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Formulation-dependent Brain and Lung Distribution Kinetics of Propofol in Rats

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Background: **Propofol when administered by brief infusion in a lipid-free formulation has a slower onset, prolonged offset and greater potency compared with an emulsion formulation. To understand these findings the authors examined propofol brain and lung distribution kinetics in rats.**

Methods: **Rats were infused with equieffective doses of propofol in emulsion (n = 21) or lipid-free formulation (n = 21). Animals were sacrificed at various times to harvest brain and lung. Arterial blood was sampled repeatedly from each animal until sacrifice. Deconvolution and moment analysis were used to calculate the half-life for propofol brain turnover (BT) and brain:plasma partition coefficient (Kp). Lung concentration-time profiles were compared for the two formulations.**

Results: **Peak propofol plasma concentrations for the lipid-free formulation were 50% of that observed for emulsion formulation, whereas peak lung concentrations for lipid-free formulation were 300-fold higher than emulsion formulation. Brain Kp calculated from tissue disposition curve and ratio of brain:plasma area under the curves were 8.8 and 13, and 7.2 and 9.1 for emulsion and lipid-free formulations, respectively. BT were 2.4 and 2.5 min for emulsion and lipid-free formulations, respectively.**

Conclusions: **Significant pulmonary sequestration and slow release of propofol into arterial circulation when administered in lipid-free vehicle accounts for the lower peak arterial concentration and sluggish arterial kinetics relative to that observed with the emulsion formulation. Higher Kp for the lipid-free formulation could explain the higher potency associated with this formulation. BT were independent of formulation and correlated with values reported for effect-site equilibration half-time consistent with a distribution mechanism for pharmacologic hysteresis. (Key words: First-pass uptake; pharmacodynamics; pharmacokinetics.)**

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EMULSIONS and non-aqueous cosolvents have been used to solubilize poorly water-soluble intravenous drugs. Non-aqueous cosolvents have been associated with hypersensitivity reactions,[1,2] venous irritation,[3] and pain on injection.[4] The incorporation of lipid-soluble drugs in lipid emulsion has been shown to reduce adverse events associated with non-aqueous solvents.[5–9] In addition to imparting potentially desirable biopharmaceutical properties, lipid emulsions have been shown to modify the disposition of cyclosporin,[10] d-α-tocopherol,[11] and other compounds.

Propofol (2,6-diisopropyl-phenol), a highly lipophilic (log octanol-water partition coefficient, 4.33[12]) anesthetic agent, is commercially formulated in a lipid emulsion (Diprivan®, Zeneca Pharmaceuticals, Wilmington, DE) for intravenous use. Propofol, when administered in emulsion, demonstrates rapid onset and produces a brief but profound level of anesthesia and a short duration of sleep after intravenous injection. It is not known whether the clinical pharmacokinetics and pharmacodynamics (PK-PD) of propofol are influenced by its lipid formulation.

We have developed a unique system of administering propofol in a lipid-free vehicle that has enabled us to examine the impact of formulation on the PK-PD of propofol in a rodent model of propofol anesthesia. A recent report from our laboratory compared the time course of electroencephalographic (EEG) effect of propofol in rats after administration of propofol formulated in either emulsion or lipid-free formulation.[13] At equivalent doses a delayed onset, a lower maximal intensity of effect and a prolonged sedative effect was

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observed for the lipid-free formulation. This sluggish effect-time profile is more in agreement with propofol's high lipophilicity. Thus it appears that intravenous formulation can have profound influence on the clinical characteristics of propofol.

In addition to altering the time course of pharmacologic effect we found that propofol pharmacokinetics assessed from arterial plasma is significantly influenced by formulation in a lipid-free vehicle.[14] When administered in the lipid-free formulation propofol central and steady state distribution volumes increased 10- and 3-fold, respectively, compared with the emulsion. To understand these formulation-induced changes in pharmacokinetics and time course of EEG effect we examined propofol brain and lung distribution kinetics in rats after short infusions in emulsion or lipid-free formulations at equieffective (EEG burst suppression) doses.

