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Pharmacodynamics and Pharmacokinetics of Propofol in a Medium-Chain Triglyceride Emulsion

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Background: **Because propofol is water insoluble, current formulations of propofol use a soybean oil emulsion. These soybean emulsions cause elevated plasma triglycerides and support bacterial growth. This study compares an alternative formulation of propofol as a 2% emulsion in a medium-chain triglyceride solution (IDD-D™ Propofol) with Diprivan®.**

Methods: **This double-blind, crossover, phase 1 study compared IDD-D Propofol with Diprivan using two consecutive protocols of 12 subjects each. Subjects in protocol 1 received a single bolus of 2.5 mg/kg, and those in protocol 2 received the same induction dose followed by a 30-min infusion at 0.2 mg · kg^{-1} · min^{-1}. Venous samples were taken for propofol concentration and biochemical measurements. Induction and emergence times were measured by termination of voluntary counting and responding to command, respectively.**

Results: **Plasma concentrations were not different between the two formulations. Induction time was 14% longer with IDD-D Propofol than with Diprivan (N = 24, protocols 1 and 2 combined, 53.3 ± 12.1 s and 46.9 ± 7.8 s, respectively; P = 0.002). Emergence time was not significantly different for protocol 1 but was marginally longer (P = 0.04) for IDD-D Propofol in protocol 2 (1,197 ± 445 s [n = 11] and 1,254 ± 468 s [n = 12], respectively). As expected because of the inherent characteristics of the formulations, plasma triglycerides were elevated for Diprivan but not for IDD-D Propofol; octanoate, a metabolite of medium-chain triglycerides, was elevated only with IDD-D Propofol. Octanoate was elevated to concentrations below those considered toxic. Plasma concentrations of other biochemical markers of medium-chain triglyceride metabolism, *e.g.*, ketones, showed no significant changes. Interestingly, there were significant differences between male and female subjects in the propofol plasma concentrations and time to awakening with both drugs.**

Conclusions: **Differences between the two propofol formulations were slight and not clinically significant. Similar gender differences in plasma concentrations and awaking times were found for both formulations.**

WHILE Propofol is commonly used for induction and maintenance of surgical anesthesia and for sedation in the intensive care unit, it nevertheless has a number of disadvantages.[1] Some of these problems stem from the need for a lipid vehicle in which to emulsify the water-insoluble drug. Current formulations use a soybean oil–based emulsion that is composed of long-chain triglycerides. This formulation supports bacterial growth[2] and causes an elevation in plasma triglycerides, particularly when the drug is given by continuous infusion for a prolonged period of time, as may be the case in the intensive care unit. The occurrence of pain on injection is also a common clinical complaint and may be related to the amount of free propofol in the aqueous phase of the emulsion.[3,4] Alternative formulations of propofol have been studied to circumvent some of these problems.[5–7]

Two intravenous formulations of propofol are currently approved in the United States: Diprivan® Injectable Emulsion 1% (AstraZeneca Pharmaceuticals LP, Wilmington, DE) and Propofol Injectable Emulsion 1% (Baxter Healthcare Corporation, Deerfield, IL). Another formulation, available outside the United States, formulates propofol in a mixture of long- and medium-chain triglycerides (Propofol-Lipuro®; B. Braun, Melsungen, Germany).[6] To address the practical limitations of these 1% propofol formulations in the clinical setting, RTP Pharma Inc. (Verdun, Quebec, Canada) is developing Insoluble Drug Delivery-MicroDroplet (IDD-D™) Propofol Injectable Emulsion 2% (abbreviated as IDD-D Propofol). IDD-D Propofol 2%, which does not contain preservative agents such as disodium edetate and sodium metabisulfite, differs from other propofol formulations in that it has inherent antimicrobial properties (IDD-D Propofol 2% meets USP antimicrobial effectiveness test <51>; unpublished company report, May 16, 2001, Michael G. Vachon, Ph.D., and Awadhesh K. Mishra, Ph.D., RTP Pharma Inc., Verdun, Quebec, Canada). In addition, IDD-D Propofol 2% uses a different oil vehicle and has lower oil content (4% of the product *vs.* 10% for the available formulations), which lessens the risk of undesirable hypertriglyceridemia during prolonged utilization. The medium-chain triglycerides forming the lipid emulsion are more rapidly metabolized[8] when compared with the long-chain triglycerides of the current soybean oil–based formulations. While medium-chain triglyceride lipid emulsions have a long history of safe use in a number of parenteral nutrition preparations, administration of medium-chain triglycerides at sufficient concentrations will result in the production of ketone bodies (acetoacetate and β-hydroxybutyrate). Concern has also been expressed over possible neurotoxic effects of high octanoate concentrations resulting from cleavage and

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incomplete oxidation from the parent triglyceride.[8,9] In this study we report the results of a phase 1 clinical trial of this new medium-chain triglyceride–containing formulation when compared with Diprivan 1%, with the hypothesis that the new formulation's clinical profile will not differ. The objectives of this study in healthy subjects were to compare the safety and tolerability of IDD-D Propofol 2% with that of Diprivan 1% by monitoring the frequency, duration, and severity of adverse events; to compare the pharmacokinetics of IDD-D Propofol 2% with that of Diprivan 1% following a slow bolus injection and a slow bolus injection followed by a 30-min infusion; and to compare the pharmacodynamics of IDD-D Propofol 2% with that of Diprivan 1% as assessed by time to induction of loss of consciousness and time to awakening.

