The Role of Drug-Lipid Interactions on the Disposition of Liposome-Formulated Opioid Analgesics *In Vitro* and *In Vivo*

Claudette R. Bethune, PhD*, Christopher M. Bernards, MD†, Tot Bui-Nguyen, BS*, Danny D. Shen, PhD*, and Rodney J. Y. Ho, PhD*†

Departments of *Pharmaceutics and †Anesthesiology, University of Washington, Seattle, Washington

Although liposome encapsulation prolongs the duration of action of epidurally administered drugs, little is known about how liposome encapsulation affects opioids differently, or about how lipid content of liposomes alters the bioavailability of epidurally-administered opioids. To address these issues, morphine, alfentanil, fentanyl, and sufentanil were loaded into D-α-dipalmitoyl phosphatidylcholine multilamellar liposomes, and incorporation efficiency and *in vitro* release rates were determined. We then determined epidural morphine and sufentanil liposomes, at two different lipid/opioid ratios, *in vivo* in a pig model in which epidural and intrathecal spaces were continuously sampled via microdialysis. Liposome encapsulation efficiency was significantly more for sufentanil (100%) than for the other opioids (25%–30%). The *in vitro* release rate was slowest for morphine, intermediate for fentanyl and alfentanil, and fastest for sufentanil. *In vivo*, morphine was released more slowly than sufentanil. It is most important to note that increasing the lipid content of morphine liposomes increased the proportion of drug reaching the intrathecal space. In contrast, increasing the lipid content of sufentanil liposomes did not alter intrathecal movement but did decrease movement into plasma. Therefore, increasing drug hydrophobicity and lipid content of the liposomes modulates drug distribution *in vivo*.

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Opioids are frequently administered epidurally to provide selective spinal analgesia in a variety of clinical situations. However, their limited duration of analgesia requires placement of an epidural catheter to permit either continuous opioid infusion or intermittent boluses. Although epidural catheterization is widely accepted, it is not without risks. In particular, bacterial colonization or infection, epidural hematoma, catheter migration into the IV or intrathecal spaces, and simple dislodgment are constant concerns.

Several groups of investigators have attempted to obviate the need for epidural cannulation by developing extended-release preparations for epidural administration of both opioids and local anesthetics. In particular, a number of laboratories, including ours, have shown that drug encapsulation in multilamellar liposomes (MLV) is an effective method of prolonging drug action in the epidural and intrathecal spaces (1–5).

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Address correspondence and reprint requests to Rodney J. Y. Ho, PhD, Department of Pharmaceutics, Box 357610, University of Washington, Seattle, WA 98195-7610. Address e-mail to Rodneyho@u.washington.edu.

Liposomes or lipid vesicles contain multiple, concentric, and spherical phospholipid bilayers separated from one another by aqueous domains, and together these bilayers encapsulate a central aqueous core. Water-soluble drugs can be encapsulated in the aqueous phase, and hydrophobic drugs may be incorporated into the lipid membrane bilayers. Drugs of intermediate hydrophobicity may be localized in both aqueous compartments and membrane bilayers. The degree or efficiency of drug loading into liposomes, assessed as percentage of drug incorporation, depends on a number of factors, including liposome size and composition (number of lipid bilayers) and the physiochemical characteristics (e.g., hydrophobicity) of drug molecules.

Several important issues with respect to the use of liposome formulations as an extended release preparation for opioids remain to be clarified. First, the efficiency of incorporation into liposomes and the kinetics of drug release from the liposome have not been thoroughly characterized for the opioids most often used clinically—morphine, alfentanil, sufentanil, and fentanyl. Second, it is not known how the hydrophobic character of these opioids affects the rate at which they are released from the liposome. Third, it is not known how the ratio of liposomal lipid to encapsulated opioid affects the kinetics of drug release *in vitro*

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or, more important, *in vivo*. Finally, it is not known whether liposome encapsulation simply alters the rate at which the drug becomes bioavailable within the epidural space or whether it also alters the pattern of drug distribution among the epidural space, cerebrospinal fluid (CSF), and plasma.

