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ORIGINAL CONTRIBUTION

Intravenous Lipid Emulsion Therapy Does Not Improve Hypotension Compared to Sodium Bicarbonate for Tricyclic Antidepressant Toxicity: A Randomized, Controlled Pilot Study in a Swine Model

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Abstract

Objectives: Tricyclic antidepressants (TCAs) are highly lipophilic medications used to treat posttraumatic stress disorder and chronic pain. Intravenous lipid emulsion (ILE) is a recent antidote for lipophilic drug overdose with unclear effectiveness. ILE has been studied in TCA overdose in small animals, and cases are reported in humans, but controlled studies in a larger animal model are lacking. Given the high lipophilicity of amitriptyline, a TCA, the hypothesis was that ILE would be more effective than the standard antidote sodium bicarbonate in improving amitriptyline-induced hypotension. The objective was to determine if ILE improved hypotension (defined by a mean arterial pressure [MAP] < 60% baseline) compared to sodium bicarbonate for amitriptyline overdose in a critically ill porcine model.

Methods: In this prospective, randomized, controlled trial, 24 female *Sus scrofa* swine weighing 45 to 55 kg were infused with amitriptyline at 0.5 mg/kg/min until the MAP reached 60% of baseline values. Animals were randomized to the experimental treatment group (ILE 7 mL/kg bolus, then 0.25 mL/kg/min) or the standard treatment group (sodium bicarbonate 2 mEq/kg plus an equal volume of saline). The primary outcome was a 50% improvement in MAP after ILE administration. We continuously monitored heart rate (HR), systolic blood pressure (sBP), MAP, and cardiac output. Electrocardiograms were recorded every 15 minutes. Serum pH, pCO_2, bicarbonate, lactate, and electrolytes were measured. Amitriptyline levels were measured by liquid chromatography/tandem mass spectrometry. Statistical methods used to detect a difference in MAP between the two treatment groups included repeated-measures analysis of variance, adjusted for treatment, time, and the interaction of treatment by time. A sample size of 12 animals per group provided a power of 0.8 and an alpha of 0.05 to detect a 50% difference in MAP.

Results: There was no difference at baseline between ILE and sodium bicarbonate groups in mean HR, sBP, MAP, or cardiac output. Mean amounts of amitriptyline to reach hypotension and time to hypotension were similar between groups. After hypotension there was no difference between groups for mean HR, sBP, MAP, or cardiac output. The median time from hypotension to death was greater for the sodium bicarbonate group (10 minutes [IQR = 6 to 61 minutes] vs. 5 minutes [IQR = 4.5 to 6 minutes] for the ILE group; p = 0.003), but overall survival was not different. One ILE and four sodium bicarbonate pigs survived. Additionally, no difference was detected in QRS intervals between the two groups. The mean (±SD) amitriptyline level in the lipid layer was 3.34 (±2.12) μg/mL, and in the aqueous layer, 4.69 (±2.44) μg/mL. The ILE fatty layer contained 38.2% of total measurable amitriptyline, while the aqueous layer contained 53.6%.

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Conclusions: Intravenous lipid emulsion treatment failed to improve amitriptyline-induced hypotension when compared to the standard treatment of sodium bicarbonate in a large animal model of severe TCA overdose. Larger groups with better survival may yield different results from the high mortality observed in this pilot study. Similar amounts of amitriptyline were found in the aqueous and lipid layers. These conclusions are limited to a single ILE regimen.

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Intravenous lipid emulsion (ILE), or lipid therapy, is a treatment for cardiotoxicity from highly lipophilic medications such as local anesthetics (bupivacaine), calcium channel antagonists, tricyclic antidepressants (TCA), and others.[1] ILE may act as a fatty "sink" or "compartment" for fat-soluble toxins that distribute into the fat layers away from the active binding sites on target organs where they disrupt critical body processes.[2] ILE may also provide an alternate energy source of fatty acids for the heart under stressed conditions, as well as affect calcium channel function. ILE's effectiveness in severe local anesthetic toxicity has been established, and clinical practice guidelines exist for its use.[3] However, ILE's effectiveness is less clear with other lipophilic agents. Some studies in small, lean animals reported that ILE improved hypotension and prolonged survival, while other reports showed no effect.[4–6] The only available human data are in case reports that are difficult to interpret due to potential confounders.