Methods

Formulations

We have previously reported the preparation of the emulsion and lipid-free formulations of propofol.[13] A brief description of these formulations is provided here.

Emulsion Formulation. This consisted of a 1:4 dilution of the commercial preparation (1 part Diprivan® 10 mg/ml to 3 parts 5% dextrose USP).

Lipid-free Formulation. Because of propofol's limited solubility, the administration of propofol in a lipid-free vehicle required the development of a unique administration system using two syringe pumps (Harvard model 22, Harvard Instruments, South Natick, MA). This lipid-free formulation is prepared *in situ* during infusion to chronically instrumented rats (see below). Propofol oil (97% pure, Aldrich Chemical Co., Milwaukee, WI) was diluted with ethanol (approximately 1:5) and placed in a 250-μl gas tight syringe on the first pump. A carrier solution, which was similar in composition to the diluted aqueous phase of the commercial emulsion preparation (1 part 22.5 mg/ml glycerol in water to 3 parts 5% dextrose USP), was placed in a 5-ml gas tight syringe on the second pump. The two solutions, propofol in ethanol and the carrier solution, were simultaneously infused into a preprimed 22-gauge mixing tee tube. The outflow of the mixing tee tube was connected to the rat's jugular cannula by a short piece of PE50 tubing. The flow rates of the component solutions were approximately 60 $\mu l \cdot min^{-1} \cdot kg^{-1}$ for the propofol in ethanol solution (pump 1) and 2.5 $ml \cdot min^{-1} \cdot kg^{-1}$ for the carrier solution (pump 2). Ethanol present in the lipid-free formulation was infused at a rate of 50 $\mu l \cdot min^{-1} \cdot kg^{-1}$. We have previously shown[13] that this dose of ethanol has no effect on animal behavior or processed EEG.

Animal Experiments

Intravenous (jugular) and intra-arterial (femoral) catheters were implanted in male Wistar rats weighing 348 ($\pm$ 36) g during isoflurane anesthesia for drug infusion and blood sampling, respectively, 24 h before the study. Propofol in emulsion (n = 21) or lipid-free vehicle (n = 21) was infused at 5 or 10 $mg \cdot min^{-1} \cdot kg^{-1}$ for 2 min, respectively. We have previously shown[13] that these doses were equieffective in producing EEG burst suppression.

Arterial blood (400 μl) was sampled at 1, 2, 3, 5, 7, 10, or 15 min from the start of the infusion. To prevent hypovolemia, sampled volume was replaced with 800 μl of saline; hematocrit never decreased below 35% during the study. The animals were divided into seven groups of three animals per group for each formulation. Animals in each group were assigned one of the following times for decapitation: 1, 2, 3, 5, 7, 10, or 15 min from the start of the infusion. Arterial blood was sampled in each animal according to the above protocol until sacrifice. The animals were decapitated immediately (within 5 s) after the last blood sample. Immediately after decapitation, brain and lung were harvested, frozen on dry ice, and stored at $-20°C$ pending assay for propofol. The animal study protocol was reviewed and approved by the Stine-Haskell Animal Care and Use Committee.

HPLC-EC Assay of Propofol from Rat Plasma and Tissues (Brain and Lung)

Propofol concentrations in rat plasma, brain, and lung were determined by a previously reported[15,16] specific and accurate reversed phase HPLC-electrochemical detection method. Briefly, for determination of propofol concentration in brain and lung, frozen tissue (0.5–1.5 g) was thawed and subdivided into 2 × 2 mm pieces. Acetonitrile—0.05 M phosphate buffer (pH 7.0) (50:50, v/v) equal to four times the tissue weight was added, and the tissue was homogenized using a Virtis Cyclone/Tempest mechanical homogenizer (Virtis, Gardiner, NY) to a uniform slurry (time dependent on tissue, three to four 10-s bursts of homogenizer). Internal standard was 2,6-*tert*-butyl-methyl phenol (Aldrich, Milwaukee, WI). Propofol in tissue homogenate (100 μl) or plasma sample (25–100 μl) was extracted into pentane, separated on a reversed-phase column (Rainin Instruments,

