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Phosphorylated oximes increase organophosphate toxicity

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Aim: Oximes are small chemical compounds utilized as treatments for organophosphate toxicity. Organophosphorus nerve agents prevent the enzyme acetylcholinesterase from performing its function, which is breaking down the neurotransmitter, acetylcholine. Nerve agents inhibit acetylcholinesterase by bonding their phosphate group to acetylcholinesterase. Oximes are used to remove the phosphate group from the nerve agent, allowing it to detach, therefore restoring the function of acetylcholinesterase. However, when this takes place, we end up with by-product known as phosphorylated oxime. Phosphorylated oximes may be dangerous because they can inhibit acetylcholinesterase more potently than organophosphates; resulting in toxicity rather than a cure. The objective of this study is to evaluate inhibitory capacity and the toxicity of phosphorylated oximes to mammalian cells.

Methods: The series of experiments conducted involved varying amounts of different oximes (K027, 2-Pralidoxime, etc.) and organophosphates (asinphos, dicrotophos, etc.) on NIH-3T3 and SH-SY5Y cells. Experiments included in-cell westerns to measure amounts of acetylcholinesterase levels, a colorimetric assay to measure acetylcholinesterase activity, and other measures of toxicity. An on-cell western blot was also developed to assess the number of acetylcholinesterase receptor neuronal cells. These experiments will examine the contributions of oximes, organophosphates, and the combination of both chemicals on acetylcholinesterase function and off- target toxicity.

Results: The results of this study suggest that the combination of nerve agents and oximes increases toxicity within neuronal cells. A colorimetric assay showed a significant decrease in the activity of acetylcholinesterase when the combination of dicrotophos and 2- PAM was added compared to dicrotophos alone. Measures of mitochondrial toxicity using the XF- 96 Flux Analyzer also showed that the combination of dicrotophos and 2- PAM detrimentally affected the cells even more than the nerve agent alone. More experiments are currently being developed to further investigate this phenomenon, and potentially explain the molecular process of this potent inhibition of acetylcholinesterase.

Conclusion: From these results, it can be determined that oximes are not a safe and viable treatment option for organophosphate toxicity because the combination of the two does more harm than good in NIH- 3T3 cells.

Discussion: The research findings in this study have the potential to change the course of how organophosphate intoxication is treated. Our goal is to improve the treatment of organophosphate toxicity to prevent the recent tragedies in Syria and Iraq from occurring in the future.

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