

# Pharmacokinetics of Propofol Administered by Target-controlled Infusion to Alcoholic Patients

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**Background:** Chronic alcoholic patients are frequently presented for anesthesia and surgery. These patients require higher doses of propofol than control patients for induction of anesthesia, but whether this is because of changes in pharmacokinetics or pharmacodynamics is not known. This study was designed to investigate the influence of chronic ethanol intake on propofol pharmacokinetics.

**Methods:** Fifteen chronic alcoholic and 15 control patients, receiving propofol by target-controlled infusion for otolaryngologic surgery, were studied. Blood propofol concentrations were measured at regular intervals during and after the propofol infusion. Nonlinear mixed-effects population models (NONMEM) examining the influence of alcoholism were constructed. The influence of recovery on propofol pharmacokinetic parameters was also addressed.

**Results:** The total amount of propofol and the predicted and measured concentrations during all phases of anesthesia did not differ between the two groups. The fact that the measured concentrations at the time of opening eyes were similar further confirmed that the potency of propofol was not modified by the alcoholic status of the patients. Chronic alcoholism was associated with only mild changes in propofol pharmacokinetics (increase in rapid intercompartmental clearance and greater interindividual variability in the central volume of distribution). The rebound in concentration frequently observed during the recovery phase could be related to decreased propofol peripheral volumes of distribution despite an increase in elimination clearance.

**Conclusions:** Chronic alcoholism induces only mild changes in the pharmacokinetics of propofol. Conversely, propofol pharmacokinetics are markedly different during anesthesia and surgery or after opening eyes in the recovery period.

THE widely used definition of chronic alcoholism is based on the definitions of E. M. Jellinek,<sup>1</sup> the World Health Organization, and the American Medical Association. "Alcoholism is a chronic, progressive treatable disease in which a person has lost control over her or his drinking so that it is interfering with some vital area of her or his life such as family and friends or job and school or health." Chronic alcoholic patients are frequently presented for anesthesia and surgery, as elective or emergency cases. It is a common belief that they

require larger doses of "anesthetic agents," even in the absence of withdrawal symptoms. Although it is commonly recommended that the dose of thiopental should be increased in alcoholic patients, no pharmacokinetic or pharmacodynamic changes could be demonstrated in chronic alcoholic patients.<sup>2</sup> Moreover, unnecessarily high doses may be deleterious in this population in whom alcohol-related cardiac disease is frequent.<sup>3</sup> In addition to sporadic case reports,<sup>4</sup> a prospective study has shown that the induction dose of propofol was increased in chronic alcoholic patients.<sup>5</sup> In that study, blood propofol concentrations at loss of consciousness did not correlate with the drinking status of the patients. This might suggest that pharmacokinetic changes are responsible for the alleged reduced potency of propofol in chronic alcoholic patients. Consequently, our study was designed to compare the pharmacokinetics of propofol, administered by target-controlled infusion (TCI) for induction and maintenance of anesthesia, in chronic alcoholic and in nonalcoholic patients.

## Materials and Methods

### Patients

After institutional approval and written informed consent, 15 alcoholic and 15 control patients, aged 18–65 yr, scheduled to undergo elective otolaryngologic surgery were planned to be included in this prospective, parallel group study to assess the influence of chronic alcohol intake on the pharmacokinetics of propofol. Three patients (two controls and one alcoholic patient) were excluded because of technical problems either with the infusion device (two patients) or with blood sampling (one patient). Therefore, to reach the required number of 15 in each group, 17 alcoholic and 16 control patients were ultimately included in the study. For a patient to be included in the alcoholic group, the following criteria had to be met: chronic daily alcohol intake greater than 75 g pure alcohol, signs of addiction to the drug such as inability to reduce alcoholic consumption despite obvious deleterious effects and morning tremor alleviated by an alcoholic beverage, biologic sequel of alcohol abuse such as erythrocyte volume greater than  $95 \mu\text{m}^3$  and  $\gamma$ -glutamyl transferase activity greater than 35 U/l, but no clinical or biologic signs of cirrhosis. Erythrocyte volume and  $\gamma$ -glutamyl transferase activity were chosen as markers of chronic alcoholism because they are easily measured, and if none of them are reliable enough on their own to support the diagnosis of alcoholism, when they are combined, their sensi-

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Received from Service d'anesthésie-réanimation chirurgicale, AP-HP, Hôpital Bichat, Paris, France. Submitted for publication July 12, 2002. Accepted for publication April 21, 2003. Supported by a grant from AstraZeneca, Rueil Malmaison, France. Presented in part at the annual meeting of the American Society of Anesthesiologists, San Diego, California, October 21, 1997.

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**Table 1. Calculation of Daily Alcohol Intake of Patients**

Beverage	Volume, ml	Alcoholic Strength, %	Milliliters Pure Alcohol = Strength $\times$ Volume/100	Grams Pure Alcohol = ml $\times$ 0.8	
Wine, beer, or cider	750	10	75	60	
Can	1,000	4	40	32	Volume = $250 \times N$
Bottle		4	0	0	Volume = $330 \times N$
Aperitif		40	0	0	Volume = $20 \times N$
Strong alcohol	20	50	10	8	Volume = $10 \times N$
Total, g				100	

Example of a patient drinking a bottle of wine, four 250-ml beer bottles, and two glasses of whisky per day.

tivity in detecting alcoholism is superior to 80%.<sup>6,7</sup> Patients were eligible for inclusion in the control group if their daily alcohol intake was less than 25 g pure alcohol, with a normal erythrocyte volume and  $\gamma$ -glutamyl transferase activity. Table 1 is used to estimate the amount of daily alcohol intake.