Woburn, MA), and detected by electrochemical detector (ESA, Bedford, MA). The intra- and inter-day variability for plasma assay were below 15% in the 0.25–10 μg/ml concentration range. For whole brain and lung assay intra-day variability were below 8% and 15% in the 1–25 μg/g and 1–2 mg/g concentration ranges, respectively.

Data Analysis

For each formulation group the arterial plasma concentrations from the animals were pooled. Subsequently a sum of two or three exponentials were fit to the pooled arterial concentration-time profiles. The area under the concentration-time curves (from 0 to 15 min) for plasma (AUC_{PLM}), brain (AUC_{BRN}), and lung (AUC_{LNG}) for each formulation were calculated from the mean concentrations at each sample point using the trapezoidal method.

Deconvolution methods were used to reveal the intrinsic disposition of propofol in the brain. Deconvolution analysis is frequently used to recover the time course of drug absorption after non-parenteral administration. The time course of the rate and extent of drug absorption (an input function) can be calculated if the concentration-time data of a drug are available after rapid bolus administration and after a non-parenteral route of administration (*e.g.*, oral, transdermal, intramuscular, epidural). In this analysis paradigm, the concentration-time course after rapid bolus administration represents the drug's whole body disposition function characterizing the drug's intrinsic whole body pharmacokinetics in the absence of any sustained drug input. The time course of drug concentrations observed after the non-parenteral route of drug administration is referred to as an output function. This observed concentration-time profile arises from the convolution or super-position of the unknown input function and the drug's intrinsic disposition function. If two of these three functions are known (input, disposition, output), a numerical method known as numerical deconvolution can recover the third.

A major aim of this study was to examine the intrinsic brain disposition of propofol. Although this disposition function cannot be directly observed, it can be recovered using piecewise deconvolution methods. The theoretical basis for the use of deconvolution in piecewise physiologic modeling was originally described by Verotta *et al.*[17] and extensively applied by Bjorkman *et al.*[18] and Ebling *et al.*[19] In this paradigm the input function to the brain is represented by the time course of drug concentration in arterial plasma. The time course of drug concentration in whole brain represent the tissue output function which resulted from the convolution of the input function and the unknown organ disposition function. Because two of the three fundamental functions are known, deconvolution methods can be applied to yield the unknown brain disposition function. This organ disposition function describes the probability of a molecule of drug being retained in the brain since it entered the organ on a single circulatory passage. Properties such as tissue:plasma partition coefficient and the half-time for transit through the tissue can be recovered from this whole brain disposition function.[17,19]

In this study constrained numerical deconvolution method,[20] identical to those reported previously,[17–19] was used to recover the disposition functions of propofol in the brain. The reader is referred to these papers for further details. The arterial plasma concentration, predicted from the fit of the sum of exponentials, at each sacrifice time was used as the input for deconvolution. The average brain concentration at each sacrifice time was deconvolved with the arterial plasma concentration time profile to reveal the propofol brain disposition function. Moment analysis[18] was subsequently used to calculate the half-time for propofol turnover in the brain and the brain:plasma partition coefficient from the disposition function of propofol in the brain for the two formulations. The brain:plasma partition coefficient of propofol was also calculated from the ratio of AUC_{BRN}/AUC_{PLM}.

