A Mixed (Long- and Medium-chain) Triglyceride Lipid Emulsion Extracts Local Anesthetic from Human Serum *In Vitro* More Effectively than a Long-chain Emulsion

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ABSTRACT

Background: Lipid emulsion infusion reverses cardiac toxicity of local anesthetics. The predominant effect is likely creation of a "lipid sink." This *in vitro* study determined the extent to which Intralipid® (Fresenius Kabi, Uppsala, Sweden) and Lipofundin® (B. Braun Melsungen AG, Melsungen, Germany) sequester anesthetics from serum, and whether it varies with pH.

Methods: Bupivacaine, ropivacaine, and mepivacaine were added to human drug-free serum (pH 7.4) at 10 μg/ml. The lipid emulsions were added, and the mixture shaken and incubated at 37°C. Lipid was removed by ultracentrifugation and drug remaining in the serum measured. Additional experiments were performed using 100 μg/ml bupivacaine and at pH 6.9.

Results: Lipofundin® extracted all three anesthetics to a greater extent than Intralipid® (34.7% *vs.*.22.3% for bupivacaine, 25.8% *vs.*.16.5% for ropivacaine, and 7.3% *vs.*.4.7% for mepivacaine). By increasing either concentration of bupivacaine or lipid, there was an increase in drug extraction from serum. Adjusting the pH to 6.9 had no statistically significant effect on the percentage of bupivacaine sequestered.

Conclusions: Bupivacaine, ropivacaine, and mepivacaine were sequestered to an extent consistent with their octanol: water partition constants (logP). In contrast with previous studies of extraction of lipids from buffer solutions, an emulsion containing 50% each of medium- and long-chain triglycerides extracted local anesthetics to a greater extent from human serum than one containing exclusively long-chain triglycerides, calling into question recent advanced cardiac life support guidelines for resuscitation from anesthetic toxicity that specify use of a long-chain triglyceride. The current data also do not support recent recommendations to delay administration until pH is normalized.

What We Already Know about This Topic

- A lipid emulsion containing only long-chain triglycerides extracts local anesthetics from pH 7.4 buffer more effectively than one containing both medium- and long-chain triglycerides
- Lipid extraction of local anesthetics from buffer was impaired at pH 7.0

What This Article Tells Us That Is New

- A lipid emulsion containing both medium- and long-chain triglycerides extracts local anesthetics from pH 7.4 serum more effectively than one containing only long-chain triglycerides
- Lipid extraction of local anesthetic from serum increased with increased local anesthetic or lipid concentration and was unaffected at pH 6.9

INCREASED bupivacaine plasma concentrations can lead to fatal cardiac toxicity. In experiments conducted by Weinberg *et al.*, both the dose and serum concentration of bupivacaine required to produce asystole were increased in rats pretreated with Intralipid® (Fresenius Kabi, Uppsala, Sweden) in comparison with control rats.[1] In addition, the dose–response curve for resuscitation was shifted to the right,

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and successful resuscitation of rats after a 15 mg/kg dose of bupivacaine was 0% in control rats and 100% in the Intralipid® infused group. This observation of lipid reversal of bupivacaine toxicity was further confirmed by systematic studies in dogs.[2]

In 2006, 8 yr after the original documentation of effect, two independent and almost-simultaneous case reports delivered this lipid therapy into clinical practice. One described a prolonged cardiac arrest attributed to bupivacaine and mepivacaine,[3] the other solely ropivacaine,[4] both ending with successful resuscitation after infusion of Intralipid®, instituted based on the reading of the experimental work from Weinberg's laboratory. This was followed by a spate of case reports describing similar scenarios with these and other local anesthetic drugs including levobupivacaine,[5–9] as well as central nervous system toxicity induced by local anesthetics.[8,10]

