



## Utility and Untoward Effects of Lipid Emulsion Therapy in Patients with Poisoning by Cardioactive Drugs

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### Abstract

Lipid resuscitation therapy is the administration of an Intravenous Lipid Emulsion Therapy (IVLET) in order to alleviate clinical manifestations of toxicity from certain overdoses, including local anesthetics, Calcium-Channel Blockers (CCB),  $\beta$ -Blockers (BB), antipsychotics, antidepressants and other drugs. CCB and BB represent two of the most important classes of cardiovascular drugs involved in producing cardiodepressive syndrome. We performed a review and critical analysis of the most recent literature to analyse consequences, use and potential adverse effects associated with this treatment modality in poisoning with cardioactive drugs.

The present evidence supports use of IVLET in local anesthetic overdoses and in lipophilic cardiotoxin intoxication-including CCB and BB-when there is an immediate threat to life, and other therapies have failed. In cases of cardiac arrest from a suspected poisoning, consider administration of intravenous lipid emulsion during the resuscitation. Patients with hypotension refractory to volume loading, correction of acidosis and calcium salts should be treated using High-dose insulin Euglycemia Therapy (HET).

Adverse effects from standard IVLET include hypertriglyceridemia, fat embolism, infection, local vein irritation, acute pancreatitis, electrolyte disturbances and hypersensitivity and allergic reactions. Meanwhile, disturbed laboratory values associated with IVLET comprise hyperlipemia, hypercoagulability, and rarely, thrombocytopenia in neonates.

IVLET may be considered for resuscitation by emergency physicians in resuscitation of severe hemodynamic compromise by lipid-soluble cardioactive xenobiotics. The purpose of this review is to highlight recent advances in our understanding of the efficacy and safety of IVLET, with special regard to its use in toxicity with cardioactive compounds.

**Keywords:** Lipid emulsion therapy; Lipid emulsion; Poisoning; Intoxication; Calcium-channel blockers;  $\beta$ -blockers

### What do we know about Lipid Emulsions?

The introduction of the first successful Intravenous Lipid Emulsion Therapy (IVLET) in the sixties was heralded as a major breakthrough in parenteral nutrition support. In the following decades, second-, third- and finally in 2000's, the fourth-generation fat emulsion were developed in accord with the changing needs which tends to increase the olive oil and fish oil content while decreasing the soybean oil mixture [1]. This fish oil-based fat emulsion is not merely a nutrient and an alternate energy source; it has also substantial anti-inflammatory effects and conveys significant pharmacological value [2]. Therefore, intravenous fat emulsions are a main component of nutrition, which helps to prevent essential fatty acid deficiency and can also be used as an alternate energy source to dextrose, avoiding the complications of excessive dextrose administration [1].

The fatty acids composing the emulsions may be saturated or unsaturated, stem from medium- and long-chain triglycerides with various pharmaceutical and metabolic activities which improved the safety and efficacy of these compounds in time [3]. Its mechanisms of action may include movement of drugs from the tissues to equilibrate in a larger circulating lipid pool (so-called 'lipid sink'), and restoration of metabolic pathways within cardiomyocytes. While the oldest available Intravenous Lipid Emulsions Therapy (IVLET) are based on pure soybean oil, rich in the proinflammatory  $\omega$ -6 polyunsaturated fatty acid linoleic acid, more recent next-generation lipid emulsions where alternative fatty acid sources such as olive and fish oil replace soybean oil to lower the content of linoleic acid seem safe and effective [4].

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By definition, IVLET is a 20% free fatty acid mixture used to deliver parenteral calories to patients unable to take oral nutrition [5]. Since 1990s IVLET has been widely studied as an antidote to local-anesthetic systemic toxicity. IVLET is the administration of a lipid emulsion to reduce the clinical manifestations of toxicity from excessive doses of certain medications, including local anesthetics, Beta-Blockers (BB), Calcium Channel Blocker (CCB), Tricyclic Antidepressant Drugs (TCAD) and other drugs [6]. Commercially available lipid injectable emulsions are marketed as 10%, 20%, and 30% oil-in-water emulsions.

The following article reviews the rationale for the introduction of IVLET as treatment for oral poisoning with cardiotoxicity and highlights a number of significant concerns based on current experimental and clinical evidence regarding its use in the emergency setting.