Methods

The study design was randomized and double-blind with a two-period crossover. Two drug administration protocols were used with 12 different subjects in each. Subjects in protocol 1 received a single bolus of 2.5 mg/kg, and those in protocol 2 received the same induction dose followed by a 30-min infusion at 0.2 $mg \cdot kg^{-1} \cdot min^{-1}$. The study was approved by the institutional review committee, and informed consent was obtained from all subjects. Each subject received both drugs in a crossover fashion, and the order (sequence) of the drug administration was randomized. At least 1 week was allowed for washout of drug and metabolites between experiments. Because of a slight difference in the color of the drugs and the different concentrations, one unblinded investigator infused the drugs into the subject out of sight of the other blinded investigators.

The subjects were admitted to the general clinical research unit the evening prior to drug administration and fasted after midnight. On the morning of the drug administration, an intravenous catheter was placed in a large forearm vein and a second one was placed in the antecubital fossa of the contralateral arm for blood sampling. Subjects were monitored with electrocardiogram, noninvasive blood pressure, and pulse oximetry, and oxygen was provided *via* an anesthesia machine. Manual positive pressure ventilation using a circle system was provided as needed to maintain a minimum respiratory rate of 4 breaths/min. In protocol 2, the electroencephalogram was monitored with the bispectral index (BIS; BIS Model A-2000, software version 2.1 upgraded to 2.21; Aspect Medical Systems, Newton, MA).

Subjects in both protocols received an induction dose of 2.5 mg/kg at a rate of 4 mg/s (manually injected). This induction dose was followed in protocol 2 by a 30-min infusion at a rate of 0.2 $mg \cdot kg^{-1} \cdot min^{-1}$ *via* syringe infusion pump. During induction, any complaints of pain were noted by one of the blinded investigators and scored as none, mild, moderate, or severe. The subject was asked to count out loud, and the time after the start of injection when the subject stopped counting was recorded as the induction time. After the bolus (protocol 1) or the termination of the infusion (protocol 2), the subject was asked, without any physical stimulation, to open his or her eyes at 1-min intervals by the same blinded investigator, and the time to following this command was recorded as the emergence time. If the subject spontaneously opened his or her eyes, then that time was recorded as the emergence time. Thirty minutes after recovery, the subject was asked to rate any pain with the drug injection, using a 0 (no pain) to 10 (worst possible pain) visual analog scale.

In protocol 1, blood samples were taken at time 0 (prior to the induction dose) and at 1, 2, 3, 4, 6, 8, 10, 20, 30, 45, 60, and 120 min after the start of the injection. In protocol 2, blood samples were taken at time 0 and at 1, 2, 5, 10, 20, 30, 32, 34, 36, 40, 50, 60, and 120 min after the start of the injection. In protocol 2, samples were also taken at time 0 and 30 min and at 1, 2, and 4 h for analysis of plasma triglycerides, cholesterol, high-density lipoprotein, lactate, β-hydroxybutyrate, acetoacetic acid, and octanoic acid (octanoate).

Blood samples were placed on ice, centrifuged and frozen immediately after they were obtained, and analyzed either in the clinical laboratories of the University of Rochester or sent to reference laboratories (propofol to Pharmakinetics, Baltimore, MD, and lactate, β-hydroxybutyrate, acetoacetate, and octanoate to the Metabolic Screening Laboratory, Dr. James D. Shoemaker, M.D., Ph.D., Associate Professor of Biochemistry and Molecular Biology, Director, Metabolic Screening Laboratory, St. Louis University, St. Louis, MO).

Data and Statistical Analysis

The sample size of 12 subjects in each protocol (total of 24 subjects) was considered sufficient to determine the pharmacokinetic profile of IDD-D Propofol and bioavailability relative to Diprivan without exposing an undue number of subjects to the new preparation. The study was designed to compare the induction and emergence times as the primary pharmacologic effects, but the measurement of the BIS was also used as a secondary outcome in protocol 2. Comparison of the pharmacokinetics was made by calculating the area under the curve, clearance, and volume of distribution, and in addition a two-compartment (biexponential) model (calculations provided by Covance, Inc., Madison, WI, using WinNonlin Professional, Pharsight Corp., Mountain View, CA) was fitted to the data and described by the half-time and volume of the fast ($T1/2\alpha$ [minutes] and V_1 [liters per kilogram]) and slow ($T1/2\beta$ [minutes] and V_2 [liters per kilogram]) components. The plasma sample at 1 min was

not used in this calculation since, for many subjects, the bolus infusion was still in progress at that time.

