Review

Intravenous Lipid Emulsions in Anticonvulsants' Toxicity

Simeonka Dimitrova Dimitrova , Stela Toshkova Dragomanova * , Gabriela Krasimirova Kehayova

Posted Date: 25 April 2024

doi: 10.20944/preprints202404.1698.v1

Keywords: intravenous lipid emulsion; acute intoxication; antiepileptics; antidote; Glasgow Coma Scale scores; QT interval

 doi:10.20944/preprints202404.1698.v1

Review

Intravenous Lipid Emulsions in Anticonvulsants' Toxicity

Simeonka Dimitrova, Stela Dragomanova * and Gabriela Kehayova

Department of Pharmacology, Toxicology and Pharmacotherapy, Faculty of Pharmacy, Medical University of Varna, Bulgaria; simeonka.dimitrova@mu-varna.bg; stela.dragomanova@mu-varna.bg; gabriela.kehayova@mu-varna.bg

* Correspondence: stela.dragomanova@mu-varna.bg

Abstract: (1) Background: In recent years, an innovative approach has emerged in the field of toxicology for managing acute intoxications caused by lipophilic substances: intravenous lipid emulsions (ILE). Through numerous experiments and case reports, the efficacy of lipid emulsions in counteracting toxicities induced by lipophilic agents, including a significant number of antiepileptic drugs (AE), has become increasingly evident. (2) Methods: Data spanning a 10-year period (2010-2020) was analyzed by searching through multiple scientific publication platforms like PubMed, Science Direct, Research Gate, and Springer Link. The study focused on reviewing relevant case reports detailing successful Intravenous lipid emulsion (ILE) administration in patients with acute intoxications with antiepileptics, specifically examining the impact of fat emulsions on neurological status, Glasgow Coma Scale (GCS) scores, and corrected QT interval concerning hemodynamic instability. (3) Results: The typical symptoms of antiepileptic toxicity include central nervous system depression, ataxia, and nystagmus. Intravenous lipid emulsion application resulted in an increase in Glasgow Coma Scale scores and enhanced recovery from drug intoxication. (4) Conclusions: This study provides a comprehensive overview of the potential utility of ILE as a component to antidote therapy in cases of acute AE poisoning involving neurotropic drugs. The process involves the engagement of various mechanisms of antitoxic activity.

Keywords: intravenous lipid emulsion; acute intoxication; antiepileptics; antidote; Glasgow Coma Scale scores; QT interval

1. Introduction

Acute medication poisoning is a significant social and health issue on a global scale [1,2]. Medicinal substances are the primary cause of hospitalization among all intoxications [3]. In children, acute drug intoxications rank second in frequency after carbon monoxide poisoning [4]. Acute drug intoxications particularly linked to the consumption of benzodiazepines, neuroleptics, and cardiovascular medications, are prevalent worldwide [5]. The prevalence of acute drug intoxication varies significantly among different countries, ranging from 2.3% to 5.4% to as high as 13.8%. In certain predominantly Asian countries, this rate can reach as high as 88.2% [6]. Poisonings involving antiepileptic (anticonvulsant) drugs, which are closely related to benzodiazepines, hold significant social importance. These medications are traditionally used to decrease the frequency, severity, and duration of seizures in epilepsy.

Most xenobiotics (from "xenos" meaning foreign and "bios" meaning "life") do not have specific antidotes. In cases of acute poisoning with drugs that have a neurotoxic effect, a range of mental and somatic-vegetative symptoms may be observed, along with potentially fatal neurological and cardiovascular complications. These symptoms result from the direct impact of toxic agents on various structures of the central and peripheral nervous system (exogenous toxicosis) or from primary damage and dysfunction of parenchymal organs and systems responsible for detoxification (endogenous toxicosis). The most severe clinical symptoms of toxic damage to the nervous system include toxic coma and acute intoxication psychoses. Toxic coma typically occurs in poisonings involving CNS depressants. It is crucial for healthcare professionals to assess the level of

 doi:10.20944/preprints202404.1698.v1

consciousness suppression and depth of unconsciousness in order to provide appropriate care. These critical conditions demand prompt intensive care, calling for the adoption of more effective strategies in everyday practice.

In recent years, a relatively new method for treating acute intoxications with lipophilic substances has been introduced in toxicological practice - the intravenous infusion of fat emulsions. This method was discovered 16 years ago during the management of systemic toxicity caused by local anesthetics, specifically Bupivacaine [7]. It relies on certain fat emulsions, when introduced in large quantities into the bloodstream, to create an extended lipid phase known as the 'lipid sink' phenomenon which absorbs and 'captures' lipid-soluble drugs, extracting them from high concentration areas such as the heart and brain. By keeping these drugs away from the site of toxic action and preventing them from binding to biological targets, this method effectively mitigates their harmful effects. Free fatty acids in the formulation help to decrease the inhibition of sodium channel transport function caused by Bupivacaine in heterologous tissue culture. This modulation of cardiac sodium channels may help in reducing the effects of local anesthetic toxicity. The suppression of sodium channels indicates a potential impact on these transporters in acute toxicity induced by other channel blockers, including certain antiepileptic medications.

Despite the increasing amount of research providing information on the positive therapeutic effects of lipid emulsion and its use as an additional treatment method for acute intoxications, there are few and insufficient reports on its alleged neuroprotective role. This innovative approach is relatively underutilized. Since 2012, intravenous lipid emulsions (ILEs) have been sporadically used in treating acute poisoning with certain neuroleptics, antidepressants, benzodiazepines, as well as more recently with cardiovascular and antiepileptic medications. A review of contemporary literature examines the available scientific studies and research on the potential role of ILE as a supplement to in-hospital therapy for acute antiepileptic drug poisonings, with a particular focus on its impact on GCS results in these cases.

Given that many of these drugs are lipophilic compounds, the goal of this study is to summarize the antidote properties and effectiveness of ILE in cases of acute poisonings involving various antiepileptic medications.

2. Materials and Methods

The research study examined clinical reports on the treatment of acute toxicity caused by antiepileptic drugs over a 10-year period (2010-2020) across different scientific publication platforms including PubMed, ScienceDirect, ResearchGate, and SpringerLink.

3. Results

3.1. Acute Intoxications with Antiepileptics

Classical antiepileptic medications work by reducing excessive excitability in the central nervous system. They achieve this by either inhibiting sodium channels or affecting GABA-ergic neurotransmission. Examples of these medications include carboxamides (such as Carbamazepine and Oxcarbazepine), valproates, benzodiazepines, and barbiturates. However, the frequent and severe side effects associated with hydantoins (like Phenytoin) limit their use. Some medications, like valproates, have multiple mechanisms of action in treating epilepsy. In addition to inhibiting the enzyme responsible for breaking down the inhibitory neurotransmitter GABA, they also block calcium channels in the hippocampus. Additional cellular mechanisms involve blocking the excitatory communication between glutamate and N-methyl-D-aspartate (NMDA) receptors, as well as inhibiting neuronal exocytosis by interacting with synaptic vesicle protein 2A (SV2A). Acute poisonings from these substances usually present with a set of three symptoms: central nervous system depression, ataxia, and nystagmus, which are indicative of their toxic effects [8].

 doi:10.20944/preprints202404.1698.v1

3.1.1. Benzodiazepines

Based on their half-elimination period ($t_{1/2}$), which determines how quickly and for how long they act, Benzodiazepines (BZDs) are categorized into the following groups: long-acting (1 to 3 days): Clorazepate, Chlordiazepoxide, Diazepam, Flurazepam; intermediate-acting (16 hours): Alprazolam, Bromazepam, Clonazepam, Clotiazepam, Lorazepam, Loprazolam, Nitrazepam, Oxazepam, Temazepam, Triazolam; short-acting (3 to 8 hours): Midazolam, Triazolam.

Benzodiazepines are lipid-soluble drugs that exert their effects by modulating GABAA receptors. They bind to a specific region of this pentameric structure of the ligand-gated ion channel, which increases the frequency of channel opening and the influx of Cl– ions. This leads to membrane hyperpolarization and reduces neuron excitability. As a result, the effects of the natural neurotransmitter gamma-aminobutyric acid (GABA) are enhanced. GABA is the primary inhibitory mediator in the central nervous system. The increased GABA neurotransmission results in anxiolytic, sedative, soporific, myorelaxant, and anticonvulsant effects, including raising the seizure threshold. Activation of GABA receptors in the peripheral nervous system decreases myocardial contractility and promotes vasodilation [9].

Benzodiazepines are classic sedative-hypnotic medications that were introduced into medical practice in the 1960s. They were developed through extensive research using the chemical structure of barbiturates as a model, with the goal of mitigating their adverse effects, broadening their therapeutic range, and reducing the risk of addiction. BZDs are commonly used to treat various sleep disorders, anxiety, withdrawal symptoms, seizures, as muscle relaxants, for pre-surgery sedation, and other conditions. Currently, there are over 50 medications in this class available worldwide. The wide range of available benzodiazepine preparations and their frequent use increase the risk of acute poisoning [10].

Numerous studies have consistently demonstrated that poisonings caused by benzodiazepines (BZDs) are the most prevalent among cases of drug intoxication [11,12]. Marinov et al. (2016) reported that they constitute 26.37% of such cases, primarily stemming from suicide attempts, and are more common among women under 30 years of age [7]. The widespread usage of BZDs is linked to an elevated risk of developing tolerance and dependence on the medication. Abuse typically occurs through the ingestion of high doses, either alone or in conjunction with other psychoactive substances, notably alcohol. While ingesting BZDs independently in toxic amounts seldom results in significant toxidrome, they do heighten the neurotoxic effects of other psychotropic agents, including alcohol. This leads to significant respiratory depression, compromised airways, and often life-threatening intoxications. Patients experiencing this type of poisoning typically exhibit hyperemia and edema of the soft membranes and brain structures. In addition to brain alterations, there is stagnation in the internal organs. Clinical symptoms of acute intoxication include central nervous system depression characterized by slurred speech, difficulty breathing, slow and shallow breaths, and suppression of the thermoregulatory center, cardiovascular instability, hypotension, ataxia, altered mental status, and consciousness disturbances ranging from somnolence to coma. Death primarily results from respiratory depression, a phenomenon uncommon in benzodiazepine poisoning alone.

3.1.2. Barbiturates

Barbiturates are functionally categorized into four groups based on their half-elimination period: those with ultrashort action (< 0.5 hours) including Methohexital, Thiamylal, and Thiopental; those with short action (3 to 4 hours) such as Hexobarbital, Nembutal, Pentobarbital, and Secobarbital; those with intermediate action (4 to 6 hours) like Amobarbital, Aprobarbital, and Cyclobarbital; and those with long action (6 to 12 hours) including Barbital and Phenobarbital [7].