### Rationale for use: Animal Studies

Animal studies show efficacy of IVLET 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"). Jamaty et al. [7] reviewed 23 animal and 50 human trials involving use of IVLET in the management of poisoning. IVLET has certain benefits in poisoning scenarios with bupivacaine, verapamil, chlorpromazine, and some TCAD and BB. Interestingly, no trial assessed the safety of IVLET in the treatment of acute poisoning.

Li et al. [8] demonstrated that late intervention (i.e., 10 min. after drugs) with epinephrine plus IVLET improved haemodynamics, but failed to alleviate deterioration of hypoxaemia and acidaemia.

### Dosing Principles

The American College of Medical Toxicology (ACMT) recommends that IVLET 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 minutes [9]. 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 hour of 12.5 ml/kg [10].

### Adverse Effects of IVLET

Nowadays, modern IVLET can be safely used in most clinical situations with some restrictions (e.g., concerning their infusion rate). The first IVLET that met the criteria for safe clinical use was based on soybean oil. However, presence or absence of protective or toxic bioactive agents such as phytosterols and tocopherol in IVLET altered balances of antioxidants can trigger complications.

Adverse effects from standard IVLET include 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 [11].

Fortunately, adverse reactions are uncommon despite widespread use of IVLET. The adverse effects encountered with the use of IVLET 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 [12]. 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 [13,14].

### Hypersensitivity to components of IVLET

Allergy to egg is known as a contraindication to the use of lipid emulsions. Hypersensitivity to egg yolk and soybean oil explained the intolerance to the emulsifier or the triglyceride source of the IVLET, respectively [15,16].

### Coagulation problems

There is currently no evidence for adverse effects based on an increased bleeding risk, and conversely, while IVLET as carriers of lipid-soluble vitamin K might counteract the effect of warfarin on prothrombin time, clinical evidence for such effects is also lacking [17].

### Pulmonary problems

Parenteral soy oil-based IVLET have been shown to induce inflammation of pulmonary vessels in a pig model, leading to pulmonary hypertension, phagocyte activation, and the formation of granulomas [18]. Also, pulmonary gas exchange can be compromised by the accumulation of lipid droplets in the microcirculation, by actions of lipid-derived mediators such as peroxides and eicosanoids, or by the diminished availability of the vascular relaxant nitric oxide. Also, one study on 13 patients with Acute Respiratory Distress Syndrome (ARDS) indicates that administration of medium- and long-chain triglycerides caused alterations in lung function and hemodynamics. Inflammatory cells possibly activated by lipids, release phospholipase A2 and platelet-activating factor, enhancing edema formation, inflammation, and surfactant alterations [19].

IVLET interferes with some laboratory measurements and may affect therapeutic drug monitoring. Analyses of creatinine, amylase and lipase, phosphate, total protein, alanine transaminase, creatinine kinase and bilirubin can become impractical following IVLET. Also, serine glucose and magnesium levels would be inaccurate with standard laboratory processes [20]. Therefore, blood samples should be collected before commencing treatment with IVLET. Interferences can be minimized by brief centrifugation at low speeds on equipment available in most advanced labs [21]. Ultracentrifugation of blood allowed for detection of a metabolic panel three hours after the infusion. Centrifuged hematocrits appeared to be higher than expected [22].

Adverse effects are encountered proportional to the infusion rate and also the total dose received [11]. Further studies for safety of use in humans and adverse events associated with IVLET are needed.

Administration of IVLET concurrent with Extracorporeal Membrane Oxygenation (ECMO) may be associated with fat deposition in the veno-arterial-ECMO circuits and increased blood clot formation [23]. Although these and other potential complications from IVLET have been reported, further research is needed to determine the risk of complications from IVLET in the setting of acute overdose.

**Table 1:** Signs and symptoms for the diagnosis and recommendations for the treatment of poisonings with cardioactive agents.