Results

Figure 1 presents the arterial plasma concentrations of propofol after administration in the lipid-free and emulsion formulations. Peak propofol arterial plasma concentrations occurred at the end of the infusion and were approximately 10 and 5 μg/ml for the emulsion and lipid-free formulations, respectively. Propofol plasma concentrations declined in a biexponential manner after termination of infusion in rats receiving the emulsion formulation indicating the presence of a rapid distribution phase (10-fold decline in 15 min). In contrast, plasma concentrations declined in a monoexponential fashion with a slow distribution phase (twofold decline over 15 min) after infusion in the lipid-free formulation. The AUC_{PLM} were 39 and 36 $\mu g \cdot ml^{-1} \cdot min$ for the emulsion and lipid-free formulations, respectively.

Figure 2 shows propofol lung concentration-time profiles. Peak lung concentrations were approximately 300-fold higher after administration of propofol in the lipid-free formulation compared with the emulsion indicating

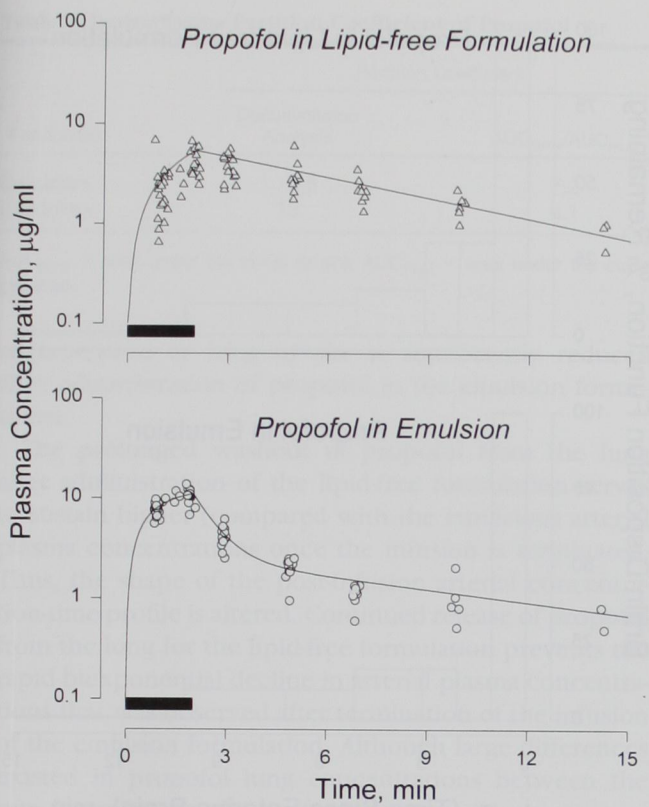

Fig. 1. Propofol arterial plasma concentration-time profiles during and after administration of propofol in lipid-free (*top panel*) and emulsion (*bottom panel*) formulations. Solid bar indicates duration of infusion (2 min). Continuous line is the polyexponential fit to the data. Symbols indicate measured plasma concentration. Post-infusion propofol concentrations decline in a biexponential manner for the emulsion formulation whereas for the lipid-free formulation concentrations exhibit a monoexponential decline.

extensive pulmonary sequestration of propofol. This high pulmonary sequestration is also reflected by the 300-fold higher AUC_{LNG} (10×10^3 *vs.* 32 $\mu g \cdot g^{-1} \cdot min$ for emulsion) observed for the lipid-free formulation.

Figure 3 presents propofol brain concentration-time profiles after administration of the two formulations. Mean peak propofol brain concentration of approximately 36 μg/g was achieved 2 min after the infusion of the emulsion formulation was started. After termination of infusion, brain concentrations declined rapidly (twofold over 6–7 min). In contrast, propofol administered in the lipid-free formulation at twice the dose of the emulsion formulation produced mean peak propofol brain concentration that was similar (about 30 μg/g). Mean peak brain concentration was observed in the 5- min sample, 3 min *after termination* of the infusion. Brain concentrations subsequently declined more slowly relative to the emulsion group. The AUC_{BRN} were 280 and 330 $\mu g \cdot g^{-1} \cdot min$ for the emulsion and lipid-free formulations, respectively.