Patients' baseline characteristics in the two groups were compared by Wilcoxon rank-sum test for continuous variables and Fisher exact test for qualitative variables. A value of  $P < 0.05$  was considered as statistically significant.

### Anesthesia

One hour before induction of anesthesia, patients received 0.15 mg/kg diazepam orally. After a bolus dose of 10  $\mu$ g/kg alfentanil followed by an infusion at a constant rate of 10  $\mu$ g  $\cdot$  kg<sup>-1</sup>  $\cdot$  h<sup>-1</sup>, anesthesia was induced with propofol using a commercial TCI device (Diprifusor<sup>®</sup>, AstraZeneca, London, United Kingdom, implemented in a Master-TCI infusion device, Fresenius Vial SA, Brezins, France) at an initial target blood concentration (TC) of 6  $\mu$ g/ml. The TC was adjusted in 0.5- $\mu$ g/ml steps to allow laryngoscopy, topical anesthesia of the vocal cords, and tracheal intubation and then at least every 15 min during maintenance according to clinical signs (TC was increased by 0.5  $\mu$ g/ml if the patient moved and/or mean arterial blood pressure increased above 130% of baseline values and/or heart rate was greater than 90 beats/min; TC was decreased if anesthesia seemed adequate or if systolic arterial pressure was less than 80 mmHg). No muscle relaxants were used. The level of hypnosis in our patients was not monitored by electroencephalographic analysis, and the adequacy of anesthesia was assessed only on hemodynamic parameters and movements in response to surgical stimuli. The lungs of the patients were ventilated to normocapnia with 50% N<sub>2</sub>O in oxygen. The alfentanil infusion was stopped at the beginning of skin closure, and TC was set to zero at the end of the dressing, when nitrous oxide administration was discontinued.

The propofol dose at loss of consciousness was recorded as well as movements in response to skin inci-

sion. Alcoholic patients frequently underwent longer surgical procedures than control patients. Consequently, the mean propofol infusion rate during the first 90 min of maintenance was calculated. The time to opening eyes after the end of propofol infusion was recorded, and blood samples were also taken at that time for measurement of blood propofol concentration.

The range of predicted alfentanil plasma concentrations from intubation to skin closure was estimated in all the patients by simulation of the infusion with Stanpump<sup>#</sup> implemented with the pharmacokinetic model of Maitre *et al.*<sup>8</sup>

Characteristics of propofol anesthesia between the two groups were compared by Wilcoxon rank-sum test. A value of  $P < 0.05$  was considered as statistically significant.

### Pharmacokinetic Analysis

Venous blood samples were drawn before propofol administration; after tracheal intubation; before each TC modification; when opening eyes on verbal command; and 2, 4, 6, 8, 10, 15, 30, 45, 60, 75, 90, 120, 180, 240, 300, 360, and 480 min after the end of propofol infusion. Propofol was measured by high-performance liquid chromatography as previously described.<sup>9</sup>

The history of propofol infusion, including all the changes in infusion rates and their times, was printed on-line for each patient. These data were implemented in the NONMEM data sheet. To reduce the amount of data, successive infusion rates were averaged when their difference was less than 10%.

The pharmacokinetic analysis was performed using the nonlinear mixed-effects modeling approach implemented in the NONMEM computer program (version V).<sup>10</sup> Propofol pharmacokinetics was best described by a three-compartment mammillary model. The population characteristics of the pharmacokinetic parameters (fixed and random effects) were estimated using the subroutines ADVAN11 and TRANS4 from the library of programs provided with the NONMEM-PREDPP package. The model was parameterized in terms of volume of the central compartment ( $V_1$ ), elimination clearance ( $Cl_1$ ), intercompartmental clearances ( $Cl_2$ ,  $Cl_3$ ), and volumes of the shallow peripheral ( $V_2$ ) and deep peripheral ( $V_3$ ) compartments.

<sup>#</sup> STANPUMP program. Available at: <http://anesthesia.stanford.edu/pkpd>. Accessed May 21, 2003.

Interindividual variability (random effects) was assessed according to a proportional error model associated with each fixed effect parameter: The  $k$ th component of the individual parameter  $p_j$  of the  $j$ th subject was modeled by  $p_j^k = \theta_{\text{mean}}^k \times \exp(\eta_j^k)$ , where  $\theta_{\text{mean}}^k$  is the population mean and  $\eta_j^k$  is assumed to be a Gaussian random variable with zero mean and variance  $\omega^2$ .

The concentration measurements profile in the  $j$ th individual was assumed to be affected by a proportional error described by the relation:  $C_{ij}(t) = f(p_j, D_j, t_{ij}) \times (1 + \epsilon_{ij})$ , where  $C_{ij}$  is the  $i$ th concentration of the  $j$ th subject;  $t_{ij}$  is the time of the  $i$ th measurement;  $D_j$  is the dosing history of the  $j$ th subject;  $f$  is the pharmacokinetic model; and  $\epsilon_{ij}$  describes the departure of the model from the observations and contains contributions from intraindividual variability, assay error, and model misspecification. The distribution of the residuals,  $\epsilon$ , is assumed to be a random Gaussian variable with zero mean and variance  $\sigma^2$ .

Empirical Bayes estimates of pharmacokinetic parameters for each subject were obtained using the POSTHOC option in NONMEM.

