The Reversal of Anticholinergic Intoxication in Man with the Cholinesterase Inhibitor VX (37670)

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(Introduced by S. A. Cucinell)

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Anticholinergic intoxication in man can be reversed by certain substances producing inhibition of the enzyme cholinesterase. Several clinical (1–4) and experimental (5, 6) reports describe the efficacy of physostigmine in reversing atropine or scopolamine poisoning; sarin and other cholinesterase inhibitors are also effective in man (6) and in animals (7). This report describes the therapeutic effectiveness of VX [*S*-(2-diisopropylaminoethyl)-ethyl methylphosphonothioate] (8), a potent anticholinesterase compound, in reversing the effects of cholinergic blocking substances in man.

A secondary purpose of the study was to investigate the effect of an oxime on the antidotal activity of the anticholinesterase. Oximes are valuable adjuncts in the therapy of poisoning by certain cholinesterase inhibitors (9, 10). Their primary action is to reactivate the inhibited enzyme, but they also seem to act by other mechanisms, possibly by a parasympatholytic activity (11), as they are of some value in instances in which they do not significantly alter the enzyme inhibition, *e.g.*, in raising the LD_{50} of neostigmine (12) or in reversing the neuromuscular block produced by neostigmine in man (13). Those having a quaternary structure (*e.g.*, pyridinium aldoxime methochloride; 2-PAMCl) would not be expected to enter the central nervous system to reverse the anticholinesterase effect there. Clinical reports have described marked and dramatic improvement in the central nervous system status of patients treated with 2-PAMCl for anticholinesterase poisoning (14, 15), yet studies on the penetratibility of 2-PAMCl into the brains of animals have been conflicting (reviewed in Ref. 10). If, indeed, the oxime reverses the CNS effects of the anticholinesterase, the antidotal benefits of the VX with respect to anticholinergic intoxication should be nullified.

Experimental. The subjects were US Army enlisted men[2] who volunteered and were accepted into the study after thorough physical, laboratory, and psychiatric examinations.[3] The investigation was thoroughly explained to them and the explanation included the facts that they would receive a drug which would produce a temporary delirium and that they might receive a very small dose of a cholinesterase inhibitor, a "nerve agent," as therapy.

The subjects were admitted to the test ward the evening before the study and remained on the ward until all signs of drug effect had dissipated. Baseline physiological and performance measures were obtained in the days before, the evening before, and the morning of the study. The physiological mea-

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[2] The volunteers in these tests are enlisted U.S. Army personnel. These tests are governed by the principles, policies, and rules for medical volunteers as established in AR 70-25 and the Declaration of Helsinki.

[3] Chest X-ray, ECG, routine urinalysis including microscopic examination, hematocrit, hemoglobin, total and differential WBC counts, serum glutamic oxaloacetic transaminase (SGOT), blood urea nitrogen (BUN), creatinine, alkaline phosphatase, bilirubin, albumin, globulin, and serum (butyryl) and red cell (acetyl) cholinesterase, MMPI, and psychiatric interview.

sures included heart rate, blood pressure, and pupil size. Because the heart rate and blood pressure changes were small at the time of therapy no definite improvement was noted and these measures are not discussed. Pupil sizes were monitored in some subjects, but most received an ophthalmic anticholinesterase to prevent the accommodative difficulty produced by the anticholinergics.

The Number Facility (NF) test, a standardized 3-min addition task, was used as the measure of cognitive performance (16). The test scores are shown as the percent of the five highest of 25 pretest trials. In our experience this score correlates well with the clinical condition of the subject: a subject who scores less than 10% is usually markedly confused and disoriented and one who scores above 75% usually appears normal, although defects in thinking and misperceptions may be detected on careful examination. Several other performance measures were used, but the scores were all highly intercorrelated and only the NF scores are shown.

Except for four subjects who received VX orally, VX was given iv in doses of 1.5–1.7 μg/kg at a concentration of 20 μg/ml. VX in these doses causes mild gastrointestinal signs and symptoms in normal subjects (8). The oxime, 2-PAMCl, was given iv at times and doses noted later. Red blood cell cholinesterase (or acetylcholinesterase) was measured by methods reported previously (17).