Although the mechanism of action of this phenomenon has not yet been fully elucidated, it is generally accepted that the predominant effect results from the fat emulsion forming a "lipid sink" that causes the drug to be absorbed out of the serum, drawing it away from the target sites of action. A previous *in vitro* study examining the solubility of local anesthetics in Intralipid® reported a high binding capacity of this emulsion,[11] consistent with its postulated efficacy of reversing toxicity induced by these drugs. This previous report also found Intralipid®, a lipid emulsion containing long-chain triglycerides, to be more effective at binding local anesthetics than Medialipide® (different trade name for Lipofundin®; B. Braun Melsungen AG, Melsungen, Germany), a lipid emulsion containing both medium-chain and long-chain triglycerides. These investigators also found that decreasing the pH of the solution from 7.4 to 7.0 impaired lipid extraction of anesthetic. However, an important limitation of this study was that bupivacaine was extracted from a buffer solution, rather than serum. Another *in vitro* study showed Intralipid® could sequester bupivacaine out of plasma obtained from EDTA anticoagulated blood.[12] However, the plasma had been diluted to 20%, and the concentration of bupivacaine (100 μg/ml) was relatively excessive with respect to common parameters of clinical toxicity. Surprisingly, this latter study did not observe a decrease in residual plasma bupivacaine with the use of a higher concentration of lipid.

Accordingly, the current investigation was undertaken to determine the relative extraction capability of a mixed (medium- and long-chain triglyceride) *versus* a long-chain lipid emulsion; whether there is an increase in extraction with increasing lipid or drug concentration; and whether variations in pH within the clinically relevant range affect lipid sequestration of anesthetic in human serum, as opposed to buffer or diluted human plasma as has been previously studied.

Materials and Methods

Materials

Human drug-free serum was obtained from Biologic Specialty Corporation (Comlar, PA). Bupivacaine, mepivacaine, ropivacaine were obtained from AstraZeneca PLC (Wilmington, DE), 20% Intralipid® was obtained from Fresenius Kabi (Uppsala, Sweden) and 20% Lipofundin® was obtained from B. Braun Melsungen AG (Melsungen, Germany). Each of these two lipid formulations are used for parenteral nutrition. Intralipid® contains exclusively long-chain triglycerides (more than 12 carbon chains), whereas Lipofundin® contains both medium-chain (6–12 carbon chains) and long-chain triglycerides (by weight, 50% of each).

The Airfuge® ultracentrifuge was from Beckman Coulter (Brea, CA). Solid-phase extraction Oasis® MCX columns were obtained from Waters Corporation (Milford, MA). The ZORBAX Eclipse XDB-C18, 4.6 × 150 mm, 5-μm column was purchased from Agilent Technologies (Santa Clara, CA) and was used in conjunction with a 1090 HPLC system with an ultraviolet/visible diode array detector from Hewlett Packard (Santa Clara, CA).

Sample Preparation

Bupivacaine, ropivacaine, or mepivacaine were added to human drug-free serum (pH 7.4) at a concentration of 10 μg/ml. 20% Intralipid® or 20% Lipofundin® were added at 1, 2, or 4% of the total volume because the recommended dosage of lipid bolus to treat anesthetic overdose is 1.5 ml/kg,#**[13] equating to approximately 3.5% of the total serum volume of the body. Multiple concentrations were used to determine the effect with respect to the volume of lipid. Once the lipid was added to the serum containing the drug, the samples were vortexed. They were then incubated at 37°C for 5 min in a water bath, and then shaken at 37°C for 5 min to ensure adequate mixing. The contents of each tube were then subjected to ultracentrifugation at room temperature using an Airfuge® at 122,000 g under 30,000 psi to separate the serum from the lipid. Serum was transferred into a fresh tube for analysis. Bupivacaine was also added at a concentration of 100 μg/ml to human drug-free serum at pH 7.4, the lipid emulsions were added, and the samples were prepared in a similar fashion. In a separate experiment using the same methodology, bupivacaine was added at 10 μg/ml to human drug-free serum at pH 6.9. Each experiment was carried out in triplicate, and the mean percent (%) decrease in serum drug concentration was calculated as the mean % decrease in the area under the curve of the chromatographic peak of the local anesthetic being studied, divided by the area under the curve of the internal standard chromatographic peak.