To investigate these issues, we encapsulated morphine, fentanyl, alfentanil, and sufentanil in MLVs and determined the incorporation efficiency and the *in vitro* release rate of each opioid. In addition, we used a previously described pig microdialysis model (6) to characterize the time course of morphine and sufentanil appearance in epidural space, CSF, and plasma after these two drugs were administered epidurally as free or soluble drug formulation and as large and small lipid/opioid ratio liposomes.

Methods

The opioids morphine, alfentanil, fentanyl, and sufentanil were supplied by the National Institute on Drug Abuse through the Research Triangle Institute (Research Triangle Park, NC). Radiolabeled fentanyl, alfentanil, and sufentanil were purchased from Janssen Biochemica (Beerse, Belgium), and ^{14}C-labeled morphine was purchased from New England Nuclear (Boston, MA).

MLV containing the study opioids and radiotracer amounts of ^{3}H-labeled sufentanil (0.014 mmol, specific activity = 9 Ci/mmol), ^{14}C-labeled morphine (0.054 mmol, specific activity = 671 μCi/mmol), ^{3}H-labeled alfentanil (0.054 mmol, specific activity = 12.5 Ci/mmol), or ^{3}H-labeled fentanyl (0.054 mmol, specific activity = 11 Ci/mmol) were prepared from D-α-dipalmitoyl phosphatidylcholine (Genzyme, Cambridge, MA) as previously described (7). Final lipid to opioid ratio (m/m) was determined to be 17:1 for morphine, 20:1 for alfentanil, 17:1 for fentanyl, and 61:1 for sufentanil.

To examine the effect of increasing the lipid/opioid ratio on *in vivo* epidural pharmacokinetics, liposomes with a larger lipid/opioid ratio (sufentanil 329:1 and morphine 37:1) were similarly prepared. These ratios represent the maximum concentrations of lipid that could be used without significantly altering the percentage of drug incorporation. No stable liposome can be formed beyond these conditions.

To determine the first-order rate of drug release from the liposomes, 500 μL of phosphate-buffered saline containing morphine, alfentanil, fentanyl, or sufentanil liposomes was added to 500 μL porcine CSF and incubated in a water bath at 37°C. At 0, 5, 10, 15, 30, 60, and 90 min and at 2, 3, 6, 22, 48, and 72 h, 20 μL of quadruplicate samples was removed and centrifuged at 22,000*g* for 10 min to separate free (supernatant) from liposome-encapsulated drug. The batched supernatant and the liposomal pellets were placed in separate scintillation vials. Hydrofluor (National Diagnostics, Mannville, NJ) scintillation cocktail (5 mL) was added and opioid concentration determined by counting radiolabeled opioid as described below.

The first-order release-rate constant (K) for each formulation was determined from the slope of linear regression of the log of free drug concentration versus time plots. The release rate half-life values were derived from the relationship half-life = $0.693/K$.

All animal studies were approved by the University of Washington Animal Care and Use Committee, and American Association of American Laboratory Accreditation Council guidelines were followed throughout. The microdialysis pig model has been described previously (6). Briefly, pigs (n = 15) weighing 10–14 kg were orotracheally intubated and their lungs mechanically ventilated with halothane (1%–2%) and nitrous oxide (70%) in oxygen. Ten animals received the small lipid/opioid ratio liposomes, and five animals received the large lipid/opioid ratio liposomes. They were enrolled in the experiments described in Tables 1 and 2, respectively. All animals received the same dose of morphine (1 mg) and sufentanil (60 μg), both as free or soluble drug and as liposome formulations.