Scopolamine hydrobromide was administered im in a dose of 24 μg/kg. Trials were then undertaken to determine the effectiveness of VX against anticholinergics producing more prolonged effects than does scopolamine. One was 3-quinuclidinyl benzilate (BZ), which was administered im in a dose of 6 μg/kg. Another anticholinergic, which has a time course similar to that of atropine, was given to a third group of subjects. Identical doses were given to non-VX-treated subjects in each case.

Results. VX given 1.5 hr after scopolamine was effective in reversing the performance and cognitive decrements produced by sco-

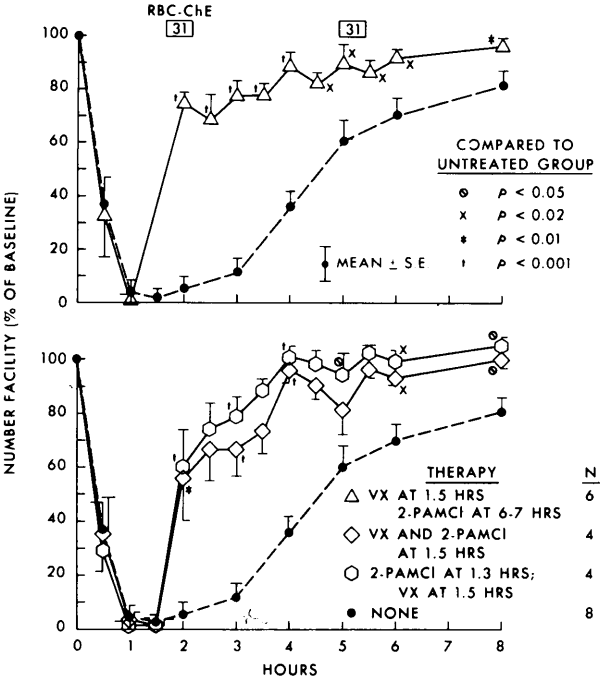

FIG. 1. The effectiveness of VX alone, VX with 2-PAMCl, and VX following 2-PAMCl in treating the central effects of scopolamine. There are no differences between the three regimens. The red blood cell cholinesterase values shown in this and the following figures are the percent of the baseline values.

polamine (Fig. 1). The results were no different whether VX was given alone (top, Fig. 1) or with or after 2-PAMCl (5 mg/kg; bottom, Fig. 1). In other subjects (data not shown), a dose of 15 mg/kg of 2-PAMCl given immediately after VX caused no change in the therapeutic effect. In all instances within minutes there was dramatic clinical improvement, and the subjects became alert, coherent, and responsive. This effect persisted throughout the time course of scopolamine; in contrast the antidotal activity of physostigmine lasts for only 2.5–3 hours (6).

The red blood cell cholinesterase of the VX-alone group was 31% of control; that of the 2-PAMCl treated groups was about 75–80%.

It has been previously noted that when scopolamine delirium is treated with physostigmine there is an initial "refractory" period of about an hour during which the therapeutic response is less than when therapy is given later (5). When VX was administered 30 min after scopolamine the initial therapeutic benefit was less than when the compound was given at 1.5 hr (Fig. 2). Again, the prior administration of 2-PAMCl did not change the therapeutic response (Fig. 2).

BZ produces pharmacological effects similar to those produced by scopolamine except that the time course is longer (7). From 5–10 hr after receiving BZ, the two placebo subjects were markedly obtunded and delirious (Fig. 3). One subject (top, Fig. 3) received VX at 8 hr and two subjects (lower 2, Fig. 3) received VX at 3 hr after BZ and each had rapid and marked improvement in his clinical status and on performance scores. This improvement lasted for 7–10 hr. Two subjects (top and bottom, Fig. 3) were given additional doses of VX (0.4 μg/kg) later in their course, but in view of the marked variability shown by the single subject who received only one dose, it is difficult to assess the value of these additional doses. Five other subjects responded to VX therapy in a similar manner (data not shown).

The third anticholinergic produces a time course of effects midway between that of scopolamine and BZ, but otherwise the effects are similar (Fig. 4). The therapeutic response to VX given iv at either 1.5 or 3 hr was quite striking and lasted for about 10 hr. However, VX given orally in equipotent doses (judging from the depression of the red cell cholinesterase activity) produced no therapeutic response and the treated subjects appeared to have a more severe and more prolonged course than the untreated.

