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Timing of decontamination and treatment in case of percutaneous VX poisoning: A mini review

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ABSTRACT

Low volatile organophosphorous nerve agents such as VX, will most likely enter the body via the skin. The pharmacokinetics of drugs such as oximes, atropine and diazepam, are not aligned with the variable and persistent toxicokinetics of the agent. Repeated administration of these drugs showed to improve treatment efficacy compared to a single injection treatment.

Because of the effectiveness of continuous treatment, it was investigated to what extent a subchronic pretreatment with carbamate (pyridostigmine or physostigmine combined with either procyclidine or scopolamine) would protect against percutaneous VX exposure. Inclusion of scopolamine in the pretreatment prevented seizures in all animals, but none of the pretreatments affected survival time or the onset time of cholinergic signs. These results indicate that percutaneous poisoning with VX requires additional conventional treatment in addition to the current pretreatment regimen.

Decontamination of VX-exposed skin is one of the most important countermeasures to mitigate the effects of the exposure. To evaluate the window of opportunity for decontamination, the fielded skin decontaminant Reactive Skin Decontaminant Lotion (RSDL) was tested at different times in hairless guinea pigs percutaneously challenged with 4× LD50 VX in IPA. The results showed that RSDL decontamination at 15 min after exposure could not prevent progressive blood cholinesterase inhibition and therefore would still require additional treatment. A similar decontamination regimen with RSDL at 90 min showed that it still might effectively increase the time window of opportunity for treatment.

In conclusion, the delay in absorption presents a window of opportunity for decontamination and treatment. The continuous release of VX from the skin presents a significant challenge for efficacious therapy, which should ideally consist of thorough decontamination and continuous treatment.

1. Introduction

Low volatile nerve agents like VX (*O*-ethyl *S*-[2-(diisopropylamino)ethyl] methylphosphonothioate) are likely to enter the body via the skin rather than via the respiratory route. These results indicate that the behaviour of OP nerve agents such as VX in the skin presents an additional challenge. In this short communication, several approaches or combinations of approaches to minimize the consequences of such an exposure will be addressed.

Effective treatment of intoxication via the skin is difficult because of unpredictable and persistent toxicokinetic behaviour. Previous studies demonstrated that after percutaneous exposure of anesthetized hairless guinea pigs to VX, maximum blood levels of VX were not reached until several hours after exposure, followed by a slow elimination [1,2]. Experimental data, obtained in hairless guinea pigs, show that exposure to VX on the skin only leads to signs of toxicity after a sign-free lag time, and that onset varies between animals. The variability in toxicokinetics has shown to lead to a delayed and variable onset of toxic signs [3–5]. The pharmacokinetics of drugs such as oximes, atropine and diazepam, are not aligned with the persistent toxicokinetics of VX [1,4,6]. The experiments described in the present paper were aimed at adapting existing concepts and protocols to enhance or aid medical countermeasures and to improve understanding of contact risk and behaviour of chemical warfare agents in the skin.

2. Hairless guinea pig model

Experiments towards investigating efficacy of interventions for percutaneous poisoning require the use of an appropriate animal model. To this end, a hairless guinea pig model is used at TNO [4]. The hairless guinea pig skin closely reflects the human skin in vitro, and parallels results found in swine skin, also for VX [7]. Whereas the swine model is the preferred large animal model for percutaneous studies, the hairless guinea pig can be regarded as an appropriate small animal model to study toxicokinetics after percutaneous VX exposure. The model is well validated, and repre-

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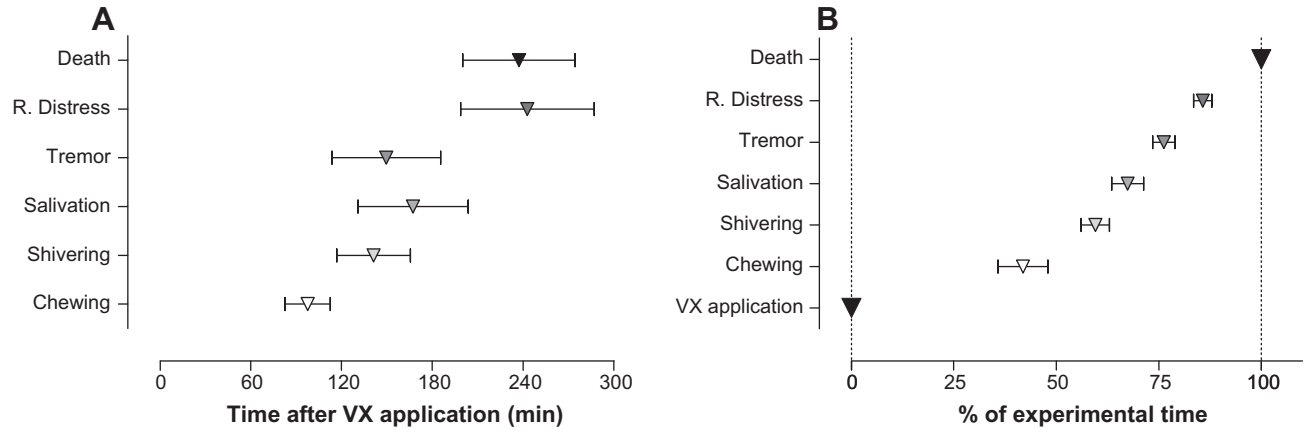

Fig. 1. (A) First appearance of cholinergic signs in individual animals (vertical axis) over experimental time (horizontal axis) between VX application (0 h) and death. (B) First appearance of cholinergic signs in individual animals (vertical axis) at percentages of total experimental time (horizontal axis) between VX application (0%) and death (100%). The average first appearances of signs ± SEM have been plotted (n = 15). Data from [4].