In clinical practice, barbiturates are primarily employed as antiepileptic agents, notably Phenobarbital, and for the induction of general anesthesia, such as Thiopental. They were extensively prescribed before the advent of benzodiazepines (BZDs), which are now more commonly used. This shift is attributed to the broader therapeutic range, reduced drug tolerance, lower potential for abuse, decreased risk of overdose, and the availability of an antidote for BZDs [13]. Barbiturates, generally,

 doi:10.20944/preprints202404.1698.v1

possess a narrow therapeutic range, meaning even a slight overdose can be life threatening, resulting in respiratory distress, severe hypotension, and hypothermia, potentially culminating in fatality. Their concurrent usage with other central nervous system depressants and alcohol exacerbates these risks. Tolerance to barbiturates develops rapidly within a few days, and prolonged use engenders both mental and physical dependence, underscoring the imperative to restrict their administration. Notably, in recent years, there has been a marked decline in the incidence of acute poisonings, attributable to diminished utilization of these substances.

Sedative-hypnotic drugs exert non-selective effects. In lower doses, they alleviate anxiety and emotional tension, while higher doses induce sedation, progressing to deep anesthesia and potentially fatal outcomes. Individual susceptibility to lethal doses of barbiturates varies. Respiratory depression, exotoxic shock, or pneumonia are the primary causes of death. Typically, clinical symptoms of poisoning manifest around 2 hours post-ingestion, peaking at 12 hours. A distinctive feature of barbiturate intoxication is hypothermia. Early mortality is linked to central nervous system depression and acute respiratory failure. Subsequently, complications may arise, including heart and kidney failure, cerebral and pulmonary edema [14]. Complications such as pneumonia, gastrointestinal bleeding, urinary tract infections, and thrombophlebitis are common during barbiturate intoxication [15].

In the context of intoxication, the predominant concern is the cerebral syndrome, which encompasses six distinct forms: cerebrotoxic, respiratory, cardio-circulatory, dysmetabolic, epidermal (occurring in severe cases alongside a comatose state), and delirium (arising during emergence from a comatose state). Based on the manifestation of these forms within the cerebral syndrome, acute poisoning is classified into four degrees: mild, moderate, severe, and extremely severe.

3.1.3. Carboxamides

Carbamazepine is frequently prescribed to manage epilepsy and various conditions such as neuropathic pain, postherpetic neuralgia, schizophrenia, and bipolar disorder in both pediatric and adult patients. Its primary modes of action involve inhibiting potential-dependent sodium channels and reducing membrane excitability. Additionally, carbamazepine impedes the reuptake of norepinephrine and acts as an antagonist for muscarinic, nicotinic, and NMDA receptors, along with central adenosine receptors. Overdosing on carbamazepine typically results in predictable, dose-dependent central nervous system depression and anticholinergic effects [16]. There is selective suppression of the motor zone of the cerebral cortex, inhibition of the transmission of excitatory impulses in the epileptogenic focus and reduction of the potential of propagation to neighboring areas.

Selective suppression of the motor zone of the cerebral cortex, inhibition of excitatory impulse transmission in epileptogenic foci, and reduction of propagation potential to adjacent areas characterize the action of Oxcarbazepine. It serves as a keto-analog of Carbamazepine and functions as a prodrug swiftly converted to 10-hydroxycarbazepine. While Oxcarbazepine was engineered to circumvent unwanted effects caused by metabolites of Carbamazepine, notable distinctions exist between the two medications. Oxcarbazepine primarily acts by blocking sodium channels but, unlike Carbamazepine, also modulates various types of calcium channels. Moreover, the involvement of hepatic CYP450-dependent enzymes in Oxcarbazepine metabolism is minimal [17].

The first reported case of Carbamazepine overdose dates back to 1967 [18]. Acute toxicity is typically observed at concentrations surpassing 40 mg/L, whereas therapeutic levels range from 4 to 12 mg/L. The toxicity progression of the drug unfolds through distinct stages: disorientation and ataxia manifest at blood concentrations of 11 to 15 mg/L; aggression and hallucinations emerge at 15 to 25 mg/L; convulsions and coma occur at levels exceeding 25 mg/L. Following the initial dose, the elimination half-life ($t_{1/2}$) is approximately 30 hours [19]. Symptoms of acute intoxication encompass dizziness, drowsiness, generalized convulsions, respiratory failure, cardiac arrhythmia, and fluctuating mental status, occasionally culminating in coma. Additionally, anticholinergic symptoms frequently manifest. Some patients may exhibit hyperchromic anemia, minor rhabdomyolysis, and

 doi:10.20944/preprints202404.1698.v1

consequent movement disorders. Notably, Carbamazepine serum levels reliably predict the severity of intoxication in cases of massive poisoning in adults. [20].

A noteworthy case involves acute Oxcarbamazepine intoxication in a 20-year-old pregnant woman with epilepsy, who deliberately ingested approximately 36 g of Oxcarbamazepine in an attempt to terminate her pregnancy. She was admitted to the Clinic for Intensive Treatment of Acute Poisonings and Toxic Allergies at Naval Hospital – Varna, presenting with slightly compromised general condition, but maintaining contact and displaying adequate responsiveness with pale skin, within 2 hours of the intoxication. Despite the situation, she remained independently mobile. Mild drowsiness and lethargy were noted. Respiratory function appeared normal, with vesicular breathing and a rate of 16 breaths/min, devoid of wheezing. Cardiovascular examination revealed no anomalies, with a heart rate of 90 beats/min and mild hypotension (blood pressure 110/70 mm/Hg). The uterine size corresponded to a pregnancy of the fifth month. Biochemical analysis indicated no elevation in liver enzyme activities (ALT, AST, GGT). Remarkably, the anticipated toxic syndrome did not manifest, and the fetus remained viable. (Apostolova V. and Zlateva S., 2019, unpublished data).

3.1.4. Valproates

Valproates (VPA) are primarily prescribed for the management of epilepsy, bipolar disorder, and the prevention of migraine headaches [21].

Acute intoxications involving VPA often result in central nervous system depression, presenting symptoms such as drowsiness, tremors, stupor, respiratory depression, metabolic acidosis, and in severe cases, coma or even death. Under controlled therapy, serum or plasma concentrations typically range from 20 to 100 mg/L, whereas acute poisoning may elevate levels to 150 to 1500 mg/L. Generalized tonic-clonic seizures are infrequent in VPA poisoning, typically occurring only with massive overdoses [22]. Moreover, cases of cerebral edema, metabolic acidosis, hypoglycemia, hypophosphatemia, hypocalcemia, and hypernatremia have been documented in such instances [23]. Furthermore, VPA inhibits the β-oxidation of mitochondrial fatty acids, thereby causing autoinhibition or saturation of its metabolism. Consequently, alternative metabolic pathways are activated, potentially leading to the production of various hepatotoxic compounds.

3.1.5. Lamotrigine

Lamotrigine is an antiepileptic medication utilized in the treatment of partial and tonic-clonic seizures, and it serves as a mood stabilizer for bipolar disorder. Its mechanism of action is multifaceted: it inhibits potential-dependent T-type calcium channels and blocks voltage-dependent sodium channels, thereby suppressing glutamate exocytosis. Additionally, it inhibits serotonin reuptake, which may underlie its antidepressant properties [24].

Patients with epilepsy or psychiatric conditions are at an elevated risk of intentional overdose. Lamotrigine toxicity primarily affects the central nervous and cardiovascular systems. The serotonin syndrome characterizes central nervous system toxicity, particularly pronounced when Lamotrigine is combined with other substances that potentiate this effect. Symptoms of CNS serotonin syndrome encompass severe depression accompanied by altered mental status, ranging from agitation to coma. Additionally, neuromuscular hyperactivity may present with hyperreflexia, ataxia, nystagmus, and generalized tonic-clonic seizures. Cardiovascular manifestations commonly include bradycardia, atrioventricular (AV) block, and tachycardia, reflecting its impact on cardiac conduction [25].

3.1.6. Hydantoins (Phenytoin)

Since its discovery in 1908, Phenytoin has been extensively studied as an anticonvulsant and is also utilized as a class IB antiarrhythmic drug. However, its narrow therapeutic index and widespread usage often result in acute intoxications [26]. Phenytoin functions by blocking membrane potential-dependent sodium channels responsible for activating neuronal action potential. Consequently, it inhibits the positive feedback, thus averting excitatory neurotoxicity [27].

 doi:10.20944/preprints202404.1698.v1

Toxicity from Phenytoin primarily manifests in the nervous and cardiovascular systems. Oral overdose predominantly induces neurotoxicity, with cardiovascular toxicity being relatively rare. Neurotoxic effects vary with drug concentration, ranging from mild nystagmus (20 to 30 mg/L) to ataxia (30 to 40 mg/L), slurred speech, vomiting, and lethargy (40 to 50 mg/L), progressing to coma and potentially death (>50 mg/L) [28]. Paradoxically, very high concentrations of the drug may trigger seizures. Cardiovascular toxicity is characterized by arrhythmias and conduction system blockade (SA and AV), albeit less frequently observed after oral ingestion [29].

3.2. Toxic Damage to the Nervous System

In clinical settings, a classification system is utilized to evaluate quantitative alterations in consciousness, outlining four levels of consciousness suppression:

Obnubilation: This represents the mildest degree of clouding of consciousness, where the patient appears lethargic and struggles to maintain focused attention.

Somnolence: Characterized by pathological sleepiness, interaction with the patient becomes challenging and incomplete. They may only comprehend basic questions and respond with brief utterances.

Sopor: At this stage, contact with the patient is nearly impossible. They may react to pain with defensive movements and produce unclear sounds or words. However, their pupils react to light, and reflexes in tendons, periosteum, skin, and mucosa remain intact. Swallowing is feasible, but there may be incontinence of pelvic contents.

Coma: Here, the patient experiences complete loss of consciousness.

Introduced in 1974 by two professors of neurosurgery at the Institute of Neurological Sciences at the University of Glasgow, the Glasgow Coma Scale (GCS) is widely employed for the objective assessment of consciousness [30]. Initially developed to evaluate consciousness levels following cranio-cerebral injuries, it is now utilized in both emergency and intensive care medicine settings, spanning from patients with acute injuries and illnesses to those in terminal conditions. Remarkably, the GCS has proven applicable even in cases of acute poisonings. As per the Glasgow Coma Scale, brain damage can be categorized as severe (values below 9), moderate (values 9 – 12), and mild (values equal to or greater than 13).

In the neurological manifestations of acute poisonings, somatic-vegetative disturbances hold significant prominence [7]. These are characterized by symmetric alterations in pupil size, disruptions in sweating, and impaired secretion from salivary and bronchial glands. Common accompanying symptoms include a muscarinic-like syndrome, featuring pinpoint pupils, excessive sweating, heightened salivation, increased bronchial secretions, bronchospasm, bradycardia, and accelerated intestinal peristalsis. Toxic mono- and polyneuritis are also frequently observed, particularly affecting the lower limbs, with symptoms including altered sensitivity, reflexes, and mobility. Morphological changes are evident in nerve cells, myelin, or the Schwann sheath.

One of the most perilous complications of exotoxic coma is cerebral edema, where factors such as hypoxia, metabolic imbalances, impaired cellular membrane transport, disruption of the blood-brain barrier, and cerebral circulation disorders play pivotal roles in its pathogenesis. The onset of cerebral edema manifests a range of neurological symptoms, including transient paralysis, epileptiform seizures, hyperthermia, bulbar disturbances, and congestive papillae.

