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Lipid Nano-Vehicles for Cyanide Antagonism: A Mini-Review

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ABSTRACT

Industrial use of cyanide makes it a common intoxicant in such settings but it is increasingly being encountered in cases of domestic fires due to the burgeoning use of novel synthetics in production processes. Since time is of crucial importance in treating cyanide intoxication, it is essential to use antidotes which are rapid-acting and facile to administer. With this in mind, our group has focused its research efforts towards identifying potential sulphur donors which perform better than those already available. Furthermore, we have focused on improving delivery kinetics of putative antidotes by using biologically relevant lipid nano-vehicles like liposomes and micelles. This review provides a vista to the development and evaluation of such formulations both *in vitro* and *in vivo*.

Keywords: Cyanide antagonism, *In vitro/in vivo* efficacy, Parenteral, Sulphur donor, Liposome, Micelle, Nanoparticle

INTRODUCTION

Apart from intentional use as a chemical warfare agent, cyanide (CN) intoxication is frequently observed in domestic fires [1]. One possible reason for this is the increased use of newly developed synthetics in production of household equipage [2]. Accordingly, increased levels of CN have been observed in nearly two-thirds of fire-related deaths making the case for the use of CN antidotes in the treatment of such patients [3]. Available antidotes include Nithiodote (comprised of a combination of sodium thiosulfate and sodium nitrite) and Cyanokit (hydroxocobalamin) each with its attendant limitations. The primary limitation of Cyanokit is that it requires a high injection volume (>200 ml). The major limitation of sodium nitrite is the formation of excess methemoglobin in certain individuals even at the recommended doses, resulting in methemoglobinemia. Furthermore, the antidotal activity of sodium thiosulfate has limitations due to its small volume of distribution, short biological half-life and high rhodanese dependence [4]. These drawbacks initiate the necessity of developing either alternative antidotes or alternative vehicles for existing antidotes which offer more attractive pharmacodynamic/pharmacokinetic parameters. Within this context, our research group has worked in both directions and identified new CN antagonists as well as novel lipid carriers for the antagonists. The following review summarizes the results of our studies in these endeavors.

Development of new sulphur donors

Efforts directed towards the discovery of novel sulphur donors that demonstrated better reactivity and lipophilicity resulted in the identification of the garlic component dimethyl trisulfide (DMTS) [5,6]. Experiments verifying the potential of DMTS as a CN antagonist were published by Rockwood [7] in which the authors demonstrated that DMTS converts CN to non-toxic thiocyanate more efficiently than sodium thiosulfate, the component of the existing therapy Nithiodote. Further, the *in vivo* antidotal efficacies of DMTS were evaluated in a mouse model of CN toxicity. Intramuscular administration of DMTS showed a threefold higher antidotal potency than an equivalent intramuscular dose of sodium thiosulfate.

DMTS is a pale-yellow liquid which is soluble in organic solvents but insoluble in aqueous solvents [8]. This makes it imperative to find appropriate solvent/carrier systems to deliver DMTS *in vivo*.

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Development of nano-vehicles for DMTS

Preliminary approaches to improve *in vivo* delivery and efficacy of DMTS adapted the use of liposomes as an extension of previous studies which had investigated the efficacies of liposomal encapsulation and co-encapsulation of cyanide antidotes in different combinations [9]. Accordingly, liposomes prepared by using combination of selected lipids were evaluated with regard to their encapsulation efficiency of DMTS with and without Rhodanese as well as thiosulfate. The optimized liposomal preparations were also used in proof-of-concept studies in a mice model of CN toxicity [10]. Results from these experiments demonstrated that DMTS was an effective sulphur donor both in the presence and absence of Rhodanese. This stand-alone efficacy of DMTS as sulphur donor led us to cast about for alternate approaches of packaging DMTS for *in vivo* delivery.

Accordingly, we decided to test micelles as putative carriers of DMTS. Micelles are spherical structures composed of a hydrophobic core and a hydrophilic corona with sizes ranging from 5 - 50 nm and earlier have been used for delivering anticancer drugs with success [11]. In our studies, micelles were prepared by hydrating polyethylene glycol phosphatidylethanolamine (PEG-PE) block co-polymers with a mixture of DMTS and distilled water. This encapsulation method allowed for a maximal injectable dose of DMTS of 12.5 mg/kg. Intramuscular administration of this formulation allowed mice to tolerate twice the LD_{50} of CN [12].

CONCLUSION

Our experiments have shown the value of DMTS as an efficient antidote for CN toxicity. Moreover, demonstration of the antidotal properties when injected intramuscularly makes it even more attractive as it obviates the need for trained personnel to administer CN countermeasures intravenously. However, its volatile property represents a limiting factor in the applicability of neat DMTS in extant clinical settings. To surmount this difficulty our research efforts are now focused on investigating formulations of DMTS which would ensure storage stability of DMTS and simultaneously improve its pharmacodynamic/pharmacokinetic properties. The cyanide antidote development with the sulphur donor DMTS is an intense and ongoing project nationwide. Efforts are focused on developing newer formulations in order to enhance bioavailability, antidotal efficacy, pharmacokinetics, pharmacodynamics properties, achieving rapid onset of action and making it available for other than intramuscular administration.

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