Figure 4 shows brain disposition functions for the two formulations of propofol obtained from deconvolution analysis. Propofol transit through the brain was rapid for both formulations. A molecule of propofol has approximately 25% probability of remaining in the brain 1 min after its entry into the tissue irrespective of formulation. Essentially a drug molecule has less than 1% probability of remaining in the brain 10 min after its entry.

Table 1 compares the half-time for turnover of propofol in the brain determined in this study with previously reported effect-site equilibration half-time ($T_{1/2}\ k_{E0}$) values of propofol after administration in the emulsion[16] and lipid-free[14] formulations. Propofol brain turnover half-times and $T_{1/2}\ k_{E0}$ were similar and not influenced by formulation.

Brain:plasma partition coefficient calculated from brain disposition curve and ratio of AUC's are reported (table 2). Propofol brain:plasma partition coefficient was high (approximately 8–9) and in agreement with its high lipophilicity. Partition coefficients calculated from both

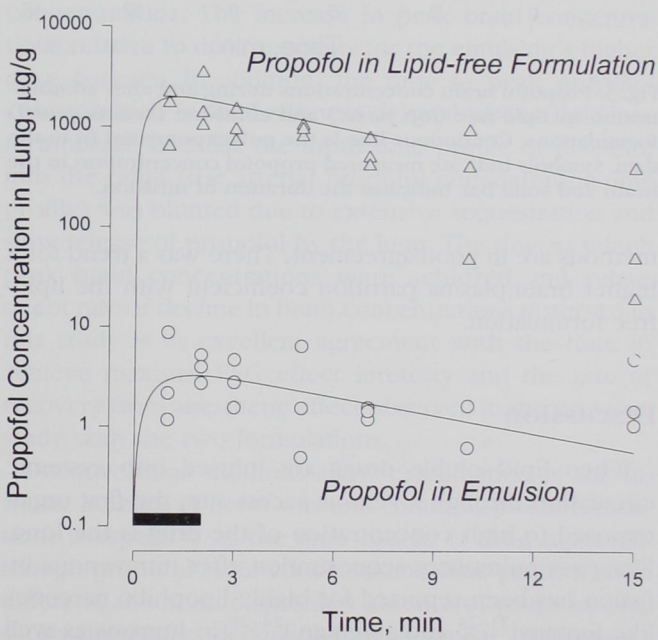

Fig. 2. Propofol lung concentrations during and after administration in lipid-free and emulsion formulations. Continuous line is the polyexponential fit to the data. Triangles and circles indicate measured propofol concentration in the lung during and after administration in lipid-free and emulsion formulations, respectively. Solid bar indicates the duration of infusion. Propofol lung concentrations were approximately 300-fold higher after administration in the lipid-free formulation compared with the emulsion formulation.

