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Short Commentary

Perspective: Considerations for Prevention and Treatment of Dermal Exposure to Toxic Organophosphorus Compounds

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Abstract

The potential benefit of polyhydroxy fullerene nanomaterials in preventing and alleviating toxicities from cholinesterase-inhibiting organophosphorus toxicants is compared to other dermal protectants.

Keywords: Dermal protectants; Fullerene nanomaterials; Organophosphate toxicity prevention; Polyhydroxyfullerenes; Skin decontamination

Introduction

Organophosphorus (OP) insecticides and nerve agents are toxicants that can cause dose-related adverse effects because they inhibit acetylcholinesterase, the enzyme responsible for the degradation of the neurotransmitter acetylcholine [1]. Since these products are lipophilic, they can be absorbed following dermal exposure. Decontamination of skin by using soap and water degrades these chemicals, but may be insufficient to prevent systemic acute effects.

Specific treatments that counteract mechanisms associated with acute toxicities that may result from OP exposure are available—atropine to decrease peripheral signs that occur when excess acetylcholine combines with its receptors in the peripheral nervous system, and pralidoxime (2-PAM) to remove the OP from the acetylcholinesterase enzyme before it has a chance to undergo covalent binding, known as 'aging'. Other, non-specific treatments, such as benzodiazepine anticonvulsants, may also be used in cases of life-threatening acute OP exposures. The only preventative treatment used is oral administration of pyridostigmine, a carbamate acetyl cholinesterase inhibitor, and that drug as well as the specific and non-specific treatments listed above, can alone cause adverse effects [1], although local benefit of ocular oximes following topical exposure of the eye to an OP nerve agent has been reported [2].

When widespread dermal OP exposure is possible, but the quantity and concentration is unknown, a desired outcome would be to decrease absorption, reducing the likelihood of acute symptoms of toxicity. Personal Protective Equipment (PPE) is useful in this regard, but requires that prospective victims know they have high probability of exposure. Use of PPE is not practical or possible in cases when large numbers of individuals are unexpectedly exposed, as occurs in agricultural accidents or terrorist attacks. As noted above, washing, especially with soap and water, is helpful but absorption of lipophilic toxicants can still occur. Some individuals may not be exposed to doses high enough to cause toxicities, but in cases of mass poisonings there is no time to make such a determination because absorption and toxicities to lipophilic OP compounds can occur rapidly, even from dermal exposures, and attention needs to be paid to those with high exposures [3].

Product comparisons and discussion

Publications from our laboratory report that polyhydroxy fullerenes, which are water-soluble carbon-containing nonmaterials, could sequester an OP compound and delay and decrease signs of acute toxicity in mice dermally exposed when the fullerene was applied at doses less than 2 mg/kg [4,5]. Sequestering the OP compound makes it unavailable so it cannot be absorbed and then inhibit cholinesterase enzymes to cause poisoning. Being sequestered does not mean the OP compound is chemically converted to an inactive product. However, decreasing and delaying OP absorption by using a water soluble product that is unlikely to itself be absorbed provides time necessary for critical evaluation of, for example, a mass poisoning scenario. The polyhydroxy fullerenes would be useful in such cases as published reports indicate that these products are not cytotoxic, not systemically absorbed following dermal exposure, and have only minimal effects when safety was assessed after administration by systemic routes [6-8]. Therefore, dermal exposure studies suggest that low doses of stable and non-toxic polyhydroxy fullerenes could be applied by nonmedical personnel in cases of suspected or actual mass exposures. The beneficial safety and potential use of low doses of these fullerenes as a preventative or early treatment of dermal OP exposure contrasts with other OP inactivating decontamination agents discussed in the paragraphs below.

