Journal of Clinical Toxicology
ISSN: 2161-0495

Karcioglu, J Clin Toxicol 2018, 8:2
DOI: 10.4172/2161-0495.1000376

Review Article Open Access

Tricyclic Antidepressant Drug Intoxication: Is there a Role for Lipid Emulsion Therapy?

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Received date: March 14, 2018; **Accepted date:** March 22, 2018; **Published date:** March 31, 2018

Abstract

Lipid resuscitation therapy is the administration of Intravenous Lipid Emulsions (ILE) with the intent of reducing the clinical manifestations of toxicity from drug overdoses; including local anesthetics, calcium-channel blockers, β-blockers, antipsychotics, tricyclic antidepressant drugs (TCAD) and other compounds. Although there are conflicting findings in the literature, ILE may be considered for resuscitation in emergency and intensive care in resuscitation of severe hemodynamic compromise by TCAD.

This article reviews recent literature to analyse consequences, and intended effects associated with this treatment modality in poisoning with TCAD.

Keywords: Lipid emulsion; Lipid emulsion therapy; Intoxication, Poisoning; Tricyclic antidepressant drugs; Amitriptylin

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Tricyclic antidepressant drugs (TCADs)

TCADs have been among the most important instruments for the treatment of depression in the last century. Highly toxic potential of the drugs has been a major drawback and resulted in substitution by alternatives in time [1]. Similar to the toxicity with opiates, analgesics, and benzodiazepines, TCAD poisonings have been highly lethal in the human being so far [2]. Toxicity with TCAD results predominantly from myocardial sodium-channel blockade and associated ventricular dysrhythmias, myocardial depression, and hypotension. Main therapy encompasses supportive care, antidysrhythmics when necessary, and systemic alkalinization with sodium bicarbonate infusion. The patients receive treatment with activated charcoal for gastric decontamination, intravenous sodium bicarbonate, intravenous lipid emulsion (ILE) therapy, and plasmapheresis.

Although clear-cut evidence has not been published to date, Toxbase recommended use of ILE when there are life-threatening arrhythmias resistant to the other "standard" modes of treatment [24]. On the other hand, Tabone et al. conducted a Best Bets literature search in 2010 and reported that there was no clear evidence about the effectiveness of ILE in TCAD overdose [25].

What are lipid emulsions?

The first successful ILE was launched in the sixties as a mainstay in parenteral nutrition. In the following decades, the new generations of fat emulsions were devised, with increasing olive oil and fish oil content while the soybean oil mixture declined [4].

ILE is a 20% free fatty acid mixture used to deliver parenteral calories to those unable to take oral nutrition [5]. ILE is administered to reduce the clinical signs of toxicity from overdoses of some medications, including local anesthetics, beta blockers, calcium channel blockers, TCADs and other drugs [6]. This article reviews the rationale for and effectiveness of the introduction of ILE as treatment for TCAD poisoning in the emergency setting.

Some mechanisms of action of ILE in the management of poisoning are believed to work for the effectiveness of ILE. The 'lipid sink' phenomenon is the most widely accepted mechanism of action for ILE, which involves surrounding a lipophilic drug molecule and rendering it ineffective [7,8]. Animal studies show efficacy of ILE in the treatment of severe cardiotoxicity associated with local anesthetics, clomipramine, and verapamil, possibly by trapping such lipophilic drugs in an expanded plasma lipid compartment ("lipid sink").

The partitioning theory, or lipid sink theory, postulates that the administration of lipids compartmentalizes the offending xenobiotic into lipid phase and away from the target receptors. The generation of a concentration gradient facilitate the removal of the offending agent from tissues via different serum concentrations [7,9,10]. Another suggested mechanism involves drug-induced disruption of cellular calcium transport and claims that the function can be restored by activating calcium channels by ILE [11]. In brief, a sufficiently lipid-soluble compound becomes bound within these oil droplets, pulling drug from target tissues and sequestering them [12].

Clinical use, dosing and drawbacks: ILE has been extensively employed in the treatment of lipophilic drug poisonings following the first successful use of ILE in non-local anesthetic poisoning by Sirianni et al. [13]. The American College of Medical Toxicology (ACMT) recommends that ILE be used for poisoned patients with hemodynamic or other instability not responding to standard resuscitation measures [6].