TCAs are highly lipophilic agents with several indications including depression, chronic pain, and migraine headaches.[7] TCA overdoses account for a large number of overdose fatalities. TCA toxicity includes hypotension, lethal cardiac dysrhythmias, seizures, and coma.[8–11] Refractory hypotension is a common cause of death in TCA-overdosed patients.

Amitriptyline is a TCA with the three-ringed structure, increased protein binding in alkalotic states, and high lipophilicity (octanol/water partition coefficient logP of 4.9), enabling it to cross cell membranes.[12] Given the high lipophilicity of TCAs, we hypothesized that ILE would be more effective than the traditional antidote, sodium bicarbonate, in improving hypotension produced by an amitriptyline overdose. TCAs are lipophilic and may respond to ILE, but to the best of our knowledge, no compelling data have been published in a large animal model.

Therefore, a randomized, controlled study in a large animal model of cardiotoxicity due to a lipophilic agent such as TCAs could provide data regarding the effectiveness of ILE for lipophilic medications other than local anesthetics. The objective of this study was to determine if ILE was more effective in improving hypotension (defined by a mean arterial pressure [MAP] < 60% baseline) compared to sodium bicarbonate for treatment of amitriptyline overdose in a critically ill swine model.

METHODS

Study Design

Using a porcine model of amitriptyline-induced hypotension, we used a randomized parallel group design with two treatment arms: ILE versus the standard antidote, sodium bicarbonate. The care and handling of animals was in accord with the American Association for Accreditation of Laboratory Animal Care guidelines, and our Institutional Animal Care and Use Committee at the Wilford Hall Ambulatory Surgical Center approved their use in this study. The U.S. Air Force Office of the Surgeon General funded the study (FWH20100172A).

Animal Subjects

Twenty-four healthy female swine weighing 45 to 55 kg were sedated and anesthetized throughout the entire protocol. Instrumentation of each swine included placement of an endotracheal tube for ventilation. Invasive hemodynamic variables were measured with an eight-French Swan-Ganz CCOmbo pulmonary artery catheter (Model 746HF8) and the Edwards Vigilance II monitor (Edwards Lifesciences). Measurements included continuous cardiac output, systemic vascular resistance (SVR), mixed venous oxygen saturation (SvO_2), central venous pressure (CVP), pulmonary artery pressure, and core temperature. The catheter ports were flushed with saline, and the catheter was placed via cut-down in the right internal jugular vein. Aortic pressure was measured continuously through the femoral artery with a Millar catheter (Millar Instruments). An 8.5-French introducer (Arrow, Reading, PA) was placed in the carotid artery for laboratory sampling, and another was placed in the femoral vein for medication administration.

Baseline values were obtained for serum electrolytes, complete blood cell count, and amitriptyline levels, as well as arterial blood gases for pH, partial pressure of carbon dioxide (pCO_2), bicarbonate, and lactate. Venous samples were obtained at hypotension and at subsequent 15-minute intervals to measure changes in serum electrolytes and lactate. Additionally, a baseline electrocardiogram (ECG) was performed to document QRS and QTc interval measurements. Temperature was maintained for all animals between 36.8 and 38°C using heating adjuncts including a warmed induction room and operating room, warm IV fluids at all times, a bed warmer during the procedure, and a warming blanket. Isoflurane was titrated to 1% to 2% to mitigate isoflurane-induced hypotension, and arterial pCO_2 was maintained between 38 and 42 mm Hg. Each animal received a bolus of 15 mL/kg warmed normal saline IV during instrumentation.

