

Clinical observation and comparison of the effectiveness of several oxime cholinesterase reactivators

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XUE SZ, DING XJ, DING Y. Clinical observation and comparison of the effectiveness of several oxime cholinesterase reactivators. *Scand J Work Environ Health* 11 (1985): suppl 4, 46–48. After passing toxicity and experimental therapeutic tests, four oxime cholinesterase reactivators [PAM (pyridine aldoxime methiodide), PAC (pralidoxime, pyridine aldoxime methylchloride), TMB₄ (trimedoxime), and DMO₄ (obidoxime, Toxogonin, LũH₆)] were compared in clinical trials. All of them proved capable of restoring erythrocyte cholinesterase activity and relieving symptoms and signs of organophosphate insecticide poisoning. Mildly and moderately poisoned patients can be treated by several injections of any one of these drugs alone, but severe cases need the synergistic action of atropine, as well as treatments for two to three consecutive days. Although response to treatment is stronger with TMB₄ and DMO₄, they are not recommended for routine treatment because of their dangerous adverse side effects.

Key terms: obidoxime, organophosphate insecticide poisoning, pralidoxime, pyridine aldoxime methiodide, treatment, trimedoxime.

Since 1958, a series of oxime reactivators has been synthesized and tested (7). After being found to be effective and safe in experimental trials, the most promising drugs have been put into routine clinical use. Several papers about them have been published in Chinese (1, 2, 3, 4, 6). This paper is an integrated summary of these reports.

Materials and methods

The clinical effects of the following antidotes have been observed in detail: PAM (pyridine aldoxime methiodide), PAC (pralidoxime, pyridine aldoxime methylchloride), TMB₄ (trimedoxime), and DMO₄ (obidoxime, Toxogonin, LũH₆).

All the drugs and their formulations were prepared by the Department of Chemical Pharmacy and the Department of Pharmaceutical Science, Shanghai First Medical College. The clinical trials were performed in Hua-Shan, Kia-Ding, Liu-Ho, among other collaborating hospitals, by special teams consisting of members of the Section of Occupational Medicine of the Hua-Shan Hospital; and the Department of Occupational Health, School of Public Health, Shanghai First Medical College; and the medical staff of the collaborating hospitals.

The subjects were selected from patients who had been poisoned by occupational exposure to parathion and demeton but who had not yet been given atropine

and other special antidotes. In the course of the treatment atropine was not used, except in very severe cases, so that the action and adverse effects of the oximes being tested could be evaluated.

Careful physical examination, blood cholinesterase activity and serum glutamate-pyruvate (SGPT) determination, and electrocardiography were performed before and after the treatment. Complaints of symptoms and adverse effects, as well as any physical signs, were carefully recorded.

Results and discussion

All the patients recovered a few days after being treated. The general features of the treatment are summarized in table 1.

Effectiveness of the oxime reactivators

All four of the drugs tested were highly effective against parathion, demeton, and thiodiphosphoric acid tetraethyl ether poisoning; less effective against Dipterex and Dichlorvos poisoning; and probably not effective against dimethoate and fenitrothion poisoning (5).

Similar to the therapeutic indices in animal experiments, these studies showed that DMO₄ has a therapeutic index that is much greater than that of TMB₄ and PAM (153 vs 77 and 12, respectively) (7). In clinical trials, the results were similar, but the differences were fewer.

Apparently, TMB₄ possesses an atropine-like effect in addition to its ordinary cholinesterase reactivator ability. DMO₄ is also more effective than PAM, but its performance in relieving central nervous system symptoms is not as powerful as had been suggested

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Table 1. General features of the oximes used for the treatment of organophosphorous insecticide poisoning.

Oxime used ^a	Number of patients	Clinical improvement	Blood cholinesterase activity (mean %)		Side effects
			Before	After	
PAM (0.6—1.0 g; intravenous; 1—4 injections/d)	33 (20 moderate and 13 mild)	Symptoms relieved in 1—2 h; remission slow in subacute cases	20	40	If undiluted formulation is used, bitterness in mouth and vertigo feeling of syncope; if diluted with saline, light-headedness
PAM (0.8 g; intravenous; 1—2 injections)	15	Symptoms controlled in 30 min; five cases recurred; mean pulse rate increase from 80 to 88/min	38	80	Nausea; bitterness in mouth; some vomiting; in some cases temporary minor T-wave changes in the electrocardiogram
TMB ₄ (0.15 g; intravenous; 1 injection)	9	Perspiration and colic relieved quickly; tremor subsided much more slowly; mean pulse rate rise from 82 to 95/min			Heavy-headedness; tension headache; facial flushing; dryness in mouth; numbness in face and limbs
DMO ₄ (0.25—0.375 g; intramuscular; 1 injection; repeat in case of recurrence)	17 (10 moderate and 7 mild)	Muscarine symptoms controlled in 15 min; nicotinic symptoms controlled in 30 min; symptoms of the central nervous system subsided in several hours	30	67	Slight distension and stinging at site of injection; distension headache; numbness; three patients had electrocardiographic changes (one 2° A-V blockage, and two atrial fibrillation)
PAC (0.5—1.0 g; intramuscular; 1—2 doses; 3—4 doses in case of recurrence)	78	Similar to occurrence after PAM; six cases recurred	52	79	Distension and stinging at site of injection; lightheadedness; nausea

^a PAM = pyridine aldoxime methiodide; TMB₄ = trimedoxime; DMO₄ = obidoxime, Toxogonin, LùH₆; PAC = pralidoxime, pyridine aldoxime methylchloride.

by some authors, who thought it would pass through the blood-brain barrier.

