Toxicology Reports 3 (2016) 202–210

Contents lists available at ScienceDirect

Toxicology Reports

journal homepage: www.elsevier.com/locate/toxrep

The possible role of intravenous lipid emulsion in the treatment of chemical warfare agent poisoning

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ARTICLE INFO

Article history:
Received 8 October 2015
Received in revised form
29 November 2015
Accepted 24 December 2015
Available online 18 January 2016

Keywords:
Intravenous lipid emulsion
Organophosphates
Sulfur mustard
Antidotes
Poisoning
Chemical Warfare agents

ABSTRACT

Organophosphates (OPs) are cholinesterase inhibitors that lead to a characteristic toxidrome of hypersecretion, miosis, dyspnea, respiratory insufficiency, convulsions and, without proper and early antidotal treatment, death. Most of these compounds are highly lipophilic. Sulfur mustard is a toxic lipophilic alkylating agent, exerting its damage through alkylation of cellular macromolecules (e.g., DNA, proteins) and intense activation of pro-inflammatory pathways. Currently approved antidotes against OPs include the peripheral anticholinergic drug atropine and an oxime that reactivates the inhibited cholinesterase. Benzodiazepines are used to stop organophosphate-induced seizures. Despite these approved drugs, efforts have been made to introduce other medical countermeasures in order to attenuate both the short-term and long-term clinical effects following exposure. Currently, there is no antidote against sulfur mustard poisoning. Intravenous lipid emulsions are used as a source of calories in parenteral nutrition. In recent years, efficacy of lipid emulsions has been shown in the treatment of poisoning by fat-soluble compounds in animal models as well as clinically in humans. In this review we discuss the usefulness of intravenous lipid emulsions as an adjunct to the in-hospital treatment of chemical warfare agent poisoning.

Contents

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http://dx.doi.org/10.1016/j.toxrep.2015.12.007

1. Introduction

Organophosphates (OPs) are cholinesterase inhibitors, that are widely used as pesticides, but still represent a major health problem in the world over [37,38]. A group of OP compounds developed as chemical nerve agents have been used in a variety of international conflicts and terror events [43,122]. Despite international efforts to outlaw their use for this purpose, they are still being used against enemy forces and innocent civilians [104]. Recently we have witnessed the devastating consequences of using the nerve agent sarin in the Syrian conflict [43,116,133].

OP poisoning leads to a characteristic toxidrome that includes muscarinic, nicotinic and central nervous system signs and symptoms [104,116,122]. Without proper antidotal treatment administered immediately after exposure, and depending on the dose, victims may suffer from convulsions, respiratory failure and ultimately, death. Currently accepted antidotal treatment includes the anticholinergic drug atropine, and a reactivator from the oxime family. Benzodiazepines are added to terminate seizures [43,122]. However, it is evident that even when given early after poisoning, the response to these antidotes is not optimal and does not prevent long-term emotional, neurological and cognitive deficiencies occurring in subjects surviving the acute poisoning. Considerable effort has focused on finding more efficient medical countermeasures [42,113,150,151].

Most of the OPs are lipophilic compounds, and as such, may remain in body tissues, especially fat, for long periods of time, mandating a prolonged medical observation time following initial antidotal treatment [38,39,94,108].

Sulfur mustard is a toxic lipophilic alkylating agent widely used in the past as a chemical warfare agent (CWA) [68,75], and recently reported to be used by the Islamic State Jihadist group ISIS [128]. It exerts its damage through alkylation of cellular macromolecules (e.g., DNA and intra- and extra-cellular proteins) and intense activation of pro-inflammatory pathways [68]. Following exposure, an on-going worsening process of vesication appears, depending on the extent of exposure and whether the victim was decontaminated in a timely manner [68]. The systems most affected are the lungs and airways, skin, and mucous membranes including the eyes. It takes several hours for many of the signs and symptoms to appear [53,68]. Once absorbed into the tissues, there are no currently available medical countermeasures to prevent the injury—apart from diminishing the extent of the injury with corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs), and certain treatment adjuncts aimed at reducing the time-to-healing of local injuries [32,53].