A femoral artery was cannulated for blood pressure measurement and blood sampling. Custom microdialysis probes (6) and an epidural catheter were placed in the lumbar (L5) and thoracic (T11) epidural space and in the immediately adjacent intrathecal space. Preliminary studies indicated that the lumbar and thoracic injection sites were far enough apart that drug administered at one site did not "contaminate" the other site (data not shown). Mock CSF (7) was pumped through the dialysis probes at 10 μL/min.

Each animal received both free or soluble opioid and liposome-encapsulated opioid. The free drug was always administered first and followed 4.5 h later by the liposomal preparation of the same opioid. At 4.5 h, most of the free or soluble drugs were cleared from the epidural space, the intrathecal space, and the systemic circulation (Fig. 1). Therefore, although some insignificant levels of residual morphine or sufentanil may have been present at the time of liposome-formulated drug administration, they did not contribute significantly to our experimental results. Each drug (1 mg morphine and 60 μg sufentanil) in a volume of 1 mL was injected by hand over 2 min, one drug at the thoracic site and the other at the lumbar site. The site at which each (morphine and sufentanil) opioid was administered (i.e., lumbar versus thoracic) was alternated between experiments.

At time 0 (or 270 min), the study drug (free or liposome encapsulated) was injected into the epidural space. Epidural and intrathecal samples were collected into scintillation vials every 5 min (50 μL samples) for 1 h and every 10 min (100-μL samples) for an

Table 1. *In Vivo* Kinetic Variables for Small Lipid/Opioid Ratio Liposomes and Free Opioid

	$t_{1/2\beta}$ (min)		C_{max} (μg/mL)		Time to C_{max} (min)		$AUC_{(0–240\ min)}$ ($\mu g \cdot min^{-1} \cdot mL$)	
Compartment	Free	Liposomal	Free	Liposomal	Free	Liposomal	Free	Liposomal
Morphine								
Epidural	41 ± 11*	119 ± 47*	59 ± 34*	8.4 ± 4.7*	5.6 ± 1.8*	34 ± 24*	1,333 ± 609*	841 ± 636*
Intrathecal	48 ± 21*	95 ± 50*	2.8 ± 1.9*	0.7 ± 1.0*	26 ± 13*	52 ± 16*	190 ± 121*	93 ± 90*
Plasma	64 ± 10*	135 ± 81*	0.0133 ± 0.0053*	0.0042 ± .002*	9 ± 4.8*	63 ± 28*	1.0 ± 0.3*	0.5 ± 0.3*
Sufentanil								
Epidural	185 ± 159	144 ± 35	0.42 ± 0.1*	0.09 ± 0.08*	7 ± 3.5*	22 ± 17*	11 ± 6.8	11 ± 12
Intrathecal	96 ± 55	160 ± 102	0.093 ± 0.24	0.02 ± 0.04	21 ± 18	32 ± 20	2.0 ± 3.9	2.0 ± 2.9
Plasma	119 ± 39	287 ± 136*	0.0006 ± 0.0003*	0.0003 ± 0.0002*	6.2 ± 5.7*	59 ± 37*	0.03 ± 0.01	0.042 ± 0.02

$t_{1/2\beta}$ = apparent terminal half-life; AUC = area under the curve.
* $P \leq 0.05$ for animals treated with liposome versus free or soluble drug formulation.

Table 2. *In Vivo* Pharmacokinetic Variables for Large Lipid/Opioid Ratio Liposomes and Free Opioid

