Current Trends in Pharmacology and Clinical Trials
ISSN: 2642-0848

Chembio Publishers
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Review Article *Volume 2; Issue 2*

Lipid Emulsion Therapy in Poisoning Via Tricyclic Antidepressant Drugs: A Systematic Review

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Received Date: May 07, 2019; **Published Date:** May 21, 2019

Abstract

Introduction: Poisoning with drugs are managed with supportive measures in conjunction with lipid resuscitation therapy i.e., intravenous lipid emulsions (ILE). The goal of this technique is to alleviate the clinical manifestations of intoxication via various molecular mechanisms. Poisonings via local anesthetics, cardioactive drugs (calcium-channel blockers and beta blockers), psychoactive drugs [antipsychotics, tricyclic antidepressant drugs (TCAD)] and some others.

Methods: This article is a review and critical analysis of the most recent literature to analyse consequences, and intended effects associated with this treatment modality in poisoning with TCAD. Online database searches were performed for randomized controlled trials published before November 2018. The search terms included lipid emulsion therapy, intoxication, poisoning, tricyclic antidepressant drugs, and names of specific compounds in TCADs. Papers were examined for methodological soundness before being included. Studies involving the use of ILE in animal studies on TCAD overdoses were summarized in a table.

Results: The initial electronic data search produced 35 potentially eligible trials; among these, 26 were discarded for some reason, and only 9 researches fulfilled the criteria based on inclusion of information set initially. Two other articles were found and enrolled in the review after a search in the references of the articles included. Thus a total of 11 articles were analyzed in the article. Eight studies (72.7%) included in the analysis commented positively on the effectiveness of ILE on TCAD overdoses.

Conclusion: 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.

Keywords: Lipid Emulsion Therapy; Lipid Emulsion; Intoxication; Poisoning; Tricyclic antidepressant drugs

Citation: Ozgur Karcioglu, et al. Lipid Emulsion Therapy in Poisoning Via Tricyclic Antidepressant Drugs: A Systematic Review. Curr Trends Pharma Clinical Trials 2019, 2(2): 180018.

Abbreviations: ILE: Intravenous Lipid Emulsion; TCAD: Tricyclic Antidepressant Drugs; ACMT: American College of Medical Toxicology; ASRA: American Society of Regional Anesthesia; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MAP: Mean Arterial Pressure; TCA: Tricyclic Antidepressants; NaHCO3: Sodium Bicarbonate.

What do we know about lipid emulsions?

The introduction of the first successful intravenous fat emulsion in the sixties has been considered an important milestone in parenteral nutrition. In the following decades, newer generations of lipid emulsions were produced in conjunction with the new requirements which tends to augment the olive oil and fish oil ingredients while reducing the soybean oil contents [1]. Saturated and/or unsaturated fatty acids forming the lipid compounds, are composed of triglycerides (medium- or long-chain) which possess differing chemical characteristics [2]. Their mechanisms of action consist of migration of the medicine from the tissues to cause an equilibrium in a larger circulating lipid pool (so-called lipid sink), and repair pathways of metabolism in cardiac myocytes. Recently developed lipid emulsion formulations contain alternative fatty acid sources such as olive and fish oil instead of previously used soybean oil in order to reduce the concentration of linoleic acid and therefore represent a safer and more efficient treatment [3].

Intravenous lipid emulsion (ILE) is a 20% free fatty acid mixture used to deliver parenteral calories topatients unable to take oral nutrition [4]. ILE is the administrationof a lipid emulsion with the intent of alleviating the findings and seerity of poisoning from overdoses of some drugs, including local anesthetics, beta blockers, calcium channel blockers, tricyclic antidepressant drugs (TCAD) and some others [5]. This review aims to highlight the evidences underlying the effect of ILE as a remedy for TCAD poisoning.

Lipid therapy triggers some mechanisms of action against toxicity which are known to account for the efficacy of ILE compounds. For example, the 'lipid sink' represents the most commonly recognized mechanism of action for ILE, which defines surrounding a lipophilic drug molecule and inibiting its hazardous effects. [6,7]. The partitioning theory conceptualizes that lipids compartmentalizes the offending xenobiotic into lipid phase and away from the target receptors. Lower serum concentrations facilitate the removal of the offending agent from tissues by the generation of a concentration gradient [6,8,9]. One of the proposed mechanisms defines drug-induced disruption of cell calcium exchange and put forth that the function can be repaired by activation of the calcium channels by ILE, which helps to augment cellular calcium [10]. In brief, a sufficiently lipid-soluble compound becomes bound within these oil droplets, pulling drug from target tissues and sequestering them [11]. Manzanares et al. conducted a meta-analysis and demonstrated that ILE may be able to decrease mortality and ventilation days in the critically ill [12]. On the other hand, because of the paucity of clinical data, they found inadequate evidence to recommend the routine use of parenteral fish oil. There is a need to determine how timing and dosing of ILE is to be changed with special regard to the type of the agent ingested [13,14].