The decrease in blood propofol concentration over time after an infusion often shows a rebound increase during recovery.<sup>11</sup> Consequently, the effect of awakening (opening eyes) on pharmacokinetics was modeled by allowing each parameter ( $V_1$ ,  $V_2$ ,  $V_3$ ,  $Cl_1$ ,  $Cl_2$ , and  $Cl_3$ ) to change after awakening.<sup>12</sup> The change in mean parameters was modeled as a percentage decrease from the initial parameter value. In the first stage of the analysis of the effect of awakening, each model parameter was sequentially allowed to change while the other parameters remained constant. The importance of these variations was evaluated based on changes in the minimum objective function (OF). A modification of a parameter after opening eyes was added to the model based on a decrease in OF, which is estimated by NONMEM as  $-2$  log likelihood of the data. The changes in OF between two nested models has a distribution that is approximately chi-square with degrees of freedom equal to the difference between the number of parameters in the full and reduced model. Thus, when the change of a parameter resulted in a decrease of the OF of at least 4 units, it was considered as significant ( $P < 0.05$ ) and included in the model. In a second stage of the analysis, the retained parameters were allowed to change simultaneously, and only the combination of parameters resulting in a further decrease of the OF of at least 8 units was retained. In addition, for each parameter whose mean was affected, it was tested whether interpatient variability was the same before and after opening eyes.

Alcohol status, age, body weight, lean body mass,<sup>13</sup> and fat body mass (weight minus lean body mass) were considered as relevant covariates to be investigated in this analysis. The influence of each covariate on the individual Bayesian estimates of the parameters obtained

from the basic model was examined. This first screening allowed the recognition of covariate/parameter associations to be included in the multivariate NONMEM model. This model was thus built forward by successively including the most significant covariates. Then, the adequacy of the model was assessed backward by removing step by step all the covariates included if their removal did not modify the OF. Covariates were added to the model based on an improvement in residual plots and a decrease in OF (duplication). A more conservative test based on a reduction of 8 units in the ( $P < 0.005$ ) was used because of the multiple comparisons that are made for this final step.

The structural model was built up using the first-order estimation method. To estimate the final parameters, the conditional estimates method of the individual etas during the computation of the OF was used, with preservation of the dependence of the error on the individual parameters (FOCE with interaction).

The model performance was assessed both numerically and graphically, using individual and population predictions. The population weighted residual and the absolute population weighted residual were calculated for each sample, using the final model and the individual covariates. The median weighted residual and the median absolute weighted residual were used as overall measures for goodness of fit of the final model.

## Results

Alcoholic and control patients had similar ages, weights, and sex ratio (table 2).

### *Propofol Anesthesia*

This study dealt primarily with propofol, and thus, the amount of opioid supplementation was kept low, with an infusion rate of alfentanil that maintained the predicted concentration at a value less than 30 ng/ml throughout the procedure. The total amount of propofol and the predicted and measured concentrations during all phases of anesthesia were not different in the two groups of patients, and this similar potency was confirmed by the fact that the measured concentration when opening eyes was not modified by alcoholic status of the patients (table 3). No relation was found between the measured blood propofol concentration at the time of surgical incision and the occurrence of movements on skin incision.

### *Pharmacokinetic Analysis*

Eight hundred thirty-five blood samples were analyzed in the 30 patients. The changes in blood propofol concentrations over time in the two groups are shown in figure 1. The pharmacokinetics of propofol in the whole

Table 2. Characteristics of the Patients

	Alcoholics (n = 15)	Controls (n = 15)	P	Normal Values
Age, yr	54.6 ± 6.5	46.9 ± 14.7	NS	
Sex ratio, M/F	13/2	10/5	NS	
Weight, kg	63 ± 10	69 ± 13	NS	
Daily alcohol intake, g	137 ± 47	9 ± 10		
γGT, U/ml	128 ± 76	27 ± 11		<35
MGV, μm <sup>3</sup>	101 ± 6	88 ± 7		80–95
Plasma creatinin concentration, μM	70 ± 10	80 ± 17	NS	45–105
Plasma protein concentration, g/l	77 ± 7	75 ± 5	NS	65–80

Data are presented as mean ± SD.

γ-GT = gamma-glutamyl transferase; MGV = mean globular volume.

population could be described by a three-compartment model, with a minimum OF of −180.23. After recovery (opening eyes), there were significant independent changes in mean  $Cl_1$ ,  $V_2$ , and  $V_3$ . When these parameters were allowed to change simultaneously with eyes opening, the minimum OF was further reduced to −267.28. The percentage change (+22% for  $Cl_1$ , −19% for  $V_2$ , and −17% for  $V_3$ ) was of the same order of magnitude for all parameters, and as a result, the OF was not significantly different (OF = −267.18) if the same magnitude of change was assumed for all the parameters. This solution being simpler, it was kept in the final model.

The introduction of alcoholism as a covariate resulted in a significant decrease in the OF when it was applied both to  $Cl_2$  and to the interindividual variability for  $V_1$  (OF = −287.41), but the other parameters were not influenced by alcoholism. Chronic alcohol intake did not influence the change in pharmacokinetic parameters estimated after opening eyes. The introduction of weight, lean body mass, or age as covariates did not improve the OF. Conversely, the introduction of fat body mass as a

covariate for both  $V_3$  and  $Cl_3$  significantly improved the OF (−295.37).

Thus, this study failed to demonstrate any major influence of alcoholism on propofol pharmacokinetics. Considering the interindividual variability, we assessed retrospectively the power of a study including 15 patients in each group to detect a difference in clearance with a test significance level of 0.05, based on the mean and SD of the Bayesian estimates of clearance values during the infusion and after opening eyes. Intraoperatively, the power to detect a 50% change in clearance was 80%, whereas after opening eyes, because of a lesser variability, the power to detect a 20% change was 99%.