Data are reported as mean ± SD except as noted. Statistical analysis was performed using STATA statistical package (Stata Corp., College Station, TX). Comparison between drugs was done *via* two-way (drug and subject) analysis of variance. Gender analysis was performed by analysis of variance with these factors: gender, subject nested within gender, drug, and drug-by-gender interaction. *P* values without correction for multiple comparisons are reported. *P* values > 0.05 are reported as not significant.

Results

All subjects tolerated both drugs well and completed both arms of the study. In protocol 1, the mean age of the 12 subjects (8 men and 4 women) was 35 ± 9.9 yr, and the mean weight was 76 ± 15 kg. In protocol 2, the mean age of the 12 subjects (6 men and 6 women) was 26 ± 8.7 yr, and the mean weight was 75 ± 12 kg. There were no adverse effects, and generally the drugs were clinically indistinguishable to the blinded investigators.

Overall, IDD-D Propofol showed higher pain scores, but no subject's pain was rated as severe. Since the subjects' rating of pain may be lessened in protocol 2 because of the length of time between induction and the rating, only the observer's rating of pain is combined between protocols 1 and 2. For the observer's rating of pain on induction (single bolus) in both protocols, with Diprivan, 21 subjects were rated as having no pain and 3 with mild pain, but with IDD-D Propofol, 11 were rated with no pain, while 10 had mild pain and 3 had moderate pain ($P = 0.007$, Pearson chi-square test). The pain visual analog scale scores for protocol 1 (single bolus) with IDD-D Propofol was 25.5 ± 14.1 and with Diprivan was 6.1 ± 8.5 ($P = 0.0006$), but for protocol 2 (single bolus plus 30-min infusion) the visual analog scale scores were lower and not significantly different (9.4 ± 16.5 and 3.1 ± 8.1 for IDD-D Propofol and Diprivan, respectively).

The averages of the plasma concentrations for protocol 1 are shown in figure 1, and the pharmacokinetic parameters are given in table 1. Missing samples (because of inability to withdraw the blood) in one subject prevented calculation of pharmacokinetic parameters in this subject. There were no apparent or statistical differences in the pharmacokinetics between the two drugs.

In one subject in protocol 2 who received IDD-D Propofol, there was an infusion pump error that caused the subject to receive an infusion dose of 0.131 mg · kg^{-1} · min^{-1}. The data from that subject are excluded from the pharmacokinetic analysis where noted by the indication of 11 subjects. Figure 2 shows the plot of the individual plasma concentrations for Diprivan and IDD-D Propofol for protocol 2. Again, there were no statistical differences between the concentrations at any time point. The results for the pharmacokinetic analysis are given in table 1. There was no significant difference by drug for any of the pharmacokinetic parameters.

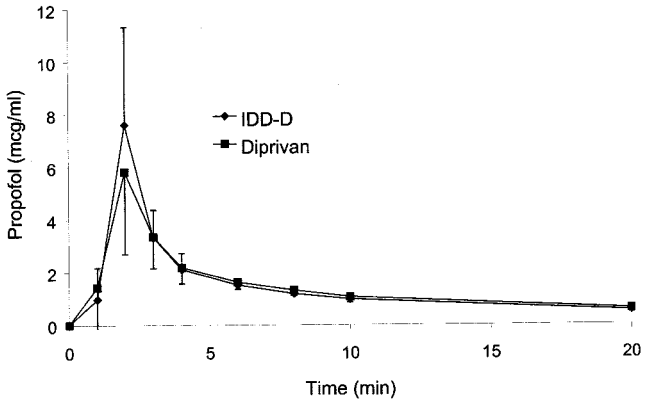

Fig. 1. Average (± SD) plasma propofol concentrations for protocol 1. There was no significant difference between the plasma concentrations of the two drugs at any of the times shown, before correcting for multiple comparisons. Most data points are the average of samples from each of the 12 subjects. There were some samples that were not obtained because of technical difficulties, but the number of patients was 9 or more for all points.

Both drugs caused the expected decrease in blood pressure with induction and infusion, but there was no significant difference. Mean baseline blood pressure was 92 ± 12 mmHg for both IDD-D Propofol and Diprivan; blood pressure decreased to 58 ± 9 mmHg in the IDD-D Propofol group (n = 11) and to 60 ± 9 in the Diprivan group (n = 12) at the end of the infusion. The heart rate was unchanged from baseline for both drugs.