Solid-phase Extraction

The serum containing the drug and a specific internal standard (table 1) was added onto Oasis® MCX columns pre-

Association of Anaesthetists of Great Britain and Ireland. Guidelines for the Management of Severe Local Anesthetic Toxicity. Available at: http://www.aagbi.org/sites/default/files/la_toxicity_2010_0.pdf. Accessed August 8, 2011.

** Resuscitation Council of the United Kingdom. Cardiac arrest or cardiovascular collapse caused by local anesthetic. Available at: http://resuscitation-guidelines.articleinmotion.com/article/S0300-9572(10)00441-7/fulltext#section–local-anaesthetics. Accessed August 8, 2011.

Table 1. High-performance Liquid Chromatography Parameters

Drug Name	Internal Standard	Mobile Phase	Flow Rate (ml/min)
Mepivacaine	Ropivacaine	0.1 M K_2HPO_4:ACN (55:45) pH9.0	3.0
Ropivacaine	Bupivacaine	0.1 M K_2HPO_4:ACN (55:45) pH7.2	2.5
Bupivacaine	Ropivacaine	0.1 M K_2HPO_4:ACN (55:45) pH7.2	2.5

ACN = acetonitrile; K_2HPO_4 = potassium phosphate, dibasic.

treated with methanol and water. Columns were washed once with 2% formic acid in water and twice with methanol. The drug was eluted with 5% ammonium hydroxide in methanol and evaporated to dryness with nitrogen in a 35°C water bath. It was then reconstituted in 100 μl of mobile phase (table 1). The recovery of bupivacaine after solid phase extraction was approximately 95%.

High-performance Liquid Chromatography

Twenty microliters of the eluate containing the drug was injected onto the C18 column using isocratic elution with a defined mobile phase and flow rate (table 1). The drugs and internal standards were detected using diode array detection at 230 nm.

Statistical Analysis

Two-tailed, two-sample Student *t* test with equal variance was used to compare the extent to which each lipid decreased the serum concentration of each drug. The mean, SD, coefficient of variation, and the 95% CI of the mean for three replicate measurements were calculated. In addition, the % of lipid added was plotted against the % decrease in serum bupivacaine concentration, and linear regression analysis was carried out to determine the correlation (R^2 value) between these variables. Statistical analyses were performed using the statistical environment R2.12.2 (R Development Core Team, Microsoft Office Excel 2003; Microsoft Corporation, Redmond, WA) and GraphPad QuickCalcs software (GraphPad Software Incorporated, La Jolla, CA). Statistical significance was designated as $P < 0.05$.

Results

Intralipid® versus Lipofundin® at a Drug Concentration of 10 μg/ml

Using 2% Intralipid®, there was a 22.3% (95% CI: 20.7–23.9%), 16.5% (95% CI: 12.4–20.6%) and 4.7% (95% CI: 1.9–7.4%) decrease in serum drug concentration of bupivacaine, ropivacaine, and mepivacaine, respectively (table 2). The between-day (n = 3) SD of decrease in drug concentration was ≤1.7% for all three drugs.

Using 2% Lipofundin®, there was a 34.7% (95% CI: 32.2–37.0%), 25.8% (95% CI: 22.7–28.8%), and 7.3% (95% CI: 4.7–10.0%) decrease in serum drug concentration of bupivacaine, ropivacaine, and mepivacaine, respectively. The between-day (n = 3) SD of decrease in drug concentration was ≤1.2% for all three drugs. Lipofundin® sequestered all three drugs to a significantly greater extent than Intralipid®; bupivacaine = 34.7% *versus* 22.3% ($P < 0.0001$), ropivacaine = 25.8% *versus* 16.5% ($P = 0.001$), and mepivacaine = 7.3% *versus* 4.7% ($P = 0.039$).