Protocol Development

We used 10 protocol development animals to determine the effective doses of TCA and ILE, as well as to test the

effects of ILE on the animal model. To determine the appropriate TCA dose, we used similar doses reported in the literature for rabbits—an equivalence of about 0.5 to 1 mg/kg/min infusion, but with amitriptyline rather than clomipramine.[4] Death ensued rapidly at the higher dose. Using a less toxic regimen (0.25 mg/kg/min) resulted in a 2-hour delay to reach hypotension, at which point death occurred precipitously despite repeat boluses of 7 mL/kg ILE 5 minutes apart. We chose 0.5 mg/kg/min and noted that humans would ingest TCAs instead of injecting them, thus likely requiring a longer time to reach toxicity. In addition, after hypotension we administered amitriptyline at 10% of the dose to simulate continued drug absorption.

To ascertain an effective ILE dose, we started with the dose recommended for humans (1.5 mL/kg bolus, followed by 0.25 mL/kg/min infusion) and increased stepwise to 7 mL/kg when no response was observed. Although the literature described higher doses in rabbit and rat models (up to 12 and 15 mL/kg, respectively), we stopped at 7 mL/kg (approximately five times the recommended human dose).[4,5] Even at 7 mL/kg the subjects' blood was milky white. We administered the 0.25 mL/kg/min infusion of ILE.

To determine the effect of ILE alone on the porcine model, we administered 7 mL/kg to two animals that had received no amitriptyline. We noted no skin flush or alteration in hemodynamic or respiratory parameters. Both survived without consequence. Necropsy was performed and showed no pulmonary emboli or other pulmonary toxicity. Furthermore, in animals intoxicated with amitriptyline, antidotal treatment with normal saline alone after reaching hypotension resulted in 100% lethality.

Study Protocol

Amitriptyline (Sigma, St. Louis, MO) 0.5 mg/kg/min was infused through a central venous line until hypotension was reached. We defined hypotension as a decrease in MAP to 60% of baseline. A continuous infusion of amitriptyline at 10% of the initial dose was then administered to the subjects to simulate continued drug absorption, along with a 10 mL/kg bolus of normal saline. The animals were then randomized (12 to each group) using an online randomization tool (www.randomization.com) to either the experimental group (to receive ILE 7 mL/kg bolus, followed by an infusion of 0.25 mL/kg/min) or the standard treatment group (to receive 8.4% sodium bicarbonate 2 mEq/kg bolus, plus an equivalent volume of normal saline). We used these doses of ILE and sodium bicarbonate based on previous studies for TCA toxicity in rabbits and rats, since no studies in large animals had been done.[4–6]

Measurements

Hemodynamic parameters (heart rate, systolic blood pressure [sBP], MAP, cardiac output, SVR, SVO_2, and CVP) were measured continuously throughout the study and for up to 60 minutes after antidote administration, when any surviving animals were euthanized with IV administration of sodium pentobarbital 100 mg/kg. We defined death as asystole when MAP was less than 20 mm Hg for 5 minutes because some animals may have had a rhythm and no measurable blood pressure or only a small pulse pressure. Laboratory data, ECGs, and serum amitriptyline levels (measured by liquid chromatography/tandem mass spectrometry [LC/MS/MS], AB SCIEX 3200 QTRAP LC/MS/MS System, Framingham, MA) were recorded every 15 minutes from study initiation to study end. At the end of the study, serum samples were centrifuged, and amitriptyline levels were determined in the total serum sample, fatty layer, and aqueous layer of the serum. A flow chart of this experimental design is shown in Figure 1.

