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MEETING ABSTRACTS

NANOTECHNOLOGY STRATEGIES USING OXIMES-LOADED LIPID NANOPARTICLES FOR BRAIN PROTECTION AGAINST ORGANOPHOSPHORUS POISONING

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Nanotechnological "two-in-one" approach using nanoparticles for packaging two oximes in single carriers and nose-to-brain delivery for brain protection against poisoning by organophosphorus agents have been developed. Strategies for designing nanocarriers for drug delivery to the CNS and crossing the BBB showed that nanoparticles based on natural and biodegradable materials are promising. Solid lipid nanoparticles (SLNs) are biocompatible, biodegradable and have very low toxicity, thereby fulfilling the requirements of preclinical safety [1]. 2-PAM and a novel reactivator of VX-, paraoxon-, and tabun-phosphylated AChE [2] a poorly water soluble 6-(5-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)pentyl)-3-hydroxypicolinaldehyde oxime (3-HPA), were loaded in SLNs to offer distinct release profile and half-life for both oximes. To increase the therapeutic time window of both oximes, SLNs with two different compartments were designed. Oxime-loaded SLNs of hydrodynamic diameter 100-160 nm and zeta potential (from -30 to -25 mV) were stable for a period of 10 months at 4ºC. SLNs displayed longer circulation time in the bloodstream compared to free 3-HPA and free 2-PAM. Oxime-loaded SLNs were suitable for intravenous administration. Paraoxon-poisoned rats ($0.8\times LD_{50}$) were treated with 5mg/kg of 3-HPA-loaded SLNs and 2-PAM+3-HPA-loaded SLNs. Brain AChE reactivation up to 30% was slowly achieved in 5 h after administration of 3-HPA-SLNs. Synergistic effect and increased reactivation up to 35% was observed with combination of both oximes.

In addition, new cationic liposomes based on L-α-phosphatidylcholine and cationic surfactant were administered via the intranasal route. These liposomes were found to reach directly central AChEs. This last approach provides evidence that reactivation of central AChEs can be achieved by a non-invasive approach that bypasses the BBB.

Keywords: Solid-Lipid Nanoparticles; Blood-brain barrier; Acetylcholinesterase; Oxime; Paraoxon

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References

1. S. Doktorovová, et al., Eur. J. Pharm. Biopharm. 108 (2016) 235.
2. T. Zorbaz, et al., Chem. Eur. J. (2018) In press