The dose most commonly used is 1.5 mL/kg of 20% lipid emulsion infused as a bolus, repeated up to twice (some authors recommend up to three times) as needed until clinical stability is achieved, and followed by an infusion of 0.25 mL/kg/min for 30 to 60 min [14]. The infusion rate may be titrated to effect if the patient's blood pressure drops. The Food and Drug Administration fixed a maximum total dose administered per 24 h of 12.5 mL/kg [15]. The upper limits of therapy in case of persistent cardiovascular collapse or hemodynamic instability have not been established so far. American Society of Regional Anesthesia (ASRA) recommends the upper limits of 10 mL/kg over 30 min (Table 1) [16].

Bolus 1.5 mL/kg (lean body mass) IV over 1 min	Continuous infusion 0.25 mL/kg/min
100 mL for a 70-kg patient	18 mL/min for a 70-kg patient
Repeat bolus for persistent cardiovascular collapse	Can double the infusion rate for persistent hemodynamic instability
	Continue infusion for at least ten minutes after hemodynamic recovery

Table 1: Current recommendation from American Society of Regional Anesthesia (ASRA) for 20% lipid emulsion.

Fortunately, adverse reactions are uncommon despite widespread use of ILE. Adverse effects from standard procedure of ILE comprise hypertriglyceridemia, fat embolism, infection, local vein irritation, acute pancreatitis, electrolyte disturbances and hypersensitivity and allergic reactions. Untoward effects can also encompass kidney injury, cardiac arrest, ventilation-perfusion mismatch, acute lung injury, venous thromboembolism, fat overload syndrome, extracorporeal circulation machine circuit obstruction, and increased susceptibility to infections [17]. In addition, practice of ILE can accompany disturbed laboratory values such that hyperlipemia, hypercoagulability, and thrombopenia in neonates.

The untoward effects encountered with the use of ILE as part of nutrition can be categorized as early or delayed reactions. Early reactions include allergic reactions, dyspnea, cyanosis, nausea, vomiting, headache, flushing, fever, sweating, sleepiness and pain in the torso, pressure over the eyes, dizziness, and irritation at the site of infusion [18]. Hepatotoxicity is typical of delayed adverse reactions which may comprise minimal elevations of enzymes or minimal parenchymal damage to fulminant liver disease presenting with jaundice and pancytopenia [19,20].

Use of ILE in TCAD overdoses: Although ILE was launched to be a rescue treatment for local anesthetic poisoning, many antipsychotic or antidepressant medications also represent treatment targets with ILE because of the lipophilicity needed to cross the blood-brain barrier and because of their structural similarity to local anesthetics. Muller et al. reported 39 cases with local anesthetic poisoning successfully reversed by ILE [21]. The second most common drug toxicity to be successfully reversed by ILE was amitriptyline, a TCAD, which was reported in six cases. It should be noted that there are contradictory reports with regard to the efficacy of ILE in the treatment of toxicity of TCAD.

Levine et al. published a systematic review on non-local anesthetic toxicity [22]. A total of 203 articles (141 for humans and 62 for animals) were included. They concluded that despite the use of ILE for multiple substances in the treatment of patients with poisoning and overdose, the effect of ILE in various non-local anesthetic poisonings is heterogenous, and the quality of evidence remains low to very low.

There is dearth of data regarding human studies about use of ILE in TCAD overdose. In a small study in which humans were given therapeutic doses of TCAD and ILE [23], patients treated with ILE developed a non-significant increase in blood level of TCAD, which would support the hypothesis that ILE attracts TCAD away from tissues by creating an expanded lipid compartment.

Although clear-cut evidence has not been published to date, Toxbase recommended use of ILE when there are life-threatening arrhythmias resistant to the other "standard" modes of treatment [24]. On the other hand, Tabone et al. conducted a Best Bets literature search in 2010 and reported that there was no clear evidence about the effectiveness of ILE in TCAD overdose [25].

Jamaty et al. reviewed 23 animal and 50 human trials involving use of ILE in the management of poisoning [26]. ILE has certain benefits in poisoning scenarios with bupivacaine, verapamil, chlorpromazine, and some TCAD and beta-blockers. The effective use of ILE for TCAD intoxication was demonstrated in a number of animal models [27-30]. However, the evidence for the efficacy of ILE in reducing mortality and improving hemodynamic, electrocardiographic, and neurological parameters in the poisoned patients is solely based on animal studies and human case reports [26].