There was a proportional corresponding increase in the % decrease in serum concentration of the bupivacaine with the addition of higher concentrations of Intralipid® or Lipofundin® (fig. 1). In addition, Lipofundin® sequestered bupivacaine to a significantly greater extent than Intralipid® at each % of lipid measured; 1% lipid = 17.1% *versus* 22.3% ($P < 0.0001$), 2% lipid = 22.3% *versus* 34.7% ($P < 0.0001$), and 4% lipid = 40.0% *versus* 46.4% ($P < 0.0004$). The between-day (n = 3) SD of decrease in drug concentration was ≤0.7% at 1, 2, and 4% Intralipid® and <1% at 1, 2, and 4% Lipofundin®.

Effect of pH on Intralipid® and Lipofundin® Sequestering Bupivacaine out of Serum

At pH 7.4, the serum bupivacaine concentration decreased by 22.3% upon the addition of 2% Intralipid® (95% CI: 20.7–23.9%) and 34.7% upon the addition of 2% Lipofundin® (95% CI: 32.2–37.0%). At pH 6.9, the serum bupivacaine concentration decreased by 23.4% upon the addition of 2% Intralipid® (95% CI: 21.2–25.6%) and 33.8% upon the addition of 2% Lipofundin® (95% CI: 31.6–35.9%). There was no statistically significant difference between the results at

Table 2. Serum Drug Concentration Decrease after Addition of Intralipid® (Fresenius Kabi, Uppsala, Sweden) or Lipofundin® (B. Braun Melsungen AG, Melsungen, Germany)

		% Decrease in Serum Drug Concentration							
Drug	Partition Constant (logP)*	2% Intralipid®	95% CI (%)†	SD (%)‡	CV (%)§	2% Lipofundin®	95% CI (%)†	SD (%)‡	CV (%)§
Mepivacaine	1.9	4.7	1.9–7.4	1.1	23.4	7.3	4.7–10.0	1.0	13.7
Ropivacaine	2.9	16.5	12.4–20.6	1.7	10.0	25.8	22.7–28.8	1.2	4.7
Bupivacaine	3.4	22.3	20.7–23.9	0.7	2.9	34.7	32.2–37.0	1.0	2.8

* Partition constant (measure of the differential solubility of a compound in octanol and water).[14] † 95% CI (%) of the mean calculated using three replicate measurements. ‡ SD calculated based upon three replicate measurements. § Coefficient of variation calculated based upon the mean and the standard deviation of three replicate measurements.

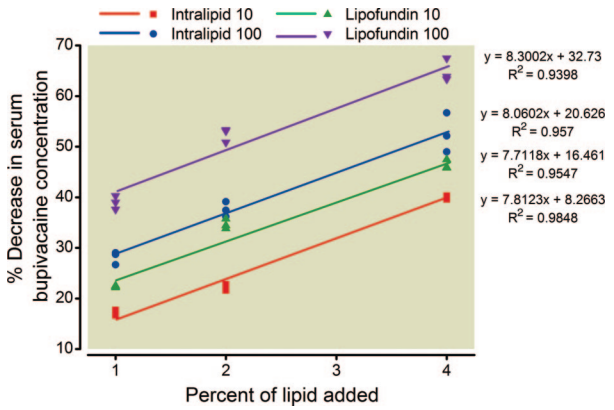

Fig. 1. Serum bupivacaine concentration decreases after addition of Intralipid® (Fresenius Kabi, Uppsala, Sweden) and Lipofundin® (B. Braun Melsungen AG, Melsungen, Germany) with varying starting bupivacaine concentrations (10 and 100 μg/ml) and varying % of lipid added (1, 2, or 4% of total volume). Intralipid 10 = Intralipid® with 10 μg/ml bupivacaine, Intralipid 100 = Intralipid® with 100 μg/ml bupivacaine, Lipofundin 10 = Lipofundin® with 10 μg/ml bupivacaine, and Lipofundin 100 = Lipofundin® with 100 μg/ml bupivacaine.