Because the same induction dose was used in both protocols, the analysis of induction time was combined (N = 24) and was 53.3 ± 12.1 s for IDD-D Propofol and 46.9 ± 7.8 s for Diprivan ($P = 0.002$). The emergence times were also slightly longer for IDD-D Propofol. In protocol 1, it was 575 ± 228 s for IDD-D Propofol and 546 ± 216 s for Diprivan (nonsignificant); in protocol 2, it was 1,197 ± 445 s (n = 11) for IDD-D Propofol and 1,005 ± 422 s (n = 12) for Diprivan ($P = 0.07$). Interestingly, if the subject in the IDD-D Propofol group in protocol 2 who received the low dose in error is included, the emergence time increases to 1,254 ± 468 s, and the difference in times barely reaches statistical significance ($P = 0.04$). This is because this subject had a relatively longer emergence time despite the lower dose. Since it would be expected that the correct larger dose would have resulted in a longer emergence time, it would appear to be conservative to include this data.

The data from the BIS monitor in protocol 2 was summarized by ensemble averaging the BIS readings after interpolating at 5-s intervals. BIS data were not obtained in one subject in the IDD-D Propofol group because of technical problems with recording the BIS

Table 1. Pharmacokinetic Parameters for Protocols 1 and 2

		Protocol 2		
	Protocol 1	Women	Men	Both
AUC ($\mu g \cdot hr^{-1} \cdot ml^{-1}$)				
IDD-D Propofol	1.22 ± 0.42 N = 10	3.9 ± 0.4 N = 6	5.6 ± 1.2 N = 5	4.7 ± 1.2 N = 11
Diprivan	1.19 ± 0.31 N = 11	3.7 ± 0.6 N = 6	5.8 ± 1.2 N = 5	4.7 ± 1.4 N = 11
Both		3.8 ± 0.5* N = 12	5.7 ± 1.2 N = 10	
CL ($l \cdot hr^{-1} \cdot ml^{-1}$)				
IDD-D Propofol	2.19 ± 0.50 N = 10	2.2 ± 0.2 N = 6	1.6 ± 0.3 N = 5	1.9 ± 0.4 N = 11
Diprivan	2.19 ± 0.41 N = 11	2.3 ± 0.4 N = 6	1.5 ± 0.3 N = 5	2.0 ± 0.6 N = 11
Both		2.3 ± 0.3* N = 12	1.5 ± 0.3 N = 10	
V_d (l/kg)				
IDD-D Propofol	3.66 ± 1.69 N = 10	5.3 ± 1.3 N = 6	7.9 ± 6.9 N = 5	6.5 ± 4.6 N = 11
Diprivan	2.80 ± 0.78 N = 11	5.1 ± 2.4 N = 6	8.5 ± 6.7 N = 5	6.7 ± 4.9 N = 11
Both		5.2 ± 1.8* N = 12	8.2 ± 6.4 N = 10	
$T_{1/2}\alpha$ (min)				
IDD-D Propofol	2.4 ± 1.6 N = 12	2.3 ± 1.4 N = 6	6.2 ± 1.4 N = 5	4.1 ± 2.4 N = 11
Diprivan	6.5 ± 9.6 N = 12	2.8 ± 1.7 N = 6	7.2 ± 1.9 N = 6	5.0 ± 2.9 N = 12
Both		2.5 ± 1.5* N = 12	6.7 ± 1.7 N = 11	
$T_{1/2}\beta$ (min)				
IDD-D Propofol	71.6 ± 54.1 N = 12	67.4 ± 13.9 N = 6	127.4 ± 40.3 N = 5	94.7 ± 41.6 N = 11
Diprivan	69.0 ± 61.9 N = 12	71.4 ± 8.6 N = 6	133.1 ± 41.0 N = 6	102.2 ± 42.8 N = 12
Both		69.4 ± 11.3* N = 12	130.5 ± 38.7 N = 12	
V_1 (l/kg)				
IDD-D Propofol	0.40 ± 0.30 N = 12	0.31 ± 0.20 N = 6	0.59 ± 0.07 N = 5	0.44 ± 0.21 N = 11
Diprivan	0.44 ± 0.22 N = 12	0.34 ± 0.17 N = 6	0.59 ± 0.11 N = 6	0.46 ± 0.19 N = 12
Both		0.33 ± 0.18* N = 12	0.59 ± 0.09 N = 11	
V_2 (l/kg)				
IDD-D Propofol	2.02 ± 1.42 N = 12	1.90 ± 0.34 N = 6	2.57 ± 0.51 N = 5	2.20 ± 0.54 N = 11
Diprivan	1.81 ± 1.27 N = 12	2.11 ± 0.89 N = 6	2.35 ± 0.61 N = 6	2.23 ± 0.74 N = 12
Both		2.00 ± 0.65 N = 12	2.54 ± 0.55 N = 11	

Mean ± standard deviation. No significant drug effect for any of the variables.