Figure 2 shows the NONMEM CONTROL file of the final model. The pharmacokinetic parameters for the final model are shown in table 4. The medians of the Bayesian estimates of the individual pharmacokinetic parameters before and after awakening, as a function of alcohol status, are shown in table 5.

The precision (median absolute weighted residual) and bias (median weighted residual) of the model were, respec-

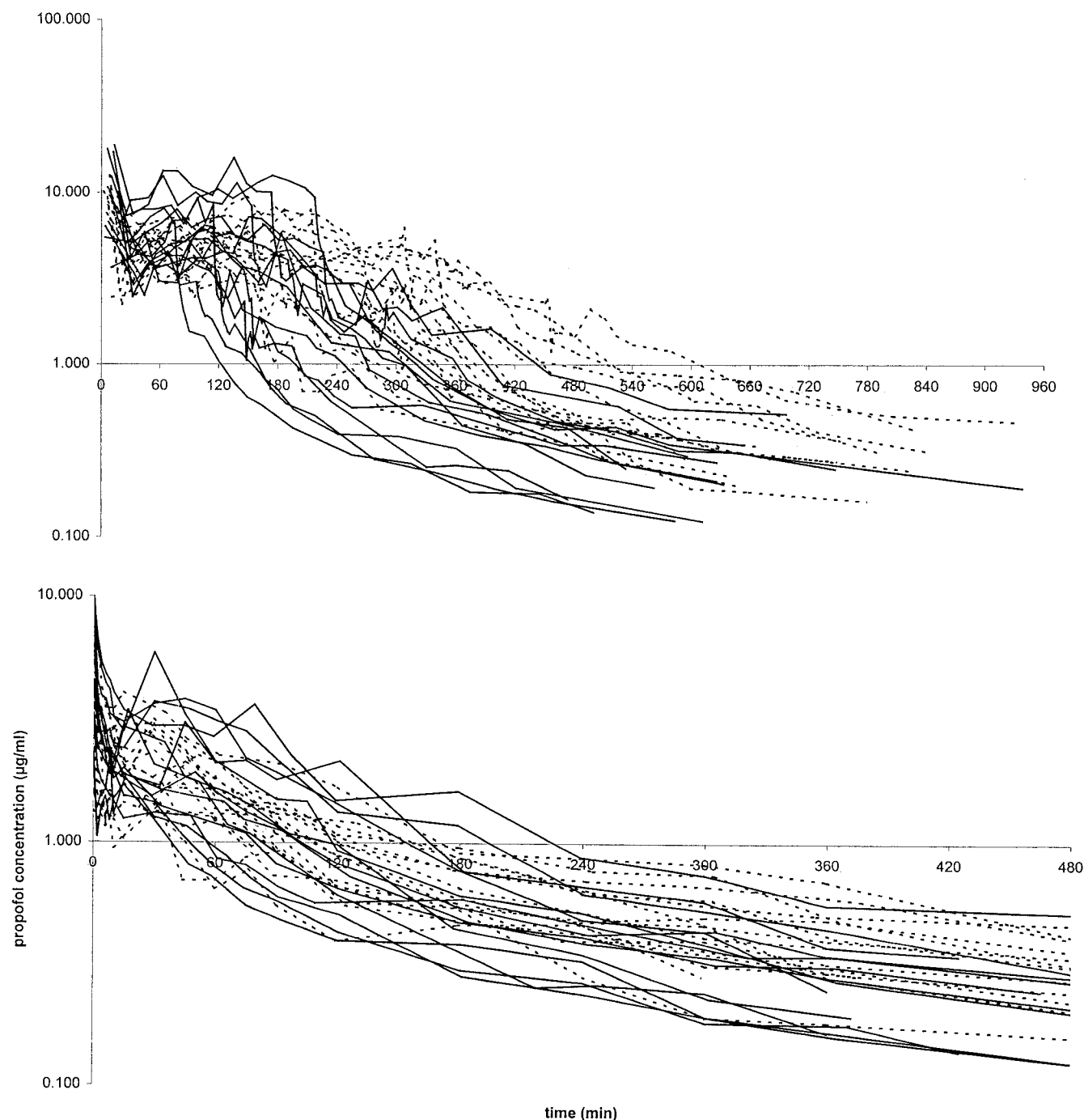
Table 3. Characteristics of Propofol Anesthesia

	Alcohol	Control	P
Induction			
Dose, mg/kg	1.81 ± 0.19	1.70 ± 0.29	NS
Time to LOC, s	63 ± 16	54 ± 13	NS
Intubation			
Time to intubation, min	8.4 ± 2.9	11.2 ± 5.1	NS
Measured concentration, μg/ml	8.33 ± 2.68	9.80 ± 5.53	NS
Incision			
Measured concentration, μg/ml	3.75 ± 1.27	4.64 ± 1.97	NS
Movements, No.	6/16	4/15	NS
Stable anesthesia			
Measured concentration, μg/ml	4.84 ± 1.48	5.65 ± 2.47	NS
Mean infusion rate, μg · kg <sup>−1</sup> · min <sup>−1</sup>	186 ± 29	178 ± 28	NS
End of anesthesia			
Duration of anesthesia, min	316 ± 151	170 ± 65	<0.01
Measured concentration at end of infusion, μg/ml	3.82 ± 1.67	5.05 ± 2.97	NS
Time to opening eyes, min	18.7 ± 12.0	23.5 ± 11.7	NS
Measured concentration at opening eyes, μg/ml	2.20 ± 0.74	2.25 ± 1.23	NS

Values are expressed as mean ± SD except where otherwise indicated.