Data Analysis

The study's primary outcome was an improvement in MAP of greater than 50% of trough values after administration of the antidote (ILE or sodium bicarbonate). Baseline hemodynamic parameters were assessed for treatment group differences using a parametric t-test. A secondary outcome was posthypotension reversal of the QRS interval widening on ECG. Other changes that are reflective of amitriptyline toxicity were also monitored

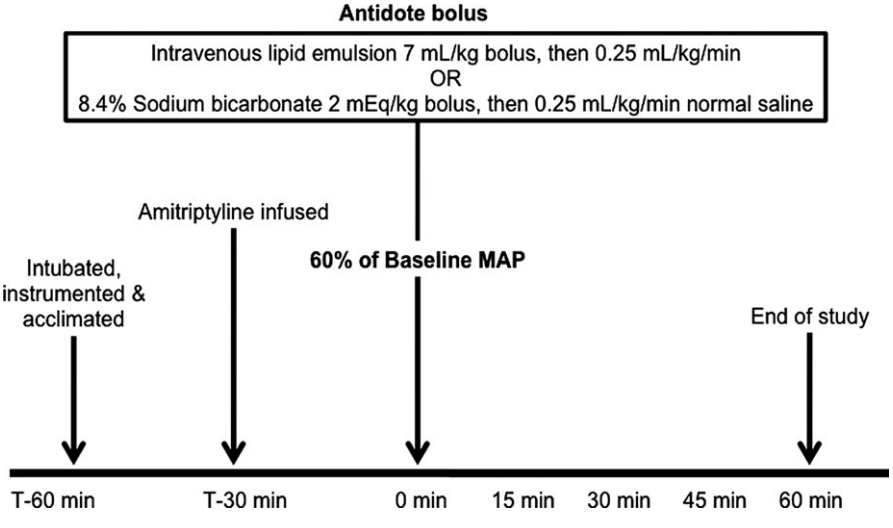

Figure 1. Sequence of study events. MAP = mean arterial pressure.

(e.g., heart rate, cardiac output, serum lactate, and serum amitriptyline levels).

The preliminary assessment of the primary outcome was via a repeated measures linear model (the MIXED model procedure) with adjustment for treatment group, time, and the treatment by time interaction with a first-order autoregressive covariance structure assumed.[13] The MIXED model procedure also appropriately managed missing data. Based on the preliminary assessment of a significant treatment by time interaction, a post hoc analysis was conducted to evaluate treatment differences during the follow-up period up to the point of 15 minutes posthypotension, at which time only one subject remained in the ILE group. Post hoc comparisons were adjusted for multiple testing using the Sidak correction method, and after adjustment, no significant differences between treatment groups were detected. Secondary analysis was preformed to assess the relationship between survival time from the point of hypotension to treatment using the Kaplan-Meier method and log-rank test.

We determined equal sample sizes of 12 animals per group would achieve a power of 0.8 to detect a 50% difference in MAP using a two-sided test at significance level of 0.05 (SAS version 9.1.3). Differences in response (e.g., improvement in amitriptyline-induced hypotension) between the two treatments were assessed with repeated measures analysis of variance adjusted for treatment, time, and the interaction of treatment by time. We compared mean values at time zero between groups for heart rate, MAP, cardiac output, serum lactate levels, QRS interval, amitriptyline dose administered, and serum amitriptyline levels.

RESULTS

At baseline there was no statistical difference between the ILE and sodium bicarbonate treatment groups (Table 1). The mean (±SD) amount of amitriptyline required to reach hypotension (ILE 14.4 ± 4.8 mg/kg vs. sodium bicarbonate 12.9 ± 4.1 mg/kg) and the mean time to reach hypotension (ILE 28:26 ± 11:34 min:sec vs. sodium bicarbonate 26:45 ± 8:30 min:sec) were not statistically different between the two treatment groups. Furthermore, the heart rate, sBP, cardiac output, and QRS intervals at hypotension were similar between groups (Table 2). In addition, there was no difference at hypotension between groups in pulse oximetry, pulmonary arterial oxygen saturation, SvO_2, or SVR.

