MEDICAL PROPHYLAXIS TO MITIGATE CHEMICAL THREATS

An Oxime Nanoformulation Designed To Cross The Blood-brain Barrier Results In More Brain Acetylcholinesterase Reactivation, Less Brain Damage, And Better Survival Rates In Paraoxon-exposed Mice

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Background Information: Organophosphates are highly toxic chemicals that inactivate acetylcholinesterase (AChE), the enzyme primarily responsible for clearing acetylcholine from synapses of the central and peripheral nervous systems. The consequent accumulation of neurotransmitter results in excitotoxicity leading to cholinergic crisis characterized by hypersecretion, tremors, convulsions, seizures, respiratory distress and even death. After initial inactivation of AChE, there is a period during which the enzyme can be reactivated. The only FDA-approved AChE reactivator is pralidoxime (a.k.a. 2-PAM). Despite substantial effort to identify reactivators with improved properties, 2-PAM is still referred to as the “gold standard”. Like ~98% of all drugs, 2-PAM does not readily cross the intact BBB, so the reactivation of AChE in the brain after organophosphate exposures remains an unmet medical need. We have developed a novel formulation of 2-PAM that comprises its encapsulation within an immuno-targeted liposomal nanocomplex designed to cross the undisrupted BBB via a normal physiological process involving the transferrin receptor. Our new formulation (termed scL-2PAM) represents the most recent application of SynerGene's platform technology called scL (for single chain Liposome), which has displayed good safety in human trials assessing two investigational anticancer agents that also utilize the scL delivery system.

Purpose, Objective, Rationale & Methods: In mice exposed to paraoxon, a deadly organophosphate derived from the pesticide parathion, we have evaluated scL-2PAM as a new and improved countermeasure via head-to-head comparisons with unencapsulated 2-PAM.

Preliminary Results & Conclusions: The duration of seizures has been linked to organophophate-induced neuropathology and to death. scL-2PAM reduced the extent and duration of cholinergic symptoms more effectively than did unencapsulated 2-PAM with a marked reduction in the time spent in convulsions resembling grand mal seizures. Our new scL-2PAM formulation was also significantly more effective than unencapsulated 2-PAM in rescuing Balb/c mice from otherwise-lethal exposures to paraoxon. This improved survival rate in mice receiving scL-2PAM was accompanied by a demonstrably higher degree of reactivation of AChE in the brain. In mice surviving paraoxon exposures, scL-2PAM significantly reduced microglial activation, a hallmark of the neuroinflammatory response to organophosphate exposures. The loss of neurons observed in mice 14 days after paraoxon exposures was also significantly reduced by scL-2PAM but not by unencapsulated 2-PAM.

Impact to the JSTO Mission and the Joint Force: Our data suggest that scL-2-PAM, if developed and made available to warfighters, has the potential not only to reduce severity and duration of cholinergic symptoms and improve survival after exposure to agents with anticholinesterase activity but also to ameliorate longer-term neurological sequelae initiated by organophosphate-induced brain damage. The fact that the scL nanodelivery system has already been in successful human trials and that scL-2PAM carries an FDA-approved drug as its payload would suggest that our new nanomedicine countermeasure should prove to be both safe and effective. If chemical reactivators with improved properties are synthesized in the future, these new countermeasures may also benefit from encapsulation within scL nanocomplexes to enhance their ability to cross the BBB.

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