The use of polyhydroxy fullerenes has advantages over other potential protectants even if the OP compound is not destroyed. This contrasts with a proposed and potentially useful mechanism for dermal decontamination after OP exposure that involves hydrolysis of OP compounds, which have unstable ester bonds. Such a reaction renders the OP compound unable to inhibit cholinesterase. Hydrolysis of OP compounds involves the use of catalytic bioscavengers such as OP hydrolase, carboxylesterase, and cholinesterase enzymes [9]. These products are usually administered by injection to treat systemic poisoning, but topical creams have been suggested to be of

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value. The unfortunate aspect associated with use of these enzymes is that detoxification is stoichiometric, and large quantities of costly enzymes are needed. Newer bioscavengers have a higher turnover rate so lower doses could be used, but they are in the design phase. Research, however, is active in this area [9]. Newer bioscavengers include phosphotriesterases that could be produced by bacteria. As with all protein therapeutics, however, potential for allergies exist [1]. Safety as well as whether these could be stored at room temperature or in conditions of high humidity for long periods of time so they could be readily available when unexpected mass poisonings occur is currently unclear. At present, this seems likely to limit their usefulness in cases of mass poisonings when both prophylaxis and treatment are necessary.

Another approach to prevention or treatment of OP poisoning caused by dermal exposure is the application of an α-nucleophile (e.g., 2-PAM) using a delivery method that can be effective when applied topically. These products have possibility of combining with OP compounds before they have opportunity to covalently bind to the acetylcholinesterase enzyme, thereby preventing poisoning. Reactivation of OP-inhibited enzyme was also reported. One such product uses a functionalized chitosan-based gel that contains the oxime 2-PAM [10]. Another approach uses 2-PAM or other oximes as α-nucleophiles covalently linked to charged scaffolds such as hydroxamic acid compounds [11]. Effectiveness has been tested *ex vivo* on porcine skin exposed to the OP compound paraoxon, and on skin of rats dermally exposed to methyl parathion. The pre-administration of oxime-containing topical gel prevented neuromuscular signs and lethality associated with dermal OP exposure of mice that followed. However, effectiveness of application the topical gel after exposure of animals that could result in acetylcholinesterase inhibition was not determined [10].Effects of pH and temperature on some of these products have been examined, although in the absence of whole animal safety experiments [11]. At present, the value of these products for post-exposure in cases of mass exposures to OP compounds is uncertain.

Even though the safety and effectiveness suggests potential use of polyhydroxy fullerenes in cases of mass OP poisonings, they are not yet commercially available. However, there is one skin decontaminant effective against OP compounds that has been approved by the U.S. Food and Drug Administration (FDA). It is called Reactive Skin Decontamination Lotion (RSDL®; Emergent Biosolutions, Gaithersburg, MD) [12]. This product is marketed as a sponge to apply after exposure to OP compounds or T-2 mycotoxin, and has been tested for its ability to decrease effects of both topical OP compounds and a sulfur mustard vesicant. It contains an α-nucleophile (Dekon 139) and 2,3-butanedione monoxime (DAM), polyethylene glycol monomethyl ether and water. The RSDL, however, cannot be used as a preventative for OP toxicity and, if used, must be rapidly removed because the product itself is toxic [13]. Another product (WoundStat™) that appeared to be effective when damaged skin was exposed to OP compounds is no longer manufactured [14]. Inorganic substances such as magnesium sulfate, glycerin, and Fuller's Earth have shown effectiveness as protectants [15,16]. The hydrophilic water-based solution of magnesium sulfate and glycerin (Dermostyx 1B1) is recommended for application to potentially exposed sensitive skin areas and has been approved for human use by the Israel Ministry of Health [15]. Glycerin, magnesium sulfate and Fuller's Earth are inexpensive and stable, but quantity needed as compared to the low effective doses for polyhydroxy fullerene protection against OP poisoning has not been reported.

Conclusion

This perspective provides a rudimentary comparison of several approaches to prevention of absorption and potential mass poisonings associated with dermal exposure to acetylcholinesterase-inhibiting OP compounds. All products have potential for usefulness, but there are advantages and disadvantages to each. The future for successful development and use of protective agents will result from continued research and experimentation.

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Conflicts of Interest

The author has no conflicts of interest.

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