	$t_{1/2\beta}$ (min)		C_{max} (μg/mL)		Time to C_{max} (min)		$AUC_{(0–240\ min)}$ ($\mu g \cdot min^{-1} \cdot mL$)	
Compartment	Free	Liposomal	Free	Liposomal	Free	Liposomal	Free	Liposomal
Morphine								
Epidural	20 ± 14*	46 ± 45*	177 ± 103*	11 ± 6*	5 ± 0	8 ± 7	1,536 ± 682*	255 ± 128*
Intrathecal	32 ± 28	46 ± 38	22 ± 7*	3.4 ± 1.4*	18 ± 21	21 ± 16	455 ± 124*	115 ± 55*
Plasma	61 ± 21*	83 ± 24*	0.013 ± 0.0034*	0.0027 ± 0.0016*	6 ± 2.2	16.4 ± 14.7	0.9 ± 0.2*	0.4 ± 0.1*
Sufentanil								
Epidural	147 ± 52	178 ± 55	0.58 ± 0.37	0.14 ± 0.01	8 ± 2.7	9 ± 2.4	14.0 ± 7.9	8.4 ± 3.6
Intrathecal	67 ± 20	121 ± 69	0.081 ± 0.078	0.016 ± 0.018	14.0 ± 8.2	22 ± 7	3.3 ± 1.7	1.7 ± 1.5
Plasma	136 ± 90	300 ± 129	0.0004 ± 0.0003	0.0001 ± 0.00002	2.6 ± 1	66 ± 57	0.027 ± 0.01*	0.021 ± 0.006*

$t_{1/2\beta}$ = apparent terminal half-life; AUC = area under the curve.
* $P \leq 0.05$ for animals treated with liposome versus free or soluble drug formulation.

additional 3 h after each injection. Arterial blood samples (3–4 mL) were collected at 0, 2, 5, 10, 20, 40, 60, 90, 120, 150, 180, and 240 min.

To determine drug concentrations in dialysate samples, 5 mL of Hydrofluor scintillation fluid was added to the samples. The samples were counted in a Packard liquid scintillation counter (Tri-Carb 2000; Packard, Downers Grove, IL) for 15 min or until the SD of disintegrations per minute was ≤2%. All samples were corrected for background.

Morphine concentration in plasma was analyzed by a selected-ion monitoring gas chromatography/mass spectrometry method originally described by Grinstead (8) (gas chromatograph model HP5890II with an HP-5MS column; mass spectrometry model HP5989A; Hewlett-Packard Co., Wilmington, DE). In our laboratory, the recovery of morphine from plasma after extraction was 95%, with a detection limit of 1.0 ng/mL and a between-run coefficient of variation of <8% between 35 and 150 ng/mL.

Quantitation of sufentanil in plasma was performed with the same gas chromatography/mass spectrometry instruments described previously by using the procedure reported by Woestenborghs et al. (9). In our laboratory, the recovery of sufentanil from plasma was 85%, with a detection limit of 0.03 ng/mL and a between-run coefficient of variation of 10% at 0.5 ng/mL.

The area under the concentration-time curves ($AUC_{0–240\ min}$) was calculated from the time of epidural drug administration to the last sample collected (240 min) in the epidural, intrathecal, and plasma compartments by using the linear trapezoidal rule (10). The terminal half-life ($t_{1/2\beta}$) of free and liposome formulations were derived from the first-order terminal phase of the concentration-time profiles. For the epidural and intrathecal compartments, the apparent $t_{1/2\beta}$ reflects the drug disappearance rate from each compartment and is not intended to estimate metabolic clearance of the drug from the systemic circulation. A minimum of five data points in the log-linear terminal phase of each profile were used to estimate half-lives.

All data are expressed as mean ± SD. Because free drug and liposomally encapsulated drug were always administered to the same animal during the same experimental session, Student's paired *t*-test (two tailed) was used to compare the pharmacokinetics of free drug with that of liposomally encapsulated drug.

