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ORIGINAL INVESTIGATION

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# Reactivation by various oximes of human erythrocyte acetylcholinesterase inhibited by different organophosphorus compounds

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**Abstract** The new bispyridinium oximes HI 6 and HLö 7 are promising antidotes against poisoning by highly toxic organophosphorus compounds, i.e. nerve agents. Until now, their ability to reactivate pesticide inhibited human acetylcholinesterase (AChE) has not been elucidated. For this purpose human erythrocyte AChE (EC 3.1.1.7) was inhibited (30 min) by chlorfenvinphos, dichlorvos, dicrotophos, heptenophos, mevinphos, monocrotophos, paraoxon, phosphamidon, trichlorfon, malaoxon, omethoate, oxydemeton-methyl or methamidophos by 85–98% of control. After removal of excess inhibitor, obidoxime, pralidoxime (2-PAM), HI 6 or HLö 7 (10, 30 or 100 μmol/l) were added and the AChE activity was measured spectrophotometrically at various times thereafter (5–60 min). The oximes significantly, but not completely, reactivated organophosphate inhibited AChE. The velocity and extent of reactivation were dependent on the oxime and its concentration. In all cases obidoxime was superior to the three other oximes, followed by HLö 7, 2-PAM and HI 6. In most cases obidoxime and HLö 7 were most effective at 10 or 30 μmol/l while 2-PAM and HI 6 needed 100 μmol/l. These data suggest that 2-PAM, HI 6 and HLö 7 are less patent than obidoxime in reactivating human AChE inhibited by organophosphate pesticides.

**Key words** Organophosphates · Oxime · Reactivation · AChE · Obidoxime · Pralidoxime · HI 6 · HLö 7

## Introduction

The adequate treatment of organophosphorus compound poisoning requires the use of different antidotes (Willems and Belpaire 1992). While it is generally accepted that anticholinergic drugs such as atropine are useful to counteract the muscarinic symptoms, the administration of oximes to reactivate organophosphate inhibited acetylcholinesterase (AChE) is discussed controversially (Karalliedde and Senanayake 1989; De Silva et al. 1992; Marrs 1993). Furthermore, there is an ongoing debate whether the monopyridinium oxime pralidoxime (2-PAM) or the bispyridinium oxime obidoxime (Fig. 1) should be recommended in organophosphorus compound poisoning.

In the past decades numerous bispyridinium oximes ("H-oximes") have been synthesised by Professor Hagedorn and coworkers at the University of Freiburg, Germany, mainly to provide an antidote which is superior to 2-PAM or obidoxime in poisoning by the highly toxic phosphonofluoridate soman (Eyer et al. 1992). Presently, the H-oximes HI 6 and HLö 7 (Fig. 1) are regarded as the most effective oximes against highly toxic nerve agents (de Jong et al. 1989; Eyer et al. 1992; Lundy et al. 1992; Worek and Szinicz 1993; Worek

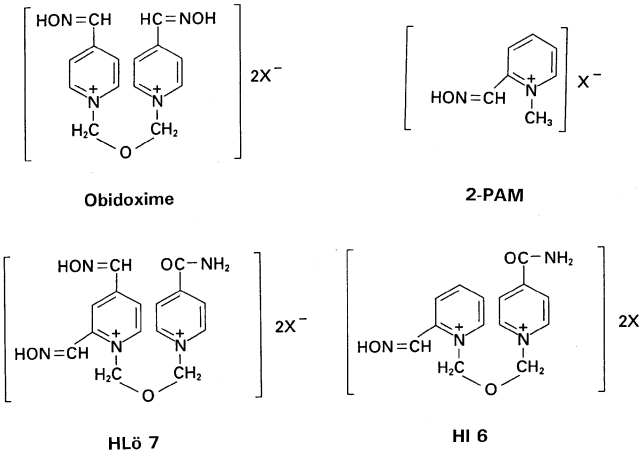


**Fig. 1** Chemical structure of obidoxime, 2-PAM, HI 6 and HLö 7

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et al. 1994a, b, 1995). In addition, Kusic et al. (1991) suggested in a recent study on the treatment of pesticide poisoned patients that HI 6 had a reasonable therapeutic effect against certain organophosphates. Due to these promising data, the present study was undertaken to compare the ability of the newer oximes HI 6 and HLö 7 with obidoxime and 2-PAM to reactivate human erythrocyte AChE inhibited by different pesticides.

## Materials and methods

### Chemicals

Human erythrocyte acetylcholinesterase type XIII (AChE, EC 3.1.1.7), pralidoxime iodide (2-PAM), acetylthiocholine iodide (ASCh) and 5,5′-dithio-bis-nitrobenzoic acid (DTNB) were purchased from Sigma (Deisenhofen, Germany). The organophosphorus compounds (95–99%, Table 1) were obtained from Promochem (Wesel, Germany). HI 6 dichloride was a generous gift of Dr. Clement (DRES, Ralston, Alberta, Canada) and HLö 7 dimethanesulfonate was a custom synthesis by J. Braxmeier (Chemical Laboratory, Döpshofen, Germany). Obidoxime dichloride and all other chemicals were products of Merck (Darmstadt, Germany).