Increase in MAP during the first 15 minutes after antidote administration was similar in the two groups (Figure 2). Within 9 minutes of hypotension and antidote administration, 11 of 12 (91.7%) ILE pigs and six of 12 (50%) sodium bicarbonate pigs died. By 17 minutes, eight of 12 (66.7%) sodium bicarbonate pigs died. There was no significant difference in mortality rates between the two groups. Comparisons between groups were stopped when 90% of the ILE pigs died. Kaplan-Meier curves were constructed to characterize survival among the treatment groups (Figure 3). The log rank test indicated a significant difference between the groups with respect to their time to death from hypotension ($p = 0.003$). The median times to death were 5 minutes for the ILE group (interquartile range [IQR] = 4.25 to 8.25 minutes) versus 10 minutes for the sodium bicarbonate group (IQR = 6 to 61 minutes). After antidote administration, the sodium bicarbonate group posttreatment levels of bicarbonate and pH increased, whereas the lactate level decreased compared to pretreatment values (all $p < 0.05$). In the ILE group, the posttreatment serum lactate increased ($p < 0.05$).

We did not detect a significant difference in the QRS interval between the two groups (Table 3). At the end of the experiment, serum amitriptyline levels were greater in the ILE arm compared to the sodium bicarbonate arm (ILE 8.76 ± 4.80 μg/mL; sodium bicarbonate 3.13 ± 1.98 μg/mL; $p < 0.0038$). Regarding amitriptyline partitioning, in the ILE group the ILE fatty layer contained 38.2% of total measurable amitriptyline, while the aqueous layer contained 53.6% (Table 3).

At no time during the study was there a difference in mean sBP, MAP, cardiac output, SVR, or QRS interval measurements between the two groups. There were transient differences in mean pulse rate at 3 and 4 minutes after hypotension, but they were similar at the end of the experiment. The subjects that died experienced cardiovascular collapse. Continuous cardiac monitoring

Table 1
Mean Values of Hemodynamic Parameters at Baseline in Each Study Arm

Parameter	Sodium Bicarbonate	IV Lipid Emulsion	p-value*
Mean arterial pressure, mm Hg	97.9 (±9.8)	101.4 (±12.4)	0.45
Heart rate, beats/min	87.9 (±20.9)	96.3 (±27.5)	0.41
Systolic blood pressure, mm Hg	118.7 (±10.8)	121.0 (±11.9)	0.62
Cardiac output, L/min	5.1 (±0.9)	6.3 (±1.8)	0.06
Oxygen saturation, %	68.4 (±10.2)	73.4 (±6.8)	0.17
QRS interval, msec	102.5 (±57.9)	89.5 (±40.8)	0.53

Data are reported as mean (±SD).
*t-test.

Table 2
Mean Values of Hemodynamic Parameters at Hypotension in Each Study Arm

Parameter	Sodium Bicarbonate	IV Lipid Emulsion	p-value*
Mean arterial pressure, mm Hg	61.4 (±5.9)	61.9 (±6.9)	0.85
Heart rate, beats/min	83.8 (±9.3)	85.6 (±9.1)	0.65
Systolic blood pressure, mm Hg	68.3 (±7.1)	68.8 (±6.9)	0.89
Cardiac output, L/min	2.7 (±0.6)	2.8 (±1.2)	0.71
QRS interval, msec	158.3 (±80.2)	113.8 (±34.5)	0.09

Data are reported as mean (±SD).
*t-test.