Because the large lipid/opioid ratio liposomes and the small lipid/opioid ratio liposomes were studied in

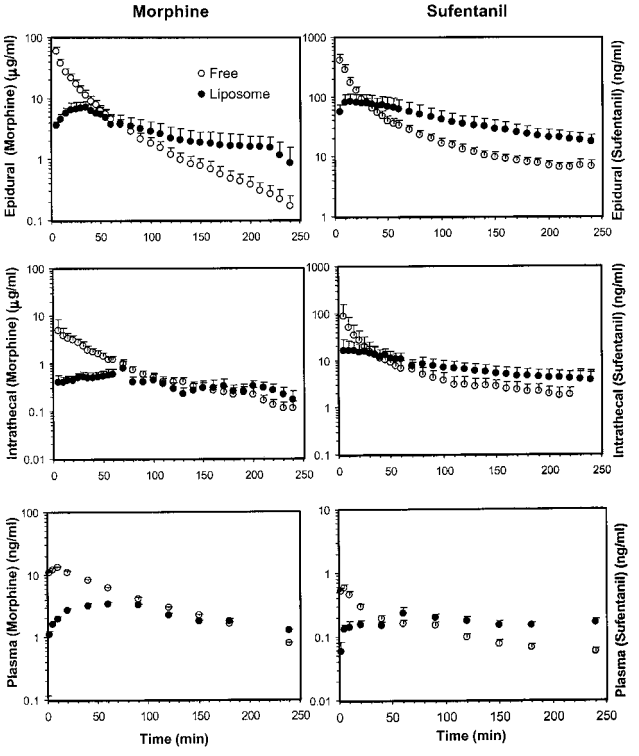

Figure 1. Concentration-time profiles after a single epidural dose of free or soluble (○) and liposomal (●) morphine sulfate and sufentanil. Liposomes with small lipid/drug ratios were given to these animals. Data for epidural, and intrathecal compartments are derived from microdialysis dialysates and represent free drug (i.e., unbound to protein or liposomes). Data points represent the mean and SEM from 10 individual pig studies.

different animals, we normalized the effect of liposomal formulation in each animal by comparing encapsulated drug with unencapsulated drug in that animal (e.g., epidural AUC of free drug divided by AUC of encapsulated drug). Differences between liposome formulations were then assessed by Student's unpaired *t*-test (two tailed). Differences for all statistical tests were considered significant for $P < 0.05$.

Results

The efficiency of drug incorporation into the liposomes was significantly greater for sufentanil (the most lipophilic opioid tested) (99% ± 5%) than for the other three drugs that did not differ from one another (morphine, 30% ± 5%; alfentanil, 25% ± 6%; fentanyl, 30% ± 4%). However, sufentanil was also released more rapidly ($t_{1/2}$ = 27.7 ± 1.8 h) than fentanyl ($t_{1/2}$ = 54 ± 1.2 h) and alfentanil ($t_{1/2}$ = 46.2 ± 4.2 h), which were both released more rapidly than morphine ($t_{1/2}$ = 1038 ± 408 h). Because sufentanil and morphine represented the extreme in encapsulation efficiency, *in vitro* liposome release rates, and lipid solubility, we chose these opioids for further testing in the *in vivo* pig model.

Figure 1 shows the mean (n = 10) concentration-time profiles in epidural, intrathecal, and plasma compartments after epidural administration of free and small lipid/opioid ratio liposomal formulations of morphine and sufentanil. As expected, when administered as free drug, morphine and sufentanil reached maximum concentrations (C_{max}) rapidly in all compartments (within 10 min), followed by an immediate decline. When administered in liposomes, morphine concentrations increased significantly more slowly in the epidural space, intrathecal space, and plasma to reach C_{max} between 30 and 60 min. For sufentanil, liposomal encapsulation also resulted in a significantly slower increase to C_{max} in plasma and epidural compartments, but not in the intrathecal compartment (Table 1).

Liposomal encapsulation also altered the magnitude of C_{max} (Table 1). Compared with free morphine, liposome-encapsulated morphine produced a C_{max} that was significantly smaller in all three sampled compartments. For sufentanil, liposome encapsulation resulted in statistically significant reductions in C_{max} only in the epidural and plasma compartments.

