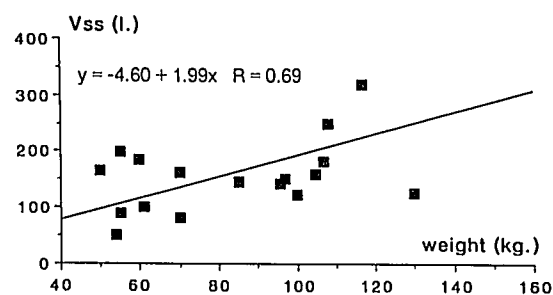


Fig. 4. Correlation between propofol Vss and body weight.

and lorazepam are two benzodiazepines primarily eliminated in the form of glucuronide. Their clearance was, respectively, 3.1 and 1.6 times greater in obese subjects than in control patients.²⁹ The influence of obesity on drug metabolism depends heavily on the metabolic pathway considered. It seems that drugs that undergo phase 1 metabolism are unaffected by obesity, as well as those that undergo acetylation, which is a phase 2 metabolic reaction. Most phase-2 reactions of glucuronidation and sulfation are enhanced.³⁰ Acetaminophen,³¹ as well as propofol in this study, display a progressively increasing clearance with increasing body weight, which implies that conjugative drug metabolizing processes may, in some way, be related to body weight. The possible role of extrahepatic conjugation in this process remains to be discovered.

As a consequence of the simultaneous increase in the Vss and the clearance, propofol elimination half life was not prolonged in obese patients, and there were no signs of propofol accumulation in those subjects,

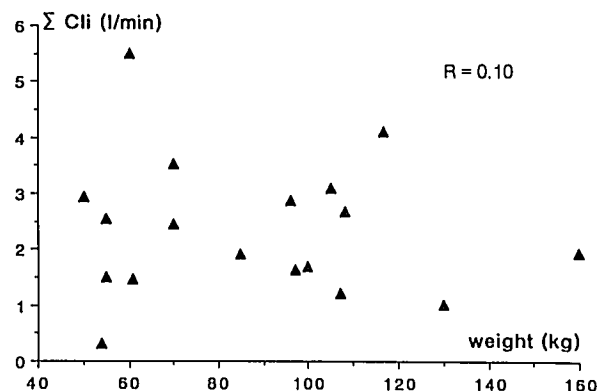


Fig. 5. Absence of correlation between propofol distribution clearance (ΣCl_i) and body weight.

Table 6. Percent Coefficient of Each Half-life

Patients	Rapid Distribution Half-life	Slow Distribution Half-life	Terminal Elimination Half-life
Obese			
1	98.6	1.3	0.06
2	96.5	2.6	0.87
3	97	2.9	0.14
4	98.7	1.2	0.17
5	91.7	7.9	0.36
6	98.6	1.1	0.22
7	98	2.0	0.06
8	92.3	7.2	0.49
Mean ± SD	96.4 ± 2.85	3.28 ± 2.72	0.30 ± 0.27
Control			
1	69.0	30.0	1.02
2	74.5	25.0	4.5
3	100		0.38
4	97.0	3.02	0.11
5	94.3	5.6	0.27
6	85.2	13.7	1.06
7	90.0	9.6	0.49
8	96.2	2.9	0.10
9	91.9	7.8	0.36
10	88.9	10.6	0.50
Mean ± SD	88.7 ± 10.0	12.0 ± 9.5	0.88 ± 1.31

nor of any prolongation of the duration of action. Obese patients opened their eyes when blood propofol concentration reached $1 \text{ mg} \cdot \text{l}^{-1}$. This value of propofol concentration when opening eyes on verbal command has already been widely reported in other categories of patients.^{5,32,33}

The empirical formula used for propofol dosage in this study provided adequate anesthetic levels, but was not supported by the present pharmacokinetic data. These pharmacokinetic data allow us to suggest that dosage of propofol for maintenance of anesthesia in obese subjects could, theoretically, be established on the same basis as in lean subjects, taking into account their actual body weight, with no specific risk of accumulation effects. However, the hemodynamic effects of larger doses of propofol remain to be assessed in obese patients.

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