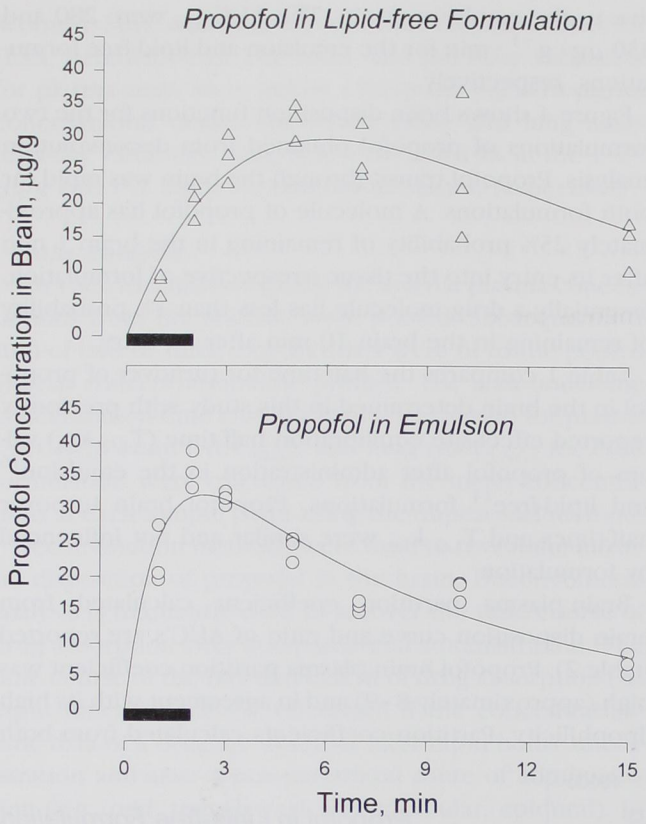

Fig. 3. Propofol brain concentrations during and after administration in lipid-free (*top panel*) and emulsion (*bottom panel*) formulations. Continuous line is the polyexponential fit to the data. Symbols indicate measured propofol concentration in the brain and solid bar indicates the duration of infusion.

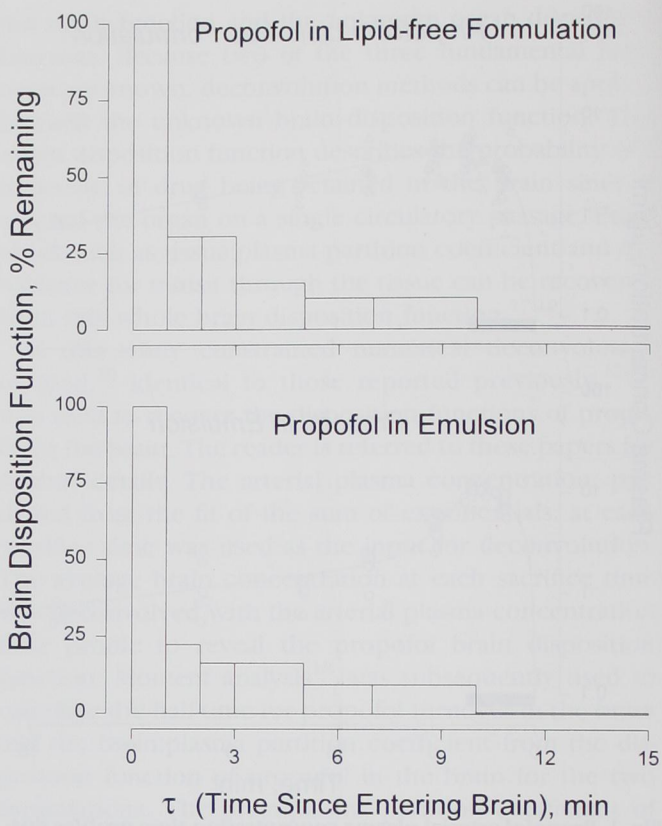

Fig. 4. Propofol brain disposition functions obtained from deconvolution of the predicted propofol arterial plasma concentrations with the average brain concentrations at the sacrifice times after administration in lipid-free (*top panel*) and emulsion (*bottom panel*) formulations. The histograms present the abstract representation of the disposition functions obtained from constrained numerical deconvolution.

methods are in good agreement. There was a trend for a higher brain:plasma partition coefficient with the lipid-free formulation.

Discussion

When lipid-soluble drugs are infused into systemic circulation through a venous access site, the first organ exposed to high concentration of the drug is the lung. First-pass pulmonary sequestration after intravenous infusion has been reported for highly lipophilic narcotics like fentanyl[21–23] and sufentanil[24–26] in humans as well as for propofol in cats.[27] The results of this study suggest that emulsion may protect propofol from excessive first-pass pulmonary sequestration (fig. 2). In the absence of emulsion, extensive lung uptake, possibly because of first-pass sequestration, appears to attenuate the rise in arterial plasma concentrations (fig. 1) during infusion. It should be noted that for the lipid-free formulation, high pulmonary sequestration may have occurred not only from propofol's intrinsically high solubility in lung but could also have potentially resulted from direct deposition of propofol oil droplets on the pulmonary capillary endothelium. The physical form of propofol, once in circulation, is not known for either formulation. Regardless of mechanism, it is clearly evident that pulmonary