For morphine, liposome encapsulation resulted in a significant increase in apparent $t_{1/2\beta}$ from all three compartments (Table 1). In contrast, liposomal encapsulation did not increase $t_{1/2}$ significantly for sufentanil. Consistent with these findings, epidural, intrathecal, and plasma $AUC_{(0-240\ min)}$ values were significantly smaller for the liposomal formulation of morphine compared with free morphine, indicating that 40%–50% of the morphine initially loaded into the liposomes remained there after 6 h. For sufentanil, $AUC_{(0-240\ min)}$ values in epidural, intrathecal, and plasma compartments were nearly equal for free and liposomal drug formulations (Table 1). Thus, all the liposome-associated sufentanil became bioavailable within the 240-min experimental period.

An additional pharmacokinetic difference between free and liposomally encapsulated drug is that free drug concentrations decreased in a biphasic manner, whereas liposomally encapsulated drug concentrations decreased in a slower, monophasic manner after C_{max} levels were reached.

Table 2 shows the within-animal comparisons between free opioid and large lipid/opioid ratio liposomes. As with the small lipid/opioid ratio liposomes, morphine encapsulation in the high lipid content liposomes significantly decreased the AUC_{240} and C_{max} in all compartments compared with the free drug. The apparent $t_{1/2\beta}$ was also increased in all compartments, but the differences reached statistical significance only in the epidural and plasma compartments. It is interesting that, unlike the small lipid liposomes, encapsulation in the large lipid content liposomes did not significantly increase the time to C_{max} for morphine in any compartment. For sufentanil, encapsulation in the

high lipid content liposomes had no significant effect on any pharmacokinetic variable in any compartment, except AUC_{240}, which was slightly but significantly less in the plasma compartment.

The more interesting and novel question addressed in this study is whether increasing the lipid/opioid ratio altered drug disposition between compartments. For morphine, increasing the lipid/opioid ratio significantly increased intrathecal AUC_{240} relative to that in the epidural space, suggesting more drug transfer from the epidural to the intrathecal space for the large lipid liposomes (Table 3). Intrathecal C_{max} relative to plasma C_{max} was significantly decreased for the large lipid/opioid ratio liposomes compared with the small lipid/opioid ratio liposomes, a finding consistent with relatively larger drug transfer into the intrathecal space relative to the plasma space. In contrast, increasing the lipid content of sufentanil liposomes did not affect the distribution of sufentanil between epidural and intrathecal spaces. However, increasing the lipid content did significantly decrease plasma C_{max} relative to both epidural and intrathecal C_{max}, suggesting a decreased drug movement into plasma.

Discussion

The purpose of these studies was to determine the efficiency with which the most commonly used opioids are entrapped within liposomes and to quantify the rate at which they are released *in vitro* and *in vivo*. More important, we sought to determine whether and how liposomal drug encapsulation and lipid/drug ratios alter the pattern of opioid distribution among epidural, intrathecal, and plasma compartments after epidural administration. An important point to bear in mind is that continuing studies in our laboratory have confirmed that there is no sequencing effect when making two consecutive injections into the pig epidural space (data not shown).

The *in vitro* data demonstrate that all four opioids studied can be entrapped in MLV with varying efficiency. We had anticipated that hydrophobicity would be the most important determinant of incorporation efficiency. However, the fact that morphine, alfentanil, and fentanyl (octanol/buffer distribution coefficients of 1, 129, and 955, respectively) had comparable incorporation efficiencies (25%–30%) suggests that this was not the case. It is noteworthy that sufentanil (octanol/buffer distribution coefficient of 1737) did have the highest incorporation efficiency (100%). The reason for this is unclear. It may be that the effect of hydrophobicity on opioid entrapment is a threshold phenomenon. That is, hydrophobic character may have little influence on entrapment efficiency below a certain threshold value, which is exceeded by sufentanil but not by the other opioids.