	Beta blockers	Calcium channel blockers
<b>Signs &amp; symptoms</b>	conduction abnormalities	myocardial depression
	decreased contractility,	hyperglycemia
	sinus node suppression,	lacticacidosis
	depressed level of consciousness,	bradycardia
	atrioventricular dissociation,	intraventricular conduction delay
	right bundle branch block,	seizures (rare)
	ventricular arrhythmias	pulmonaryoedema (rare)
	intraventricular conduction delay	insulindeficiency
<b>IVLET</b>	hemodynamically unstable patients due to overdoses with BB must receive IVLET	
	advocated as useful treatment in patients with refractory shock or who are periarrest with incremental doses.	
<b>HET</b>	1.5 mL/kg of 20% lipid emulsion infused as a bolus, repeated up to twice, followed by an infusion of 0.25 mL/kg/min for 30 to 60 min.	
	first-line therapy for hypotension and/ or cardiogenic shock resulting from toxicity with CCB and/or BB.	
	in refractory shock or periarrest situations, incremental doses of high-dose insulin can be beneficial.	
<b>Glucagon</b>	Moderate chronotropic and inotropic benefits	is not recommended except for cases in extremis in overdoses of CCB
	Standard advanced cardiac life-support	Standard advanced cardiac life-support
<b>Other mainstay therapies</b>	Catecholamine infusions	intravenous fluid administration
	ventilatory support	extracorporeal cardiac assist devices
	intravenous fluid administration	venoarterial ECMO (in cardiac arrest)
	Transcutaneous or transvenous pacing	

## Clinical Use

Clinical efficacy of IVLET is firmly established in many reports to resuscitate patients with cardiotoxicity from local anesthetic systemic toxicity [6,24]. Recently, IVLET has emerged as treatment options for severe toxicity from BB and CCB. Resuscitation *via* IVLET seems to be an effective treatment for toxicity induced by lipophilic medications and may be useful in treating systemic toxicity all ages and almost all clinical scenarios, including pregnant patients [25]. Some researchers reported that IVLET has also been beneficial in neonates and children [26,27]. Administration of an exogenous lipid compound is expected to provide an additional pharmacologic compartment in which highly lipid-soluble drugs can partition, thus reducing drug burden at target tissues [28].

Some mechanisms of action of IVLET in the management of poisoning are believed to work for the effectiveness of IVLET. The 'lipid sink' phenomenon is the most widely accepted mechanism of action for IVLET, which involves surrounding a lipophilic drug molecule and rendering it ineffective [29,30]. Another suggested mechanism involves drug-induced disruption of cellular calcium transport and claims that the function can be restored by activating calcium channels by IVLET, which helps to increase intracellular calcium [31].

Mechanism of effects of the IVLET on local anesthetic agents are primarily based on droplet formations as well as changes in cell metabolism involving survival cell pathway, on functional properties and on direct hemodynamic parameters [32]. In recent years, some researchers put forth a novel mechanism to eliminate toxic agents *via* "functional nanogels" based on poly (N-isopropylacrylamide) for effectively scavenging compounds [33]. Acid-functionalized nanogels were found to bind cationic drugs such as local anesthetics and thus

have the potential to treat the overdoses.

A retrospective chart review showed a 55% survival to discharge in patients with cardiovascular collapse and extremely poor predicted outcome after receiving IVLET for cardiotoxicity drug ingestions [34]. In a small randomized controlled trial with a total of 30 patients in the setting of non-local anesthetic drug overdose, IVLET was demonstrated to increase GCS while interestingly, lowering the blood glucose [35]. It was recently claimed that IV Intralipid protects against ischemia-reperfusion injury and decreases the myocardial infarct size when it is administered at the beginning of reperfusion [36].

Animal studies and clinical reports guide the contemporary use of IVLET in treatment of overdoses caused by local anesthetic and non-local anesthetic, lipophilic medications. It seems reasonable to assume that a victim of cardiac arrest would not be harmed if IVLET is employed as a "last gasp" in resuscitation [24].

Lipid rescue has led to a reduction in fatalities associated with severe systemic toxicity of local anesthetic compounds, but continued research is necessary for a better mechanistic understanding.

## Hyperinsulinemia Euglycaemia Therapy (HET)

The key to the management of CCB and BB toxicity rests with aggressive supportive care of the circulation including expedient use of HET. Insulin promotes glucose use and storage and inhibits glucose release, gluconeogenesis and lipolysis. Its use in humans is supported by a systematic review, and efficacy has been demonstrated in clinically serious poisonings [37]. Supplemental insulin provides metabolic support to the heart during shock by promoting carbohydrate metabolism. Following beta-blockade, insulin increased myocardial glucose uptake and improved function [38]. Clinical studies of HET

consistently show beneficial effects of HET in cardiotoxicity drug poisonings [39].