Unconsciousness is a prevalent occurrence in emergency departments, with various conditions besides acute poisoning potentially leading to impaired consciousness. Exogenous intoxications, metabolic imbalances, and cerebral injuries are among the primary culprits behind the comatose state.

Coma entails a complete loss of consciousness endured for an extended period. It is essential to differentiate coma from syncope, characterized by brief, transient loss of consciousness lasting from seconds to minutes, and from stupor, wherein reactivity remains intact despite a subdued state of wakefulness, typically observed in mental illnesses such as schizophrenia. Coma can manifest suddenly, even in individuals previously considered healthy. Extensive clinical investigations have

 doi:10.20944/preprints202404.1698.v1

underscored the pivotal role of identifying and quantifying toxic substances through chemical-toxicological analysis of blood and urine for precise diagnosis [31].

3.3. Lipid Emulsions

3.3.1. Historical Data

The experimental use of intravenous lipid emulsion (ILE) dates back to the 18th century. In 1712, William Courten made the initial attempt by administering parenteral fats, infusing intravenous olive oil into a dog. Unfortunately, the dog succumbed within hours to respiratory distress attributed to fat embolism [32]. Subsequently, in 1869, Wentzel and Perco, following possible animal experiments, subcutaneously injected fat into a severely asthenic patient suffering from Potts disease [33]. In 1873, Hodder in Toronto employed intravenous milk infusion to treat cholera in three patients, with two of them recovering [34].

The first systematic endeavors to apply artificial fat emulsion to humans occurred in Japan between 1920 and 1930. In the United States, despite ongoing discussions, no documented results were recorded until 1950. The first clinical and experimental data on the utilization of lipid emulsion derived from cottonseed oil were not published until 1957 [35]. However, post-infusion, this elicited acute side effects of clinical significance, including fever, liver damage, jaundice, and bleeding, leading to the cessation of its application.

In 1963, Swedish physician and nutrition researcher Arvid Wretlind pioneered the development of the first Intravenous Lipid Emulsion (ILE) for human intravenous administration [36]. Over nearly six decades, it has remained the most widely used ILE, benefiting millions of patients worldwide. Initially, these emulsions were primarily utilized as an effective glucose-free energy source to mitigate the adverse effects associated with high dextrose intake. They serve two primary functions: providing a source of energy and supplying essential fatty acids in parenteral nutrition regimens for patients [37].

Intravenous fat emulsion plays a crucial role as an energy source for patients receiving parenteral nutrition, fulfilling 30% to 50% of their non-nitrogen caloric needs, equivalent to approximately 20% to 30% of total calories or 9 kcal/g of energy. The caloric content of intravenous lipid emulsions varies depending on their concentration [38,39].

3.3.2. Composition of ILE

A fat emulsion designed for intravenous administration typically comprises vegetable oil dispersed in water, along with one or two emulsifiers to ensure emulsion stability. Recent years have seen extensive studies on various fats and triglycerides. Initially, five ILEs were introduced, incorporating cotton or soybean oil. Different phospholipids serve as emulsifiers. To achieve the necessary isotonicity with blood, the aqueous phase commonly includes glucose, sorbitol, or glycerol. Lipids within these emulsions exist as dispersed particles abundant in triglycerides, stabilized by phospholipids, with particle sizes akin to chylomicrons (200÷400 nm). Triglycerides are predominantly derived from vegetable oils or fish oil, found in newer emulsions with concentrations ranging from 10% to 30% [40].

The fatty acid composition varies among different emulsion types.

3.3.3. Neuroprotective Role of ILEs

There is a scarcity of studies in the literature regarding the utilization of ILEs in acute drugs intoxications. Information regarding their protective effects against ethanol-induced neurotoxicity remains limited. However, one study revealed a beneficial effect in cases of acute ethanol intoxication, wherein brain tissue was shielded from the deleterious effects of induced oxidative stress after ILE administration [41]. The likely rationale behind this protective effect of emulsions predominantly stems from their high content of triglycerides containing both saturated and unsaturated fatty acids. Unsaturated fatty acids are known to serve as scavengers in reactive oxidative stress scenarios.

 doi:10.20944/preprints202404.1698.v1

Moreover, ILEs have been observed to directly interact with cell membranes and induce structural alterations, thereby reducing the release of free radicals into the extracellular environment [42].

3.3.4. Application of ILE in Acute Drug Intoxications

There is a notable absence of rigorous and comprehensive clinical trials involving ILE, including both single and double-blind studies. Scientific literature primarily consists of case reports or case series detailing purported positive effects of intravenous ILEs in acute poisonings involving numerous substances, albeit lacking reliable evidence. However, synthesizing information from these reports offers valuable clinical insights into specific toxic syndromes, shedding light on the typical course of overdose and its response to lipid therapy.

ILEs are believed to possess the capacity to ameliorate the condition of patients experiencing acute intoxication with lipophilic medicinal substances. Animal studies and select human reports delineate their utility in treating poisonings involving substances such as Clomipramine, Verapamil, Propranolol, Bupropion/Lamotrigine, and Quetiapine/Sertraline. Additionally, according to Moshiri et al., ILEs have demonstrated successful outcomes in acute poisonings involving various drugs with potential impacts on the nervous and cardiovascular systems, including antiepileptics [43] (refer to Table 1).

Table 1. Use of ILEs in acute drug intoxications.

Drug group		Drug	Application in humans	Application in animals
Local anesthetics		Bupivacaine	18	10
		Ropivacaine	13	
		Mepivacaine	2	
		Lidocaine	4	
		Lupivacaine	1	
		Propofol	1	
Antidepressants	TCA	Amitriptiline	5	1
		Clomipramine	1	4
		Imipramine	1	
		Doxepin	1	
	TeCA	Mirtazapine	1	
		Amoxapine	1	
	SSRIs	Fluoxetine	1	
		Sertraline	1	
	SNRIs	Venlafaxine	1	
	Others	Bupropion	1	
Calcium channel blockers		Verapamil	5	6
		Diltiazem	1	
		Amlodipine	3	
		Nifedipine	1	
Beta-blockers		Propranolol	1	3
		Atenolol	2	1
		Carvedilol	2	
	Non-BDZ	Zopiclone	1	

 doi:10.20944/preprints202404.1698.v1

Sedative-hypnotics	BDZ	Midazolam	1	
Antipsychotics		Quetiapine	3	
		Haloperidol	2	1
		Chlorpromazine		1
Antiepileptics		Carbamazepine	1	
		Lamotrigine	1	
		Thiopental	1	
Organophosphorus compounds		Paraoxon		1
		Diazinon		1
Other		Digoxin	1	
		Cyclobenzaprine	1	
		Ketorolac	1	
		Ivermectin		1
		Ethanol	2	
		Amphetamine	1	
		Hydroxychloroquine	1	
		Flecainide	1	
		Lithium	1	

TCA – tricyclic antidepressants; TeCA – tetracyclic antidepressants; SSRIs – selective serotonin reuptake inhibitors; SNRIs – selective norepinephrine reuptake inhibitors; BDZ – benzodiazepines.

3.4. Mechanisms of Antidotal Action of ILE in Acute Systemic Toxicity

3.4.1. "Lipid Sink" Phenomenon

A widely accepted mechanism of action for Intravenous lipid emulsions is the "lipid sink" phenomenon, first identified by G. Weinberg in 1998 [44]. This concept revolves around certain ILEs, when introduced in significant quantities into the bloodstream, creating a lipid phase capable of absorbing ("capturing") lipophilic xenobiotics. By extracting these substances from areas of high concentration, particularly the heart and brain, the lipid phase prevents their binding to targets, thus thwarting their toxic effects.

The distribution of drugs from regions of high concentration to those of lower concentration adheres to pharmacokinetic principles. Lipid infusion establishes an expanded lipid phase, facilitated by the concentration gradient, which drives the migration of substances from the aqueous plasma phase of blood and tissues to the lipid phase of the emulsion. This setup ensures the swift removal of toxic agents from sites of high accumulation, such as the brain and heart, facilitating their incorporation into the lipid fraction via blood plasma. This mechanism not only shifts the equilibrium from the end organ to the plasma but also accelerates metabolism and promotes the distribution or sequestration of drugs away from their targets. Consequently, the concentration of lipophilic toxic agents decreases in tissues, elucidating the organ-protective effect of ILEs. This process of redistribution is commonly referred to as the "lipid sink" or "lipid shuttle". Emulsified fat droplets form the lipid phase in which lipophilic substances, such as local anesthetics, are theoretically incorporated, effectively moving the toxicant away from critical organs like the heart and brain [45]. In an experimental in vitro rat model, G. Weinberg et al. (1998) demonstrated through high-performance liquid chromatography that radiolabeled Bupivacaine, when added to lipid-treated rat plasma, exhibited preferential incorporation into the lipid phase with a partition coefficient of 11.9 [44]. Subsequent experiments conducted in 2006 using an isolated heart model to simulate Bupivacaine toxicity illustrated that infusion of ILE not only expedited the removal of radiolabeled

 doi:10.20944/preprints202404.1698.v1

Bupivacaine from myocardial tissue and enhanced its elimination rate but also reinstated drug-induced asystole [46]. According to the authors, these findings support the hypothesis that Bupivacaine partitions into the emulsion and substantiate the concept of a "lipid sink", although they do not preclude the existence of other potential mechanisms of action.

Concrete evidence supporting the lipid sink model is furnished by the studies conducted by Mazoit et al. (2009), revealing that ILE bind substantial quantities of lipid-soluble local anesthetic [47]. Complementing this in vitro experiment, Niiya et al. (2010) observed that pretreatment of pigs with an ILE shielded them against Amiodarone-induced hypotension [48]. Moreover, through ultracentrifugation of plasma to segregate the lipid-bound drug fraction, it was discerned that Amiodarone exhibited a preference for partitioning into the newly formed lipid phase. This observation constitutes direct substantiation of the "lipid sink" effect, as the resultant lipid-free aqueous phase exhibited lower Amiodarone concentrations compared to control animals administered saline instead of lipid. Samuels et al. (2012) assessed the efficacy of fractionation by examining the impact of drugs with varying lipid solubility on blood methemoglobin production [49]. They found that the addition of fat emulsion notably decreased the process induced by most lipid-soluble drugs, although it failed to suppress the process induced by less lipid-soluble drugs. This underscores the significance of the lipid sink in mitigating the adverse physiological effects associated with drug toxicity.

Collectively, these studies lend support to the hypothesis that "lipid uptake" plays a pivotal role not only in the treatment of Bupivacaine toxicity but also in the management of other lipophilic substances. However, the findings of other experiments challenge the notion of "lipid uptake" as the primary mechanism of action of ILEs. For instance, Litonius et al. (2012) conducted a study measuring Bupivacaine concentrations in the blood of volunteers who received small doses of the local anesthetic followed by either ILE or a control infusion of Hartmann's solution [50]. Their results indicated no discernible difference in the concentration of free (non-lipid or protein-bound) bupivacaine compared to controls, suggesting the absence of a "lipid sink" effect. Conversely, the infusion of ILE significantly shortened the plasma half-life of the anesthetic by more than 40%, implying a beneficial impact on the drug's distribution in peripheral tissues.