Hydrophobicity appears to have a clearer effect on the rates at which the tested opioids were released from liposomes *in vitro*. Morphine, the most hydrophilic drug, had the slowest release rate, whereas sufentanil, the most hydrophobic drug, exhibited the fastest release rates. Alfentanil and fentanyl, with intermediate octanol/buffer distribution coefficients, had intermediate release rates. These findings may offer some insight into the distribution of these opioids in liposomes. Specifically, given morphine's high aqueous solubility, it is likely that it is entrapped within the aqueous interior of the liposome. Egress from the liposome would require that morphine traverse multiple lipid bilayers, which would be expected to be a slow process given morphine's hydrophilic character. In contrast, sufentanil would be expected to preferentially partition into the lipid bilayers. Because the outermost lipid bilayers have the largest volume, they should contain the largest amount of sufentanil; consequently, sufentanil's release should be rapid.

Consistent with its behavior in the *in vitro* arm of the study, sufentanil was released more rapidly *in vivo* than was morphine. The fact that AUCs for sufentanil were not different in any compartment indicates that all of the encapsulated sufentanil had been released over the 240-minute study period. In contrast, less than half of the encapsulated morphine had been released over the same time period. As with morphine, the monoexponential decrease in sufentanil concentration in each compartment and the lack of secondary peaks suggest that the drug was released at a relatively constant rate. It is not clear why encapsulation in large lipid/opioid ratio liposomes did not also alter sufentanil's C_{max} or the time required to reach C_{max} in the epidural space. The most likely explanation is that a larger proportion of the encapsulated sufentanil resides in the outer lipid bilayers in these large lipid/opioid ratio liposomes and is therefore more rapidly released into the epidural space.

The most striking and novel finding of this study relates to the effect of increasing the liposomal lipid/opioid ratio on drug movement between compartments. For morphine, increasing the lipid content resulted in a significantly larger transfer of drug into the intrathecal compartment relative to the amount of drug present in the epidural compartment over the same time period. The mechanism for this is unclear, but previous *in vitro* studies by Bernards and Kern (11) and Ummenhofer and Bernards (12) provide a possible explanation. These investigators demonstrated that esters of fatty acids (including palmitate from which our liposomes were prepared) increase the meningeal permeability of hydrophilic drugs (e.g., morphine) but not hydrophobic drugs (e.g., sufentanil) *in vitro*. Given that there was significantly more dipalmitoyl phosphatidylcholine present in the large

Table 3. Effect of Lipid/Opioid Ratio on Intercompartmental Pharmacokinetic Variables

	Intrathecal/epidural AUC ratio		Plasma/intrathecal AUC ratio		Plasma/epidural AUC ratio	
Lipid/opioid ratio	Morphine	Sufentanil	Morphine	Sufentanil	Morphine	Sufentanil
Small	0.14 ± 0.14*	0.13 ± 0.13	4.39 ± 2.11	0.15 ± 0.15	0.98 ± 0.57	0.02 ± 0.03
Large	0.486 ± 0.167	0.19 ± 0.12	3.85 ± 0.93	0.07 ± 0.07	0.86 ± 0.50	0.003 ± 0.001
	Intrathecal/epidural C_{max} ratio		Plasma/intrathecal C_{max} ratio		Plasma/epidural C_{max} ratio	
	Morphine	Sufentanil	Morphine	Sufentanil	Morphine	Sufentanil
Small	0.14 ± 0.13*	0.13 ± 0.11	4.24 ± 2.2*	0.09 ± 0.08*	0.60 ± 0.37	0.01 ± 0.01*
Large	0.36 ± 0.15	0.15 ± 0.06	0.93 ± 0.73	0.04 ± 0.04	0.93 ± 0.73	0.00082 ± 0.00019

* $P < 0.5$ for small lipid/opioid ratio liposomes compared with large lipid/opioid ratio liposomes.
AUC = area under the curve.

lipid content liposomes, it is possible that fatty acid esters released from the liposomes could have partitioned into the arachnoid matter, thereby increasing local meningeal permeability. Increased meningeal permeability is one possible explanation for the observation that morphine content was larger in the intrathecal space relative to the epidural space for large lipid content liposomes. Regardless of the mechanism, the potential clinical significance of this finding is that encapsulation of morphine in appropriately formulated liposomes may offer a mechanism to both prolong the drug's duration of action as well as increase the fraction of drug reaching the intrathecal space while simultaneously reducing the relative amount of drug reaching the plasma.