Table 1. Half-time for Propofol Turnover in Brain and Effect–Site Equilibration

Formulation	Tissue Distribution Study [half-time for propofol turnover in brain (min)]	Pharmacokinetic–Pharmacodynamic Study [$T_{1/2}$ k_{E0} (min)]
Emulsion	2.4	1.7*
Lipid-free	2.5	2.0†

* Dutta *et al.* (1997).[16]

† Dutta and Ebling (1997).[14]

Table 2. Brain:Plasma Partition Coefficient of Propofol

Formulation	Partition Coefficient	
	Deconvolution Analysis	AUC_{BRN}/AUC_{PLM}
Emulsion	8.8	7.2
Lipid-free	13	9.1

AUC_{BRN} = area under the curve (brain); AUC_{PLM} = area under the curve (plasma).

sequestration or lung uptake is significantly reduced after administration of propofol in the emulsion formulation.

The prolonged washout of propofol from the lung after administration of the lipid-free formulation serves to sustain higher (compared with the emulsion) arterial plasma concentrations once the infusion is terminated. Thus, the shape of the post-infusion arterial concentration-time profile is altered. Continued release of propofol from the lung for the lipid-free formulation prevents the rapid biexponential decline in arterial plasma concentrations that was observed after termination of the infusion of the emulsion formulation. Although large differences existed in propofol lung concentrations between the two formulations, the post-infusion arterial plasma concentrations differed only twofold. If propofol freely partitions between lung and arterial blood, the lung:blood partition coefficient must be large. The possibility exists that a significant portion of the total load of propofol initially sequestered in the lung after administration of the lipid-free formulation may be irreversibly trapped or exhaled as propofol vapor and thus may not available for redistribution into the arterial circulation. Studies with extended sampling of blood and lung could potentially resolve whether propofol's pulmonary disposition is governed by simple partitioning in the absence of the emulsion carrier.

Independent of formulation, a rapid $T_{1/2}$ k_{E0} is requisite for the effect-site (and brain) concentrations to rapidly track the changing propofol arterial plasma concentration profiles for both formulations. We have previously shown that the effect-site equilibration half-time ($T_{1/2}$ k_{E0}) for the two formulations are similar (table 1). This supports the hypothesis that alterations in systemic pharmacokinetics is primarily responsible for the formulation-dependent differences in the effect-time profiles. The redistribution of propofol from brain to blood during the rapid distribution phase appears to be responsible for the brisk termination of propofol effect with the emulsion formulation. For the lipid-free formulation the rate of decline in arterial plasma concentrations during this distribution phase is slower. The higher post-infusion arterial plasma concentration sustains transfer of drug into the brain and prolongs effect duration.

Propofol *dose potency* in rats receiving the lipid-free formulation was previously reported to be less than half of the potency of the emulsion formulation.[13] Maximal EEG effect intensity was achieved at approximately 2 min after a 2-min infusion of the emulsion formulation, whereas the effect intensity time profile after administration in the lipid-free formulation appeared to have significant inertia; peak effect intensity occurred 3 min after termination of the brief infusion. Recovery from anesthesia appeared more sluggish. The results obtained from this tissue disposition study provide a potential explanation for this phenomenon.