Clinical Use and Dosing

Lipid-soluble drugs are known to be highly toxic. ILE has been extensively employed in the treatment of lipophilic drug poisonings followingthe first successful use of ILE in non-local anesthetic poisoning published in 2008 by Sirianni et al [15]. The use of ILE to ameliorate lipid-soluble drug toxicity by sequestering the drug in an intravascular lipid compartment has been demonstrated in different animal models. The American College of Medical Toxicology (ACMT) raise that this treatment is to be utilized for intoxicated unstable patients not responding to standard resuscitation measures [5]. ILE treatment is mostly employed via a dose of 1.5 mL/kg of 20% lipid emulsion administered as a bolus, which is to be repeated up to twice or three times for titration as necessary till hemodynamic stabilization is noted. The bolus infusion can be followed by an maintenance administration of 0.25 mL/kg/min for up to one hour [16]. A daily maximum total dose of 12.5 mL/kg is advocated by The Food and Drug Administration [13]. The upper limits of 10 mL/kg (in half an hour) have been recommended by the American Society of Regional Anesthesia (ASRA). (Table 1) [17].

1. Bolus 1.5 mL/kg (lean body mass) IV over 1 min
- 100 mL for a 70-kg patient
- Repeat bolus for persistent cardiovascular collapse
2. Continuous infusion 0.25 mL/kg/min
- 18 mL/min for a 70-kg patient
- 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: [18].

Tricyclic Antidepressant Drugs

Since 1950s, TCAD have been among the most important instruments for the treatment of depression. To date, their toxic potential has been a major drawback and resulted in substitution by alternatives [19]. TCADs are substantial contributors to the mortality rate due to drug overdose, alongside opiates, analgesics, and benzodiazepines [20]. TCAD overdose leads to a true emergency with a high death toll. Toxicity with TCAD results primarily from blockage of myocytes' sodium channels and consequent ventricular arrhythmias, myocardial depression, and low blood pressure. Aggressive supportive care, antidysrhythmics when necessary, and systemic alkalinization are among essentials of treatment.

Sodium channel blockage is also associated by antimuscarinic and alpha-adrenoceptor antagonistic effects in those intoxicated with TCAD compounds. Remarkably wide QRS complexes that may resemble ventricular dysrhythmias are encountered in ECG tracings. A landmark prospective study pointed out that in these patients with severe intoxication via TCAD, a QRS shorter than 100 ms can be seen as a predictor of favorable outcome, whereas a QRS greater than 100 ms was linked with a boosted propensity to seizures, and greater than 160 ms accompanies an increased risk of dysrhythmias [21]. This article is a review and critical analysis of the most recent literature to analyse consequences, and intended effects associated with this treatment modality in poisoning with TCAD.

Methods

Online database searches were performed for controlled trials published before July 2018, on the effectiveness of the ILE treatment on TCAD intoxication. A literature search via electronic databases was carried out for the last twenty years on English Language papers. The research question was: "Is intravenous lipid emulsion therapy effective in subjects with poisoning via tricyclic antidepressant drugs?"

Search methodology

A literature search in the Cochrane Controlled Trials, PubMed, ClinicalKey, EMBASE, and BIOSIS has been undertaken on the published experimental studies. Online searches were performed using the following keywords and terms: *lipid emulsion therapy, intoxication, poisoning, tricyclic antidepressant drugs, and names of specific compounds in TCADs.* The papers were examined for methodological soundness before being analyzed. In addition, the reference lists of retrieved articles were used to generate more papers and search terms

Studies involving the use of ILE in subjects with TCAD overdoses were summarized in the Table 2.

