

INTRAVENOUS LIPID INFUSION IN TOXICOLOGICAL PRACTICE

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ABSTRACT

The use of intravenous lipid emulsions (ILEs) is a relatively new method of treatment in toxicology. Initially, it was applied to control the resistant to other therapeutic methods systemic toxicity of local anesthetics. In the last decade this therapeutic method has been approved and recommended. Thereafter, attempts have been made to clarify the effect of ILEs in cases of acute intoxications with lipophilic xenobiotics, other than the local anesthetics.

Keywords: *intravenous lipid emulsion, ILE, systemic toxicity, acute intoxications, lipophilic xenobiotics*

INTRODUCTION

Intravenous lipid emulsions (ILEs) infusion has been applied in clinical practice for more than 50 years. Its main designation was for parenteral nutrition, as a source of energy and essential fatty acids in hospitalized adults and children (1).

The first reports about ILEs administration are related to reducing the toxicity of local anesthetics in experimental animals. Local anesthetics are widely used for topical anesthesia, infiltration anesthesia, nerve block, including epidural and spinal anesthesia. Local-anesthetic systemic toxicity (LAST) is

the most dangerous complication in their application in medical practice. This life-threatening complication is a result of resorption or intravascular injection of the local anesthetic. The frequency of LAST is not high - 1:1000 (2), with clinical manifestations including arrhythmias, seizures, changes in consciousness to coma, cardiac arrest. A number of fatal cardiac arrest cases have been associated with the systemic toxicity of local anesthetics, such as bupivacaine and etidocaine (3). Often conventional treatment of these complications is ineffective (4).

Under experimental conditions, pretreatment of rats with ILEs protects bupivacaine-induced cardiotoxic effects. It was found that administration of 20% ILEs in rats after intravenous bolus dose administration of bupivacaine caused an increase in LD⁵⁰ from 12.5 mg/kg to 18 mg/kg compared to the control animals. All rats receiving lipid emulsion (LE) after a bolus dose of 15 mg/kg bupivacaine survived and all animals in the control group not receiving LE died (5).

In another experimental study, injection of bupivacaine at a dose of 10mg/kg caused the death of all

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dogs in the control group. Electrocardiogram (ECG) and blood pressure were normalized in animals receiving 20% of LE and they survived (6).

ILES was administered for the first time in clinical practice in 2006 to treat systemic toxic effects caused by local anesthetics bupivacaine and mepivacaine. After application of these anesthetics for a brachial plexus block, the electrocardiogram showed asystole. Heart rate and blood pressure were normalized 15 seconds after intravenous administration of 100 ml of 20% lipid solution. The patient recovered completely without neurological sequelae and cardiovascular changes (7). Subsequent reports demonstrate the beneficial effect of ILEs on LAST, often after unsuccessful standard resuscitation (8,9). Soon after administration of ropivacaine for axillary plexus block, a female patient experienced generalized tonic-clonic seizures, followed by asystole. Standard resuscitation measures were unsuccessful and 10 minutes later she received a bolus dose of ILEs, followed by lipid infusion. The patient restored normal heart rhythm, ECG and blood pressure. Four days later the patient was discharged from the hospital completely recovered (10). Five minutes after administration of bupivacaine and ropivacaine before total knee arthroplasty a patient experienced ventricular tachycardia and arterial pressure of 60/30 mm Hg, which were not overcome by standard performed resuscitation. Blood pressure was normalized and a sinus rhythm was recorded on the ECG 4 minutes after the patient received two bolus doses of 250ml 20% LE each. The patient recovered without further sequelae (11). A patient began to have generalized clonic-tonic seizure 20 seconds after sciatic nerve block with bupivacaine which was controlled with midazolam, followed by ventricular tachycardia that was not managed with amiodarone. A bolus dose of LE and electrical defibrillation followed by lipid infusion were administered. The ventricular tachycardia persisted for a few minutes, and after two hours the normal neurological status was restored. The complete recovery of the patient and the prevention of cardiovascular collapse were associated with rapid administration of ILEs (12).

ILES also restored neurological impairment and symptoms of LAST, including seizures and altered mental status and the benefits of their application are not limited to the cardiovascular system

(13). The administration of ILEs to treat neurotoxicity and ventricular ectopic activity effectively prevented progression to cardiac arrest (14).

