A Toxidromic Approach for Chemical Medical Countermeasure Development

Characterization of Nerve Agent Intoxication in a Novel Genetically Modified Mouse Model

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Mice and other rodent models exhibit greater resistance to chemical warfare nerve agent (CWNA) intoxication than do humans and non-human primates. This is directly attributed to the presence of carboxylesterase (CaE), an endogenous bioscavenger in rodent blood plasma but not in that of humans and non-human primates. In order to create an improved small animal model of CWNA intoxication that is more representative of the human response, the gene encoding serum carboxylesterase (Es1) in C57BL/6J mice was deleted to generate a genetically modified strain of mice, Es1 knock out (Es1 KO), which no longer expresses a functional form of the protein. Removal of serum carboxylesterase represents only one piece of a gestalt in vivo model for predicting human CWNA susceptibility. Testing medical countermeasures to CWNA intoxication primarily involves targeting acetylcholinesterase (AChE), the enzyme that hydrolyzes acetylcholine to terminate nerve signaling. When AChE is inhibited by CWNAs, the resulting cholinergic crisis can quickly lead to death. AChE is found in all species, but recent research has found significant biochemical differences between rodent and human AChE. Therefore, another genetic modification was made to the Es1 KO mouse strain to incorporate expression of the human form of AChE in place of the mouse form of this enzyme. This new mouse strain (KIKO) should be a more predictive model of not only human intoxication by CWNAs, but also human responses to CWNA countermeasures such as oximes and other AChE reactivators. This study evaluates the median lethal dose (MLD) of G- and V-type CWNA nerve agents in both male and female C57BL/6J wild type (WT), Es1 KO, and KIKO adult mice as part of an initial effort to characterize this novel animal model. Results indicate that while there was no significant difference in V-agent MLDs across genotypes, G-agent MLDs of KIKO and Es1 KO mice are significantly lower than those of WT mice. In the ongoing endeavor to better protect the warfighter, KIKO mice are a promising model for CWNA intoxication and countermeasure development. Their use may also allow for more rapid evaluation of new drugs as part of the regulatory approval process. (The experimental protocol was approved by the IACUC at the USAMRICD, and all procedures were conducted in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals (NRC, 2011), and the Animal Welfare Act of 1966 (P.L. 89-544), as amended.)