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RECOMMENDED COMBAT DRINKING WATER STANDARDS FOR ORGANOPHOSPHORUS NERVE AGENTS

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ABSTRACT

Organophosphorus (OP) nerve agents may be used on an integrated battlefield and U.S. Army preventive medicine and quartermaster personnel are required to ensure the safety of drinking water supplies in such combat situations. Accordingly, research was performed to develop improved drinking water standards for OP nerve agents. This research yielded recommended interim drinking water standards for OP nerve agents for consumption rates of 5 and 15 L/d and exposure periods lasting up to seven days. The emphasis in developing these standards was the protection of soldiers against any performance degradation that would impede their ability to accomplish combat missions. The relationship between pharmacokinetic parameters and toxic responses were established for OP nerve agents for the oral route of exposure only and soman (GD) and VX were identified as being the OP nerve agents of most concern in field-drinking-water supplies. Inhibition of red blood cell cholinesterase (RBC-ChE) was linked to the potential for performance degradation, however, actual toxicological interactions probably occur at cholinergic synapses (i.e., junctions between nerves or nerves and muscles), which cannot be monitored in vivo. In the absence of prophylactic pretreatment with substances such as carbamates, the recommended standards correspond to 50% inhibition of RBC-ChE and are 12 and 4 μg/L for 5 and 15 L/d consumption rates, respectively. If prophylactic pretreatment with a carbamate is used, then RBC-ChE will be inhibited prior to exposure, and the recommended standards correspond to 20% inhibition of RBC-ChE, which correspond to 4.7 and 1.6 μg/L for 5 and 15 L/d consumption rates, respectively.

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INTRODUCTION

The potential use of organophosphorus (OP) nerve agents, such as tabun (GA), sarin (GB), soman (GD), or VX, on an integrated battlefield necessitates the development of improved field drinking water standards for this category of chemical agent. Monitoring field drinking water supplies to determine if the water complies with these standards for OP nerve agents will ensure that water contaminated with such substances does not contribute to troop incapacitation or

casualty. Also, U.S. Army water-treatment equipment that has the inherent capacity to reduce the concentration of OP nerve agents in water from maximum levels down to concentrations at or below the standards will make it possible for such water to be consumed without degrading performance. The methodology used to develop improved field water quality standards for OP nerve agents is provided and the resulting standards are presented. These standards are designated as recommended interim drinking water standards for the following reasons. First, the toxicity of OP nerve agents seems to differ depending on route of administration[1,2,3] and the effects of OP nerve agents may not be parallel in different species of laboratory animals.[4] Second, the dose-response data available in the literature for oral exposure by humans to OP nerve agents are very limited. Finally, the methodology and standards that are described must receive approval of the military surgeons and major user communities before they are adopted for use by United States forces in combat.

METHODOLOGY

The development of recommended interim field drinking water standards for OP nerve agents is based on the relationship between inhibition of acetylcholineserase (AChE) bound to red blood cells (RBC-ChE) and toxicity.[5,6,7] The inhibition of AChE at cholinergic synapses (i.e., junctions between nerves or nerves and muscles), which cannot be monitored in vivo, is regarded as the principal mechanism by which OP nerve agents induce acute toxicity.[8] An exponential single-compartment model was used to quantitatively link the effects of sublethal doses of an OP threat agent on RBC-ChE, even after repetitive administration, to the potential for adverse health consequences and to take into account the recovery from such effects. The development of recommended interim field drinking water standards for OP nerve agents also takes into consideration the following criteria and limitations.

- Only oral exposure to OP nerve agents in field drinking water supplies for a maximum of 7 d is of concern--no other exposure routes are considered and water is assumed not to be a primary target (no sabotage).

- Exposed military personnel are considered to be adequately immunized, fed, and clothed; to possess no physiological/psychological burdens; to be 70 kg, male and female, and between 18 and 55 years old.

- Possible chronic or reversible health effects after a maximum combat exposure period of 7 d are not addressed nor are the toxicities of hydrolysis products or any byproducts of water-treatment.

- Unique methods of agent delivery (e.g., thickeners and encapsulation) are not considered.

- On the basis of limited human data presented in the literature,[5,6,7] the toxicological endpoint that will ensure no performance decrement for general military occupational specialties is 50% depression of RBC-ChE.

- The capabilities of current agent-detection equipment and exisiting water-treatment equipment do not drive the development of the recommended standards.

- Standards also will allow for any prescribed prophylactic treatment with carbamates that would depress RBC-ChE prior to exposure to OP threat agents and will address both 5 and 15 L/d consumption rates.

RESULTS AND DISCUSSION

Equation 1 was derived from the exponential single-compartment model and was used to determine the concentration of an OP nerve agent in field water, C (μg/L), that corresponds to a particular level of depression of RBC-ChE, Q (%),

$$C = \frac{Q\ r\ W}{k\ [1-\exp(-rt)]\ D}\ , \qquad (1)$$

where r = the recovery rate from toxicity (d^{-1}); k = a conversion factor describing the potency of a dose [(%RBC-ChE depression x kg/μg)]; t = the maximum time over which repetitive dosing from field drinking water takes place (i.e., 7 d); W = the standard weight of military personnel (i.e., 70 kg); and D = the daily drinking water consumption rate (i.e., 5 or 15 L/d). The values for k and r are compound specific and were derived using the limited empirical data available[1,2,5,9-12] and by making conservative assumptions with regard to the application of these data.

For VX, k is 20 (% x kg)/μg and r is 0.4 d^{-1}; for GD, k is 10 (% x kg)/μg and r is 0.05 d^{-1}; for GB, k is 5 (% x kg)/μg and r is 0.1 d^{-1}; and for GA, k is 1 (% x kg)/μg and r is 0.1 d^{-1}. Based on these pharmacokinetic parameters, VX is the most potent of the OP nerve agents (i.e., highest k value) and GD is the OP nerve agent for which recovery from toxic effects is the slowest (smallest r value). Substitution of the parameter values for each OP nerve agent into Eq. 1 for Q values equal to 50% or 20%, depending on whether or not pretreatment with carbamates is anticipated, yields concentrations for GD that are lower than for any of the other OP threat agents. This is because GD is eight times more effective than VX in inhibiting recovery from toxicity.

Because the method for detecting OP nerve agents in field water is nonspecific, recommended field drinking water quality standards for OP nerve agents are based on concentrations of GD corresponding to either 50% RBC-ChE depression or 20% RBC-ChE depression. In the absence of prophylactic pretreatment with substances such as carbamate compounds, the recommended interim field drinking water standards for a 7-d exposure period are based on GD inhibition of RBC-ChE to 50%. These concentrations are 12 and 4 μg/L for 5 and 15 L/d consumption rates, respectively. If prophylactic pretreatment with a carbamate is used, the RBC-ChE will be inhibited prior to exposure and the recommended interim standards for a 7-d exposure period are based on GD inhibition of RBC-ChE of only 20%. These concentrations are 4.7 and 1.6 μg/L for 5 and 15 L/d consumption rates, respectively.

CONCLUSIONS

Pharmacokinetic analyses indicate that the OP nerve agents VX and GD are of most concern in field water. While GD is only half as potent as VX, it is eight times more effective than VX in preventing recovery from toxicity. Therefore, GD is a more effective cumulative poison than VX, and recommended field drinking water standards for OP nerve agents are based on concentrations of GD corresponding to either 50% or 20% RBC-ChE depression.

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