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Combination delivery of two oxime-loaded lipid nanoparticles: Time-dependent additive action for prolonged rat brain protection

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ABSTRACT

A novel approach for brain protection against poisoning by organophosphorus agents is developed based on the combination treatment of dual delivery of two oximes. Pralidoxime chloride (2-PAM) and a novel reactivator, 6-(5-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)pentyl)-3-hydroxy picolinaldehyde oxime (3-HPA), have been loaded in solid-lipid nanoparticles (SLNs) to offer distinct release profile and systemic half-life for both oximes. To increase the therapeutic time window of both oximes, SLNs with two different compartments were designed to load each respective drug. Oxime-loaded SLNs of hydrodynamic diameter between 100 and 160 nm and negative zeta potential (−30 to −25 mV) were stable for a period of 10 months at 4 °C. SLNs displayed longer circulation time in the bloodstream compared to free 3-HPA and free 2-PAM. Oxime-loaded SLNs were suitable for intravenous (*iv*) administration. Paraoxon-poisoned rats (0.8 × LD_{50}) were treated with 3-HPA-loaded SLNs and 2-PAM + 3-HPA-loaded SLNs at the dose of 3-HPA and 2-PAM of 5 mg/kg. Brain AChE re-activation up to 30% was slowly achieved in 5 h after administration of 3-HPA-SLNs. For combination therapy with two oximes, a time-dependent additivity and increased reactivation up to 35% were observed.

1. Introduction

Multidrug combination therapy is one of the promising approaches for treatment of chronic diseases. Nanotechnological “two-in-one” approach using nanoparticles for packaging multiple drugs in single carriers allows the improvement of drugs' bioavailability, with the simultaneous decrease of administered doses and adverse side-reactions [1–4]. Nanoparticles exhibit targeted delivery of drugs and modified release profile and, when loaded with two drugs, may foster synergistic therapeutic outcomes [2]. To date, prevention of irreversible brain damages after acute organophosphorus (OP) poisoning is still a difficult problem, in particular in case of delayed medical care [5]. OP threat has become increasingly important due to acts of terrorism around the globe that have increased markedly in recent decades, and due to the proved use of these agents against civilian populations in Iraq and Syria. The acute toxicity of OPs results from covalent inhibition, phosphylation, of acetylcholinesterase (AChE). Low OP doses do not induce clinical manifestations of cholinergic impairment. It is accepted that clinical signs of poisoning appear when cholinesterase activity drops below 50% [6]. Severe signs, in particular convulsions, appear when AChE activity of poisoned patients is below 10–20% [7]. In humans, brain AChE activity < 10% is associated with respiratory failure and death [8]. Thus, the current emergency treatment of acute OP poisoning consists in administering a combination of AChE reactivator (quaternary oximes), atropine as anticholinergic drug to protect muscarinic receptors, and an anticonvulsant to prevent irreversible brain damage [5,9]. However, current quaternary oximes are unable to reactivate phosphylated AChE in the central nervous system (CNS)

Abbreviations: AChE, acetylcholinesterase; BBB, blood brain barrier; OP, organophosphorus agent; BChE, butyrylcholinesterase; 2-PAM, Pralidoxime chloride; SLN, solid lipid nanoparticle; SNC, central nervous system

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