LOC = loss of consciousness; NS = not significant.





**Fig. 1.** (Top) Evolution over time of the measured propofol concentrations in control (dashed lines) and in alcoholic (dotted lines) patients over the entire sampling period. The infusion time was longer in the alcoholic patients. (Bottom) Evolution over time of the measured propofol concentrations in control (dashed lines) and in alcoholic (dotted lines) patients during the postinfusion sampling period.

tively, 60.1% and -6% (fig. 3), and that of the individual Bayesian estimates were 9.55% and 0.77%. The weighted residuals are plotted against time for each individual in figure 4, and the ratio of the measured over predicted concentrations calculated for each sample are given in figure 5. The best, median, and worst fits, based both on individual median absolute weighted residuals calculated

from the final population model estimations and on the individual Bayesian estimates, are shown in figure 6.

## Discussion

Despite that chronic alcoholism is a common disease worldwide, its influence on the pharmacokinetics of

```

SSUBS ADVAN11 TRANS4
$PK
DEC1 = THETA(7)

V1 = THETA(1)*(EXP(ETA(1))*ALC+EXP(ETA(10))*(1-ALC))
CCL = THETA(2)
VV2 = THETA(3)
Q2 = (THETA(4)*ALC+THETA(8)*(1-ALC))*EXP(ETA(4))
VV3 = THETA(5)+THETA(9)*FBM
Q3 = (THETA(6)+THETA(10)*FBM)*EXP(ETA(6))

IF (TIME.GT.OUVY) THEN
V2 = VV2*(1-DEC1)*EXP(ETA(7))
V3 = VV3*(1-DEC1)*EXP(ETA(8))
CL = CCL*(1+DEC1)*EXP(ETA(9))
ELSE
V2 = VV2*EXP(ETA(3))
V3 = VV3*EXP(ETA(5))
CL = CCL*EXP(ETA(2))
END IF

VSS= V1+V2+V3
S1 = V1
K = CL/V1
K12 = Q2/V1
K21 = Q2/V2
K13 = Q3/V1
K31 = Q3/V3

$ERROR
Y = F*(1+EPS(1))
IPRED = F
IRES = DV - F

```

Fig. 2. NONMEM CONTROL file of the final model.

Table 4. Pharmacokinetic Parameters for the Final Model

	Value	Interpatient Variability, CV %	SE, %
Model parameter during anesthesia			
$V_1$ , l	$\theta_1$	40 (non-ALC), 83 (ALC)	
$V_2$ , l	$\theta_3$	27	
$V_3$ , l	$\theta_5 - \theta_9 \cdot \text{FBM}$	89	
$Cl_1$ , l/min	$\theta_2$	36	
$Cl_2$ , l/min	$\theta_4 \cdot \text{ALC} + \theta_8 \cdot (1 - \text{ALC})$	69	
$Cl_3$ , l/min	$\theta_6 - \theta_{10} \cdot \text{FBM}$	36	
Model parameter after opening eyes			
$V_2$ , l	$\theta_3 \cdot (1 - \theta_7)$	10	
$V_3$ , l	$\theta_5 \cdot (1 - \theta_7)$	20	
$Cl_1$ , l/min	$\theta_2 \cdot (1 + \theta_7)$	14	
ALC = alcoholic (1 if yes, 0 if no)			
Parameter estimates			
$\theta_1$	8.02		22
$\theta_2$	1.17		5.7
$\theta_3$	54.7		19
$\theta_4$	1.34		39
$\theta_5$	280		19
$\theta_6$	0.513		14
$\theta_7$	0.37		25
$\theta_8$	1.20		18
$\theta_9$	3.53		62
$\theta_{10}$	0.00363		104
Residual variability, %	18		39

ALC = alcoholic; CV = coefficient of variation; SE = standard error.

anesthetic drugs has not been extensively studied. Indeed, most studies have specifically excluded patients with cirrhosis of the liver. Swerdlow *et al.*<sup>2</sup> investigated the pharmacokinetics and pharmacodynamics of thiopental in 11 patients with a history of excessive alcohol intake compared to 9 control patients or volunteers who were social drinkers. The alcoholic population had consumed ethanol 9–17 days before the study, with no evidence of acute intoxication or acute withdrawal at the time of the study, and was therefore similar to our own alcoholic population. The authors found no differences in thiopental pharmacokinetic and pharmacodynamic parameters between alcoholics and nonalcoholics. Sporadic reports of increased propofol requirements at induction of anesthesia have been published.<sup>4</sup> There is a single prospective clinical study<sup>5</sup> that found differences in propofol requirements as a function of drinking habits but could not differentiate pharmacokinetic or pharmacodynamic causes for this observation. In our study, the amount of propofol required (in conjunction with a low concentration of alfentanil) to maintain anesthesia in both alcoholic and nonalcoholic patients was not different, but the absence of monitoring of depth of anesthesia together with venous rather than arterial blood sampling precluded any detailed pharmacodynamic analysis.