the different pH values for Intralipid® (22.3% *vs.* 23.4%; $P = 0.17$) and Lipofundin® (34.7% *vs.* 33.8%; $P = 0.31$), respectively. The between-day (n = 3) SD of decrease in drug concentration was ≤ 0.98% for both Intralipid® and Lipofundin®.

Effect of Increasing Bupivacaine Concentration on Intralipid® and Lipofundin® Sequestration

At 10 μg/ml bupivacaine, the decrease in the serum bupivacaine concentration was 17.1% (95% CI: 15.8–18.4%), 22.3% (95% CI: 20.7–23.9%), and 40.0% (95% CI: 39.1–41.0%) when 1, 2, or 4% Intralipid®, respectively, was added (fig. 1). At 100 μg/ml bupivacaine, the decrease in the serum bupivacaine concentration was 28.1% (95% CI: 25.0–31.3%), 37.6% (95% CI: 33.9–41.2%), and 52.6% (95% CI: 43.0–62.2%) when 1, 2, or 4% Intralipid®, respectively, was added, a significantly larger decrease in bupivacaine concentration than at 10 μg/ml bupivacaine ($P < 0.0002$, $P < 0.0001$, and $P = 0.005$ for 1, 2, and 4% Intralipid®, respectively).

At 10 μg/ml bupivacaine, the decrease in the serum bupivacaine concentration was 22.3% (95% CI: 21.9–22.8%), 34.7% (95% CI: 32.2–37.1%), and 46.4% (95% CI: 44.1–48.7%), respectively, when 1, 2, or 4% Lipofundin®, respectively, was added (fig. 1). At 100 μg/ml bupivacaine, the decrease in the serum bupivacaine concentration was 39.0% (95% CI: 35.7–42.3%), 52.4% (95% CI: 49.0–55.8%), and 64.9% (95% CI: 59.3–70.5%) when 1, 2, or 4% Lipofundin®, respectively, was added; there was a significantly larger decrease in bupivacaine concentration than at 10 μg/ml bupivacaine ($P < 0.0001$, $P < 0.0001$, and $P < 0.0002$ for 1, 2, and 4% Lipofundin®, respectively). In addition, at 100 μg/ml bupivacaine concentration, Lipofundin® sequestered the bupivacaine to a significantly greater extent than Intralipid® at 1, 2, and 4% lipid added; 1% lipid = 39.0% *versus* 28.1% ($P < 0.0006$), 2% lipid = 52.4% *versus* 37.6% ($P < 0.0003$), and 4% lipid = 64.9% *versus* 52.6% ($P = 0.009$). The between-day (n = 3) SD of decrease in drug concentration at 100 μg/ml bupivacaine was ≤3.9% at 1, 2, and 4% Intralipid® and <2.3% at 1, 2, and 4% Lipofundin®.

Table 3. Drug Information

Drug Name	pKa*	logP Value†
Mepivacaine	7.9	1.9
Ropivacaine	8.2	2.9
Bupivacaine	8.2	3.4

* Acid dissociation constant measured at 25°C.[15] † Partition constant (measure of the differential solubility of a compound in octanol and water).[14]

Discussion

We have shown that Intralipid®, and to a significantly greater extent, Lipofundin®, appears to extract bupivacaine, mepivacaine, and ropivacaine, and sequester these drugs out of human serum in an *in vitro* model. The relative degree of extraction was bupivacaine > ropivacaine > mepivacaine, which is as might be predicted based on the partition constants (logP) of these drugs (logP = 3.4, 2.9, and 1.9, respectively; table 3).[14] The logP is a measure of the differential solubility of a compound in octanol and water, and thus is a measure of how hydrophobic a substance is, with higher logP values indicating greater hydrophobicity. Accordingly, we found that to some extent, extraction parallels relative lipophilicity as so determined,[14–15] although there are likely additional as-yet-undetermined factors that determine the utility of lipid in sequestering these drugs, and consequently the ability to reverse clinical toxicity.