Discussion. VX, a potent cholinesterase inhibitor, is effective in reversing the manifestations of anticholinergic produced delirium in man; its antidotal effect lasts from 7–10 hr. Since VX is not known to have other pharmacological activity, this strongly suggests that its antidotal activity is related to its ability to inhibit cholinesterase. The inhibited enzyme cannot hydrolyze acetylcholine and this substance then accumulates to overcome the cholinergic blockade.

This also suggests that the effects of certain compounds which block acetylcholine

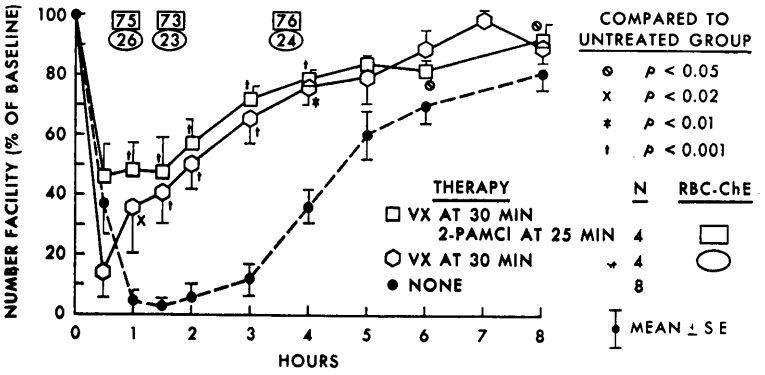

FIG. 2. The effectiveness of VX, administered at 30 min, in treating the central effects of scopolamine. The administration of 2-PAMCl did not reduce the effects of VX.

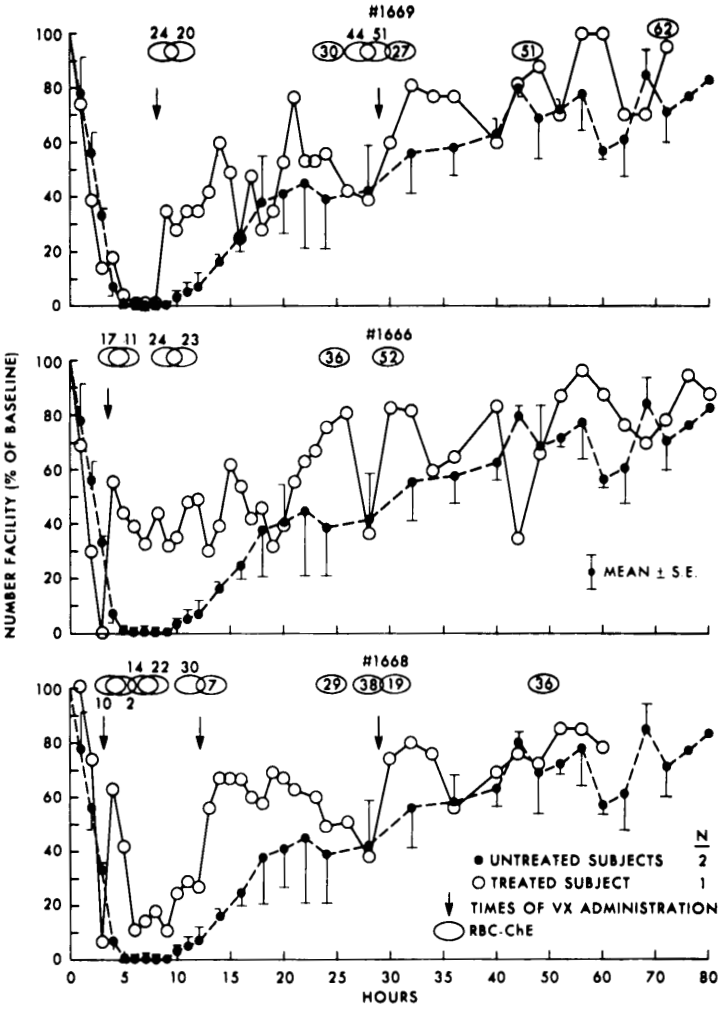

FIG. 3. The effectiveness of VX in reversing the central effects of BZ in three subjects.

are due primarily if not entirely to their anticholinergic properties.

An oxime, in doses which readily reactivated the circulating VX-inhibited cholinesterase, did not reverse the therapeutic benefits of VX. This may be because adequate amounts of oxime did not enter the CNS, although these doses (5–15 mg/kg) have been reported to be clinically effective (14, 15). The oxime given prophylactically did not prevent the CNS activity of the anticholinesterase compound, which was desirable under the circumstances of this investigation. However, this suggests a limitation on the prophylactic use of oximes to protect against anticholinesterase intoxication.