* $P < 0.0001$ *versus* male subjects.

N = number of subjects; AUC = area under the curve; CL = clearance; V_d = volume of distribution; $T_{1/2}\alpha$ = distribution time constant, bi-exponent model; $T_{1/2}\beta$ = elimination half time, bi-exponent model; V_1 = central compartment volume; V_2 = peripheral compartment volume.

data. The subject who received the erroneous infusion rate was not included; therefore, n = 10 for the IDD-D Propofol group, and n = 12 for the Diprivan group. The values and the time course of the BIS readings were similar for both drugs (fig. 3). The time to minimum BIS and the minimum BIS value were 117 ± 38 s and 16 ± 7 for IDD-D Propofol and 113 ± 27 s and 17 ± 6 for Diprivan, respectively (nonsignificant for both). At the time of the infusion termination, the average BIS reading (averaged over the last minute of data prior to the end of the infusion) was not significantly different: 34.2 ± 3.9 for IDD-D Propofol and 36.2 ± 3.9 for Diprivan.

The plasma concentrations of triglycerides confirmed the expected differences (fig. 4). Octanoate is a significant metabolite of medium-chain triglycerides; it was

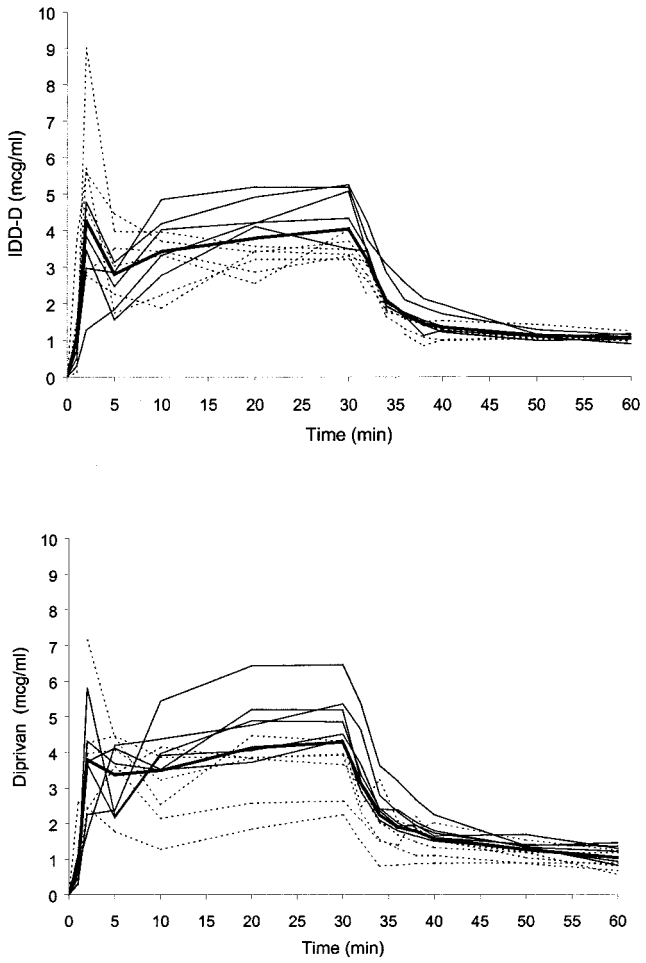

Fig. 2. Individual plasma measured plasma concentrations for IDD-D Propofol (*top*) and Diprivan (*bottom*). Male subjects are shown with a solid line and female with a dotted line. The mean is given with the heavy solid line. Breaks in the lines are at missing data points. There was no significant difference between the mean plasma concentrations of the two drugs at any of the times shown.

