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From Bupivacaine to Intralipid: Leading Edge

Abstract

Recent ILT success stories led to many experiments to find out intralipid mechanism of action. Intralipid as a Lipid-Emulsion not only has been introduced as an effective treatment for LA toxicities but also has shown its effectiveness in reversal of other toxicities as well. Although the story of intralipid started with Bupivacaine but it is going to be a safe treatment option.

Keywords: Intralipid; Local anesthetic; Bupivacaine; Cardiotoxicity; Resuscitation; Cardiac arrest; Lipid emulsion

Review Article

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Introduction

Intravenous lipid emulsion therapy was introduced as a treatment for local anesthetic toxicity it has shown couple of reversing and therapeutic efficacies for a number of different drug toxicities. In recent papers many different applications of Intralipid or oil containing products-Lipid Emulsion-have successfully experimented in critical care patients. In 1998 Dr. Weinberg began working on the effects of local anesthetics and discovered that an infusion of lipid emulsion not only protect against but also correct local anesthetic cardiac toxicity. The first case report of successful Lipid Rescue was published in 2006. Reportedly lipid infusion was successful in reversing neurological signs of toxicity from local anesthetics. With appearing more evidences for intralipid different applications there is a hope that many types of drug-induced CNS or cardiac toxicities could be treated by Lipid Rescue effect as a safe treatment option. Since identification of lipid resuscitation therapy in 1998 as a treatment for LA toxicity by Weinberg [1], many studies and experiments have been performed in order to explore more the mechanism of this novel treatment. Intralipid has been used as a source of energy and essential fatty acids for parenteral nutrition. Intralipid is an emulsion of soy bean oil, egg phospholipids and glycerin, and is available in 10%, 20% and 30% concentrations. The 30% concentration has not been approved for direct intravenous infusion. Intralipid and other balanced lipid emulsions provide essential fatty acids. In this review some of the novel applications of Intralipid have introduced.

Local Anesthetics /Cardioprotection

Intralipid was introduced by Dr. Weinberg as an effective treatment for reversing cardiotoxicity due to local anesthetics [1]. Although Lipid Sink theory was the primary theory for mechanism of action but couple of different theories have come to the table to discuss (Figure 1). They showed that Lipid treatment accelerates recovery from Bupivacaine-induced asystole in the isolated rat heart, reduces Bupivacaine content, and increases cardiac Bupivacaine washout [2]. Rat and dog studies showed that lipid emulsions could be used in establishing normal sinus rhythm and maintaining oxygenation after Bupivacaine-induced arrest [3]. Intralipid was used successfully to treat the refractory hypotension following epidural anaesthesia [4]. Lou et al. [5] evaluated the Mechanism of Intralipid-Mediated Cardioprotection and concluded that active metabolite, Palmitoylcarnitine, Generates Reactive Oxygen Species (ROS) and Activates Reperfusion Injury Salvage Kinases. They suggested ROS as active cardioprotective metabolite of Intralipid [5].

Eghbali group demonstrated that post-ischemic treatment with Intralipid prevents the opening of mitochondrial permeability transition pore and protects the heart through glycogen synthase kinase-3 β [6]. In another experiment they concluded that ILP not only prevents the development of PAH and RV failure but also rescues preexisting severe PAH [7]. They also showed that Intralipid is effective in reducing the infarct size and improving the cardiac functional recovery [8].

Toxicities

Interestingly Intralipid has been successful in reversing other toxicities as well [9-12]. Herring reported successful treatment of Naproxen overdose in dogs with Lipid emulsion [13]. Rodríguez et al. [14] used Lipid emulsion successfully in a 26 year old male who had hypotension and bradycardia because of medication overdose (Amlodipin, Metoprolol, Lisinopril) and was unresponsive to treatment with saline, calcium, glucagon, and vasopressors. In this patient, Intralipid prevented renal replacement therapy correcting both metabolic abnormalities and volume overload [14]. Matsumoto et al. [10] reported successful treatment of a commatos 24 year old woman due to overdose of chlorpromazineand mirtazapine with combination of intralipid with adrenalin [10]. According to Mc Beth case report severe hemodynamic instability resulting from myocardial irritability in a Female with overdose of Hydroxychloroquinetoxity was treated by intralipid and hemodialysis use [15].

In a recent study Weinberg group reported successful

treatment of cocaine induced cardiotoxicity. They showed Lipid emulsion can delay progression of cocaine cardiac toxicity both invivo and isolated hearts perfused in langendorff system in rats [16]. Intralipid has also been successful in treating pesticides intoxications [17,18]. Put together Intralipid or lipid emulsion has shown strong "soap like effect" in removing different toxicities.