VX administered orally was ineffective in reversing anticholinergic delirium under the conditions of this investigation. Other studies[4] have shown that physostigmine is also ineffective when administered orally in doses equivalent to those given parenterally, but is effective when given orally in larger doses. When given orally VX is absorbed more slowly than after intravenous administration; the concentration of VX in the blood is probably too low to drive much of the compound into the brain. This was also suggested by an earlier study (8) in which subjects receiving VX iv had more signs and symptoms than subjects receiving VX orally although the

[4] Sidell, F. R., unpublished data.

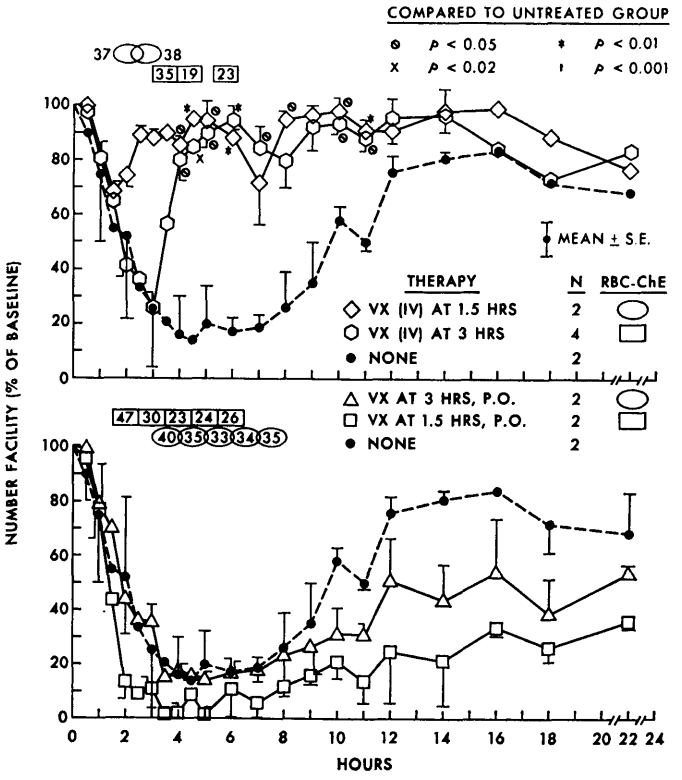

FIG. 4. The effect of VX given iv in reversing the central effects of this anticholinergic is in contrast to its ineffectiveness when given orally.

red blood cell cholinesterase depression was slightly greater in the latter group.

The finding that VX and certain other cholinesterase inhibitors [physostigmine and sarin (6)] are effective antidotes to the peripheral and central manifestations of intoxication by belladonna-like compounds is in contrast to the results of many earlier investigations. The ineffectiveness of anticholinesterase compounds as antidotes was widely promulgated in reports and textbooks, one of which states ". . . anti-ChE agents have been advocated to antagonize the peripheral effects of atropine, but are of doubtful value. Certainly they do not influence the central effects of the poison. . . ." (18). VX, physostigmine, and sarin possess two properties which many compounds examined earlier do not: (1) they cross the blood–brain barrier, and (2) they inhibit a significant amount of "true" or acetylcholinesterase at the doses administered.

Although it is unlikely that VX will be commonly employed as an antidote, it is likely that less potent compounds having these properties will be developed for clinical use.

Summary. VX, a potent cholinesterase inhibitor, effectively reversed the central effect (delirium) produced by scopolamine and two synthetic anticholinergic compounds in man when VX was administered iv. The therapeutic effectiveness of VX was not diminished by the previous, simultaneous, or subsequent administration of pralidoxime chloride which restored the red blood cell cholinesterase inhibition produced by VX. However, VX administered orally in a dose that produced equivalent red blood cell cholinesterase depression was ineffective.

We wish to thank the nurses and technicians of the Clinical Research Branch for the ward care of the subjects. We also thank J. S. Ketchum for helpful suggestions during the study, S. A. Cucinell for constructive comments on the manuscript, and Marion P. Royston for editorial assistance.

Part of this report was presented at the April

1973 meeting of the Federation of American Societies of Experimental Biology, Atlantic City, New Jersey.

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Received April 16, 1973. P.S.E.B.M., 1973, Vol. 144.