In cases of mild and moderate poisoning, the effectiveness of the oximes, when used alone, were comparable to that of atropine. In severe cases, atropine should be used simultaneously with an oxime. The combined therapeutic action of the oximes and atropine is highly synergistic.

PAC, DMO₄, and TMB₄ can be given by intramuscular injection with almost the same effectiveness and speed as when given by the intravenous route. This characteristic makes them valuable in rural clinics staffed only by the "barefoot doctors."

Restoration of blood cholinesterase activity

In 1959 and 1965, in clinical trials, the recovery of blood cholinesterase activity was estimated by a rapid tintometric method. But in other years it was measured more precisely by the electrometric method. In 1963, the whole blood cholinesterase activity was determined; in 1964 erythrocyte and plasma cholinesterase activity was measured separately after centrifugation of the samples.

Recovery from poisoning and the restoration of cholinesterase activity were parallel.

As shown by the results of separate measurements, erythrocyte cholinesterase activity returned to normal quickly after the administration of the oximes; how-

ever, the plasma cholinesterase activity did not change significantly.

The changes in the blood cholinesterase activity are shown in figures 1 and 2.

Side effects of the oximes

The side effects of PAM and PAC were rather mild when these drugs were used in recommended doses, but, when they were injected very quickly or in high doses, the patient's respiration was inhibited, and breathing immediately became very slow and shallow. Because of the rapid decline of the concentration of oximes in the circulating blood, the patient's breathing returned to normal quickly.

The side effects of TMB₄ and DMO₄ were more prominent than those of PAM and PAC. The side effects of TMB₄ were similar to the effects of a large dose of atropine (such as palpitation and dilatation of superficial capillaries) and those of DMO₄ (eg, possible atrial irritability, A-V blockage, and ventricular instability). Since our dosage schedule was strictly controlled, some severe reactions described by others in patients treated with extraordinarily large doses have not yet occurred in our trials, eg, hepatotoxicity in the case of TMB₄ and fatal cardiac arrhythmia after the administration of DMO₄. Because of these adverse effects, TMB₄ use is now banned, and DMO₄ is only used in small doses. Probably DMO₄ may be helpful

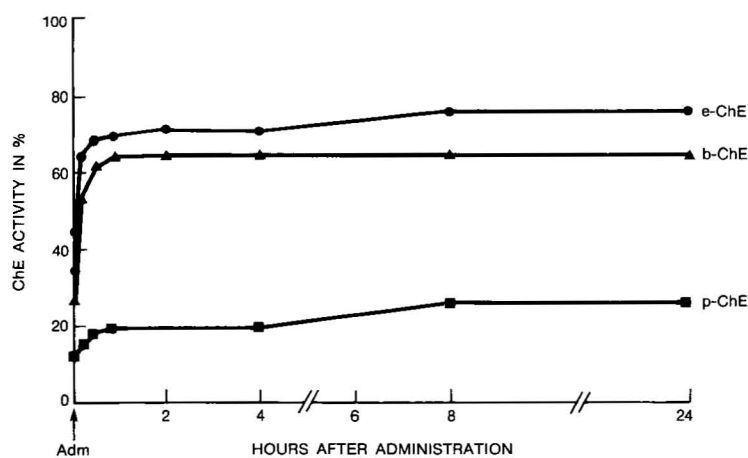


Figure 1. Restoration of cholinesterase (ChE) activity after the administration of the oximes in nonrecurrent cases. (e-ChE = erythrocyte cholinesterase activity, b-ChE = whole blood cholinesterase activity, p-ChE = plasma cholinesterase activity, Adm = administration)

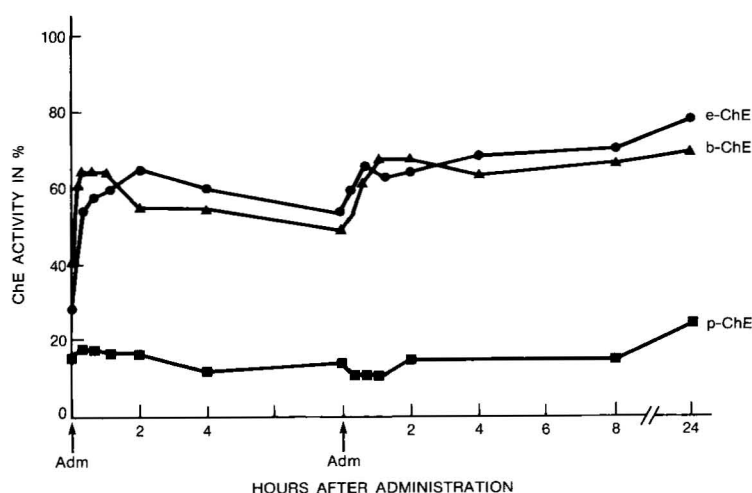


Figure 2. Restoration of cholinesterase (ChE) activity after the administration of the oximes in recurrent cases. (e-ChE = erythrocyte cholinesterase activity, b-ChE = whole blood cholinesterase activity, p-ChE = plasma cholinesterase activity, Adm = administration)

in making a combined formulation of antiorganophosphorous-ester remedies because of its high reactivating potency.

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