After a lumbar plexus block with ropivacaine and lidocaine, a patient developed ventricular tachycardia. ILEs were infused at the start of tachycardia, normal vital indications and ECG were restored very quickly. This allowed surgical intervention to proceed without complications (15). ILE infusion is an acceptable therapy for LAST resistant to standard therapy (16).

MECHANISM OF ILE EFFECTS

The exact mechanism of action of ILEs is not yet fully clarified (17,18). Most authors accept the so-called a phenomenon of "lipid sink" (4,5,19,20,21,22,23). Rapid administration of ILEs as a bolus dose creates a new, enlarged lipid phase that absorbs lipophilic xenobiotics and prevents their binding to target receptors. The resulting concentration gradient causes a decrease in the concentration of the lipophilic xenobiotics in the tissues (5,21). Decreased serum concentration of the xenobiotic leads to its extraction from the tissues to the aqueous plasmatic phase and subsequently to the lipid phase (4,24), reducing its tissue toxicity (22).

The second hypothesis about the effect of ILEs is related to improved metabolism of cardiomyocytes. Under aerobic conditions, fatty acids are the main energy substrate for oxidative phosphorylation in myocytes. That is how approximately 80-90% of adenosine triphosphate (ATP) is synthesized in heart cells (25). Local anesthetics block the transport of fatty acids and, respectively, their oxidation in cardiomyocytes (26,27). ILEs increase intracellular fatty acids restoring their oxidation and ATP synthesis (4), thus improving myocardial contractility (28). However, the metabolic hypothesis does not explain the cerebro-protective effects of ILEs as neurons have limited ability to metabolize fatty acids.

According to the third hypothesis, ILEs restore heart function by increasing the concentration of intracellular calcium. This leads to a direct positive inotropic effect (29) as fatty acids activate calcium channels (30). Probably, the three potential mechanisms mentioned have synergistic action after administration of ILEs (19).

THERAPEUTIC EFFECTS OF ILE ADMINISTRATION

The practical application of ILEs in LAST is specified in the guidelines of the Association of Anaesthetists of Great Britain and Ireland (AAGBI), the American College of Medical Toxicology (ACMT) and the American Society of Regional Anesthesia and Pain Medicine (ASRA). In case of development of LAST, cardiopulmonary resuscitation (CPR) is initiated. It should not be prolonged, and should be followed by a bolus dose of 1.5ml/kg of Intralipid 20% for one minute, followed by intravenous infusion of Intralipid 20% at a dose of 0.25ml/kg/min for 30-60 minutes. If necessary, in case of non-stabilized circulation, the bolus dose is repeated twice in 5-minute intervals. If the patient is unresponsive, the infusion rate should be increased to 0.5ml/kg/min. The infusion continues for 10 minutes upon stabilization of hemodynamics. For the first 30 minutes, up to 10ml/kg Intralipid 20% may be applied to the patient (31,32,33). Some authors report the effective administration of lower than recommended LE doses, by infusion of 10% lipid solution (34) or a short-term infusion of 200 ml of 20% lipid solution administered after the initial regular bolus dose (35).

Following the promising results of the use of ILEs for the treatment of LAST, the efforts were recently directed towards the use of ILEs also in cases of intoxications with other lipophilic xenobiotics (36,37), as ILEs could be effective antidotes in acute exogenous intoxications with various xenobiotics (38). The first announcement about the effect of ILEs in humans beyond LAST is related to the treatment of severe combined oral intoxication with the antidepressant bupropion and the antiepileptic drug lamotrigine (39). Ten hours after drug ingestion, the patient began to have seizures and cardiac arrest with ventricular fibrillation. CPR was initiated, which did not restore heart function. A bolus dose of 100 ml of Intralipid 20% was administered 70 minutes later, pulse appeared after one minute and the sinus rhythm was restored 15 minutes later.

In subsequent reports the therapeutic effect of ILEs in acute intoxications with calcium antagonists, beta blockers, tricyclic antidepressants, antipsychotics (2,4,40,41,42) is demonstrated. There is no specific antidote for most of these substances (37).

Following an oral administration of the antipsychotic quetiapine and antidepressant sertraline - a selective serotonin reuptake inhibitor, the patient's level of consciousness deteriorated - Glasgow coma scale (GCS) 3 points and he became hypotensive. Four hours later the patient was administered 1.5ml/kg 20% lipid infusion in a bolus dose. Fifteen minutes later consciousness improved considerably - GCS 9 points, allowing to avoid endotracheal intubation. After 12h all vital indices were normalized (43).