Application of HET switches cardiac cell metabolism from fatty acids to carbohydrates. HET increases the intracellular transport of glucose, lactate and oxygen into myocardial cells, thus improving myocardial contractility. HET is commonly recommended as a first-line treatment in these poisonings, to improve myocardial contractility, and should be instituted early when myocardial dysfunction is suspected [40]. HET provided improved haemodynamic stability and survival compared to calcium, adrenaline or glucagon alone, not only in animal models of verapamil and propranolol poisoning [41,42], but also in human studies [43]. Animal studies have established HET as superior to conventional treatment across multiple hemodynamic parameters including improved coronary artery blood flow, contractility, cardiac output, and overall survival.

Levine et al. [44] reported the management and outcome of a series of 48 patients with non-dihydropyridine CCB overdose, at a single center. They concluded that hypotension was common and managed with the use of multiple vasopressors and without HET in a majority of the sample.

HET is administered in patients with CCB and/or BB poisoning, regular insulin is given at a dose of 1 U/kg IV bolus followed by an infusion at 1 U/kg/h to 10 U/kg/h, concurrent with infusion of 50% dextrose 50 ml to maintain euglycaemia. Although the optimal regimen is still to be determined, bolus doses up to 10 U/kg and continuous infusions as high as 22 U/kg/h have been administered with good outcomes and minimal adverse events.

In a study by Kerns et al. [41] a combination of high dose insulin and glucose increased coronary blood flow, reversed myocardial failure, and improved survival in BB poisoning in dogs. Doepker et al. [45] described successful reversal of cardiogenic shock *via* combined therapy with HET and IVLET after intentional ingestions of CCBs and BBs. This therapy is supported by animal work and multiple human case reports, but a randomized controlled trial is lacking.

Glucagon use is controversial in the treatment. There are scarce data supporting efficacy of glucagon in either CCB or BB toxicity. Graudins et al. [40] indicated that high-dose glucagon infusions have provided moderate chronotropic and inotropic benefits in BB poisoning. Due to the plenty of vials often required, it is frequently difficult to source adequate stocks of glucagon for use in poisoning cases. Therefore, its use in the treatment of CCB or BB poisoning is not recommended except for cases in extremis.

- 1) Start HET concurrently with calcium, glucagon, or norepinephrine, if necessary,
- 2) Stop dextrose infusion if blood glucose is <400 mg/dl,
- 3) Titrate dextrose infusion to maintain blood glucose 100 mg/dl to 250 mg/dl,
- 4) Monitor blood glucose q 20-30 min until stable, then q 1-2 hr
- 5) Potassium replacement not needed unless <2.5 mEq/l

### **Use in Oral Poisoning with Cardiotoxicity Medications other than Local Anesthetics**

Cardiovascular drugs including CCB, BB, and digoxin sodium channel blocker poisonings are associated with potentially life-

threatening toxicity. American Poison Control Centers report cardiovascular drugs as the substance category with the third fastest rate of increase in terms of exposures [46]. The most common nonlocal anesthetic xenobiotics which warranted administration of IVLET to date are TCAD and verapamil [47].

Forsberg et al. [48] have recently conducted a meta-analysis culminating 94 cases with oral poisoning and pointed out that the weak and contradictory scientific evidence for lipid rescue being an effective antidote and its increasingly reported adverse effects, it is reasonable to strictly limit its use in clinical practice.

The response to IVLET in clinical intoxication with BBs and CCBs is variable. In most cases, IVLET was administered as a 'rescue therapy' in verapamil or diltiazem poisoning, or as a part of poly-drug intoxications that included BBs with CCBs. In some cases a treatment effect was reported in minutes after IVLET, while the difference is delayed for several hours in others [22,49,50]. Most of the literature data involves adult cases; nonetheless, IVLET has been applied in neonates and adolescents, with generally positive outcomes [31].

Table 1 summarizes signs and symptoms for the diagnosis and recommendations for the treatment of poisonings with cardioactive agents.