In a recently published study, an *in vitro* model was used to determine the binding capacity of Intralipid® and Lipofundin® for bupivacaine and ropivacaine.[11] Using this model, Mazoit *et al.* reported that bupivacaine was sequestered into the lipid emulsions from the experimental buffer (containing sodium chloride, sodium phosphate, and calcium chloride) more efficiently than ropivacaine, and that Intralipid® was more effective than Lipofundin® at sequestering these drugs. The results presented herein thus mirror the relative extraction of bupivacaine and ropivacaine, but differ with respect to the relative effectiveness of Lipofundin® and Intralipid®. The reason for this discrepancy is not obvious, although it might be based on the difference in media, as our model measured the decrease in drug concentration in human serum, rather than buffer, which was used to replicate as closely as possible the "real-life" situation. The most obvious difference between these solutions would be the potential for protein binding in serum, which may differentially affect the results. Other factors may be important; for example, diluting the lipid in buffer may function to stabilize the emulsion by increasing the surface charge of the chylomicron-like droplets,[11] as well as the size of the chylo-

microns formed, the volume/surface area relationship, and the half-life of the chylomicrons in the respective solutions.

Mazoit *et al*. indicated that steady state between the lipid and bupivacaine was reached at approximately 1–3 min of shaking and was not altered when shaken for up to 20 min.[11] In the current study, shaking was carried out for 5 min, and therefore our experiments were likely carried out at steady state. This previous study also reported that the ability of lipid emulsion to bind anesthetic drugs increased when the temperature of the buffer was increased from 20°C to 37°C. Accordingly, the experiments documented here were performed at 37°C, to optimize the clinical relevance of our findings. In addition, in the previous report, when pH was adjusted down from 7.4 to 7.0, the affinity of the lipid emulsion for the anesthetics decreased.[11] Our findings conflict with these data, as we observed that a decrease in pH from 7.4 to 6.9 did not significantly alter the binding capacity of either Intralipid® or Lipofundin® for bupivacaine. Again, the cause of this discrepancy might be related to differences in composition of experimental solutions. For example, a decrease in pH may serve to reduce lipid extraction but this might be counteracted in our model, which incorporates serum rather than buffer, by an associated decrease in the α 1-acid glycoprotein binding of bupivacaine.[16] This effect might allow more free drug to be sequestered by the lipid thus explaining the similar lipid extraction across this range of pH. However, only total drug was measured in this study and not free drug, and further experiments would be required to confirm this mechanism.

Another *in vitro* study described the interaction of bupivacaine with Intralipid® as shown by a decrease in drug concentration in 20% human plasma by 37% and 36.4%, respectively, upon the addition of 1 and 4 mg/ml of the lipid emulsion.[12] The decrease in bupivacaine concentration we observed when serum containing bupivacaine at 10 μg/ml was mixed with 2% Intralipid® concentration (approximately 1.6 mg/ml) was decreased (22.3%), but with 4% Intralipid® (approximately 3.3 mg/ml) the anesthetic extraction was comparable (40.0% decrease in bupivacaine concentration). When we increased the bupivacaine concentration to 100 μg/ml, the concentration used in a previous study, the decrease in bupivacaine concentration with 2% and 4% Intralipid® was 37.6% and 52.6%, respectively. Our results indicate that the greater the concentration of Intralipid®, the more drug is sequestered out of serum (with constant drug concentration), and the greater the drug concentration, the higher percentage extraction by Intralipid® (with constant Intralipid® concentration). Our observation of increased drug extraction with increasing concentration of lipid thus conflicts with this previous *in vitro* study. We cannot explain this discrepancy, but our observation of greater efficacy with higher concentrations of lipid is intuitively attractive, is consistent with the lack of saturation observed with these concentrations of lipid,[11] and is consistent with experimental studies of lipid resuscitation.[1] Our observation of greater extraction at higher bupivacaine concentration might possibly reflect decreasing percentage of protein-bound anesthetic at the higher concentration, as it has been shown that α 1-acid glycoprotein binding is near saturated at our higher bupivacaine concentration.[17]

