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Novel Substituted Phenoxyalkyl Pyridinium Oximes Alone And In Combination With 2-pam Provide Improved Survival And Attenuation Of Op-induced Toxic Signs In Rats And Guinea Pigs

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A platform of substituted phenoxyalkyl pyridinium oxime acetylcholinesterase reactivators (US patent 9,277,937) was synthesized with the objective of improving penetration of the blood-brain barrier and consequently providing neuroprotection from organophosphate-induced neuropathology. Using lethal level challenges of highly toxic organophosphate anticholinesterases, nitrophenyl isopropyl methylphosphonate (NIMP) and nitrophenyl ethyl methylphosphonate (NEMP), in male rats, the combination of 2-PAM plus novel oxime, both administered at the 2-PAM human molar equivalent dosage, provided improved 24-hr survival percentages of 60-87% compared to 40% for 2-PAM alone with NIMP and 53 -100% compared to 30% for 2-PAM alone for NEMP with statistically significant odds ratios of 1.7-9.7 for NIMP and 2.5-69.1 for NEMP compared to 2-PAM alone. Some of our novel oximes resulted in a shorter time to cessation of seizure-like behavior than 2-PAM, providing behavioral support for the premise of their brain penetration. Some of the oximes also provided histological evidence of protection of brain architecture that 2-PAM did not. This attenuation of signs of toxicity and neuroprotection might be in part the result of the considerably longer circulating half-lives of some of our novel oximes (3-15 hr) compared to 2-PAM (40-70 min as reported in the literature). Therefore these novel oxime reactivators in a combination with 2-PAM provide attenuation of signs of OP poisoning with highly toxic organophosphates, that could result in better outcomes for the warfighter including protection of the brain. Supported by NIH CounterACT U01 NS107127 and U01 NS123255.

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