Liver

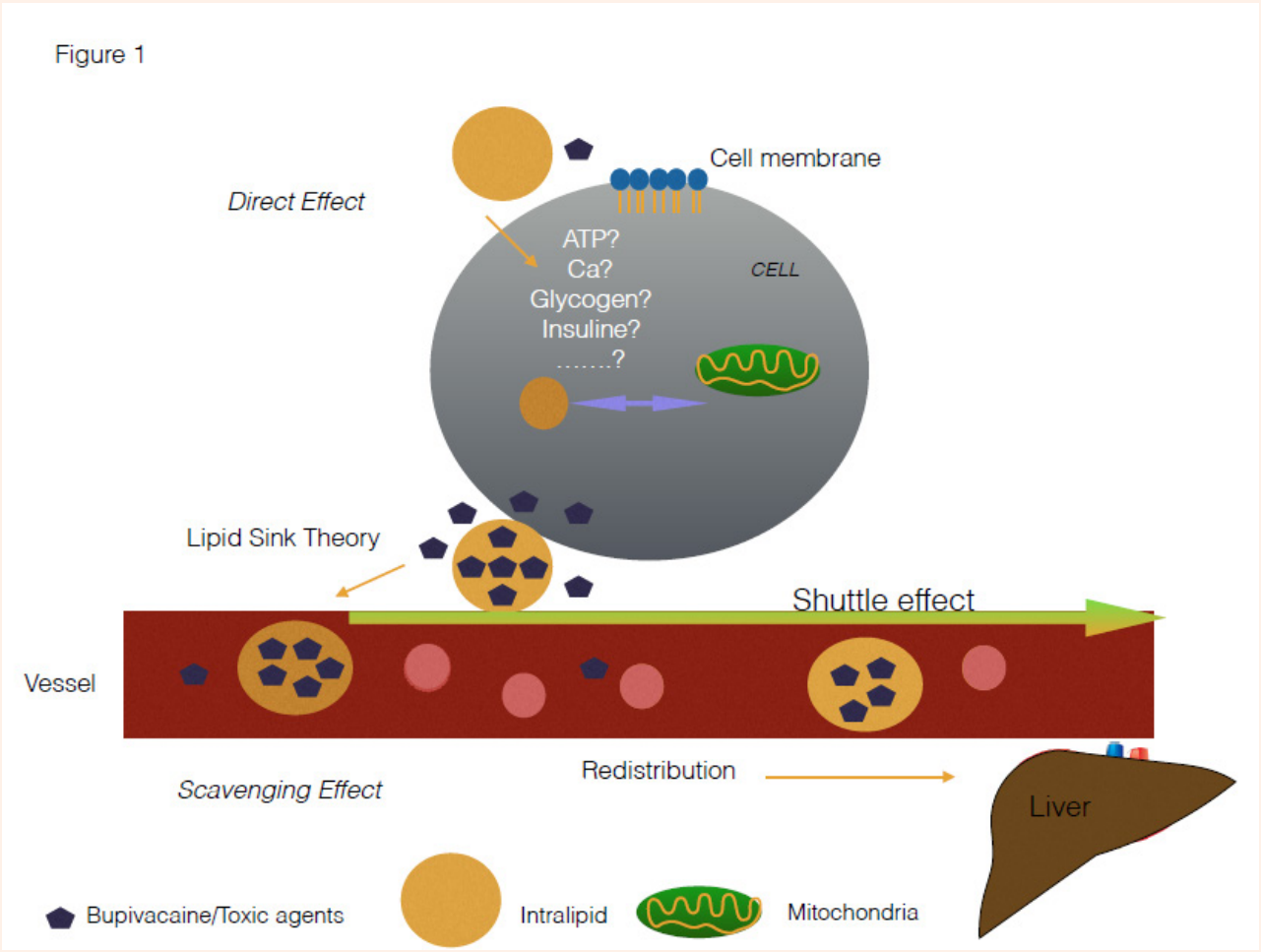

Figure 1: A hypothetical mechanism of actions for Lipid emulsion.

The upper figure shows unknown probable Intracellular effects of Lipid emulsion. The adjacent blood vessel highlights scavenging effect and Lipid Sink theory which removes Bupivacaine/Toxic agents through Lipid emulsion. The lower part of the figure shows accelerated-Shuttel Effect term used by Dr. Weinberg- redistribution and metabolism of Lipid emulsion-Bupivacaine/toxic agent complex to the liver.

Zheng et al. [19] suggested that Intralipid could decrease hepatic ApoM levels. They showed rats receiving Intralipidhad increased FFAs and decreased glucose infusion rates and ApoM gene expression [19]. Xiao group showed Infusion of Intralipid, unlike saline, did not affect plasma glucose concentration or EGP. They concluded there are important interspecies differences between humans and rodents with respect to the gut-brain-liver axis [20]. Stephens showed that Lipid infusion reduced whole-body glucose disposal by 20% and the muscle fractional synthetic rate increased during saline infusion, although no change occurred during lipid infusion in this regard. They suggested increased muscle availability may contribute to anabolic resistance in insulin-resistant conditions by damaging translation initiation. In another study during hyper insulinemia without lipid, glucose infusion rate (GIR) was lowest. Lipid infusion reduced GIR in all subjects. But in lipid group, fat oxidation was higher with lipid oversupply. They concluded enhanced mitochondrial performance with exercise is related to better metabolic flexibility and insulin sensitivity when faced with lipid overload [21].

Immune system

Sanches evaluated the effects of increasing the energy availability from dextrose and lipid treatments on the pro-inflammatory response to LPS in steers. Their experiment Showed increased circulating non-esterified fatty acids with a lipid emulsion modulates the pro-inflammatory response in steers [22].

Anti cancer drugs

In a recent study Intralipid decreased Platinum-Containing Anti-Cancer Nanodrugs (Pt) accumulation in the liver, spleen, and kidney through reducing reticuloendothelial system (RES) uptake and increased the bioavailability of the nanodrug [23].

Obstetrics-Gynecology

Meng Lili. evaluated effectiveness and potential mechanisms of Intralipid in treating unexplained recurrent spontaneous abortion. They suggested Intralipid as an alternative to IVIG [24].

Conclusion

Although fat emulsion have been used in patient care for several decades, as a source of calories, it has shown an important rescuing effect in many toxicities as well as Bupivacaine cardiotoxicity. Several experiments is still necessary to elucidate the underlying mechanism of action and consequent novel applications.

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