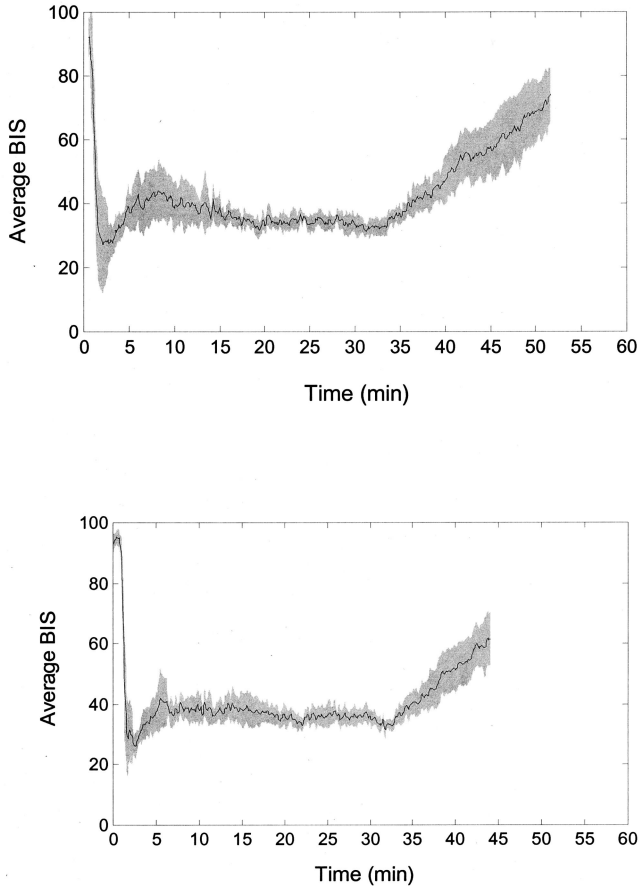

Fig. 3. Ensemble average of the bispectral index (BIS) readings in protocol 2 for IDD-D Propofol (*top*, n = 10) and Diprivan (*bottom*, n = 12). The individual BIS readings were interpolated at 5-s intervals and then averaged across subjects. The mean is shown and the shaded area is ± 2 SEM, representing approximately 95% confidence intervals. The infusion was terminated at 1,800 s. BIS readings when the subject aroused became unstable, and the ensemble averaging was terminated at the shortest time with a stable reading.

elevated in the IDD-D Propofol group but not in the Diprivan group. In one of the male subjects, the reference laboratory reported elevated concentrations of octanoate when he received Diprivan but not when he received IDD-D Propofol. In this subject, the triglyceride value (performed on a different sample in the University of Rochester clinical laboratories) was apparently correct (elevated during Diprivan and unchanged for IDD-D Propofol). While the statistical results are not affected regardless of how this subject's data are handled, for the purposes of this analysis, we deleted the data from this subject assuming that it was erroneous. The data from the subject receiving the incorrect infusion rate of IDD-D Propofol is not included. Plasma concentrations of cholesterol, high-density lipoprotein, lactate, acetoacetate, or β-hydroxybutyrate did not demonstrate any large or consistent changes with either formulation of propofol.

It has been reported that there are gender differences affecting the awakening time from propofol.[10] The plasma concentrations for each subject shown in figure 2 indicates that the female subjects tended to have a higher initial peak but a lower final concentration. Since there was no difference between the two drugs, the data were combined and plotted by gender in figure 5. While the initial peak was higher in females, the difference was not significantly different; however, the plasma concentrations at 20 and 30 min were significantly lower in female subjects, and this difference persisted after the infusion was terminated. Table 1 also gives the comparison between female and male subjects for calculated pharmacokinetic parameters; only V_2 did not show a statistical difference.

Table 2 compares the awakening time, plasma concentration at the end of the infusion, and the BIS level at the same time between male and female subjects. There was a highly significant difference in the wake-up times between the male and female subjects. This difference was greater than the difference between the two drugs.

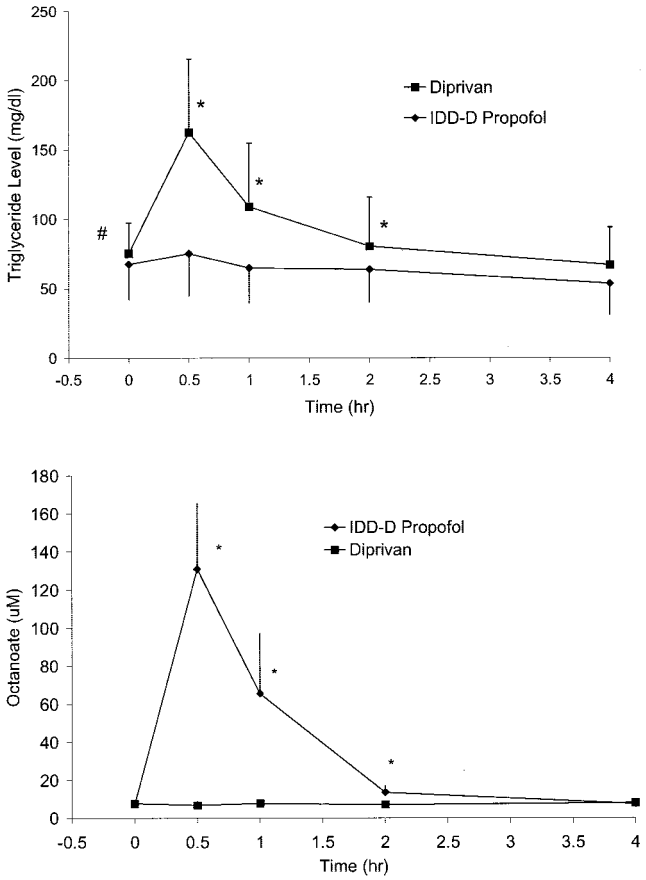

Fig. 4. Average plasma triglyceride (*top*) and octanoate (*bottom*) concentrations for subjects in protocol 2. For triglycerides, n = 12 for IDD-D Propofol and n = 11 for Diprivan; for octanoate, n = 10 for IDD-D Propofol and n = 11 for Diprivan. *$P < 0.006$ and #$P = 0.04$, difference between the two drug formulations at the given time.