Examination of brain disposition revealed that mean peak brain concentration (fig. 3) was similar after administration of the emulsion formulation even though the dose of propofol was half compared with the lipid-free formulation. Extensive pulmonary sequestration after administration of the lipid-free formulation reduced the peak arterial and consequently the achieved peak brain concentrations. The increase in peak brain concentrations relative to dose accounts for the emulsion's higher *dose potency.* In addition, the time to peak propofol concentration in the brain was delayed for the lipid-free formulation because the input time profile of propofol into the brain (the arterial propofol concentration-time profile) was blunted due to extensive sequestration and slow release of propofol by the lung. The time at which peak brain concentrations were achieved and subsequent rate of decline in brain concentrations observed in this study is in excellent agreement with the time to achieve maximal EEG effect intensity and the rate of recovery from anesthetic effect observed in the previous study with the two formulations.

Deconvolution methods allow examination of the intrinsic kinetics of brain washout (brain disposition function) irrespective of the time course of drug input. Although propofol brain concentration time profiles were different, the brain disposition kinetics of propofol (fig. 4) obtained after deconvolution is similar for the two formulations. This indicates that turnover of propofol in the brain is not influenced by formulation.

After transient input, drug concentration in arterial plasma is not necessarily equal to the concentration in the hypothetical effect-site due to blood:brain distribution delays. For drugs that have concentration-effect relationships that can be characterized by direct acting

pharmacodynamic models a first order rate constant (k_{E0}) is frequently invoked to describe this disequilibrium. Interestingly, the half-time for turnover in the brain (table 1) is comparable with the half-time for equilibration between the plasma and apparent effect-site ($T_{1/2}$ k_{E0}). This indicates that the time course of propofol in the effect-site is kinetically indistinguishable from that observed in whole brain. Propofol $T_{1/2}$ k_{E0} appears to represent more than a simple empiric factor to adjust for hysteresis. The excellent agreement between $T_{1/2}$ k_{E0} and the half-time for propofol turnover in brain is consistent with a distribution mechanism for pharmacologic hysteresis and suggests an actual physiologic realization of this empirical pharmacokinetic-pharmacodynamic parameter proposed by Sheiner.[28] To our knowledge this correlation between $T_{1/2}$ k_{E0} and tissue turnover have been made for thiopental,[19,29] morphine,[30] meperidine,[30] alfentanil,[30] fentanyl,[30] and now propofol.

The brain:plasma partition coefficients (or solubility) calculated by two different methods (deconvolution analysis and ratio of AUC's; table 2) were high and consistent with propofol's lipophilicity. Both methods indicated a trend for higher brain solubility with the lipid-free formulation. Consistent with this observation is the previously reported twofold increase in the *steady state potency* of the propofol after administration in the lipid-free formulation. The *steady state or intrinsic potency* of a drug can be characterized by the concentration-effect relationship (pharmacodynamics) determined after collapsing any effect hysteresis. This recovered concentration-effect relationship is independent of the pharmacokinetics and other distribution effects (*e.g.*, effect-site turnover, lung and brain uptake, and disposition). The higher intrinsic potency of the lipid-free formulation indicates that for a given steady state plasma concentration of propofol, a more intense effect is elicited by this formulation compared with the emulsion. The increase in brain solubility observed with the lipid-free formulation could explain in part the *higher steady state potency* reported[14] for this formulation compared with the emulsion. In this study we measured the total plasma concentration of propofol after administration of the two formulations. It is possible that formulation-dependent changes in free fraction may also explain the observed differences in the brain:plasma partitioning of the drug between the two formulations.

In conclusion, comparison of the two formulations reveals that emulsion reduces pulmonary sequestration or uptake, produces higher peak plasma concentrations of propofol at lower doses, and allows rapid redistribution of propofol from the brain to systemic circulation. The extensive pulmonary sequestration observed with the lipid-free formulation is responsible for the lower plasma concentrations and the delay in the time to peak concentrations in the brain. These phenomena can account for the higher *dose potency* of the emulsion formulation as well as the delay in time to maximal effect, sluggish offset of sedative effect and higher *steady state potency* previously observed[13,14] with the lipid-free formulation. The half-times for turnover of propofol in the brain were similar to the effect-site equilibration half-times ($T_{1/2}$ k_{E0}) and independent of formulation.

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