Chronic alcoholism was associated with few changes in the pharmacokinetics of propofol because only the intercompartmental clearance to the shallow peripheral

**Table 5. Individual Empirical Bayes Parameters Estimates before and after Opening Eyes on Verbal Command**

Parameter	Control Patients		Alcoholic Patients	
	Before	After	Before	After
$V_1$ , l	7.32 (4.40–13.52)	7.32* (4.40–13.52)	10.27 (2.04–23.60)	10.27* (2.04–23.60)
$V_{SS}$ , l	350 (153–785)	182 (126–218)	326 (165–652)	193 (162–215)
$V_2$ , l	53.2 (37.8–84.3)	34.1 (32.1–36.3)	54.9 (40.1–98.3)	34.4 (33.5–34.8)
$V_3$ , l	266 (85–739)	139 (87–173)	251 (77–598)	151 (120–165)
$Cl_1$ , l/min	1.174 (0.529–2.785)	1.628 (1.279–1.743)	1.301 (0.679–1.697)	1.618 (1.457–1.700)
$Cl_2$ , l/min	1.115 (0.687–3.004)	1.115* (0.687–3.004)	1.275 (0.357–4.382)	1.275* (0.357–4.382)
$Cl_3$ , l/min	0.427 (0.256–0.738)	0.427* (0.256–0.738)	0.436 (0.266–0.921)	0.436* (0.266–0.921)

Data are presented as median (range).

\* No influence of opening eyes on the parameter.

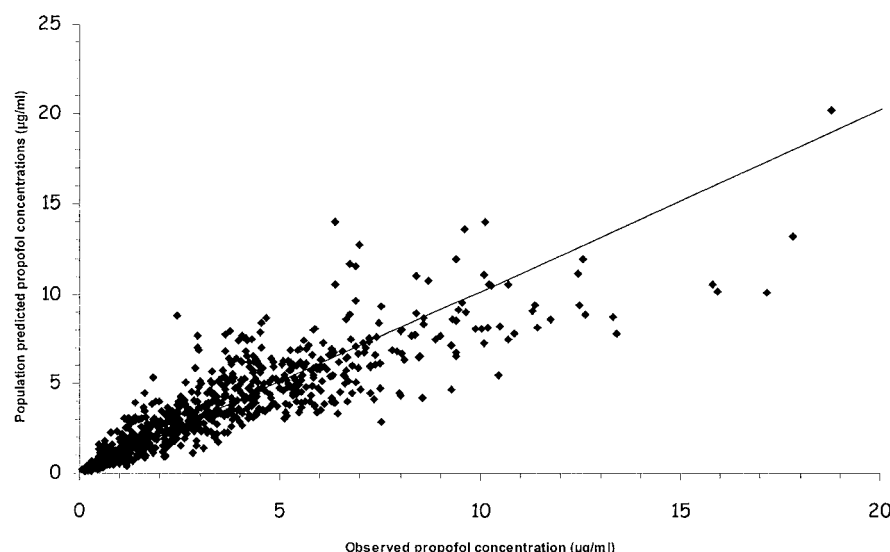
compartment was significantly altered, and interindividual variability of the volume of the central compartment was significantly greater in the alcoholics. These findings may be related to the heterogeneity of the alcoholic population,<sup>14</sup> to the vasomotor changes induced by chronic alcohol intake,<sup>15,16</sup> and to the fact that chronic alcoholism is frequently associated with heavy smoking. Our results are in good accordance with those of Liu *et al.*<sup>17</sup> in rats selected for differential ethanol sensitivity.

It has been demonstrated that weight and age were significant covariates of propofol pharmacokinetics.<sup>18,19</sup> However, in our population, weight and age were purposely kept within a narrow range, which explains why the introduction of those covariates did not significantly improve our model. Similarly, our alcoholic noncirrhotic patients did not have abnormal levels of plasma protein concentrations, specifically albumin.

Coadministered drugs might influence pharmacokinetics and modify comparisons if their behavior differed as a function of the alcoholic status of the patients. Propofol has a flow rate dependent clearance, and thus, pharmacokinetic interaction occurs mainly through hemodynamic changes. The heart rate and blood pressure

profiles were not different in our two groups of patients. Pharmacokinetic interactions between propofol and alfentanil have been described. Propofol is a potent enzyme inhibitor, and because alfentanil has an intermediate clearance dependent on the CYP450 activity, when propofol and alfentanil are infused simultaneously, alfentanil concentrations are increased by approximately 20%.<sup>20,21</sup> Alfentanil (which in this study was used at very low dosages) has no influence on the pharmacokinetics of propofol.

The pharmacokinetics of propofol described in this study before awakening are in good agreement with previously published results.<sup>18,19</sup> Nevertheless, no study so far has attempted to model what happens on recovery, despite the fact that the increase in propofol concentration at that time is common knowledge and was evident in early publications on propofol pharmacokinetics.<sup>11</sup> This phenomenon has been described with other lipophilic drugs<sup>22</sup> but without any clear explanation. When no more drug is administered to a patient, a rise in plasma drug concentration may be related to a release of the drug from some sort of depot, to a decrease in peripheral protein binding or to changes in peripheral distribution. Clearance changes alone would



**Fig. 3.** Plot of the propofol concentrations predicted by the final population model versus the measured propofol concentrations.