There was also a significant difference in the plasma concentration but not in the BIS levels at the time of the termination of the infusion.

Discussion

Propofol has become the induction agent of choice when speed of awakening without any "hangover" is important.[1] It is also increasingly administered as a continuous infusion to maintain anesthesia or provide sedation for patients requiring intensive care. Since the drug is extremely insoluble in water, it is necessary to formulate it in a lipid-based emulsion. The currently marketed products contain propofol as a 1% emulsion in a soybean-based lipid. This formulation contains the long-chain triglycerides from the soybean base. While this formulation has been clinically very useful, it has some drawbacks, including pain on injection, elevation of plasma triglyceride concentrations during prolonged infusion, and the risk of bacterial contamination.[1,2]

This new RTP formulation of propofol attempts to address some of these issues by changing the emulsion

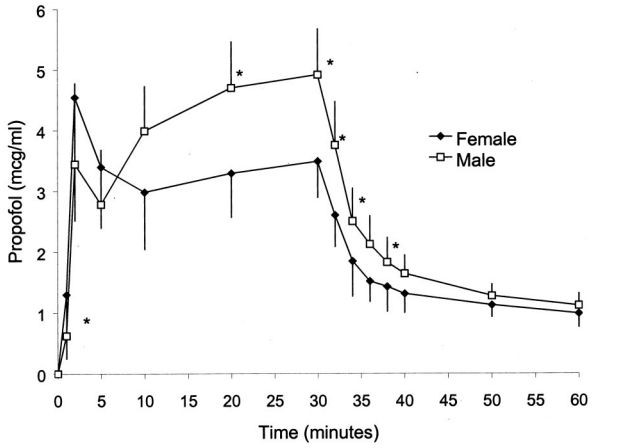

Fig. 5. Average plasma propofol concentrations for protocol 2. Concentrations for Diprivan and IDD-D Propofol combined for men *versus* women. *$P < 0.01$ difference between men and women at indicated time point.

base. In this formulation, propofol is a 2% oil-in-water emulsion stabilized with phosolipids, where the oil phase comprises a mixture of medium-chain triglycerides (C_8 and C_{10} fatty acids, primarily caprylic and capric acids). The lack of long-chain triglycerides in the formulation precludes their elevation in the plasma following a prolonged infusion. However, this new formulation may result in changes in pharmacodynamic or pharmacokinetic properties of propofol.

The plasma concentrations for both drugs were similar in both protocols, indicating no pharmacokinetic difference between the two formulations. Although peak drug

Table 2. Comparison of Waking Times, BIS Values, and Plasma Concentrations at the End of the Infusion for Women *versus* Men in Protocol 2

	Women	Men	Both
Time to awaking (s)			
IDD-D Propofol	931 ± 250 N = 6	1517 ± 427 N = 5	1197 ± 445 N = 11
Diprivan	777 ± 378 N = 6	1234 ± 352 N = 6	1005 ± 422 N = 12
Both	853 ± 316 N = 12	1362 ± 396 N = 11	
BIS			
IDD-D Propofol	34.1 ± 2.9 N = 6	34.3 ± 5.6 N = 4	34.2 ± 3.9 N = 10
Diprivan	36.6 ± 5.2 N = 6	35.8 ± 2.3 N = 6	36.2 ± 3.9 N = 12
Both	35.5 ± 4.2 N = 12	35.2 ± 3.7 N = 10	
Concentration (μg/ml)			
IDD-D Propofol	3.5 ± 0.3 N = 6	4.7 ± 0.8 N = 5	4.0 ± 0.8 N = 11
Diprivan	3.5 ± 0.8 N = 6	5.1 ± 0.8 N = 6	4.3 ± 1.2 N = 12
Both	3.5 ± 0.6 N = 12	4.9 ± 0.8 N = 11	

Mean ± standard deviation. No significant drug effect for any of the variables. $P < 0.001$ *versus* male subjects.

BIS = Bispectral Index; N = number of subjects.

concentrations following the initial bolus injection were higher for IDD-D Propofol, these differences were not significant because of the expected individual variability. None of the calculated pharmacokinetic parameters showed a significant difference, and the values are similar to those reported by Shafer *et al.*,[11] who also analyzed venous samples.