A limitation of this study is that we measured total drug remaining in the serum after the lipid was removed and not the protein-bound, or indeed free drug. Bupivacaine is approximately 92% protein bound.[18] Based on our data, the addition of 2% Intralipid® would distribute 22% of the bupivacaine into the chylomicrons of the lipid (table 2). Accordingly, we would estimate that approximately 81% of the original total concentration of bupivacaine would be bound to serum proteins, and the remaining 7% is free in the plasma water. Performing the same estimation with ropivacaine, which is roughly 94% protein- bound,[18] approximately 17% would be distributed in the chylomicrons, 78% protein-bound and 5% is free in the plasma water. With respect to mepivacaine, which is only 77% protein-bound,[18] approximately 5% would be distributed in the chylomicrons, 73% protein-bound, and 22% is free in the plasma water after addition of 2% Intralipid®.

Our observation that extraction of bupivacaine with Lipofundin® is more complete than with mepivacaine or ropivacaine is supported by previous reports, and it may help explain the results of a study using an isolated rat heart model.[19] After induction of cardiac arrest by local anesthetic, recovery times of heart rate and rate-pressure product (to 90% of baseline values) were significantly shorter with the administration of Lipofundin® in bupivacaine-induced cardiac toxicity, but not in ropivacaine- or mepivacaine-induced toxicity. Certainly, additional work is required to understand the clinical relevance of such findings.

The apparent efficacy of lipid emulsion in resuscitation after local anesthetic-induced cardiac arrest has been widely reported in the literature, and there is some experimental evidence to suggest it may have an acceptable therapeutic index.[20] Although there is a report of an increased amylase concentration in a patient who made a full recovery (and did not require any further intervention),[21] there have been no reports to date of any apparent long-term significant adverse effects of this therapy. Lipid rescue has already gained the endorsement of professional bodies in their guidelines for treatment of severe local anesthetic drug toxicity,#**[13] as almost all reports document successful outcomes. However, in one case report, Intralipid® failed to reverse central nervous system toxicity during the use of ropivacaine and mepivacaine,[22] and it should be obvious that there is a potential for bias in the published literature in that clinicians might be reticent to report resuscitation failures.

In summary, we have shown that Intralipid® and Lipofundin® sequester bupivacaine, and to a lesser extent ropivacaine and mepivacaine out of serum in an *in vitro* model, in a rank order consistent with their respective partition constants. Lipofundin®, a lipid emulsion containing 50% each

of medium-and long-chain triglycerides, sequestered all three drugs to a significantly greater extent than Intralipid® (long-chain triglycerides only) from human serum, which is in contrast with previous studies describing extraction from a buffer solution. These findings call into question the current advanced cardiac life support guidelines specifying use of a long-chain triglyceride emulsion for lipid rescue,[23] although further *in vivo* studies that confirm a significant improvement in resuscitation from local anesthetic toxicity with Lipofundin® are obviously required before drawing any confident conclusions. In addition, our data suggest that normalization of pH before administration of lipid rescue may not improve drug extraction. There is a growing body of evidence that lipid treatment can be effective for a wide spectrum of toxic drugs that are commonly taken in overdose,[24] for which there are no reliable antidotes, and this model may prove useful to predict how well lipid emulsion sequesters other drugs out of serum.

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