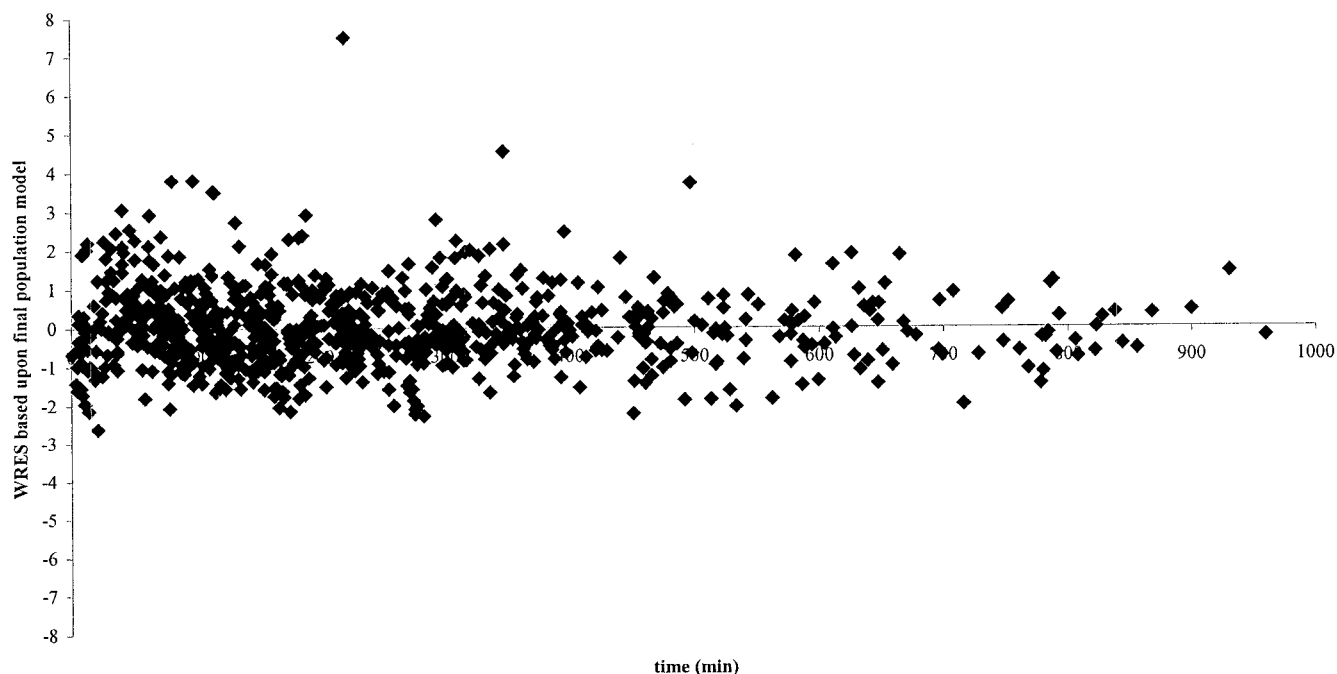


Fig. 4. The population weighted residual (WRES) from the final population model as a function of time.

induce mainly a change in the decrease slope but cannot account for a rise. For fentanyl, it has been hypothesized that the drug was released from a lipid depot at recovery,<sup>23</sup> but the pharmacokinetics of propofol are characterized by a very slow return from the deep compartment ( $k_{31}$  is small when compared to  $k_{10}$ ), which should preclude any significant increase in blood con-

centration at recovery. Modifications in protein binding during recovery are difficult to determine, specifically because nowadays, intraoperative control over hypocapnia reduces the relative importance of postoperative respiratory acidosis. Another hypothesis is that the cardiac output and regional blood flows are modified during recovery, when the cardiovascular sympathetic drive is

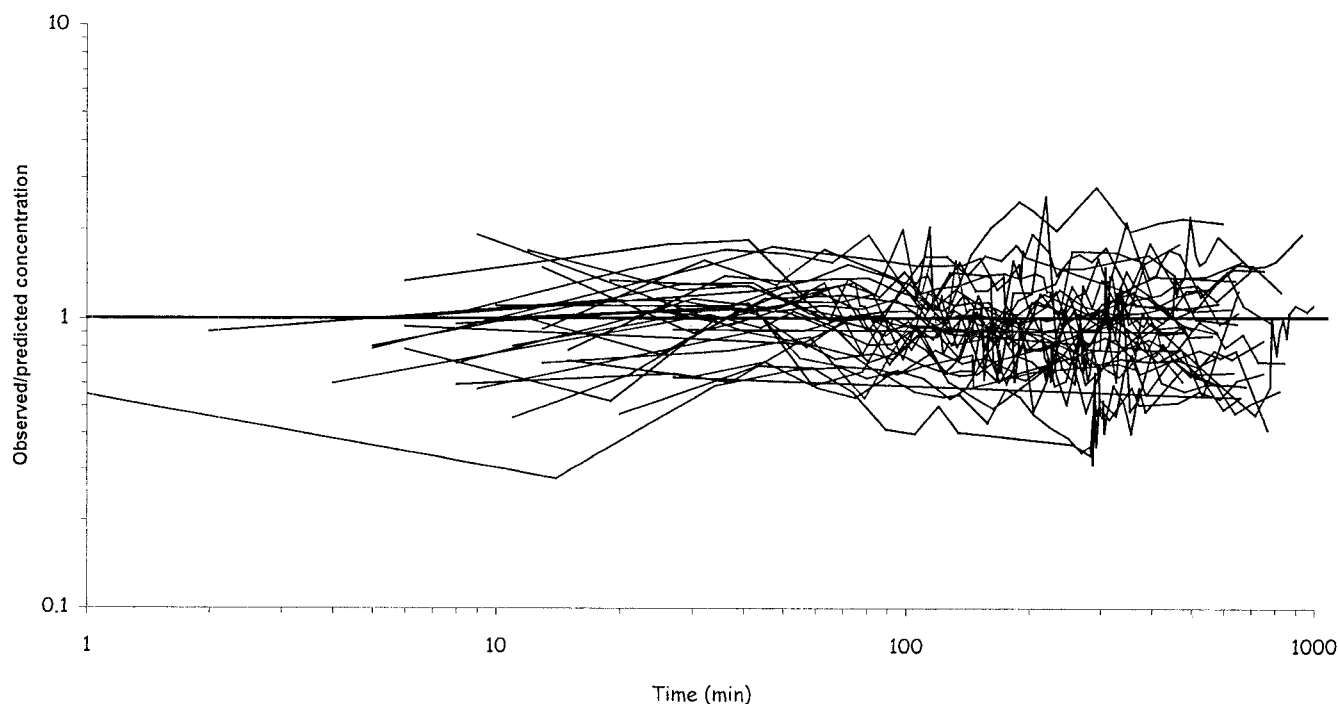


Fig. 5. Ratio of measured propofol concentrations to propofol concentrations predicted by the final population model as a function of time.