Assessment of quality and risk of bias

"Grading of Recommendations Assessment, Development and Evaluation" (GRADE) guidelines were used to assess and score eligible clinical studies regarding the quality of evidence. This scale rates the researches in accord with risk of bias, publication bias, consistency, directness and precision [14]. With respect to the GRADE, the studies were assigned to one of four groups (A to D, respectively): High, moderate, low and **v**ery low quality. Table 2 provides a summary of this rationale; grading and levels of evidence which is also recognized as "Sackett's original evidence based approach".

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Results

The electronic data search produced 35 potentially eligible researches and among these, 26 were discarded for some reason, and only nine trials fulfilled the criteria based on inclusion of information set initially. Among those excluded from the review, 11 were case reports, 2 were case series, 7 were reviews, 5 were involved in other drug intoxications and focused on irrelevant subjects, and one was written in Japanese. In addition, two other articles were found and enrolled in the review after a search in the references of the articles included (Fig. 1).

Thus the data in the table were elicited from 11 articles. Table 2 gives a comprehensive list of the 11 animal studies on the use of ILE in poisoning with TCAD and their main characteristics. All studies had been designed as interventional and experimental researches. Level of evidence as evaluated with respect to GRADE system yielded a 'C' for all articles, which means low level of evidence (The true effect may be substantially different from our estimate of the effect)[22]. Eight articles (72.7%) included in the analysis commented positively on the effectiveness of ILE on TCAD overdoses.

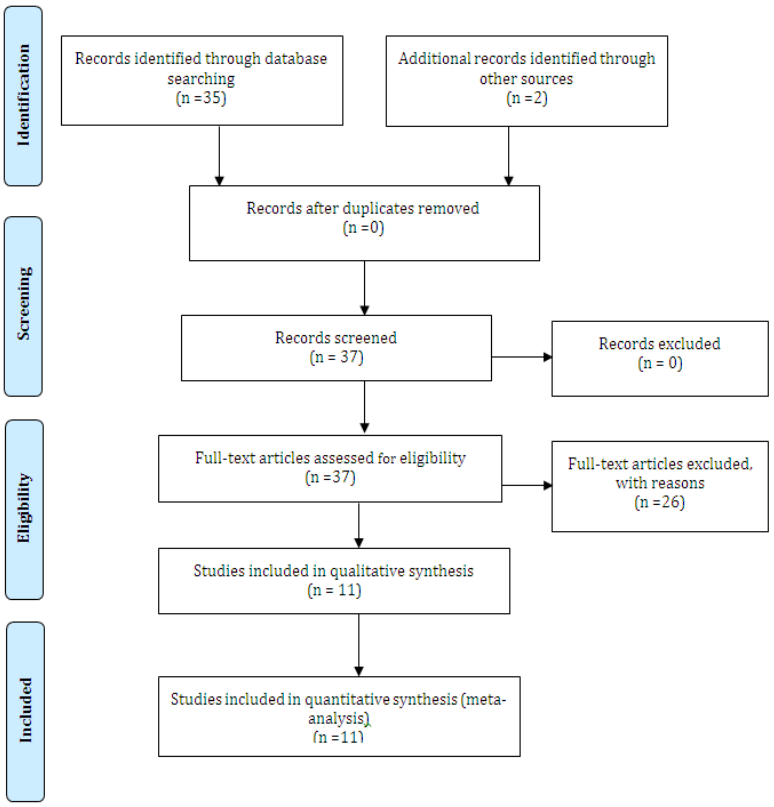

Figure.1. PRISMA 2009 Flow Diagram

Investigator(s), date, reference #	Sample size	Design and Quality of evidence*	Objectives	Results	Notes, conclusions
Heinonen et al. 2013 [23]	20 pigs	I, E, C	To investigate the effect of ILE on plasma and tissue concentrations of amitriptyline and haemodynamic recovery, when ILE was given after TCAD distribution into tissues.	Arterial plasma total amitriptyline concentrations were higher in the ILE than in the control group ($p < 0.03$) from 20 min. on after the start of the treatment infusions. ILE reduced brain amitriptyline concentration by 25% ($p = 0.038$) and amitriptyline concentration ratios brain/arterial plasma ($p = 0.016$) and heart/arterial plasma ($p = 0.011$).	ILE, administered after an initial amitriptyline tissue distribution, was able to entrap amitriptyline back into plasma from brain and possiblyfrom other highly perfused, lipid-rich tissues.
Perichon et al. 2013 [24]	20 rats	I, E, C	To investigate the effects of ILE-infusion on drug concentration and haemodynamics in the early/ absorptive phase after oral poisoning.	ILE infusion significantly decreased the survival compared to other treatments (10% ILE vs 70% bicarbonate vs 70% Hartmann's solution, $p = 0.005$).	Treatment with ILE early after oral amitriptyline overdose resulted in worse survival and no improvement in hemodynamics. In addition, blood