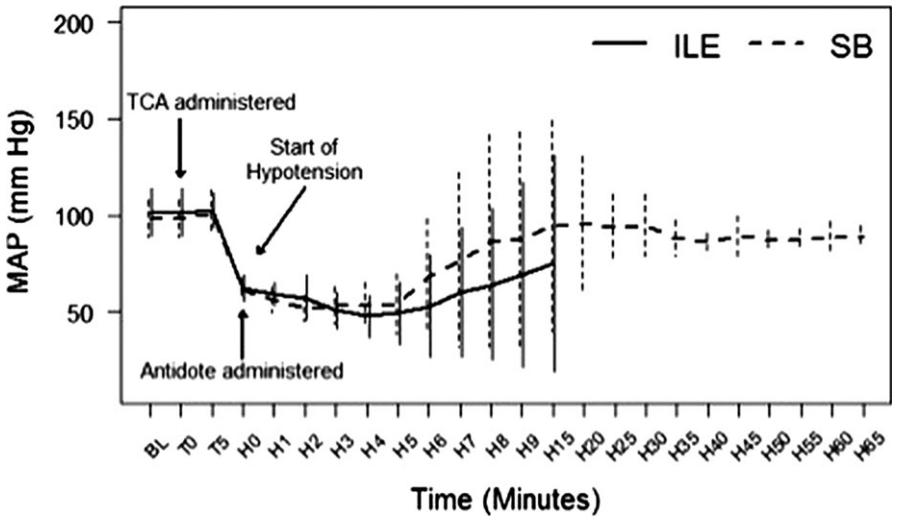

Figure 2. Effect of ILE versus sodium bicarbonate treatment on MAP after hypotension. *Bars* = SDs. BL = baseline; H = time of hypotension in minutes; ILE = intravenous lipid emulsion; MAP = mean arterial pressure; SB = sodium bicarbonate; T = time study began in minutes; TCA = tricyclic antidepressant.

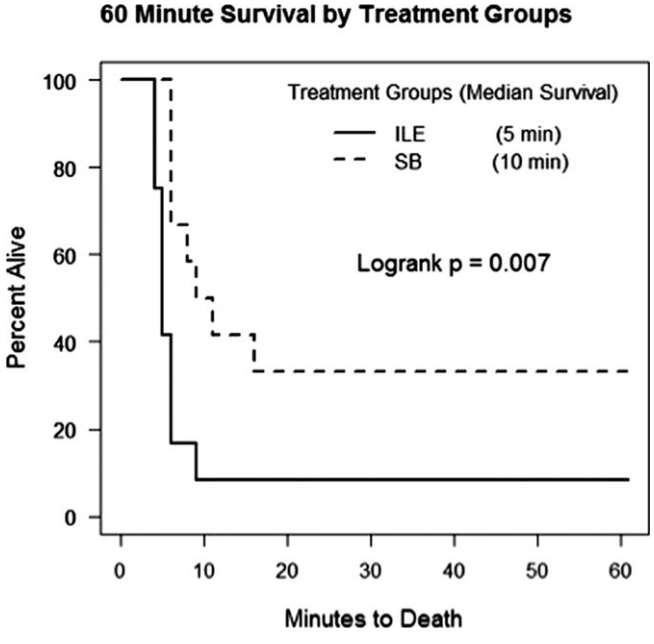

Figure 3. Kaplan-Meier curve characterizing time to death from hypotension by drug treatment group. ILE = intravenous lipid emulsion; SB = sodium bicarbonate.

showed wide complex rhythms that became sinusoidal in few of these animals. In most subjects, however, cardiovascular collapse occurred before the QRS could widen significantly. The physiologic parameters were measured only in surviving animals.

DISCUSSION

In contrast to our negative study for ILE therapy, Harvey and Cave[4] reported a transiently significant higher MAP in small, lean rabbits exposed to clomipramine (a TCA) after ILE administration compared to sodium bicarbonate. Both Bania and Chu[5] and Yoav et al.[6] showed improved survival in rats and rabbits intoxicated with TCAs when pretreated or cotreated with ILE (respectively) compared to normal saline and not sodium bicarbonate.

Table 3
Mean Values of Select Parameters at Death

Parameter	Sodium Bicarbonate	IV Lipid Emulsion
QRS interval, msec	104 (±71)	144 (±34)
Amitriptyline level, μg/mL		
Total	3.13 (±1.98)	8.76 (±4.80)*
Aqueous	–	4.69 (±2.44)
Fatty layer	–	3.34 (±2.12)

Data are reported as mean (±SD).
*$p < 0.0038$.