After a suicidal attempt with 6000 mg of quetiapine, 400 mg of citalopram - a serotonin reuptake inhibitor antidepressant, and 45 mg of bromazepam, a patient became to have seizures evolving into status epilepticus and ventricular tachycardia. Due to life-threatening arrhythmia and seizures, 15ml/kg of 20% Lipofundin were administered, followed by 200 ml intravenous infusion over the next two hours. After the bolus dose, the ventricular tachycardia and convulsions were completely managed (35). The antidote effect of ILEs in acute intoxications with quetiapine was also demonstrated by other authors (44,45).

ILEs have been successfully administered in acute intoxications with other neuroleptics - olanzapine, haloperidol. A patient with cardiac arrest after haloperidol administration is treated with ILEs and sinus rhythm is restored (46). ILEs are powerful alternative to extracorporeal methods of treatment of acute carbamazepine intoxications (47).

One of the few randomized, controlled clinical trials on the effect of ILEs in patients with drug intoxications indicates that ILEs significantly improve consciousness (GCS) and reduce blood glucose levels (34). Severe intoxications with tricyclic antidepressants, particularly amitriptyline, are often manifested by ventricular arrhythmias, shock, and cardiac arrest. They are often refractory to treatment. In such clinical cases beneficial response to ILE was registered (48,49,50).

Calcium antagonists, and in particular verapamil, are widely used for the treatment of hypertensive disease, angina pectoris and arrhythmias. Acute intoxications with them are uncommon but severe and with high lethality (51). Cardiovascular shock is often refractory to treatment. In these cases, ILEs should be administered without delay as there are re-

ports of their positive effect in these intoxications (51,52,53,54). ILEs have been successfully applied in acute amlodipine intoxications (55,56,57).

Beta blockers are also commonly used in clinical practice to treat arterial hypertension, angina pectoris, heart failure, arrhythmias, migraine. ILEs are recommended in cardiac arrest and severe hypotension, refractory to ongoing therapy. A visible positive effect in asystole and hypotension, resistant to other inotropic agents in poisonings with propranolol, bisoprolol, carvedilol, nebivolol, atenolol (41) and metoprolol (58) is reported. The combined intoxications with beta blockers and calcium antagonists often cause cardiogenic shock due to myocardial depression and rhythm-conduction disorders. An additional mechanism of the etiopathogenesis of shock is vasodilatation caused by calcium antagonists. The treatment of these severe forms of poisoning also includes ILEs (59,60).

Intoxications with organophosphorus pesticides (OPs) take the lead as causes of fatal outcome in acute poisonings. Most of these pesticides are liposoluble. ILE infusions are a new potential method for the treatment of such intoxications (61,62,63). A patient who has swallowed parathion with a suicidal intention has a depressed consciousness - GCS 6 points, ventricular tachycardia followed by ventricular fibrillation and CPR undertaken was unsuccessful. Thirty minutes after the cardiac arrest, a bolus dose of Intralipid 20% of 1.5ml/kg was administered twice every two minutes. Fifteen minutes later, the width of the ECG QRS complex was normalized and the sinus rhythm was restored (64).

One of the most commonly used herbicides is glyphosate (Roundup). In conventional treatment-resistant intoxications with persisting hemodynamic instability, ILEs are recommended (65, 66), after which the patient is completely recovered and is discharged from the hospital without complications. A clinical study (67) established the antidote effect of ILEs in glyphosate intoxications. None of the patients treated with 20% of LE developed arterial hypotension or other complications, while 41% of the patients in the control group developed complications. Based on these results, the authors recommend ILEs as an effective treatment approach in severe glyphosate intoxications.

Despite the optimistic results of these and other reports on the effects of ILEs in acute intoxications with liposoluble xenobiotics other than topical anesthetics, this method is currently recommended only in cardiac arrest and life-threatening toxicity (68).

CONCLUSIONS

1. ILE infusion is a new method for the effective treatment of LAST resistant to conventional resuscitation therapy.
2. Application of ILEs in acute intoxications with xenobiotics other than topical anesthetics is recommended in life-threatening complications only.
3. ILEs may be applied in every hospital and the method is cost effective.

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