					amitriptyline concentrations were higher in the ILE-treated group.
Varney et al. 2014 [25]	24 pigs	I, E, C	To determine if ILE improved hypotension (defined by MAP < 60% baseline) compared to NaHCO3 for amitriptyline overdose in the critically ill.	The median time from hypotension to death was greater for the NaHCO3 group (10 minutes vs. 5 minutes for the ILE group; p = 0.003), but overall survival was not different. One ILE and four NaHCO3 pig ssurvived.	ILE treatment failed to improve amitriptyline-induced hypotension when compared to the standard treatment of NaHCO3 in the porcine model of severe TCA overdose.
O'Sullivan et al. 2014 [26]	56 pigs	I, E, C	To investigate the efficacy of the drugs and drug combinations (Epinephrine, Vasopressin and ILE) administered with CPR.	The animals treated with vasopressin were more likely to survive than those that did not receive vasopressin, and the groups that received ILE were more likely to survive than those that did not receive ILE.	Vasopressin alone was shown to be the most effective treatment in the management of desipramine overdose. ILE treatment was also associated with higher survival than the others.
Cave et al. 2013 [27]	15 rabbits	I, E, C	Compare resuscitation with tailored liposomes, 20% ILE, and NaHCO3, in a model of clomipramine toxicity.	Thirty-minute MAP was greatest in ILE-treated animals: 61 mmHg ILE, 43 mmHg liposomes, and 10 mmHg NaHCO3 (all p = 0.02).	Both ILE and tailored liposomes improved hemodynamics compared with NaHCO3 in clomipramine-induced cardiotoxicity in rabbits. Higher 30-min MAP was seen in the ILE group.
Harvey et a.l 2007 [28]	30 rabbits	I, E, C	To compare resuscitation with ILE versus NaHCO3 in a rabbit model of clomipramine toxicity.	Mean difference in MAP between ILE- and NaHCO3-treated groups was 19.4 mmHg and 11.5 mmHg at 5 and 15 minutes. Spontaneous circulation was maintained in all ILE-treated rabbits. All animals in the NaHCO3-treated group developed pulseless electrical activity and expired at 10 minutes.	ILE resulted in more rapid and complete reversal of clomipramine-induced hypotension compared with NaHCO3. Additionally, ILE treatment prevented circulatory collapse in severe clomipramine toxicity.
Harvey et al. 2014 [29]	20 rabbits	I, E, C	To seek for additional benefit with plasma exchange (PE) therapy undertaken	Greater survival was observed in animals treated with ILE from both LE and LE+PE groups. Mean PE of 52% circulating volume returned	The survival rate is higher in animals treated with ILE. Intravascular lipid sequestration of

			after ILE, hypothesising enhanced blood carriage of lipophilic toxin to increase yield when combined with extracorporeal elimination	only 0.04% of the administered clomipramine load in LE+PE group animals.	clomipramine appears an inadequate sole explanation for the beneficial effects of ILE.
Chapman et al. 2017 [30]	20 rats	I, E, C	To investigate if ILE would augment acidic pH gradient liposome supported peritoneal dialysis (LSPD) or not.	There were significantly higher intraperitoneal concentrations of amitriptyline and extraction ratio for peritoneal blood flow (ERs) in the two groups treated with LSPD (Group B, $p = 0.02$, Group C, $p < 0.01$ vs. Group A). There was no observed effect for ILE on intraperitoneal amitriptyline concentration or ERs ($p > 0.20$).	LSPD increased the amitriptyline concentration in the dialysate. No further increase was noted with ILE. Exploratory analysis suggests LSPD may be driven by total rather than free drug concentrations.
Harvey M et al. 2009 [31]	20 rabbits	I, E, C	To document plasma and peritoneal diasylate clomipramine concentration after resuscitation with ILE in a model of clomipramine-induced hypotension.	MAP was greater in lipid-treated rabbits ($p = 0.020$). ILE was associated with elevated plasma clomipramine concentration and reduced initial volume of distribution (Vd; 5.7 L/kg lipid vs. 15.9 L/kg saline; $p = 0.0001$). Also, peritoneal diasylate clomipramine concentration was greater in ILE-treated animals.	Amelioration of TCA-induced hypotension with ILE is associated with reduced initial Vd and elevated plasma clomipramine concentration consistent with IV drug-lipid sequestration. Concomitant peritoneal dialysis with ILE enhances clomipramine extraction.
Litonius et al. 2012 [32]	20 pigs	I, E, C	To study the effect of ILE on the plasma concentration of amitriptyline and hemodynamic recovery in a model of amitriptyline intoxication.	ILE prevented the decrease in plasma total amitriptyline concentration, resulting in a 90% higher ($p<0.001$) total concentration and significantly ($p=0.014$) lower free fraction of plasma amitriptyline in the Lipid group (1.1%) compared with the Control group (3.0%) at 30 min.	A marked entrapment of amitriptyline by ILE was detected but this did not improve the pigs' hemodynamic recovery from severe intoxication.
Tsuji et al. 2018 [33]	10 rats	I, E, C	To assess the effectiveness of the ILE for treating clomipramine overdoses in a rodent model of	The blood concentration of clomipramine was significantly higher in the ILE group than in the placebo group. The ratio of the concentration of	The distribution of clomipramine from blood to tissue was suppressed by ILE. ILE therapy was concluded to be a