A few human case reports of TCA ingestion show dramatic recoveries after ILE administration following multiple other interventions; however, no studies exist proving its effectiveness.[14,15] This may be due to publication bias, or simply a lack of evidence of ILE's effectiveness.[16]

It is unclear why we found no difference between ILE and sodium bicarbonate in mitigating amitriptyline-induced hypotension. Swine provide a cardiovascular model similar to human physiology.[17] Nevertheless, Weinberg and Rubenstein[18] suggested that the porcine model may be problematic due to complement-mediated hypersensitivity to ILE. Studies describe an acute immune toxicity displaying hypersensitivity reactions that involve the complement system instead of IgE termed "complement activation–related pseudoallergy" or CARPA. These anaphylactoid reactions are more commonly seen with liposomal drugs and micellar

solvents containing amphiphilic lipids that serve as carriers for potent anticancer agents (e.g., doxorubicin, daunorubicin, paclitaxel) rather than in lipid emulsion alone.[19,20] In addition, a search of PubMed revealed no articles on CARPA associated with ILE as a single agent in any animal model. Furthermore, in our protocol development animals, we infused several animals with ILE alone and evaluated for hypotension and other adverse effects; we detected none. In one of 24 swine in our study we observed cutaneous flushing after ILE administration (a "constant feature of hypersensitivity" per Weinberg and Rubenstein). However, this animal did not manifest any temporally related increased hypotension, dysrhythmias, decrements in cardiac output, or respiratory abnormalities after ILE delivery, and it survived the study.

A potential explanation is a difference in ILE redistribution in swine compared to humans. Presumably, highly lipophilic agents deposit in body fat (large volume of distribution). The large lipid stores in swine should, therefore, be protective. However, we did not detect this in our experiment. Studies that employed small, lean animals (rodents and rabbits) responded more favorably to ILE.[4–6] No published reports address this possibility. In addition, there may be a difference in the way humans and swine metabolize the lipid droplets, although this has not been reported.[21]

Alternatively, the lack of ILE response in swine to a highly lipophilic agent like TCAs may be because the animals were too critically ill to allow sufficient time for ILE to establish a gradient and draw amitriptyline away from saturated myocardial receptors. Perhaps the ILE could sequester only a limited critical mass of amitriptyline, or there may have been a transport problem into fat stores, that when superseded would result in excess amitriptyline available to the heart. The half-life of ILE is 30 to 60 minutes and varies according to the subject's clinical status, ILE dose given, and droplet size.[22] Smaller droplets are cleared more readily. However, in human case reports, ILE is generally administered late in resuscitation attempts.[14,15] This was a severe TCA toxicity model. It is possible that a less toxic model may have produced different effects.

Furthermore, it is possible that death may have resulted from a cause other than amitriptyline-induced cardiotoxicity (e.g., pulmonary toxicity), but we did not observe a large decrease in pulse oximetry, pulmonary arterial oxygen saturation, or SvO_2. In addition, there was no increase in respiratory rate or acute decrease in cardiac output indicating massive pulmonary emboli. All animals were similar in these respects making this less likely. We performed necropsy on the protocol development animals, and no pulmonary toxicity was noted.

Our results are congruent with those of Litonius et al.[12] who reported that ILE did not improve hemodynamic parameters (pulse rate, MAP, cardiac output) or survival compared to Ringer's acetate in a medium-sized (29 kg) swine model. In fact, the ILE group trended toward worse survival than the Ringer's acetate group (2 vs. 5, respectively) despite the ILE group sequestering a greater concentration of amitriptyline compared to the aqueous (i.e., free serum) level. Litonius et al.[12] suggested that the higher circulating level of entrapped amitriptyline in the lipid emulsion is reversible and may expose critical, vulnerable cardiac receptors to greater concentrations of cardiotoxic amitriptyline. This may partly explain the lack of effectiveness with ILE in our study as well.

Consistent with another study we found that ILE did not improve QRS interval widening expected from TCA-induced sodium channel blockade compared to sodium bicarbonate.[4] The short survival period after hypotension may have obscured this finding.

The ILE did not appear to protect the subjects from amitriptyline-induced cardiotoxicity. The improved lactate levels in the sodium bicarbonate group compared to the ILE group either may be associated with a direct effect of treating an acidotic hypotensive state with an alkaline agent (sodium bicarbonate) or could be associated with a transiently improved survival (10 minutes vs. 5 minutes), allowing greater clearance of lacticemia. On the other hand, the more compromised hemodynamic state in the ILE group likely contributed to higher lactate levels and poor clearance, indicating a periarrest state.