Following successful laboratory reports on resuscitation from Bupivacaine toxicity, the efficacy of lipid infusion has been investigated in animal models of overdose with various other drugs. Naturally, attention has been directed towards substances that frequently cause acute poisonings, such as TCAs, beta-blockers, and calcium channel blockers. The publication by Sirianni et al. (2008), detailing the administration of an Intravenous Lipid Emulsion (ILE) in patients with severe cardiotoxicity resulting from Bupropion and Lamotrigine intoxication, along with numerous studies conducted on animal models, provides impetus to expand the use of ILE for treating acute poisoning involving other lipophilic drugs as Verapamil, Diltiazem, Amlodipine, Quetiapine, Sertraline, Haloperidol, Lamotrigine, Olanzapine, Propranolol, Atenolol, Nebivolol, Doxepin, Dosulepin, Imipramine, Amitriptyline, and others [51]. It is important to acknowledge that not all reports subscribe to the hypothesis that the direct mechanism of action of Intravenous Lipid Emulsion (ILE) is responsible for toxicological reversal. Nonetheless, researchers concur that the administration of oil emulsions demonstrates efficacy in cases involving lipophilic agents, albeit varying in amounts and concentrations. Harvey and Cave (2012) supported the effectiveness of this therapeutic approach in managing multidrug overdose [52]. They documented a case involving profound neurological and cardiovascular manifestations in acute Tricyclic Antidepressant (TCA) intoxication. A 51-year-old man weighing 75 kg, with a medical history of ischemic heart disease, chronic back pain, and depression, ingested unknown quantities of multiple pharmaceuticals (including Quetiapine, Citalopram, Metoprolol, Quinapril, and Acetylsalicylic acid), including Amitriptyline exceeding 43 mg/kg (>65×50 mg tablets) deliberately as an act of self-poisoning. The clinical presentation of symptoms was characteristic of TCA-cardiotoxicity. Following unsuccessful active therapy to mitigate the developing shock, a 100 mL bolus of 20% ILE was administered, followed by an additional 400 mL over 30 minutes. This intervention restored hemodynamic stability, eliminating the need for further vasopressor medication. Blood levels tested were consistent with the "lipid sink"

 doi:10.20944/preprints202404.1698.v1

playing a significant role in the observed improvement. Based on the patient's recovery history and laboratory parameter dynamics, the authors concluded that ILE likely contributed significantly to the favorable outcome of the case.

Fettiplace and Weinberg (2018) meticulously delineated the concentration-dependent restoration of cardiovascular function [53]. They asserted that the mechanism of action of Intravenous Lipid Emulsion (ILE) relies on the tissue concentration of the drug. Improvement in cardiovascular function is not anticipated until Bupivacaine concentrations drop below threshold levels for channel blockage, with recovery contingent upon the redistribution of the drug from the heart to the muscles and liver. The incorporation of lipids facilitates the expedited removal of the drug from cardiac tissue. The primary advantage of ILE lies in its cleansing effect. According to this study, in the bloodstream, Bupivacaine exists as a combination of neutral and cationic (positively charged) forms, with the positively charged ions binding to plasma proteins, such as albumin, through electrostatic interactions. The introduction of lipids provides a third phase (lipid + plasma) for Bupivacaine binding. Lipid droplets consist of a monolayer shell of phospholipid (and some phytosterols) surrounding hydrophobic triglyceride cores. Through lipophilic partitioning, the amphiphilic Bupivacaine molecule integrated into the membrane or transported into the hydrophobic core. Additionally, the positively charged molecules will adhere to the negatively charged phospholipids on the droplet surface due to electrostatic forces. Weinberg (2012) discovered that integrating intravenous lipid emulsion application into the treatment protocol for mixed acute intoxication involving lipophilic drugs led to a reduced requirement for intubation and shorter stays in the intensive care unit compared to patients in the control groups who were treated without fat emulsion [54].

It is widely accepted that two potential mechanisms of action, namely partitioning and enhanced metabolism, are believed to explain the beneficial effects of lipid infusion in bupivacaine toxicity. However, in recent times, additional evidence has emerged suggesting several other significant potential mechanisms of action.

3.4.2. Impact on Bioenergy

According to this theory, the rapid infusion of a substantial amount of fatty acids (bolus administration) offers an energy substrate for myocardial dysfunction. Lipids serve as a primary energy source for cardiac cells under normal aerobic conditions, suggesting that the administration of intravenous lipid emulsion may directly influence cardiac function. Thus, it was proposed that the high lipid load could potentially compensate for the potent inhibition of fatty acid metabolism caused by Bupivacaine. Stehr et al. (2007) presented the initial evidence supporting this theory [55]. They demonstrated in isolated rat hearts that, despite the lipid content being insufficient to significantly lower the local anesthetic concentration in the perfusate, ILE could mitigate Bupivacaine-induced depression of cardiac function. Preventing the oxidation of fatty acids inhibits the lipid reversal of Bupivacaine-induced cardiac toxicity. Enhanced metabolism was linked with supplementary cytoprotective effects, which mitigate mitochondrial permeability, a pivotal stage in programmed cell death.

Local anesthetics and other potentially cardiotoxic drugs can hinder fatty acid transport in cardiomyocyte mitochondria by inhibiting the enzyme carnitine-acylcarnitine translocase [56]. It's believed that high plasma triglyceride levels can counteract this inhibition.

In a contrasting approach, Rahman et al. (2011) discovered that in rodents, lipid infusion decreased reperfusion injury during cardiac ischemia [57]. Incorporating metabolic inhibitors into experimental protocols decreases the probability of mitochondrial permeability activation and apoptosis induction.

Theoretically, intravenous lipid emulsion could augment intracellular fatty acid content, thereby counteracting the diminished adenosine triphosphate (ATP) production resulting from local anesthetic blockade. It's conceivable that the therapeutic effect of ILE stems from an elevation in intracellular fatty acid levels, which also contributes to enhanced ATP synthesis in cardiomyocytes. Given that fatty acids serve as a primary substrate for oxidative phosphorylation under aerobic

 doi:10.20944/preprints202404.1698.v1

conditions, generating roughly 80-90% of cardiac ATP, their impaired transport leads to diminished ATP production, adversely impacting cardiomyocyte viability and potentially inducing cardiac toxicity [58]. ILE infusion enhances contractility by fostering improved fatty acid oxidation. Consequently, ILE may sufficiently elevate intracellular fatty acid content to counteract or alleviate the reduction in cardiac ATP synthesis.

3.4.3. Activation of Calcium Channels

Another potential mechanism of action of intravenous lipid emulsion (ILE) in acute poisonings involves the direct activation of voltage-dependent calcium channels, leading to an elevation in intracellular calcium levels and subsequent stimulation of cardiac activity. Supporting this hypothesis is a study by Huang et al., demonstrating that long-chain fatty acids enhance calcium currents in cardiac myocytes [59]. Interestingly, ILEs exhibit a rapid onset of action in vivo, suggesting that their direct cardiotonic effects may also contribute to their mechanism of action.

Elevated levels of calcium in cardiomyocytes produce a direct positive inotropic effect, as demonstrated in a study by Gueret et al [60]. The authors investigated the impact of Intralipid treatment on verapamil toxicity in rats and found that standard therapy with ILE enhances hemodynamic stability and survival in an animal model of severe verapamil toxicity.

3.4.4. Affecting the Enzyme Translocase

One vital cardiac protein with enzymatic properties is carnitine-acylcarnitine translocase, which facilitates the transport of acyl-CoA-bound fatty acids across mitochondrial membranes for their oxidation. This transfer of fatty acids, possessing long hydrocarbon chains, across the inner mitochondrial membrane occurs via the shuttle mechanism, aided by the low molecular weight transporter carnitine.

Carnitine exists in two forms, L- and D-, with the L-form being physiologically active. L-carnitine, closely associated with fat metabolism, plays a crucial role in preventing the accumulation of lactic acid in muscle cells. A study conducted by Seong-Ho Ok et al. explored the effects of lipid emulsions on various enzymes including carnitine palmitoyltransferase I (CPT-I), carnitine acylcarnitine translocase (CACT), and carnitine palmitoyltransferase II (CPT-II), as well as mitochondrial dysfunctions induced by toxic doses of local anesthetics [61]. The findings suggest that lipid emulsion mitigates levobupivacaine-induced inhibition of CACT, potentially through the sequestration of levobupivacaine mediated by lipid emulsion.

3.4.5. Inotropic Effect

Intravenous administration of lipid emulsion (LE) has been proposed to exert a positive inotropic effect. Stehr et al. (2007) demonstrated that lipid infusion produced a positive inotropic effect in the isolated rat heart and reversed bupivacaine-induced cardiac depression at lipid levels below those required to reduce the concentration of bupivacaine in the aqueous phase [54]. The infusion of lipid emulsion can induce a direct cardiotonic effect both in vivo and in isolated rat hearts. Although the exact mechanism behind this phenomenon remains unknown, its action is notably rapid, making lipid emulsion a preferred choice for acute poisoning situations.

The administration of ILE "reversed" Bupivacaine-induced cardiodepression at concentrations too low to facilitate the "lipid sink" phenomenon, suggesting a metabolic explanation for the positive effect, as proposed by Fettiplace and Weinberg (2018) [58]. According to their theory, lipid emulsion significantly contributes to cardiovascular recovery through an additional cardiotonic effect. The triglycerides and phospholipids present in the lipid emulsion exert a favorable influence on the cardiovascular system (CVS) either directly on the heart or the vascular system. This effect becomes evident only after the concentration of the respective drug falls below the threshold required for blocking the ion channels. In cases of acute toxicity leading to asystole and cardiovascular collapse, circulating lipid "droplets" of the lipid emulsion can extract the drug from the tissue, thereby restoring cardiac function. These lipid droplets facilitate the rapid redistribution of the drug to

 doi:10.20944/preprints202404.1698.v1

skeletal muscle and the liver, where it undergoes conjugation and subsequent excretion. This hypothesis was supported by a prospective, randomized experiment that involved rats anesthetized with isoflurane and treated with a bolus infusion of ILE [62]. The study revealed that the lipid emulsion induced a swift and positive inotropic effect, leading to a faster and more pronounced increase in aortic flow and arterial pressure compared to the control group.

3.4.6. Other Mechanisms

According to Mottram et al. (2011), free fatty acids mitigated Bupivacaine-induced inhibition of transport function of sodium channels in heterologous tissue culture [7]. Their findings suggest that the modulation of cardiac sodium channels may play a role in alleviating the effects of local anesthetic toxicity. The suppression of sodium channels by these fatty acids implies an impact on these transporters, potentially extending to acute toxicity induced by other blockers of these channels, including certain antiepileptic medications.

Lipid-based resuscitation presents a far more intricate clinical landscape than initially perceived. At present, the impacts of intravenous lipid emulsion (ILE) administration can be categorized into intracellular (metabolic, signaling), intravascular (sequestration, sink), and membrane (channel) effects. It is plausible that forthcoming research endeavors will unveil all the primary beneficial effects of ILE and delineate their respective contributions to the treatment of acute intoxications involving various xenobiotics. An overview of these mechanisms is provided in Table 2.