The stability of the organophosphorus compounds and oximes was regularly checked by GC and HPLC. Stock solutions of the organophosphates (in 2-propanol) and of the oximes (in 67 mM phosphate buffer, pH 7.4) were prepared, stored at –80°C and appropriately diluted just before the experiment.

### Methods

#### *Reactivation experiments*

AChE was inhibited by incubating a mixture of 300 µl enzyme solution (approximately 2.5 U/ml) in 67 mmol/l phosphate buffer (pH 7.4) and of 5 µl of an organophosphorus compound in 2-propanol (for final concentration, see Table 1) at 37°C. After 30 min, the AChE activity decreased by 85–98% and excess inhibitor was removed by extraction with *n*-hexane as described (Eyer et al. 1992). Immediately afterwards, 20 µl aliquots of the incubate were added to 3 ml of 67 mmol/l phosphate buffer (pH 7.4) containing 0.25 mmol/l DTNB and an oxime (10, 30 or 100 µmol/l, see Table 1). After incubation at 37°C for various time intervals (5, 10, 20, 40, 60 min)

**Table 1** Chemical structure of the organophosphorus compounds and oximes. $C_{final}$ gives the final concentration of the compound during inhibition or reactivation

| Type | Name | CAS-No. | Chemical structure | $C_{final}$ |
|---|---|---|---|---|
| Phosphate | Chlorfenvinphos | 479–90–6 | 2-chloro-1-(2,4-dichlorophenyl) vinyldiethylphosphate | 16 µmol/l |
| | Dichlorvos | 62–73–7 | 2,2-dichlorovinyldimethylphosphate | 40 µmol/l |
| | Dicrotophos | 141–66–2 | *O*,*O*-dimethyl-*O*-[2-(*N*,*N*-dimethylcarbamoyl) -1-methylvinyl]-phosphate | 10 µmol/l |
| | Heptenophos | 23560–59–0 | (7-chlorobicyclo[3.2.0]hepta-2,6-dien-6-yl) dimethylphosphate | 50 µmol/l |
| | Mevinphos | 7786–34–7 | (2-methoxycarbonyl-1-methylvinyl) dimethylphosphate | 16 µmol/l |
| | Monocrotophos | 6923–22–4 | *O*,*O*-dimethyl-*O*-(1-methyl-2-methyl-carbamoylvinyl)phosphate | 160 µmol/l |
| | Paraoxon | 311–45–5 | *O*,*O*-diethyl-*O*-4-nitrophenylphosphate | 160 nmol/l |
| | Phosphamidon | 13171–21–6 | *O*-(2-chloro-2-diethylcarbamoyl-1-methylvinyl)-*O*,*O*-dimethylphosphate | 1.6 mmol/l |
| Phosphonate | Trichlorphon | 52–68–6 | *O*,*O*-dimethyl-2,2,2-trichloro-1-hydroxyethylphosphonate | 100 µmol/l |
| Phosphorothioate (*S*-substituted) | Malaoxon | 1634–78–2 | *O*,*O*-dimethyl-*S*-[1, 2-bis-(ethoxycarbamoyl)-ethyl]-phosphorothioate | 4 µmol/l |
| | Omethoate | 1113–02–6 | *O*,*O*-dimethyl-*S*-methylcarbamoyl-methylthiophosphate | 830 µmol/l |
| | Oxydemeton-methyl | 301–12–2 | *O*,*O*-dimethyl-*S*-2-ethylsulphinyl-ethylthiophosphate | 50 µmol/l |
| Phosphorothioamidate (*S*-substituted) | Methamidophos | 10265–92–6 | *O*,*S*-dimethylphosphoroamidothioate | 160 µmol/l |
| Oxime | Obidoxime | 114–90–9 | 1,1′-(oxydimethylene)bis(4-hydroxy-iminomethylpyridinium) dichloride | 10–30–100 µmol/l |
| | 2-PAM | 94–63–3 | 2-(hydroxyiminomethyl)-1-methylpyridinium iodide | |
| | HI 6 | 34433–31–31 | 1-[[[4-(aminocarbonyl)pyridinio]methoxy] methyl]-2-[(hydroxyimino)methyl] pyridinium dichloride | |
| | HLö 7 | 120103–35–7 | 1-[[[4-(aminocarbonyl)pyridinio]methoxy] methyl]-2,4-bis[(hydroxyimino)methyl] pyridinium dimethanesulfonate | |