It is unclear why the total serum amitriptyline levels at the time of death were greater in the ILE group compared to the sodium bicarbonate group. The higher lactate levels in the ILE group may have contributed to a more acidotic state than in the sodium bicarbonate group. Acidosis increases the fraction of ionized amitriptyline, which may theoretically slow diffusion across membranes and prolong redistribution time. This may have resulted in higher measurable amitriptyline levels in the serum of the ILE group. Another potential explanation relates to the state of amitriptyline measured—free or protein-bound. Alkalinization decreases the percentage of free amitriptyline by up to 20% over a pH range of 7 to 7.4 and by up to 42% over a pH range of 7.4 to 7.8.[23]

Finally, after centrifugation and extraction, the measurable amitriptyline concentration in the lipid layer was less than in the aqueous layer. This contrasts with Litonius et al.[12] who found a greater level of amitriptyline in the lipid layer. Despite the sequestered amitriptyline, there was no improvement in hypotension. Perhaps the longer amitriptyline infusion time in our study allowed a greater degree of equilibrium between the serum lipid compartment and the animals' innate lipid stores. Regardless of this finding, ILE exerted no apparent beneficial effect on limiting amitriptyline accessibility to myocardial receptors and produced similar results to ours. In our study, there was no evidence that ILE formed a "sink" to sequester amitriptyline from active, vulnerable receptor sites. It is possible that a lower amitriptyline dose and/or a greater ILE amount administered may have had a significant effect on outcomes. This study represented a severe toxicity model and only tested a single dose of amitriptyline and ILE.

The high mortality rate resulted in a lack of power in our final analysis. Significant differences in MAP between the treatment groups may be present, but we could not detect them. In future studies we will use our

estimated mortality rate to create a buffer in the sample size to account for this difference as is done in clinical trials to account for drop-out rates.

LIMITATIONS

Our study employed a porcine model. Given the infrequency of amitriptyline-induced hypotension in patients presenting for emergency care, the potential confounding effect of coingested medications, and the variation in resuscitation practices, a controlled animal study is a practical way to study the effect of ILE. In addition, regulatory and logistic concerns would make a randomized controlled trial of ILE and sodium bicarbonate in humans difficult to accomplish. Animal models may not perfectly replicate what happens in humans, but the porcine cardiac model closely mirrors human cardiac physiology.[17,18,24]

A second limitation of an animal model is potential adverse events not seen in humans. However, we did not detect adverse events associated with a porcine hypersensitivity syndrome.[18] Also, we did not measure complement levels.

Third, our study had a small sample size and high death rate and was unable to achieve statistical significance despite the a priori power analysis. The high fatality rate may be due to the toxicity of amitriptyline or individual variation in animals. A larger sample size may have detected a smaller difference in hypotension recovery, but there is no guarantee of a lower death rate.

Fourth, we administered amitriptyline by the IV route instead of oral route, as would typically occur after overdose. By this means we were able to control the rate and amount of amitriptyline each subject received.

Fifth, we studied only one ILE dose. A greater or lesser dose of ILE bolus or infusion may have produced different results. However, 7 mL/kg has been used in previous studies. A wide range of doses (2.5–15 mL/kg) has been used for TCA toxicity with variable results.[4–6,25]

Finally, we did not include a control arm. However, in our protocol development animals, we found that treatment with saline alone for amitriptyline toxicity was 100% lethal. In addition, animals treated with ILE alone and not given amitriptyline had 100% survival.

CONCLUSIONS

In this large-animal model of amitriptyline-induced cardiotoxicity, intravenous lipid emulsion failed to improve hypotension compared to sodium bicarbonate. Similar amounts of amitriptyline were found in the serum aqueous and lipid layers. This pilot study represents a severe tricyclic antidepressant overdose model with high mortality. Larger groups with better survival may yield different results. These conclusions are limited to a single intravenous lipid emulsion regimen.

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