#### **Beta blockers**

BBs reduce the facilitation of calcium entry into cardiomyocytes produced by increased CAMP, resulting in negative chronotropic and inotropic effects. The resultant effect is a direct depressant action on the myocardium, resulting in conduction delays, bradycardia and reduced contractility with little or no effect on peripheral vasculature. BB ingestions can cause significant morbidity and mortality when taken in overdose, especially if another cardioactive agent has also been ingested. Agents with membrane stabilizing effects are particularly dangerous. Love et al. [51] reported a prospective cohort of 280 BB exposures reported to 2 regional poison centers. They demonstrated that the single most important factor associated with cardiovascular morbidity is a history of a cardioactive coingestant, primarily CCB, TCAD, and neuroleptics. Also, exposure to a BB with membrane stabilizing activity is associated with an increased risk of cardiovascular morbidity. In one large series of patients with BB overdose, 30% to 40% of patients remained asymptomatic and only 20% developed severe toxicity. Most of the life-threatening presentations or deaths that have been reported in the literature are due to overdosage of propranolol or sotalol [52].

Typical manifestations of intoxication are conduction abnormalities and decreased contractility, sinus node suppression, while depressed level of consciousness, atrioventricular dissociation, right bundle branch block, ventricular arrhythmias and intraventricular conduction delay have also been encountered. Continuous cardiac monitoring and a 12-lead electrocardiogram are essential to identify cardiac conduction abnormalities.

The treatment of suspected cardiogenic shock in BB and CCB poisoning follows similar therapeutic principles. HET and catecholamine infusions form the mainstay of therapy to improve inotropy and chronotropy in both instances [40]. Supportive management may include airway and ventilatory support, intravenous fluid administration, early implementation of HET and administration of inotropes. Transcutaneous or transvenous pacing may be tried in cases with profound bradycardia, but often is of limited benefit. The indications for initiation of HET in CCB and BB

overdose are not well defined. This therapy is being advocated as first-line therapy for hypotension resulting from toxicity [52]. Severe cases potentially benefit from the use of cardiac ultrasound and invasive pressure monitoring to guide management.

In recent years, there has been growing evidence supporting use of IVLET to treat poisonings with some lipophilic substances including nonlocal anesthetics [53]. IVLET is thought to be particularly useful in the treatment of hemodynamically unstable patients due to overdoses with BB. IVLET has been administered with apparent effect in cases of hypotension or asystole unresponsive to other inotropes in propranolol, bisoprolol, carvedilol, nebivolol and atenolol poisoning [54].

After “classical” therapies (IV fluids, atropine, high dose insulin and glucose, and vasopressors) have failed to restore hemodynamic stability, IVLET has been used successfully in documented cases of severe BB overdose [45,55,56]. In BB poisoning, IVLET has been administered with apparent effect in cases of hypotension or asystole unresponsive to other inotropes in propranolol, bisoprolol, carvedilol, nebivolol and atenolol poisoning [54].

### Calcium channel blockers

CCBs directly inhibit voltage-gated L-type calcium channel opening and calcium influx into myocardial and vascular smooth muscle cells. Non-dihydropyridine CCB i.e., diltiazem and verapamil generally depress contractility and conduction more markedly, compared with the dihydropyridine group of CCB (e.g., nifedipine, amlodipine).

CCB are also considered metabolic poisons. The heart is dependent on free fatty acids for energy. In CCB overdose, the heart becomes more dependent on carbohydrates for energy, and insulin release from the pancreas is blocked. As a result, the ability of the heart to use the preferred energy substrate efficiently is exacerbated [57-59]. This determines appearance of hyperglycemia and lactic acidosis and further depressing the myocardial contractility.

Verapamil and diltiazem are lipophilic, non-dihydropyridine CCBs that have particular cardioselectivity, and are more toxic than dihydropyridine antagonists (such as amlodipine and nifedipine). The majority of serious cases and deaths result from the ingestion of nondihydropyridine CCB i.e., verapamil and diltiazem.

The severity of toxicity is affected by a number of factors, including the amount and characteristics of the drug ingested, underlying heart disease and previous health status of the victim, co-ingestion if any, age of the victim(s) and the time taken to initiate the treatment. Ingestion of toxic amounts of standard preparations typically produces symptoms within 2 h, although maximal toxicity may not occur for up to 6 h to 8 h [52]. CCBs can cause symptoms of cerebral hypoperfusion, such as syncope, lethargy, lightheadedness, dizziness, altered mental status, seizures and coma. Negative inotropic and chronotropic effects are common and peripheral vasodilation can also contribute to hypotension [60].

Extracardiac toxicity (such that pulmonary oedema, hyperglycaemia, lactic acidosis, seizures) is encountered rarely and herald worse outcomes. Children with suspected ingestion of even a single tablet of some CCB may require ICU observation for up to 24 hours. In addition, CCB poisoning often results in metabolic derangements resembling diabetes including acidemia, hyperglycemia, and insulin deficiency.