The induction times were similar. Although the 6.4-s longer time with IDD-D Propofol was statistically longer, it is not clinically significant, and the time to the peak BIS effect was the same for both drugs. Both the induction times and the time to minimum BIS are similar to those found by Flaishon *et al.*[12] following a 2-mg/kg induction dose given over 20 s. An explanation for this difference may also be found in the work of Kazama *et al.*[13] In a study of induction time with a wide range of induction infusion rates using 1% undiluted and 0.05% diluted propofol, they found that the more concentrated propofol had a longer induction time. In our protocol, the induction dose of the drug was calculated on a milligram-per-kilogram basis (2.5 mg/kg), but the speed of injection was not (4 mg/s). This resulted in induction dose rates (protocols 1 and 2 combined) of 196 ± 33 and 267 ± 45 mg · kg^{-1} · h^{-1} adjusted for lean body mass (calculated using the formulas given by Kazama *et al.*[13]; at approximately these rates, Kazama *et al.*[13] found an induction time of 51 ± 5 s for undiluted propofol and 34.1 ± 3.2 s for the diluted propofol. If these results apply to the more concentrated IDD-D Propofol, then the longer induction time may be largely explained by this concentration difference. In addition, Van Hemelrijck *et al.*[14] gave Diprivan at a slightly slower rate than we did and found the induction time to be 75 ± 25 s.

While the difference in emergence times was only marginally statistically significant in protocol 2 and not significant in protocol 1, there was a tendency for IDD-D Propofol to prolong emergence slightly. However, a complete interpretation of this result must be tempered by the fact that we obtained only venous plasma samples and that there may be a significant difference between arterial and venous propofol during (arterial greater than venous) and after (venous greater than arterial) continuous infusions.[15] Determining the pharmacodynamics of a drug with only venous samples may lead to erroneous conclusions.[16] However, the longer awaking time for IDD-D Propofol may indicate that it is slightly more potent.

While in our protocol we did not find any major differences between IDD-D Propofol and Diprivan, we did observe large differences between our male and female subjects. The emergence time was faster for women, and the plasma concentrations at the termination of the infusion were statistically significantly lower. This leads us to conclude that this gender difference is primarily a result of pharmacokinetic differences, which are shown by the differences in pharmacokinetic parameters (table 1). However, since the BIS levels at the termination of the infusion were the same for these different plasma concentrations, there may also be a gender-related difference in pharmacodynamic effect. Stepwise multiple regression analysis of the awakening time showed that gender ($P = 0.002$) and BIS at the time of termination of the infusion ($P = 0.02$) and drug ($P = 0.07$) were the most significant factors, while the octanoate and drug concentrations at the end of the infusion and lean body mass were not significant. While some previous reports have not shown gender to be a significant cofactor (in addition to lean body mass) in a pharmacokinetic analysis,[17] others have.[11] It seems that the gender difference may be both a pharmacokinetic and a pharmacodynamic effect.[10,18] In this study, the gender-related difference was larger than the differences found between the propofol formulations.

Medium-chain triglyceride administration to humans has been extensively studied and is without significant toxicity when given either orally and parenterally.[9] However, there has been some indication that octanoate concentrations of 3–8 μmol/ml in animals[9] can cause somnolence and coma, and infusion of a large dose (plasma concentrations > 10 μmol/ml) of octanoate in Rhesus monkeys also caused somnolence and coma.[19] However, a 6-h infusion in human volunteers of a 10% solution of a lipid emulsion containing 75% medium-chain triglycerides was without any neurologic effects, and the plasma concentrations reached 2–3 μmol/ml.[20] The highest concentration seen in our study, 0.189 μmol/ml, is well below these concentrations. While the octanoate concentration has returned almost to normal by 90 min after the termination of the infusion, clinical trials with larger doses (longer infusions) will be needed to determine the pharmacokinetics of this metabolite; it will be important to monitor for any possible neurologic effects. Although large doses of medium-chain triglycerides can result in the formation of ketone bodies, there was no elevation in β-hydroxybutyrate or acetoacetate seen with IDD-D Propofol.

Pain on injection was not one of our primary outcome variables, but there seemed to be slightly more pain on injection with IDD-D Propofol. This difference in reported pain might have been caused by an increased amount of free propofol in the 2% formulation, since pain has been related to the amount of free propofol in the injectate.[3] In contrast to the common reporting of severe pain in the operating room, the general pain concentrations were low in this study, most likely because of the use of a large antecubital vein. We did not use any common clinical technique to reduce pain (*e.g.*, mixing with lidocaine). The fact that the injection was made relatively slowly may have resulted in less pain than might occur with a more rapid injection into a more peripheral vein.[4] Larger clinical trials, using techniques more commonly used in clinical practice (*e. g.*, use of a

small hand vein) will be needed to determine if there is more injection pain with this formulation and if it is caused by the higher propofol concentration.

In this phase 1 trial involving 24 normal, healthy subjects, we found that the new formulation of propofol was well tolerated and generally indistinguishable from one of the current propofol formulations (Diprivan 1%). We did find strong gender differences in emergence time and pharmacokinetics that were similar for both drugs. Since the new formulation may have significant advantages, further clinical trials are warranted.

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