It is interesting to note that increasing the lipid content of the sufentanil liposomes resulted in a significant decrease in plasma C_{max} relative to both the epidural and intrathecal spaces. The mechanism for this is unclear. However, if confirmed in humans, the significance of this finding is that encapsulation of sufentanil in large lipid content liposomes may offer a way to decrease systemic uptake relative to intrathecal transfer and thereby decrease systemic side effects that are related to peak drug concentration.

In conclusion, we found that liposomal encapsulation of morphine resulted in a sustained release preparation that prolonged the drug's presence in plasma, epidural, and intrathecal compartments. In contrast, liposomal encapsulation of sufentanil did not result in an important prolongation of the drug's presence in any sampled compartment. However, encapsulation in high lipid content liposomes did reduce plasma C_{max} relative to C_{max} in the other compartments. More important was our finding that liposome composition does not simply affect the rate at which a drug becomes bioavailable in the epidural space; it can also alter the intercompartmental distribution of the drug after it is released. This finding suggests a novel method to effect some control over the relative distribution of epidurally administered drugs.

References

1. Boogaerts J, Lafont N, Carlino S, et al. Biodistribution of liposome-associated bupivacaine after extradural administration to rabbits. Br J Anaesth 1995;75:319–25.
2. Bernards C, Luger T, Malmberg A, et al., Liposome encapsulation prolongs alfentanil spinal analgesia and alters systemic redistribution in the rat. Anesthesiology 1992;77:529–35.
3. Yaksh T, Provencher J, Rathbun M, et al. Pharmacokinetics and efficacy of epidurally delivered sustained-release encapsulated morphine in dogs. Anesthesiology 1999;90:1402–12.
4. Wallace M, Yanez A, Ho RJY, et al. Antinociception and side effects of liposome-encapsulated alfentanil after spinal delivery in rats. Anesth Analg 1994;79:778–86.
5. Kohn F, Malkmus S, Brownson E, et al. Fate of the predominate phospholipid component of DepoFoam drug delivery matrix after intrathecal administration of sustained-release encapsulated cytarabine in rats. Drug Delivery 1998;5:143–51.
6. Ummenhofer WC, Arends RH, Shen DD, Bernards CM. Comparative spinal distribution and clearance kinetics of intrathecally administered morphine, fentanyl, alfentanil, and sufentanil. Anesthesiology 2000;92:739–53.
7. Bui T, Faltynek C, Ho RJY. Differential disposition of soluble and liposome-formulated human recombinant interleukin-7: effects on blood lymphocyte population in guinea pigs. Pharm Res 1994;11:633–41.
8. Grinstead GF. A closer look at acetyl and pentafluoropropionyl derivatives for quantitative analysis of morphine and codeine by gas chromatography/mass spectrometry. J Anal Toxicol 1991;15:293–8.
9. Woestenborghs R, Michielsen L, Heykants J. Rapid and sensitive gas chromatographic method for the determination of alfentanil and sufentanil in biological samples. J Chromatogr 1981;224:122–7.
10. Gibaldi M. Clinical pharmacokinetics. 3rd ed. Philadelphia: Lea & Febinger, 1984:315–6.
11. Bernards CM, Kern C. Palmitoyl carnitine increases the transmeningeal flux of hydrophilic but not hydrophobic compounds in vitro. Anesthesiology 1996;84:392–6.
12. Ummenhofer WC, Bernards CM. Acylcarnitine chain length influences carnitine-enhanced drug flux through the spinal meninges in vitro. Anesthesiology 1997;86:642–8.