Table 2. Mechanisms of antidote activity of ILE in acute intoxications.

Mechanism	Species	Method	Medicine	Reff.
"Lipid sink"	Rat (plasma)	*In vitro*	Bupivacaine	[44]
	Rat (isolated heart)	*In vitro*	Bupivacaine	[46]
	Pig	*In vivo*	Amiodarone	[48]
	Human	*In vivo*	Bupivacaine	[50]
	Human	*In vivo*	Bupropion + Lamotrigine	[51]
	Human	*In vivo*	TCA	[52]
Impact on bioenergy	Rat (isolated heart)	*In vitro*	Bupivacaine	[55]
	Rat (heart tissue)	*In vitro*	Bupivacaine	[56]
	Rat	*In vivo*	Ischemia	[57]
	Mice (isolated heart)	*In vitro*	Ischemia	[58]
Activation of calcium channels	Pig	*In vitro*	Nifedipin	[59]
	Rat	*In vivo*	Verapamil	[60]
Affecting the enzyme translocase	Rat	*In vitro*	Levobupivacaine, Bupivacaine, Rropivacaine, Mepivacaine	[61]
Inotropic effect	Rat (isolated heart)	*In vitro*	Bupivacaine	[54]
	Rat (isolated heart)	*In vitro*	Isofluran	[62]
Inhibition of sodium channels	Cell line	*In vitro*	Bupivacaine	[7]

3.5. Effects of ILEs in Acute Intoxications with Antiepileptics

There is scientific evidence regarding the efficacy of fat emulsions in acute poisoning involving antiepileptic drugs. The primary mechanisms of action of antiepileptics are associated with enhancing inhibitory GABAergic neurotransmission, decreasing excitatory glutamatergic system activity, and blocking voltage-dependent sodium channels, thereby mitigating excessive excitability

 doi:10.20944/preprints202404.1698.v1

in the brain. These drugs may operate through one or a combination of the aforementioned mechanisms.

It has been observed that the administration of intravenous lipid emulsion in patients with severe intoxications can reverse the progression of clinical symptoms of poisoning and potentially save lives. The effectiveness of ILE was demonstrated in a retrospective study involving 75 patients with acute exogenous intoxications at KILOOT-VMA-MBAL – Varna, spanning the period from 2010 to 2020 [39]. Among these patients, six received intravenous lipid emulsion as an adjunct therapy alongside the standard treatment regimen, while the remaining patients underwent only standard resuscitation and detoxification protocols. Throughout the treatment process, the intoxication and toxic sopor were managed, and positive trends were observed in controlling cerebrotoxic and cardiovascular syndromes, without significant CNS depression or complications.

3.5.1. Effects of ILE in Barbiturate Intoxications

Although a specific antidote for barbiturate toxicity remains elusive, several publications have explored the potential clinical utility of intravenous lipid emulsion as a countermeasure [63]. Initially, ILE administration reduced the duration of anesthesia induced by Thiopental in rats. According to Moshiri et al. (2018), in rats experiencing acute toxicity induced by Phenobarbital (100 mg/kg), the administration of 18.6 mL/kg ILE resulted in increased muscle strength and prolonged survival time among the rodents, although it did not affect overall mortality rates [64]. However, the average survival time of animals in the ILE group was notably higher compared to those treated with saline.

Due to the limited use of the drug as an antiepileptic in recent years, there is a lack of clinical data available on isolated acute poisonings where intravenous lipid emulsion administered as an antidote. However, a groundbreaking report by Hameed et al. (2020) shed light on the use of ILE in pediatric patients experiencing severe life-threatening poisoning with benzodiazepines, barbiturates, and tricyclic antidepressants [65]. In this report, an 11-year-old girl was admitted unconscious with a GCS of 4/15 (E1V1M2), displaying moderately dilated and slowly reactive pupils along with metabolic acidosis. After Flumazenil was administered as an antidote for benzodiazepine poisoning, ILE therapy was initiated with 2 boluses of 1.5 ml/kg over 5 minutes. Remarkably, the patient's GCS improved to 12/15 (E4M5V3) after the second bolus, and lipid infusion was continued for the next 6 hours. Ultimately, the patient regained a full GCS status of 15/15 without any neurological deficit. This sequence of events provides substantial evidence supporting the role of ILE therapy in the successful management of acute combined barbiturate intoxications.

3.5.2. Effects of ILE in Lamotrigine Intoxications

Lamotrigine intoxication is characterized by the inhibition of voltage-gated sodium channels, the release of aspartate and glutamate, and the reuptake of serotonin. This blockade of sodium channels typically presents with ECG abnormalities, while serotonin toxicity manifests as intermittent myoclonus, confusion, tachycardia, hypertension, hyperreflexia, clonus, and prolonged QRS interval [24].

Following a systematic review of published cases of Lamotrigine overdose in both adults and children, Alyahya et al. (2018) concluded that in patients aged ≤ 3.5 years, ingestion of the antiepileptic drug at doses exceeding 525 mg may result in severe CNS depression and seizures [66,67].

In 2008, Sirianni et al. at Riddle Memorial Hospital in Media, Pennsylvania, documented the utilization of ILE in a 17-year-old girl who experienced seizures and cardiovascular collapse due to an intentional overdose involving Bupropion, Lamotrigine, and Amphetamine [51]. After 70 minutes of unsuccessful standard cardiopulmonary resuscitation, a 100 ml bolus of 20% ILE was administered. Remarkably, within a minute after the infusion, a pulse was detected, leading to an improvement in cardiovascular status and subsequent recovery of neurological function.

Below are individual cases illustrating successful intravenous ILE treatment following acute Lamotrigine intoxication. In 2012, Moore et al. documented the inaugural case of ILE administration alleviating severe neurological symptoms in acute Lamotrigine toxicity in humans [68]. The patient,

 doi:10.20944/preprints202404.1698.v1

a 23-year-old man who ingested approximately 13 g of Lamotrigine and 18 g of Fludrocortisone in a suicide attempt, exhibited continued severe toxicity during his three-day hospitalization, marked by agitation, restlessness, and persistent ECG abnormalities due to the elevated Lamotrigine level. Following the administration of ILE, initially as a bolus followed by a 40-minute infusion, there was a notable improvement in the patient's mental state, with decreased agitation and restlessness. By the fifth day, he regained consciousness but remained disoriented to time and place, with alterations in gait.

Similarly, in 2012, Castañares-Zapatero et al. employed ILE as an adjunctive therapy in intentional Lamotrigine overdose cases where toxic ECG changes were unresponsive to bicarbonate therapy [69]. The 50-year-old patient lost consciousness and developed ECG abnormalities, including QRS-interval prolongation with left AV-block. After the infusion of 20% ILE, a prompt recovery of cardiac conduction was observed, demonstrating the efficacy of ILE as an adjunctive treatment in Lamotrigine overdose scenarios.

Following combined intoxication from Quetiapine and Lamotrigine ingestion, a 17-year-old girl experienced a spectrum of symptoms including depression of mental status, hypotension, tachycardia, and an exceedingly prolonged QT-interval with decreased heart rate, as documented by Klučka et al. in 2019 [70]. In response, intravenous ILE administration resulted in the normalization of the QT interval within 30 minutes, indicating the prompt efficacy of ILE in mitigating the cardiac effects of the intoxication.

3.6.3. Effects of ILE in Benzodiazepine Intoxications

Several studies have highlighted the prevalence of benzodiazepine poisonings as the most common form of drug intoxication [71–73]. As noted by Marinov et al. (2016), they account for approximately 26.37% of cases, predominantly stemming from suicide attempts and notably affecting women under 30 years of age [74].

The standard treatment protocol for acute benzodiazepine intoxication involves the administration of the specific antidote Flumazenil intravenously, with repeat doses if necessary. Patients typically regain consciousness within 1-2 minutes following Flumazenil administration in cases of pure benzodiazepine intoxication [75]. Flumazenil stands out as a highly effective antidote and can serve as a valuable diagnostic tool for suspected benzodiazepine poisoning [76]. Hemodialysis has proven ineffective in treating benzodiazepine intoxications, and prognosis tends to be less favorable in cases involving elderly individuals.

Several studies have documented the successful utilization of intravenous lipid emulsion in treating acute intoxications involving benzodiazepines in combination with other medications between 2010 and 2020. In a case outlined by Hillyard et al. (2010) [77], a 55-year-old man was admitted to the hospital with depressed consciousness attributed to Zopiclone and an extended-release formulation of Venlafaxine (with an ingestion of 1.8 g of Venlafaxine and an unspecified quantity of Zopiclone prior to admission). Initially, the patient's consciousness, as measured by the Glasgow Coma Scale, was recorded at 10 (moderately severe), but it decreased to 3 (severe) after four hours. Following a 30-minute infusion of ILE, the patient's GCS improved to 11, obviating the need for assisted breathing. Subsequently, the patient was discharged from the hospital two days later.

Dagtekin et al. (2011) documented a case of combined intoxication in a 44-year-old woman who deliberately overdosed on Lamotrigine, Diazepam, and Venlafaxine (an antidepressant) [78]. The patient experienced coma, convulsions, marked stiffness, and hyperreflexia. Despite undergoing hemodialysis, her condition remained unchanged. However, after receiving an intravenous bolus of ILE, the rigidity and hyperreflexia rapidly resolved. Subsequently, the patient experienced an uneventful recovery.

Orr and Bailie (2010) detailed a similar case involving combined intoxication with benzodiazepines (BZDs), influenced by the administration of ILE [79]. In this scenario, a 34-year-old man consumed high doses of liposoluble drugs along with other toxic substances, including Diazepam, Temazepam, Citalopram, and an unspecified amount of Perindopril, Doxazosin, and Amlodipine, a combination drug containing Codeine and Paracetamol, and 500 ml of ethylene glycol.

 doi:10.20944/preprints202404.1698.v1

Upon admission, he presented with hypotension, tachycardia, and GCS score of 5. Standard antidote therapy yielded no response, resulting in metabolic acidosis and reduced renal function. However, within thirty minutes of receiving the ILE bolus injection, the patient's GCS score improved. He was discharged on day 12 with restored neurological status and renal function.

Additionally, a case of BZD self-poisoning during labor, successfully treated with ILE, has been documented [80]. The patient experienced altered mental status during labor, which subsequently improved following the administration of ILE.

3.6.4. Effects of ILE in Carbamazepine Intoxications

Carbamazepine poisoning typically results from overdose and is commonly associated with cardiac, neurological, and respiratory complications. Symptoms often include diplopia (observed in most patients with blood levels above 7 μg/mL), ataxia, and dysarthria. In severe cases, coma, hypotension, respiratory depression, cardiac arrhythmias, and seizures may manifest. Unfortunately, there is currently no specific antidote available for carbamazepine poisoning.