Amitriptyline: Many reports in which amitriptyline overdoses were treated with ILE have been published to date [30-36]. There were no differences in ECG parameters and no severe cardiac arrhythmias occurred. Thus ILE was able to entrap amitriptyline back into plasma from brain and possibly from other highly perfused, lipid-rich tissues. In spite of the entrapment, there was no difference in haemodynamics between the groups.

Gosselin et al. published "evidence-based recommendations on the use of ILE therapy in poisoning" with a variety of culprit drugs including amitriptyline and other TCAD [37]. In their "executive summary of indications regarding the use of ILE in poisoning" they recommended to use ILE if other therapies fail/in last resort in life-threatening toxicity. In non-life-threatening toxicity, on the other hand, they did not suggest using ILE as part of treatment modalities.

Varney et al. conducted a randomized, controlled pilot study in a swine model to compare efficacy of ILE with standard treatment of sodium bicarbonate to reverse amitriptyline-induced hypotension in the course of severe TCAD overdose [38]. They reported that ILE failed to improve hypotension when compared to the standard treatment of sodium bicarbonate in this model. On the other hand, in a rodent model of TCAD oral poisoning, Perichon et al. administered ILE 30 min after oro-gastric administration of amitriptyline and compared the effects with 70% bicarbonate vs 70% Hartmann's solution [39]. Treatment with ILE early after oral amitriptyline overdose resulted in worse survival and no improvement in haemodynamics. The authors pointed out that either drug absorption from the gastrointestinal tract was facilitated or drug redistribution was delayed when ILE was instituted early after oral poisoning.

Rabbit models have demonstrated the effectiveness of lipid as a treatment for IV TCAD toxicity [27,40,41]. Furthermore, in pig studies, lipid is shown to entrap amitriptyline into the plasma, which fits into the scavenging theory. Heinonen et al. used ILE in the management of severe amitriptyline poisoning in a pig model and indicated that a significant (25%) decrease in brain amitriptyline

concentrations were noted following treatment with 20% ILE when compared to Ringer's acetate administration [42].

Desipramine: As a member of the TCAD family, toxic ingestion of desipramine triggers fatal dysrhythmias and a systole. O'Sullivan et al. compared the efficacy of the drugs and drug combinations given concurrent with cardiopulmonary resuscitation in pigs with desipramine overdose [43]. They reported that animals treated with ILE + vasopressin were more likely to survive than those treated only with ILE, and the groups that received ILE were more likely to survive than those not treated with ILE. In the present study, ILE infusions were not as beneficial as expected in desipramine poisoning.

Clomipramine: Harvey and Cave compared efficacy of resuscitation with ILE *versus* sodium bicarbonate in a rabbit model of clomipramine toxicity [27]. Infusion of ILE led to more rapid and complete reversal of clomipramine-induced hypotension compared with sodium bicarbonate. Additionally, ILE infusion prevented cardiovascular collapse in a model of severe clomipramine toxicity.

In a rabbit model of clomipramine toxicity, Cave et al. reported that both ILE and tailored liposomes improved hemodynamic recovery compared with bicarbonate in clomipramine-induced cardiotoxicity in rabbits [44]. ILE group also had higher 30-minute blood pressure readings. In another model of TCAD toxicity, Harvey et al. sought for additional benefit with plasma exchange therapy undertaken subsequent to ILE treatment, hypothesising enhanced blood carriage of lipophilic toxin clomipramine to increase yield when combined with an extracorporeal mode of elimination [45]. Plasma exchange performed in conjunction with administration of ILE failed to result in significant extracorporeal clomipramine elimination and ILE resulted in greater survival.

Dothiepin (Dosulepin): So far, only a few case reports have been published to extrapolate efficacy of treatment with ILE in dothiepin overdose and cardiotoxicity [46,47].

Conclusion

Acute poisoning with TCAD is difficult to treat and consists mainly of haemodynamic and ventilatory support. Clinical efficacy of ILE is firmly established in many reports to resuscitate patients with cardiotoxicity from systemic toxicity of different compounds in the TCAD family. ILE is a potential antidote for this phenomenon under extreme circumstances. Further research concerning the safety of ILE is needed before it is recommended as the first choice treatment modality for acute TCAD overdose.

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