**Introduction**

Nerve agents are organophosphorus compounds used as chemical weapons. They inhibit the enzyme acetylcholinesterase (AChE), causing accumulation of the neurotransmitter acetylcholine (ACh). Cholinergic crisis results, producing secretions, seizures, and cardiorespiratory failure (Sidell, Newmark, & McDonough, 2008). Treatment often relies on an anticholinergic, an oxime, and an anticonvulsant. Anticholinergics (i.e., atropine) block the effects of excessive ACh. When administered soon after poisoning, oximes (i.e., 2-PAM) can reactivate AChE to normal function. Anticonvulsants (i.e., diazepam) can reduce the severity of seizures (McDonough & Romano, 2007). The safety of drugs utilized against nerve agent poisoning must be evaluated in animal models prior to human use. Operant behavioral tests in rodent species provide a sensitive means of evaluating safe doses of potential therapeutics. This study characterized the behavioral safety of several candidate compounds using an avertively motivated psychomotor test in guinea pigs to determine safety ratios. It was hypothesized that compounds which demonstrated large safety ratios within the guinea pig model may be viable for human use against organophosphorous intoxication.

**Materials and Methods**

Sixteen guinea pigs were trained under a discriminated active avoidance procedure (Gemini System, San Diego Instruments, Inc., San Diego, CA, USA). Each of 50 trials began with an inter-trial interval of 20 ± 5 s followed by the onset of the warning stimuli. If the subject ambulated within the first 5 s, 1.25 mA shock was avoided. The subject ‘escaped’ from shock if ambulation occurred between 5 and 15 s, and ‘no response’ if ambulation did not occur.

Half of the guinea pigs received atropine sulfate (ATR; 0.17-1.0 mg/kg), scopolamine hydrobromide (SCP; 12.5-100 µg/kg), and ketamine hydrochloride (KET; 2.5-20 mg/kg) while the other half received pyridine-2-aldoxime methylchloride (2-PAM; 25-77 mg/kg), 1,1'-methylenebis[4-(hydroxylimethyl) pyridinium] DMS (MMB-4; 100-562 mg/kg), and anti-pyruvialdehyde 1-oxime (MINA; 30-180 mg/kg). Drug administration occurred on Tuesdays and Fridays with control injections on Thursdays. Non-injection control sessions occurred on Mondays and Wednesdays. Drugs were injected intramuscularly in the laterodorsal thigh at a volume of 0.25-0.50 mL/kg. The effect of dose within each drug was analyzed using repeated-measures ANOVA. The median effective dose (ED$_{50}$) for behavioral disruption was calculated by using logistic regression. The safety ratio was then formulated by dividing the ED$_{50}$ for behavioral disruption by a known therapeutic dose (TD). Drug administration occurred on Tuesdays and Fridays with control injections on Thursdays. Non-injection control sessions occurred on Mondays and Wednesdays. Drugs were injected intramuscularly in the laterodorsal thigh at a volume of 0.25-0.50 mL/kg. The effect of dose within each drug was analyzed using repeated-measures ANOVA. The median effective dose (ED$_{50}$) for behavioral disruption was calculated by using logistic regression. The safety ratio was then formulated by dividing the ED$_{50}$ for behavioral disruption by a known therapeutic dose (TD).

**Results**

Based on Figure 1, 2-PAM (≥ 51.43 mg/kg, ≤ 70% avoids) slightly reduced performance, but only ketamine (≥ 10 mg/kg, ≤ 76% avoids) and MINA (≥ 120 mg/kg, ≤ 38% avoids) led to significant reduction.

**Conclusions**

The present data indicated that all compounds tested were safe at the intended therapeutic doses. As depicted in Table 1, the oximes had safety ratios ranging from 3 to 29. The anticholinergics had safety ratios between 2 and 4. Ketamine, a dissociative anesthetic, had a safety ratio of only 1.51. However, ketamine would only be administered in cases of active convulsions when the victim would already be incapacitated. The results supported the safety of novel therapeutics under investigation. This study further demonstrated the utility of operant testing methods using guinea pigs for assessing the behavioral safety of nerve agent countermeasures. The discriminated avoidance procedure was quickly acquired by guinea pigs, making it cost-effective. Drug effects were not confounded by food motivation, and the procedures can be replicated easily. Future studies should evaluate the efficacy of therapeutics in mitigating behavioral impairments following nerve agent exposure.

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**References**


