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## A Toxidromic Approach for Chemical Medical Countermeasure Development

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### **The Benefit of Novel Non-oxime Bispyridinium Compounds for the Standard Antidotal Treatment of Nerve Agent-Poisoned Mice**

Jiri Kassa, Faculty of Military Health Sciences, University of Defense, Hradec Kralove, Czech Republic

Christopher M. Timperley, Defence Science and Technology Laboratory (Dstl), Porton Down, Salisbury SP4 0JQ, United Kingdom

Mike Bird, Defence Science and Technology Laboratory (Dstl), Porton Down, Salisbury SP4 0JQ, United Kingdom

Rebecca L. Williams, Defence Science and Technology Laboratory (Dstl), Porton Down, Salisbury SP4 0JQ, United Kingdom

Chris Green, Dstl

John EH Tattersall, Defence Science and Technology Laboratory (Dstl), Porton Down, Salisbury SP4 0JQ, United Kingdom

The aim of this study was to evaluate the influence of three newly-developed bispyridinium antinicotinic compounds (MB408, MB442, and MB444; MB compounds) on the therapeutic efficacy of a standard antidotal treatment (atropine in combination with an oxime) of acute poisoning by two nerve agents (sarin and cyclosarin) using *in vivo* methods. The therapeutic efficacy of the standard antidotal treatment (atropine in combination with an oxime) with or without one of the bispyridinium non-oxime compounds was evaluated by determination of the 24 h LD50 values of the nerve agents studied. The efficacy of tested antidotes was expressed as a protective ratio A (LD50 value of nerve agent in protected mice/LD50 value of nerve agent in unprotected mice) and as a protective ratio B (LD50 value of nerve agent in mice treated with atropine, an oxime and MB compound/LD50 value of nerve agent in mice treated with atropine and oxime without MB compound). To evaluate the influence of the bispyridinium non-oximes on the time to death of nerve agent-poisoned mice, the animals were poisoned intramuscularly with supralethal doses of nerve agents studied. The animals were monitored for signs of poisoning up to 6 h, and times of death were noted. The results showed that the addition of all tested non-oximes increased the therapeutic efficacy of atropine in combination with an oxime against sarin poisoning; however, the differences were not significant. They also positively influenced the number of surviving mice 6 h after supralethal poisoning with sarin. In the case of cyclosarin, they were also slightly beneficial for the treatment of acute poisoning. In addition, the higher dose of MB444 was able to significantly increase the therapeutic efficacy of standard antidotal treatment of poisoning with cyclosarin. The benefit of the tested bispyridinium non-oxime compounds was dose-dependent. Based on the obtained data, we can conclude that the addition of MB compounds to the standard antidotal treatment of acute nerve agent poisoning was beneficial for the antidotal treatment of sarin or cyclosarin poisoning although their benefit at 24 h after poisoning was not significant with the exception of the higher dose of MB444 against cyclosarin. On the other hand, all MB compounds studied were able to markedly decrease the number of animals dying within 1 and 6 h after supralethal poisoning with the chosen nerve agents (especially sarin). Given the typically steep probit slope for the dose-lethality relationship for nerve agents, such modest increases in protection ratio could provide significant survival benefit. Due to their presumed mechanism of action in antagonizing the effects of excess acetylcholine on muscarinic and nicotinic postsynaptic receptors, the combination of MB compound, atropine and oxime should be expected to counteract the acute toxicity of all nerve agents regardless of their chemical structure. However, the benefit of the bispyridinium non-oxime compounds may vary according to the type of nerve agent, and must be evaluated carefully. The obtained results could contribute to the effectiveness of medical protection of warfighters in the case of exposure to nerve agents.