Current evidence is not in support of lipid rescue therapy in local anaesthetic systemic toxicity

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It is now 10 years since the first case reports of the use of intravenous lipid emulsion (ILE) as treatment for local anaesthetic systemic toxicity (LAST). In spite of very scarce data on efficacy, safety and mechanism of action, this novel therapy was enthusiastically adopted by anaesthesiologists, clinical toxicologists and emergency medicine physicians worldwide. However, recent thoroughly performed systematic reviews, preceded by the description of the applied methodology, suggest that reliable evidence in support of the usefulness of ILE in LAST or non-local anaesthetic poisonings is still not available. While there seem to be some anecdotal indications which might suggest potential benefits of ILE in LAST, the evidence is quite heterogeneous (very low quality), and so far the usefulness of ILE in LAST is unproven. The human data on ILE in LAST consist only of some 70 positive case reports, plus one small human volunteer case series, and no randomized and controlled studies in patients. The number of case reports with no effect of ILE represents only about 5% of all case reports of the use of ILE in LAST suggesting a strong publication bias.

Animal studies are also nonsupportive regarding the usefulness and success of ILE therapy since effective doses of ILE in experimental animals need to be much higher than the guideline recommended doses for patients, i.e., an initial bolus of 20% Intralipid® (Fresenius Kabi AB, Uppsala, Sweden) 1.5 ml/kg followed by an infusion of 0.25 ml/kg/min for 30 min, with additional boluses up to a total amount of 10 ml/kg (American Society of Regional Anesthesia and Pain Medicine) or 12 ml/kg (Association of Anaesthetists of Great Britain and Ireland). In fact, the high doses (volumes) of 20% or 30% Intralipid® in animal studies would be impossible to administer rapidly enough to a human patient, and would violate profoundly the pharmacopoeial recommendation of intravenous nutritional lipid emulsion administration, both regarding dose and rate of administration; the risk of adverse effects of ILE would rise. The adverse effects of ILE (Intralipid®) in treatment of poisonings have been largely ignored. In healthy human volunteers, who have received ILE according to current guideline recommendations, adverse reaction have been very rare and mild. In patients occasionally very severe complications have been observed, such as pancreatitis and ARDS. Rapid intravenous lipid emulsion infusion may also result in a complex fat overload syndrome. Acute hypersensitivity reactions (soy allergy), known from reports of...
nutritional use of ILE have not been diagnosed in LAST patients treated with ILE. The lipoaemic blood interferes for hours with certain laboratory analyses which may be relevant for the patient’s treatment. ILE in the circulating blood may cause filter collapse in renal replacement therapy and fat depositions in VA-ECMO circuits.

The possible mechanisms of action of ILE in LAST have remain at the level of theory and suggestion. Notably, the initially suggested mechanism of action of lipid rescue, i.e., the production of a lipid sink which sequesters hydrophobic local anaesthetic molecules in plasma has been questioned by several authors, recently also by the lipid rescue guideline committee members in the UK. The presently used local anaesthetics are not lipophilic enough (partition coefficient in octanol-water, logP = 2–3). Instead other possibilities have been suggested, e.g., that lipid emulsion in blood could serve as a vehicle and carry drug molecules to well-perfused organs like the lungs and the skeletal muscle. Other suggested, but unverified mechanisms include cardiac inotropy induced by activation of cardiac calcium channels by fatty acids, reduction of sodium channel inhibition by free fatty acids, stimulation of cardiac mitochondrial respiration through fatty acid oxidation, and systemic vascular β1-adrenergic receptor activation.

Although a few case reports suggest that ILE could have had an antidotal effect in local anaesthetic toxicity of the CNS, also here evidence is lacking. Recovery from moderate and even severe CNS-LAST occurs spontaneously relatively quickly without further problems, as long as the patient rapidly receives proper abortive (seizures) and supportive (respiration and circulation) care.

According to current evidence, it can be concluded that there is not sufficient support for a role of ILE in treating LAST. Relying only on indirect animal testing results is not enough. Strong treatment recommendations in this type of problem cannot be based on case reports. Fortunately, LAST in patients receiving regional anaesthesia is rare. Optimal training in regional anaesthesia will minimize the incidence of LAST. Education to maintain a high degree of clinical suspicion of LAST and routines for aggressive resuscitative interventions is our speciality’s mandate.

References