According to Ghannoum et al. (2014), conventional treatment approaches may prove ineffective in reducing absorption and enhancing the elimination of overdose, particularly with delayed-release formulations [81]. Consequently, extracorporeal clearance is recommended for managing carbamazepine toxicity, despite its lipophilic nature (Log *P* of 2.5), which traditionally makes it less amenable to hemodialysis. Toxic doses of carbamazepine can induce cardiac depression, possibly attributed to the blockade of cardiac sodium channels. Agulnik et al. (2017) proposed that neurotoxicity might arise from the hyperpolarization of mitochondrial membranes [82]. This suggests that carbamazepine toxicity at elevated doses can lead to mitochondrial dysfunction. There are isolated reports detailing the successful use of intravenous lipid emulsion in acute intoxications involving the classical antiepileptic drug Carbamazepine. Agulnik et al. reported an analogous case of carbamazepine intoxication in another 15-year-old girl who displayed impaired mental status (GCS 5) and severe acidosis. The patient experienced seizures and severe EEG changes indicative of significant cortical dysfunction. Treatment involved a therapeutic regimen comprising ILE, hemodialysis, plasmapheresis, continuous veno-venous filtration, and endoscopic intestinal decontamination. Remarkably, the patient achieved full recovery without any organ or neurological complications. In a case described by Hirose et al. (2014), a 15-year-old girl presented with acute Carbamazepine and Mirtazapine intoxication, exhibiting respiratory depression and seizures [83]. ILE was administered, and the patient was discharged without complications after 8 days.

Avcil et al. (2015) documented a case of poisoning in a young man who ingested 2.8 grams of extended-release Carbamazepine [84]. The patient presented with confusion and depression (GCS 12), along with mild hypotension, tachycardia, and a prolonged QT interval. In response, a bolus administration of intravenous lipid emulsion was followed by a four-hour infusion, in conjunction with multiple doses of activated charcoal and intravenous saline hydration. Remarkably, within 60 minutes of the ILE bolus administration, the patient regained consciousness and orientation. He was discharged from the intensive care unit on the third day without any neurological or cardiac complications. Sohn (2017) proposed that the reduction of carbamazepine toxicity mediated by lipid emulsion might be attributed to the restoration of inhibited sodium channels in the excitatory conduction system of the heart, as well as the correction of mitochondrial dysfunction [85].

3.6.5. Effects of ILE in Valproate Intoxications

The central nervous system symptoms associated with acute Valproic acid (VPA) intoxication, characterized by dysfunction, can manifest as mild drowsiness progressing to coma and potentially fatal cerebral edema. Caution is particularly advised when administering VPA salts to critically ill patients with hypoalbuminemia, uremia, or those receiving medications that can displace valproate from its albumin binding sites [86]. Such medications include Acetylsalicylic acid, Ibuprofen, Propofol, and others, including intravenous lipid emulsions. These substances interact with valproate at the level of plasma protein binding, leading to an increase in the free fraction of the antiepileptic drug. This interaction mechanism, resulting in elevated non-albumin-bound drug fractions,

 doi:10.20944/preprints202404.1698.v1

underscores the incorporation of ILE into the treatment regimen for acute poisoning, with the objective of expediting the elimination of the toxic agent from the body.

Intentional ingestion, often for suicidal purposes, or insufficient therapy monitoring and control, can result in poisoning with sodium valproate, as well as with phenytoin, commonly prescribed for antiepileptic treatment. Some reports suggest that an overdose of sodium valproate tablets may lead to delayed toxicity characterized by clinical symptoms arising when hyperammonemia develops [87].

While there are rare instances of intravenous lipid emulsion, use in clinical practice within intensive care units for acute valproate intoxications, limitations exist due to risks of incompatibility and drug interactions identified in certain studies [88]. Consequently, combined administration of sodium valproate and ILE via the same infusion line is not recommended.

3.6.6. Effects of ILE in Phenytoin Intoxications

Phenytoin metabolism is known to follow first-order kinetics at lower doses and zero-order kinetics at higher doses, posing challenges in managing its toxic effects due to prolonged elimination from the body [89].

A single publication documented the administration of intravenous lipid emulsions in a case of mixed intoxication involving phenytoin and sodium valproate in a 28-year-old woman [90]. She presented for treatment 10 hours after ingesting the two drugs, following gastric lavage. Upon admission, she exhibited consciousness with nystagmus, diplopia, and uncontrollable speech, along with a prolonged QT interval on ECG. The cardiotoxic manifestations were addressed with ILE infusion, and due to low GCS score, the patient required intubation and mechanical ventilation. By day 9, Phenytoin plasma levels had risen, with the patient remaining irritable and unresponsive to commands, eventually experiencing cardiac arrest and hypothermia. As her condition worsened, plasmapheresis was initiated to reduce phenytoin levels, resulting in a twofold decrease in medication concentration. A day after the cardiac arrest, the patient exhibited spontaneous eye opening with persistent nystagmus. By day 21, the phenytoin plasma concentration measured 8.2 µg/mL.

A summary of the effect on GCS values and CVS of ILE in acute intoxications is given in (Table 3).

Table 3. Effect of ILE on GCS and CVS in acute intoxications.

Medicine	Species	Results on GCS	Results on CVS	Reff.
Lamotrigine + Bupropion + Amphetamine	Human	Positive	Positive	[51]
Phenobarbital	Rat	Positive	Negative	[64]
Phenobarbital + BDZ+TCA	Human	Positive	-	[65]
Lamotrigine + Fludrocortisone	Human	Positive	Positive	[68]
Lamotrigine	Human	Positive	Positive	[69]
Lamotrigine + Quetiapine	Human	Positive	Positive	[70]
Zopiclone + Venlafaxine	Human	Positive	-	[77]

 doi:10.20944/preprints202404.1698.v1

Diazepam + *Lamotrigine* + *Venlafaxine*	Human	Positive	Positive	[78]
Diazepam + *Temazepam* + *Citalopram* + *Perindopril* + *Doxazosin* + *Amlodipine* + *Codeine* + *Paracetamol* + *Ethylene glycol*	Human	Positive	Positive	[79]
Carbamazepine	Human	Positive	Positive	[82]
Carbamazepine + *Mirtazapine*	Human	Positive	Positive	[83]
Carbamazepine	Human	Positive	Positive	[84]
Phenytoin + *Valproate Sodium*	Human	Positive	Positive	[90]

4. Conclusion

The widespread use of drugs from these groups today, combined with their severe consequences and potential for mortality, highlights the critical need for scientists to investigate and implement more effective strategies in clinical practice.

It is proposed that the utilization of intravenous lipid emulsions (ILEs), known for their affordability, accessibility, safety, and efficacy, in the management of poisonings caused by other lipid-soluble toxic agents, holds promise for therapeutic intervention. However, due to its limited application in toxicological clinical practice thus far, the available scientific literature, particularly case reports, detailing their effects in acute exogenous intoxications with neurotropic substances, including medications, remains scarce. Additionally, there is a dearth of experimental data elucidating the precise mechanism of action of ILEs in acute intoxications.

Treatment with ILEs as adjunctive therapy in poisoning from neurotropic drugs has been associated with improvements in Glasgow Coma Scale (GCS) scores and enhanced recovery from drug intoxication. Multiple mechanisms of antitoxic action are believed to be implicated in this process.

Author Contributions: Conceptualization, S.Dimitrova, S.Dragomanova and G.Kehayova; methodology, S.Dimitrova, S.Dragomanova; software, S.Dragomanova, S.Dimitrova; validation, S.Dimitrova, G.Kehayova, S.Dragomanova; investigation, S.Dimitrova; resources, S.Dimitrova, G.Kehayova; data curation, S.Dragomanova; writing—original draft preparation, S.Dimitrova, S.Dragomanova; writing—review and editing, G.Kehayova, S.Dimitrova, S.Dragomanova; visualization, S.Dragomanova; supervision, S.Dragomanova. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding

Institutional Review Board Statement: Not applicable

Informed Consent Statement: Not applicable
Data Availability Statement: No data available