Intravenous lipid emulsions (ILE) were introduced in the early 1960's as an energy substrate and calorie source containing essential fatty acids, given parenterally as a nutritional supplement in patients with major injury, infection or nutritional depletion [14,99]. It is widely used in neonatal intensive care, where infants are frequently dependent on intravenous nutrition in the early weeks of life [137]. For more than a decade, ILE were shown to be effective in the treatment of poisonings by fat-soluble compounds, especially local anesthetics. ILE has been shown to rapidly reverse the clinical toxicity induced by a variety of compounds with diverse kinetics and mechanisms of action [17,20,21,23,117,142,143,145,149].

Recently, Zhou et al. [154] proposed to use a combination of ILE and charcoal hemoperfusion in patients with severe OP poisoning. They suggest that with this strategy, caregivers can remove the OP, decrease the amount of antidotes needed, reduce possible side-effects of the drugs, and meanwhile provide an additional energy substrate for the victims. We have found no evidence in the literature on the use of ILE in the treatment of sulfur mustard injury.

In this review we will discuss the potential role of ILE as an adjunct to the in-hospital treatment of CWA poisoning.

2. Proposed mechanisms of action

The exact mechanisms by which ILE exert their beneficial effects are not fully understood, and several have suggested synergistic effects of several mechanisms [47,48,61]. The mechanisms of action can be divided into intravascular, membrane, and intracellular effects [149]. The original theory explaining the mechanism of lipid rescue was that of "lipid sink", suggesting sequestration of lipophilic compounds to an expanded intravascular lipid phase, extracting the offending agent from the target tissue, and reversing the toxicity [61,117,118,143,149]. In support of this theory, toxic drug levels were shown to decrease more rapidly in tissues following the administration of ILE [35,63,98,144,148,149], and intravenous lipid emulsions were shown to bind lipid-soluble drugs in vitro [51,89]. Other hypotheses relate to the mechanism by which ILEs facilitate cardiac rescue from drug poisoning. These include (1) increasing myocardial energy substrate delivery and a direct cardiotonic effect of ILE on the poisoned heart, thus improving cardiac function (a so-called metabolic effect) [7,57,117,126,130,143,149], and (2) an effect of ILE on calcium ion channels through high levels of long-chain fatty acids, leading to increased cardiomyocyte calcium and positive inotropic effect which improves the heart contractility [54,66,105]. The latter theory seemed unlikely in view of evidence of the inhibitory effects of fatty acids on Ca^{2+} ion intake by neurons [48]. Recently, the cardioprotective action of the long-chain fatty acids in Intralipid® was found to involve Ca^{2+}-homeostasis and rescue signaling pathways that regulate the opening of the mitochondrial permeability transition pore (mPTP) [103,112]. This activity requires fatty acid metabolism and involves production of reactive oxygen species (ROS) by the mitochondria which, in turn, activates rescue pathways [81,134]. The relative contribution of the "lipid sink" and other mechanisms to the beneficial effect of ILE on systemic bupivacaine toxicity has been studied using physiologically-based pharmacokinetic and pharmacodynamic (PBPK/PD) modeling [131]. Pharmacokinetic analysis has shown that the amount of bupivacaine sequestered from the heart and brain tissues by standard ILE infusion is too low to account for reversal of toxicity, suggesting that additional mechanisms must be involved [76]. A later study, combining dose-response of the effect of ILE in bupivacaine-poisoned rats with PBPK/PD modeling, has shown that ILE exerts its beneficial effect by three mechanisms operating in concert: lipid scavenging of the drug, a volume effect, and the cardiotonic effect, which was found to be essential for reversal of toxicity [46]. Support for the theory suggesting combined action of these mechanisms is found in the recent detailed mechanistic study by Fettiplace et al. [47]. This study suggested that the "lipid sink" concept is inaccurate, and replaced it with the more accurate "lipid shuttle" mechanism [48]. Additional mechanisms besides lipid sequestration extend the range of action of ILE to less lipophilic compounds.

3. The use of ILE in over-dose and poisonings

In recent years, several review articles summarized current experience in animal models and in humans [17,20,23,70,100,117,149], showing repeatable positive effects, suggesting a role for ILE as an antidote for poisoning by lipophilic compounds. Efforts have been initiated to collect all data in a global registry (e.g., http://www.lipidrescue.org and http://www.lipidregistry.org) [23,117,149]. In the recent LIPAEMIC report, Cave et. al. [24] summarized the results from three years of operation (2009–2012) of the lipid rescue registry. The first successful use