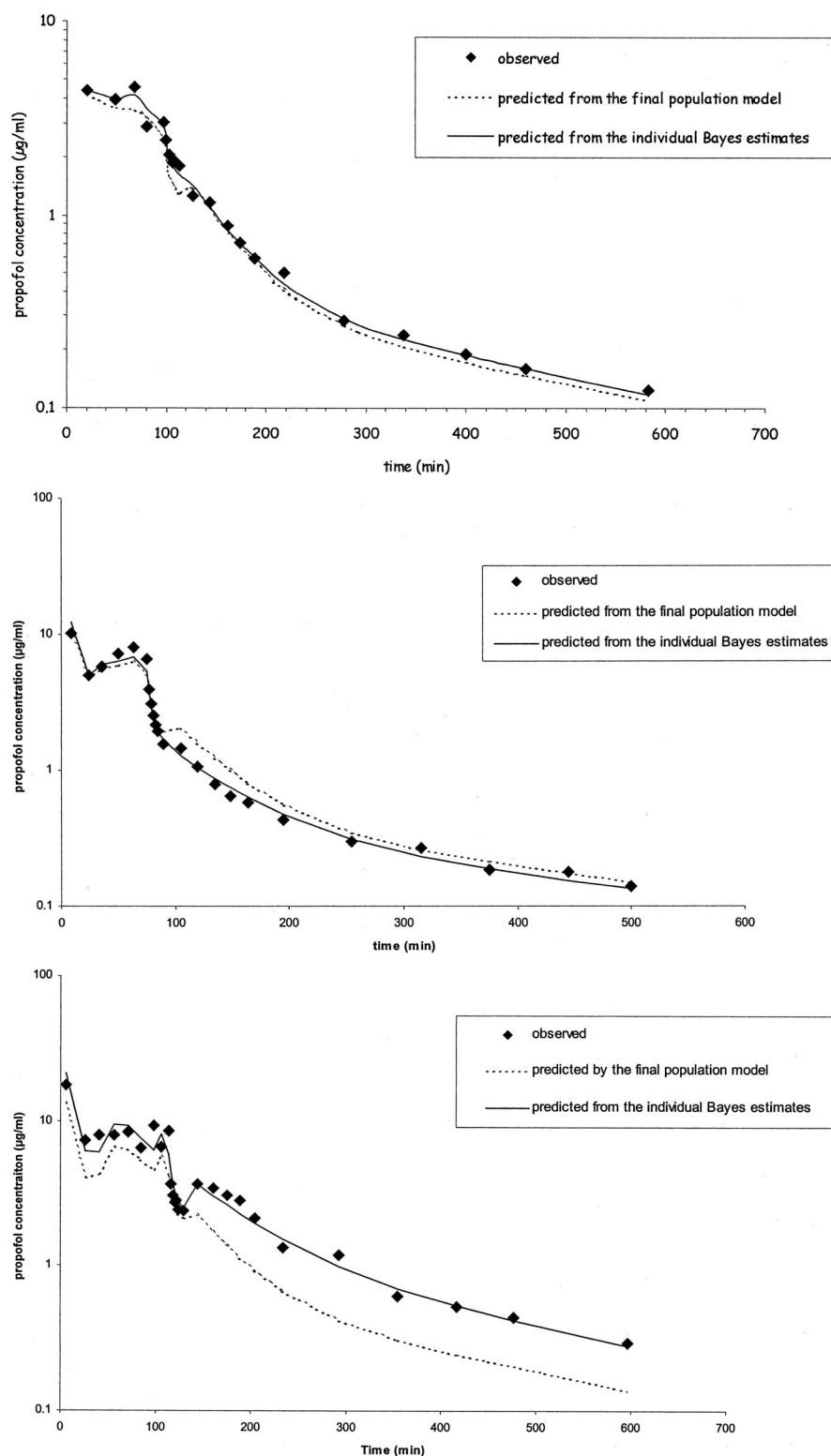


Fig. 6. (Top) Best, (center) median, and (bottom) worst individual performances.

increased.<sup>19</sup> Our findings of an increase in clearance with recovery (and propofol clearance depends on hepatic blood flow, which in turn varies with cardiac output) associated with reduced distribution volumes of the peripheral compartments support this hypothesis. Clearance is increased but cannot completely blunt this

phenomenon. The interindividual variability of the pharmacokinetic parameters is larger during anesthesia than after opening eyes, and this in turn might be due to variations in sympathetic response both to anesthetic drugs and to surgical stimuli. These findings may explain the high performance error of pharmacokinetic models

established during general anesthesia when they are applied to TCI devices for use during conscious sedation.<sup>24,25</sup>

Chronic alcoholism induces only mild changes in the pharmacokinetics of propofol. Conversely, propofol pharmacokinetics are markedly different during anesthesia and surgery or after opening eyes in the recovery period.

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