Acknowledgments: Not applicable

Conflicts of Interest: The authors declare no conflicts of interest

 doi:10.20944/preprints202404.1698.v1

References

1. Zohre, E.; Ayrik, C.; Bozkurt, S.; Koze, A.; Narci, H.; Cevik, I.; Toker, I.; Demir, F.; Ovla, D. Retrospective Analysis of Poisoning Cases Admited to the Emergency Medicine. *Arch Iran Med*. **2015**; *18*(2):117-122.
2. Piekarska-Wijatkowska, A.; Czyzewska, S.; Kotwica, M.; Krakowiak, A. Epidemiology of acute poisonings during 2002-2011 in Toxicology Unit, Department of Occupational Medicine and Toxicology, Nofer Institute of Occupational Medicine, Lodz, Poland. *Przegl Lek*. **2013**; *70*(10):848-51.
3. Yaylaci, S.; Genc, A.B.; Demir, M.V.; Cinemre, H.; Tamer, A. Retrospective evaluation of patients at follow-up with acute poisoning in Intensive Care Unit. *Niger J Clin Pract*. **2016** Mar-Apr; *19*(2):223-6.
4. Karadeniz, H.; Birincioglu, I.; Turna, O.; Ketenci, H.C.; Beyhun, N.E. Fatal poisoning of childhood in the Eastern Black Sea region of Turkey (2009-2013). *J Forensic Leg Med*. **2015** Aug; *34*:109-12.
5. Patel, S.R. Toxicologic emergencies in the intensive care unit: management using reversal agents and antidotes. *Crit Care Nurs Q*. **2013**; *36*(4): 335-44.
6. Marinov, P. Acute poisonings - a modern view, IK Steno, MU- Varna. ISBN: 978-954-449-953. **2018**: 91.
7. Mottram, A.R.; Valdivia, C.R.; Makielski, J.C. Fatty acids antagonize bupivacaine-induced I(Na) blockade. *Clinical toxicology*. **2011**; *49*:729–33.
8. Ramael, S.; De Smedt, F.; Toublanc, N.; Otoul, C.; Boulanger, P.; Riethuisen, J.M.; Stockis, A. Single-dose bioavailability of levetiracetam intravenous infusion relative to oral tablets and multiple-dose pharmacokinetics and tolerability of levetiracetam intravenous infusion compared with placebo in healthy subjects. *Clin Ther*. **2006** May; *28*(5):734-44.
9. Araújo, É.J.F.; Rezende-Júnior, L.M.; Lima, L.K.F.; Silva-Júnior, M.P.D.; Silva, O.A.; Sousa Neto, B.P.; Almeida, A.A.C.; Gutierrez, S.J.C.; Tomé, A.D.R.; Lopes, L.D.S.; Ferreira, P.M.P.; Lima, F.D.C.A. Pathophysiological investigations, anxiolytic effects and interaction of a semisynthetic riparin with benzodiazepine receptors. *Biomed Pharmacother*. **2018**; *103*:973-981.
10. Ameline, A.; Richeval, C.; Gaulier, J.M.; Raul, J.S.; Kintz, P. Detection of the designer benzodiazepine flunitrazolam in urine and preliminary data on its metabolism. *Drug Test Anal*. **2019** Feb; *11*(2):223-229.
11. Hutton, J.; Dent, A.; Buykx, P.; Burgess, S.; Flander, L.; Dietze, P. The characteristics of acute non-fatal medication-related events attended by ambulance services in the Melbourne Metropolitan Area 1998-2002. *Drug Alcohol Rev*. **2010**; *29*(1):53-8.
12. Vallersnes, O.M.; Jacobsen, D.; Ekeberg, O.; Brekke, M. Patients presenting with acute poisoning to an outpatient emergency clinic: a one-year observational study in Oslo, Norway. *BMC Emerg Med*. **2015** Aug; *13*: 15-18.
13. Agulnik, A.; Kelly, D.; Bruccoleri, R.; Yuskaitis, C.; Burns, M.; Kohane, D. Severe carbamazepine overdose treated with lipid emulsion therapy, hemodialysis, and plasmapheresis. *Crit. Care Med*. **2015**; *43*(12):154; doi: 10.1097/01.ccm.0000474439.78867.75.
14. Roberts, D.M. and Buckley, N.A. Enhanced elimination in acute barbiturate poisoning—a systematic review. *Clin Toxicol (Phila)*. **2011**; *49*: 2–12.
15. Hadden, J.; Johnson, K.; Smith, S.; Price, L.; Giardina, E. Acute barbiturate intoxication. Concepts of management. *JAMA*. **1969**; *209*(6):893-900. DOI:10.1001/jama.1969. 031601900 15004.
16. Spiller, H.A. Management of carbamazepine overdose. *Pediatr Emerg Care*. **2001**; *17*(6):452–456pmid:11753195.
17. Schmidt, D.; Elger, C.E. What is the evidence that oxcarbazepine and carbamazepine are distinctly different antiepileptic drugs? *Epilepsy Behav*. **2004** Oct; *5*(5):627-35. doi: 10.1016/j.yebeh.2004.07.004. PMID: 15380112.
18. Ferrey, A.E.; Geulayov, G.; Casey, D.; Wells, C.; Fuller, A.; Bankhead, C.; Ness, J.; Clements, C.; Gunnell, D.; Kapur, N.; Hawton, K. Relative toxicity of mood stabilisers and antipsychotics: case fatality and fatal toxicity associated with self-poisoning. *BMC Psychiatry*. **2018** Dec; *18*(1):399.
19. Nelson, L.; Lewin, N.; Howland, M.; Hoffman, R.; Goldfrank, L.; Flomenbaum, N. Goldfrank's Toxicologic Emergencies. 9th Ed. New York, NY: McGraw-Hill; **2011**.
20. Hojer, J.; Malmlund, H.O.; Berg, A. Clinical features in 28 consecutive cases of laboratory confirmed massive poisoning with carbamazepine alone. *J Toxicol Clin Toxicol*. **1993**; *31*(3):449–458pmid:8355320.
21. Rossi, S. ed. (**2013**). Australian Medicines Handbook (2013th Ed.). Adelaide: The Australian Medicines Handbook Unit Trust. ISBN 978-0-9805790-9-3.
22. Eeg-Olofsson, O.; Lindskog, U. Acute intoxication with valproate. *Lancet*. **1982**; *1*:1306.
23. Doyon, S. Anticonvulsants. Goldfrank's Toxicologic Emergencies8th, NE Flomenbaum, LR Goldfrank, RS Hoffman, MA Howland, NA Lewin, LS Nelson. McGraw Hill, New York; **2006**; 737–739.
24. Sagud, M.; Pivac, N.; Mustapic, M.; Nedic, G.; Peles, A.; Kramaric, M.; Jakovljevic, M.; Muck-Seler, D. The effect of lamotrigine on platelet serotonin concentration in patients with bipolar depression. *Psychopharmacology (Berl)*. **2008**; *197*: 683–685.
25. Iqbal, M.; Basil, M.; Kaplan, J.; Iqbal M. Overview of serotonin syndrome. *Ann Clin Psychiatry*. **2012**; *24*: 310–318.

26. Drugs and Lactation Database (LactMed) [Internet]. National Library of Medicine (US); Bethesda (MD): **2006**. Phenytoin.
27. Yaari, Y.; Selzer, M.E.; Pincus, J.H. Phenytoin: mechanisms of its anticonvulsant action. *Ann Neurol.* **1986** Aug; *20*(2):171-84.
28. Hamed, S.A. The auditory and vestibular toxicities induced by antiepileptic drugs. *Expert Opin Drug Saf*. **2017** Nov; *16*(11):1281-1294.
29. Guldiken, B.; Rémi, J.; Noachtar, S. Cardiovascular adverse effects of phenytoin. *J Neurol*. **2016** May; *263*(5):861-870.
30. Teasdale, G.; Jennett, B. Assessment of coma and impaired consciousness. A practical scale. *Lancet*. **1974**; *2*(7872):81–4. doi:10.1016/S0140-6736(74)91639-0
31. Zlateva, S.; Marinov, P.; Sabeva, Y.; Jovcheva, M. An investigation on the relationship between the comatose state and the serum levels of the toxic agents in patients with acute exogenic intoxications. *J of IMAB. Annual Proceeding (Scientific Papers)*, **2007**; *1*:79-80.
32. Vinnars, E. and Wilmore, D. History of parenteral nutrition. *JPEN*. **2003**; *27*(3): 225-231.
33. Mayer, J.; Hallberg, D.; Holm, I.; Obel, A.L.; Schuberth, O.; Wretlind, A. Fat Emulsion for Complete Intravenous Nutrition: Experimental Studies, Part 1. *Postgrad. Med*. **1967**; *42*(2), A-71-A-76. https://doi.org/10.1080/00325481.1967.11696248.
34. Hodder, E. Transfusion of milk in cholera. *Practitioner*, **1873**, 10, 14
35. Meyer, C.E.; Fancher, J.A.; Schurr, P.E.; Webster, H.D. Composition, preparation and testing of an intravenous fat emulsion. *Metabolism-clinical and Experimental*. **1957** Nov; *6* (6 Pt 2):591–596.
36. Isaksson, B.; Hambraeus, L.; Vinnars, E.; Samuelson, G.; Larsson, J. In memory of Arvid Wretlind 1919–200. *Scand J Food Nutr*. **2002**; *46* (3): 117–118, ISSN 1102-6480 117.
37. Calder, P.C.; Jensen, G.L.; Koletzko, B.V.; Singer, P.; Wanten, G.J. Lipid emulsions in parenteral nutrition of intensive care patients: Current Thinking and Future Directions. *Intensive Care Med*. **2010**; *36*: 735–749.
38. Teitelbaum, D.; Btaiche, I.; Coran, A. Chapter 12 - Nutritional Support in the Pediatric Surgical Patient. *Pediatric Surgery* (7th Edition) **2012**: 179-199; https://doi.org/10.1016/B978-0-323-07255-7.00012-X.
39. Dimitrova, S. Study of the Effects of Intravenous Lipid Infusion in Acute Intoxications with Some Xenobiotics. **2021**; http://repository.mu-varna.bg/handle/nls/1135
40. Carpentier, Y.A.; Dupont, I.E. Advances in intravenous lipid emulsions. *World J Surg*. **2000**; *24*: 1493–7. doi: 10.1007/s002680010267.
41. Basarslan, S.K.; Osun, A.; Senol, S.; Korkmaz, M.; Ozkan, U.; Kaplan, I. Protective Effects of Intralipid and Caffeic Acid Phenyl Esther (CAPE) on Neurotoxicity Induced by Ethanol in Rats. *Turk Neurosurg*. **2017**; *27*(1):66-73. doi: 10.5137/1019-5149.JTN.14463-15.2.
42. Hartert, M.M.; Dupont, G.D.; Hans, P.; Deby, C.; Lamy, M. Protective activity of propofol, Diprivan® and Intralipid against active oxygen species. *Mediators of Inflamm*. **1998**; *7*: 327–333.
43. Moshiri, M.; Etamad, L.; Fadaei, H.; Heydarabadi, M. Lipid emulsions in the treatment of acute poisoning: a mini-review of human and animal studies. **2012**; http://www.csen.com/lipid.ppt.
44. Weinberg, G.L.; VadeBoncouer, T.; Ramaraju, G.A.; Garcia-Amaro, M.F.; Cwik, M.J. Pretreatment or resuscitation with a lipid infusion shifts the dose-response to bupivacaine-induced asystole in rats. *Anesthesiology*. **1998** Apr; *88*(4):1071-5. doi: 10.1097/00000542-199804000-00028. PMID: 9579517
45. Fettiplace, M.R.; Lis, K.; Ripper, R.; Kowal, K.; Pichurko, A.; Vitello, D.; Rubinstein, I.; Schwartz, D.; Akpa, B.S.; Weinberg, G. Multi-modal contributions to detoxification of acute pharmacotoxicity by a triglyceride micro-emulsion. *J Control Release*. **2015**; *198*:62–70.
46. Weinberg, G. Lipid infusion resuscitation for local anesthetic toxicity: proof of clinical efficacy. *Anesthesiology*. **2006**; *105*:78, doi:10.1097/00000542-200607000-00005.
47. Mazoit, J.X.; Le Guen, R.; Beloeil, H.; Benhamou, D. Binding of long-lasting local anesthetics to lipid emulsions. *Anesthesiology*. **2009**; *110*:380–6.
48. Niiya, T.; Litonius, E.; Petaja, L.; Neuvonen, P.J.; Rosenberg, P.H. Intravenous lipid emulsion sequesters amiodarone in plasma and eliminates its hypotensive action in pigs. *Ann Emerg Med*. **2010**; *56*:402–8.
49. Samuels, T.L.; Willers, J.W.; Uncles, D.R.; Monteiro, R.; Halloran, C.; Dai, H. In vitro suppression of drug-induced methemoglobin formation by Intralipid® in whole human blood: Observations relevant to the 'lipid sink theory'. *Anesthesia*. **2012**; *67*:23–32.
50. Litonius, E.; Tarkkila, P.; Neuvonen, P.J.; Rosenberg, P.H. Effect of intravenous lipid emulsion on bupivacaine plasma concentration in humans. *Anesthesia*. **2012** Jun; *67*(6):600-5. doi: 10.1111/j.1365-2044.2012.07056.x.
51. Sirianni, A.J.; Osterhoudt, K.C.; Calello, D.P.; Muller, A.A.; Waterhouse, M.R.; Goodkin, M.B.; Weinberg, G.L.; Henretig, F.M. Use of lipid emulsion in the resuscitation of a patient with prolonged cardiovascular collapse after overdose of bupropion and lamotrigine. *Ann Emerg Med*. **2008** Apr; *51*(4):412-5, 415.e1. doi: 10.1016/j.annemergmed.2007.06.004.