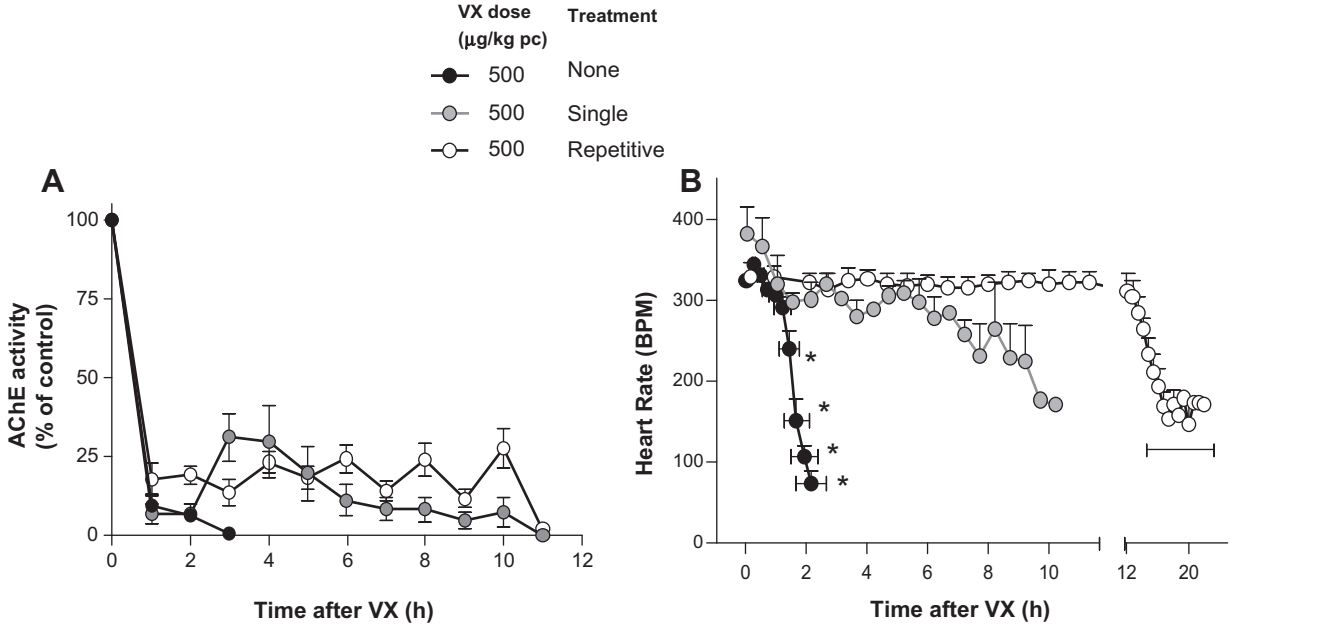

Fig. 2. (A) Acetylcholinesterase activity in blood of animals exposed to VX (500 µg/kg pc). (B) Heart rate after pc VX exposure (500 µg/kg). Untreated animals (black dots, n = 6), animals treated with three autoinjector doses at once (grey dots, n = 6), and animals repetitively treated with autoinjector doses (open dots, n = 6) (Averages + SEM). *p < 0.05, significantly different from initial heart rate. Repeated measures ANOVA followed by Dunnet's post hoc test. Data from [4].

sentative results from previous experiments are shown in Fig. 1. VX (500 µg/kg in IPA; 15.6 µl/kg) was applied on the belly of hairless guinea pigs (n = 15). For experimental details see [4]. In the model, the first clinical signs appeared in a gradual fashion, starting with chewing and shivering at 15–220 min and 55–374 min, respectively. This was followed by more heavy tremors at 75–122 min, after which most animals developed respiratory distress shown by heavy breathing [3,4]. The average survival time was 237 ± 37 min, with a minimum of 96 min and a maximum of 560 min, indicating a large variation in the development of signs of poisoning.

In an attempt to correct for the large variation in an objective way, we calculated the first appearance of the cholinergic signs versus the % of time elapsed between VX application (0%) and death (100%) (Fig. 1(B)). On average, the onset time of the first occurrence of each sign was predictive for the time of the occurrence of more severe signs, and signs occurred always in a similar sequence. Chewing occurs at 41 ± 6% of the total survival time, followed by shivering and salivation at 59 ± 3% and 67 ± 4% of survival time, respectively. On average, animals started showing tremor at 76 ± 3% and the most severe symptom, respiratory distress, was only seen shortly before death at 85 ± 2% of total time.

This analysis showed the onset time of clinical signs following percutaneous VX application to be a reliable predictor for the time course and presence of more severe signs and death. Using this approach in the present study, it was shown that compensation of the variable and delayed absorption through the skin by normalizing the time factor, minimized inter-individual variability in the first occurrence of clinical signs increasing the value of the animal model [4].

3. Repetitive treatment

The slow absorption of VX by the skin into the circulation does not parallel the short biological half-lives of the current medical