The treatment of suspected cardiogenic shock in BB and CCB poisoning comprise similar principles. Expedient and aggressive administration of charcoal and whole bowel irrigation should be instituted to prevent systemic absorption after a substantial overdose. In addition, HET and catecholamine infusions form the mainstay of therapy to improve inotropy and chronotropy in both instances [40]. Patients with evidence of shock caused by vasodilation will probably benefit most from a vasoconstrictor such as norepinephrine or phenylephrine. Patients with severe bradycardia or atrioventricular block need pulse rate support. Optimizing serum calcium concentration can confer some benefit to improving myocardial function and vascular tone after CCB poisoning. Intravenous infusions of inotropic agents such as dobutamine or phosphodiesterase inhibitors are used for signs of heart failure or cardiogenic shock. Acidemia worsens CCB toxicity, and sodium bicarbonate treatment improves hemodynamics [61].

IVLET has been promoted as a treatment for the most toxic ones of the CCBs non-dihydropyridine lipid-soluble CCB, including verapamil and diltiazem. Many reports indicated IVLET is effective in sequestering the toxic compound and thus alleviating the hazards of the free drug [62]. The use of IVLET appears justified in cases refractory to conventional therapy in felodipine poisoning [63].

French et al. [64] showed that administration of Intralipid® was associated with a decrease in serine verapamil levels once the lipid had been removed from the sample, demonstrating that Intralipid® was effective in removing verapamil from the serum. In clinical terms, IVLET administration was followed by normalization of the patient's blood pressure, although there is a notable confounding effect of other vasoactive drugs given concurrently. In a very recent review, St-Onge et al. [65] culminated data on the treatment of CCB poisoning and although the level of evidence was very low, a stepwise management is recommended. In addition, in patients with refractory shock or who is peri arrest, incremental doses of high-dose insulin and IVLET were advocated as useful modalities.

Systematic reviews of IVLET for acute poisoning have found the overall quality of studies supporting this treatment to be low or very low but human case reports provide some evidence of benefit in patients with toxicity from verapamil, BB, some tricyclic antidepressants, bupivacaine, chlorpromazine and flecainide [7,66,67]. IVLET may have a useful role in the treatment of patients who are hemodynamically unstable from such poisonings [45,49,68,69]. High-dose insulin and extracorporeal life support were the interventions supported by the strongest evidence, although the evidence is of low quality [37].

In cases of severe cardiogenic shock and/or cardiac arrest attributed to poisoning with CCB, extracorporeal cardiac assist devices have resulted in successful recovery. Other treatments used in refractory hypotension include IVLET for lipophilic CCB and BB poisoning [40].

All symptomatic patients should be admitted for monitoring. Because of the potential for delayed toxicity, patients ingesting sustained-release products should be admitted for 24 hours to a monitored setting, even if asymptomatic [70].

The recommendations of a multi-national expert workgroup were published recently [65]. Based on possible hemodynamic improvement documented in animal studies [71-73], case series [45,74] and case reports [47,66], the workgroup suggested the use

of IVLET. However, this is not recommended earlier in therapy in the absence of cardiac arrest, given the inconsistent response and the concern of potentially increasing the absorption of medications still present in the gastrointestinal tract by changing the distribution of the CCB. The workgroup felt that there were insufficient data to recommend a specific dose regimen of lipid-emulsion therapy [65].

### Therapy for patients in cardiac arrest

For therapy of CCB-poisoned patients in cardiac arrest, the workgroup recommends, in addition to standard advanced cardiac life-support provided to nonpoisoned patients, the use of IV calcium, even if previously administered, IVLET if not administered previously.

For therapy of CCB-poisoned patients in cardiac arrest, the workgroup suggests the use of IVLET, even if previously administered, and venoarterial ECMO [65].

### Conclusion

Clinical efficacy of IVLET is firmly established in many reports to resuscitate patients with cardiotoxicity from systemic toxicity of various agents. Animal studies and clinical reports guide the contemporary use of IVLET in treatment of overdoses caused by local anesthetic and non-local anesthetic, lipophilic medications. More specifically, IVLET can reliably reverse toxicity from CCB and BB. It seems reasonable to assume that a victim of cardiac arrest caused by cardioactive agents would not be harmed if IVLET is employed as a "last gasp" in resuscitation.

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