			intoxication.	clomipramine in liver/serum was significantly lower in the ILE group than in the placebo group. There was a significantly faster elimination rate for clomipramine in peripheral blood in the ILE group.	promising strategy for the management of overdoses of this group of lipophilic drugs

Table 2. Main characteristics of the animal studies on the use of ILE in poisoning with TCAD which were reviewed in the present study.
***Design: I; interventional, E: experimental**
Level of evidence (GRADE system) [22]
Grade A: High level of evidence (The true effect lies close to our estimate of the effect.)
Grade B: Moderate level of evidence (The true effect is likely to be close to our estimate of the effect, but there is a possibility that it is substantially different.)
Grade C: Low level of evidence (The true effect may be substantially different from our estimate of the effect.)
Grade D: Very low level of evidence (Our estimate of the effect is just a guess, and it is very likely that the true effect is substantially different from our estimate of the effect.)

Discussion

Utilization of lipid emulsions in TCAD poisoning

ILE has been introduced as a rescue therapy against local anesthetic overdoses, but many psychoactive medicines also represent treatment targets with ILE because of the lipophilicity necessitated to cross the blood-brain barrier and for their chemical similarity to local anesthetics. Thirty-nine cases with local anesthetic poisoning were described to have been successfully reversed by ILE [34]. The second most common drug toxicity to be successfully reversed by ILE was amitriptyline. Of note, there are contradictory reports with regard to the efficacy of ILE in the treatment of toxicity of TCAD. A systematic review was performed on cardioactive and TCAD overdoses on 200+ articles [25]. They noted that despite the use of ILE for many concurrent intoxicating agents in the treatment of patients with intoxications, the effect of ILE in different overdoses is unpredictable, and the quality of evidence is found to be low.

Few data can be found in relation to clinical studies on the utilization of lipid emulsions in poisoning with antidepressants. Minton et al. administered patients treatment doses of TCAD and ILE, and reported that blood levels of TCAD demonstrated only a small unimportant rise in those treated with ILE [36]. This finding can be interpreted to support the attraction of antidepressant compounds by ILE away from tissues by forming an enlarged compartment of lipids. Well-established databases such as Toxbase advocate administration of ILE in case of hemodynamic unstability triggered by serious arrhythmias resistant to the known "traditional" treatment modalities [37]. However, very few clear-cut evidence were published on the issue. A BestBets literature search was performed in 2010 and the authors wrote that there was no clear evidence about the efficacy of ILE in poisoning with TCAD compounds [38].

Jamaty et al. reviewed 23 animal and 50 human trials describing benefits and drawbacks of ILE in the treatment of overdoses [39]. ILE has remarkable advantages in poisoning with bupivacaine, verapamil, chlorpromazine, and certain TCAD and beta-blockers. The optimal and efficient utilization of ILE for antidepressant overdoses has been defined in numerous animal models [28,40,41,42]. The efficiency of ILE in lowering mortality in those with overdoses is generally based on animal models and case presentations [39].

Amitriptyline

Management of amitriptyline overdoses with ILE have been published in numerous articles to date [42-48]. ECG findings were similar in the reports and no lethal cardiac arrhythmias occurred. Thus ILE must have entrapped amitriptyline into plasma from central nervous system and some other organs. However, there has been no improvement regarding hemodynamic states between the treatment arms.