52. Harvey, M.; Cave, G. Case report: successful lipid resuscitation in multi-drug overdose with predominant tricyclic antidepressant toxidrome. *Int J Emerg Med*. *2012*; 5:8.
53. Fettiplace, M.R.; Weinberg, G. The Mechanisms Underlying Lipid Resuscitation Therapy. *Reg Anesth Pain Med*. **2018**; *43*:138-149.
54. Weinberg, G.L. Lipid Emulsion Infusion: Resuscitation for Local Anesthetic and other Drug Overdose. *Anesthesiology*. **2012** July; *117*(1): 180–187. doi:10.1097/ALN.0b013e31825 ad8de.
55. Stehr, S.N.; Ziegeler, J.C.; Pexa, A.; Oertel, R.; Deussen, A.; Koch, T.; Hübler, M. The effects of lipid infusion on myocardial function and bioenergetics in l-bupivacaine toxicity in the isolated rat heart. *Anesth Analg*. **2007** Jan; *104*(1):186-92. doi: 10.1213/01.ane.0000248220.01320.58. PMID: 17179268.
56. Weinberg, G.L.; Palmer, J.W.; VadeBoncouer, T.R.; Zuechner, M.B; Edelman, G.; Hoppel, C.L. Bupivacaine inhibits acylcarnitine exchange in cardiac mitochondria. *Anesthesiology*. **2000** Feb; *92*(2):523-8. doi: 10.1097/00000542-200002000-00036.
57. Rahman, S.; Li, J.; Bopassa, J.C.; Umar, S.; Iorga, A.; Partownavid, P.; Eghbali, M. Phosphorylation of GSK-3beta mediates Intralipid- induced cardioprotection against ischemia/reperfusion injury. *Anesthesiology*. **2011**; *115*:242–53.
58. Cave, G.; Harvey, M.; Castle, C. The role of fat emulsion therapy in a rodent model of propranolol toxicity: A preliminary study. *JMT*. **2006**, *2*: 4-7. 10.1007/BF03161005.
59. Huang, J.M.; Xian, H.; Bacaner, M. Long-chain fatty acids activate calcium channels in ventricular myocytes. *Proc Natl Acad Sci U S A*. **1992**; *89*: 6452–6456
60. Gueret, G.; Pennec, J.P.; Arvieux, C.C. Hemodynamic effects of intralipid after verapamil intoxication may be due to a direct effect of fatty acids on myocardial calcium channels. *Acad Emerg Med*. **2007**; *14*(8):761. doi:10.1197/j.aem.2007.04.006.
61. Ok, S.H.; Kang, D.; Lee, S.H.; Kim, H.J.; Ahn, S.H.; Sohn, J.T. Lipid emulsions attenuate the inhibition of carnitine acylcarnitine translocase induced by toxic doses of local anesthetics in rat cardiomyoblasts. *Hum Exp Toxicol*. **2022**; 41:9603271211065978.
62. Fettiplace, M.R.; Ripper, R.; Lis, K.; Lin, B.; Lang, J.; Zider, B.; Wang, J.; Rubinstein, I.; Weinberg, G. Rapid cardiotonic effects of lipid emulsion infusion*. *Crit Care Med*. **2013** Aug; *41*(8):e156-62. doi: 10.1097/CCM.0b013e318287f874.
63. Russell, R.L.; Westfall, B.A. Alleviation of barbiturate depression. *Anesth Analg*. **1962**; *41*:582-585.
64. Moshiri, M.; Aftabi, F.; Esmaeili, M.; Etemad, L.; Hosseinzadeh, H. Intravenous Lipid Emulsion Increased Muscles Power and Survival Time of Phenobarbital in Intoxicated Rats. *JIMC*. **2018**; *1*(1):29-33.
65. Hameed, A.; Sara, F.; Tayyab, H.; Maryam, B. H. Intravenous Lipid Emulsion Therapy In Paediatric Poisoning. *JBUMDC*. **2020**; *10*(1):81-83
66. Southam, E.; Kirkby, D.; Higgins, G.A.; Hagan, R.M. Lamotrigine inhibits monoamine uptake in vitro and modulates 5-hydroxytryptamine uptake in rats. *Eur J Pharmacol*. **1998**; *358*(1):19-24.
67. Fleurat, M.; Smollin, C. Case files of the University of California San Francisco medical toxicology fellowship: Lamotrigine toxicity. *JMT*. **2012**; *8*(1):52-8.
68. Moore, P.; Urquhart, M.; McMillion, D.; Donovan, J.; Burkhart, K.; Cantilena, L. Severe lamotrigine neurotoxicity treated with Intralipid emulsion therapy. *LVHN Scholarly Works*; Department of Emergency Medicine. **2012**; Available from: https://scholarlyworks.lvhn.org/emergency-medicine/?utm_source-scholarlyworks.lvhn.org%2Femergency-medici %2F210&utm_medium=PDF & u tm_campaign= PDF CoverPages.
69. Castanares-Zapatero, D.; Wittebole, X.; Huberlant, V.; Morunglav, M.; Hantson, P. Lipid Emulsion as Rescue Therapy in Lamotrigine Overdose. *JEM. J. Emerg. Med.* **2012**; *42*(1): 48-51.
70. Klučka, J.; Juřenčák, T.; Kosinová, M.; Stourac, P.; Kratochvíl, M.; Sedláčková, Y.; Tomáš, N.; Pelclova, D.; Jabandžiev, P. Intralipid infusion in paediatric patient with quetiapine and lamotrigine intoxication. *Monatshefte für Chemie - Chemical Monthly*. **2019**; 150. 10.1007/s00706-019-02423-5.
71. Islambulchilar, M.; Islambulchilar, Z.; Kargar-Maher, M.H. Acute adult poisoning cases admitted to a university hospital in Tabriz, Iran. *Hum Exp Toxicol***. 2009**; *28*(4):185-90.
72. Hutton, J.; Dent, A.; Buykx, P.; Burgess, S.; Flander, L.; Dietze, P. The characteristics of acute non-fatal medication-related events attended by ambulance services in the Melbourne Metropolitan Area 1998-2002. *Drug Alcohol Rev***. 2010**; *29*(1):53-8.
73. Krayeva, Y.V.; Brusin, K.M.; Bushuev, A.V.; Kondrashov, D.L.; Sentsov, V.G.; Hovda, K.E. Pre-hospital management and outcome of acute poisonings by ambulances in Yekaterinburg, Russia. *Clin Toxicol (Phila).* **2013**; *51*(8):752-60.
74. Marinov, P.; Zlateva, S.; Bonchev, G.; Ivanov, D.; Georgiev, K.; Sabeva, Yu.; Yovcheva, M. Acute poisoning with benzodiazepines and other hypnotics & etiologic cause, sex/age distribution and clinical outcome. *J of IMAB*. **2016** Oct-Dec; *22*(4):1371-1374.DOI: https://doi.org/10.5272/ jimab.2016, 224.1371.

 doi:10.20944/preprints202404.1698.v1

75. Martens, F.; Köppel, C.; Ibe, K.; Wagemann, A.; Tenczer, J. Clinical experience with the benzodiazepine antagonist flumazenil in suspected benzodiazepine or ethanol poisoning. *J. Toxicol. Clin. Toxicol.* **1990**; *28*(3):341-56.
76. Vukcević, N.P.; Ercegović, G.V.; Segrt, Z.; Djordjević, S.; Stosić, J.J. Benzodiazepine poisoning in elderly. *Vojnosanit Pregl*. **2016** Mar; *73*(3):234-8.
77. Hillyard, S.G.; Barrera-Groba, C.; Tighe, R. Intralipid reverses coma associated with zopiclone and venlafaxine overdose. *Eur. J. Anaesthesiol*. **2010** Jun; *27*(6):582-583. DOI: 10.1097/eja.0b013e3283357049.
78. Dagtekin, O.; Marcus, H.; Müller, C.; Böttiger, B.W.; Spöhr, F. Lipid therapy for serotonin syndrome after intoxication with venlafaxine, lamotrigine and diazepam. *Minerva Anestesiologica*. **2011** Jan; *77*(1):93-95.
79. Orr, K.; Bailie, R. The use of Intralipid in the management of a mixed overdose. *JICS*. **2010**; *11*(4): 268-269.
80. Berman, D.J. A case of local anesthetic toxicity that wasn't: lipid rescue from self-administered benzodiazepine overdose in labor. *Int J Obstet Anesth.* **2020**; *42*:109-111.
81. Ghannoum, M.; Yates, C.; Galvao, T.F.; Sowinski, K.M.; Vo, T.H.; Coogan, A. Gosselin, S.; Lavergne, V.; Nolin, T.D.; Hoffman, R.S. Extracorporeal treatment for carbamazepine poisoning: systematic review and recommendations from the EXTRIP workgroup. *Clin. Toxicol. (Phila*). **2014**; *52*: 993-1004.
82. Agulnik, A.; Kelly, D.P.; Bruccoleri, R.; Yuskaitis, C.; Ebrahimi-Fakhari, D.; Sahin, M.; Burns, M.M.; Kohane, D.S. Combination Clearance Therapy and Barbiturate Coma for Severe Carbamazepine Overdose. *Pediatrics.* **2017**; *139*(5). pii: e20161560. doi: 10.1542/peds.2016-1560.
83. Hirose, T.; Onishi, M.; Nakae, H.; Ogura, Y.; Shimazu, T.A. case of acute carbamazepine toxicity manifesting as respiratory depression and seizures 12 hours later. The 34th Western Japan Local Meeting of the Annual Meeting of the Japanese Toxicology Society. *Toxicol. Research*. **2014**; *27*: 373 – 382.
84. Avcil, M.; Ozluer, Y.E.; Karaman, K.; Kapci, M.; Kantekin, B. Treatment of Severe Carbamazepine Intoxication with Intravenous Lipid Emulsion Therapy. *J Pharmacol Clin Toxicol*. **2015**; *3*(3):1052.
85. Sohn, J.T. Lipid emulsion treatment for carbamazepine toxicity. *Pediatrics*. **2017**; https://pediatrics.aappublications.org/content/lipid-emulsion-treatment-carbamazepine-toxi-city.
86. Riker, R.R.; Gagnon, D.J.; Hatton, C.; May, T.; Seder, D.B.; Stokem, K.; et al. Valproate protein binding is highly variable in ICU patients and not predicted by total serum concentrations: a case series and literature review. *Pharmacotherapy*. **2017**; *37*(4):500–8.
87. Pons, S.; Gonzva, J.; Prunet, B.; Gaillard, T.; Brisou, P.; Vest, P. Acute Overdose Of Enteric Coated Valproic Acid And Olanzapine: Unusual Presentation And Delayed Toxicity. *Clin Toxicol (Phila).* **2012** Apr.; *50*(4):268.
88. Piwowarczyk, L.; Tomczak, S.; Antkowiak, P.; Jelińska, A.; Stawny, M. Sodium Valproate Incompatibility with Parenteral Nutrition Admixtures—A Risk to Patient Safety: An In Vitro Evaluation Study. *Pharmaceutics*. **2022**; *14*(2):371.
89. Eadie, M.J.; Tyrer J.H. Anticonvulsant Therapy – Pharmacological Basis And Practice. 3rd Edn. New York: Churchill Livingstone, **1989**: 51–135.
90. Yarramalle, S. P.; Munta, K.; Rao, S. M.; Hemanth, C.; Dhanalakshmi S.; Parate, S. Phenytoin and sodium valproate intoxication and management, a case report. *Int. J. Adv. Res*. **2017**; *5*(4): 1610-1621; ISSN: 2320-5407.