Gosselin et al. launched "evidence-based recommendations on the use of ILE therapy in poisoning" with various medications, also involving TCAD [49]. In the "executive summary of indications regarding the use of ILE in poisoning" the authors advocated to use ILE as a last chance in severe life-threatening intoxication.

In accord with these findings, Mithani et al. conducted a retrospective case review on 36 patients treated with ILE in Canada and failed to show a clinically important

improvement in MAP after ILE administration [50]. They interpreted that ILE must remain an alternative treatment for hemodynamically unstable patients with TCAD intoxication only after conventional procedures have failed, until future research defines its efficacy.

In a randomized, controlled study in a swine model to compare efficacy of ILE in conjunction with standard NaHCO3 administration to normalize shock states triggered by amitriptyline poisoning in the course of life-threatening TCAD intoxication, authors pointed out that ILE failed to improve hypotension when compared to the "standard" NaHCO3 regime [25]. In a rodent model of TCAD oral poisoning, Perichon et al. informed that treatment with ILE early after oral amitriptyline overdose led to poor survival without any normalization in haemodynamics [24]. Some other rodent (rabbit) models have proved the efficacy and usefulness of ILE as a treatment for intravenous TCAD overdoses [28,51,31]. Likewise, in swine models, ILE treatment is demonstrated to entrap amitriptyline into the plasma, in accord with the scavenging theory. For example, Heinonen used ILE in the treatment of severe amitriptyline poisoning in a swine model and concluded that an important (one-fourth) reduction in brain amitriptyline concentrations were documented after infusion of 20% ILE when compared to treatment with Ringer's acetate [23].

Desipramine

As a member of the TCAD family, toxic doses of desipramine trigger lethal cardiac arrhythmias and asystole. Authors investigated the effectiveness of the drug treatments administered during cardiopulmonary resuscitation in animals overdosed by desipramine [26]. Survival rate of the pigs administered ILE+vasopressin was higher than those received only lipids, and the groups administered lipids survived more frequently than those managed without ILE.

Clomipramine

In a study about the efficacy of resuscitation with ILE compared to sodium bicarbonate in a rabbit model of clomipramine toxicity, Harvey et al. reported that infusion of ILE resulted in a more expedient reversal of clomipramine-induced shock states [28]. Cave et al. compared the detoxification effect of 20% ILE with sodium bicarbonate, in a rabbit model of clomipramine toxicity [27]. They reported that both ILE and tailored liposomes improved hemodynamic recovery compared with bicarbonate in clomipramine-induced cardiotoxicity in rabbits. Greater 30-minute blood pressure readings were observed in the ILE group. Likewise, in a very recent study, Tsuji et al. used a rat model of clomipramine toxicity and noted that the distribution of clomipramine from blood to tissue was suppressed by ILE. Therefore, ILE therapy was concluded to be a promising strategy for the management of overdoses of this group of lipophilic drugs. Harvey et al sought for advantages with plasma exchange carried out after lipid therapy and reported that administration of ILE was associated with higher survival rates in the rabbit model of TCAD toxicity [29]. Interestingly, plasma exchange undertaken concurrent with ILE treatment was not accompanied by substantial extracorporeal elimination of clomipramine. Lipid sequestration of the TCAD compound seems to be an insufficient sole explanation for the favorable effects of ILE.

Dothiepin (Dosulepin)

Blaber et al. reported a case of dothiepin overdose causing refractory cardiovascular collapse, which was successfully reversed with ILE treatment [52]. Boegevig et al. reported a successful acute reversal of potential life threatening QRS complex widening and prolonged QT interval following dosulepin overdose using ILE 20% in an unstable patient [18]. To date, only a number of case reports are present to generalize the recommendation of treatment with ILE in dothiepin overdose and cardiotoxicity.

Conclusion

Acute intoxication via TCAD is a challenging entity which mainly encompasses haemodynamic and ventilatory supportive measures. Effectiveness of ILE is noted in many reports to resuscitate patients with cardiotoxicity from systemic toxicity of TCAD compounds. ILE is a potential antidote for this phenomenon under extreme circumstances. However, the safety of ILE remains to be tested and approved in broad multicentric population-based studies before it is advocated to be the first choice treatment for TCAD poisonings.

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