**Table 2** AChE activity at the end of the inhibition period

| *O*rganophosphorus compound | AChE activity (% of control activity) |
|---|---|
| Chlorfenvinphos | 5.52 ± 0.15 |
| Dichlorvos | 5.93 ± 0.55 |
| Dicrotophos | 11.32 ± 0.48 |
| Heptenophos | 4.58 ± 0.16 |
| Mevinphos | 8.99 ± 0.21 |
| Monocrotophos | 8.34 ± 0.23 |
| Paraoxon | 2.76 ± 0.10 |
| Phosphamidon | 4.65 ± 0.16 |
| Trichlorphon | 7.61 ± 0.71 |
| Malaoxon | 7.26 ± 0.17 |
| *O*methoate | 5.25 ± 0.20 |
| *O*xydemeton-methyl | 10.06 ± 0.43 |
| Methamidophos | 4.80 ± 0.07 |

100 µl ASCh (67 mmol/l phosphate buffer, pH 7.4, final concentration 1 mmol/l) were added and the increase in extinction was measured at 405 nm and 37°C in a spectrophotometer (Cary 219, Varian, Darmstadt, Germany) according to Ellman (1961). The enzyme activities were corrected for spontaneous hydrolysis of ASCh and for oxime-induced hydrolysis of the substrate and were referred to control runs performed in a similar manner without inhibition by organophosphates.

*Statistics*

The data, expressed as means + SE ($n = 6$, each), are presented as percent of the control values. Differences between groups were tested by Wilcoxon, Mann, and Whitney *U*-test and within-group differences were checked by Wilcoxon matched pairs test. A $p < 0.05$ was considered to indicate a significant difference (Sachs 1974).

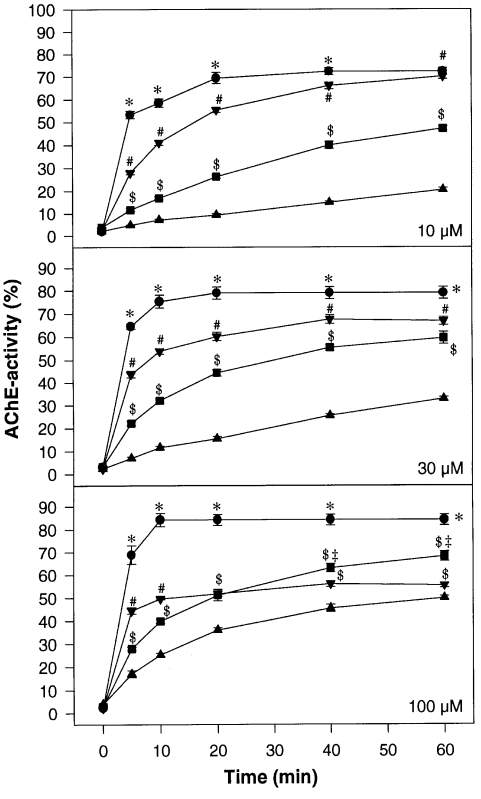


**Fig. 2** Reactivation of paraoxon inhibited human AChE by obidoxime (*circle*), 2-PAM (*square*), HI 6 (*triangle up*) or HLö 7 (*triangle down*) at 10 µmol/l (*upper panel*), 30 µmol/l (*middle panel*) or 100 µmol/l (*lower panel*) of the respective oxime. The data are shown as % of control activity in means ± SE ($n = 6$, each). Differences between groups were tested by Wilcoxon, Mann and Whitney *U*-test. * $p < 0.05$ to 2-PAM, HI 6 and HLö 7; # $p < 0.05$ to 2-PAM and HI 6; $ $p < 0.05$ to HI 6; ‡ $p < 0.05$ to HLö 7

## Results

The oximes obidoxime, 2-PAM, HI 6 and HLö 7 reactivated human erythrocyte AChE inhibited by different organophosphorus compounds without reaching the control level (Figs 2–4). There were substantial differences in reactivating potency among the oximes and organophosphorus compound used.

Obidoxime (10, 30 or 100 µmol/l) was significantly more effective than the other oximes in reactivating paraoxon inhibited AChE and its reactivation rate was most rapid (Fig. 2). This oxime increased the AChE activity to 55–68% of the control value within 5 min, and the maximum level was reached after 10 (100 µmol/l) to 40 min (10 µmol/l). HLö 7 (10 µmol/l) was almost as effective as obidoxime in reactivating paraoxon inhibited AChE (Fig. 2). However, the reactivation rate was slower and the maximum level (70%) was only reached after 60 min. The reactivation appeared to decrease with higher concentrations of HLö 7 and at 100 µmol/l only 50% of control activity was measured. 2-PAM (10–100 µmol/l) resulted in a nearly dose dependent increase in AChE activity, but the values remained significantly lower compared to obidoxime and HLö 7 (10 and 30 µmol/l). HI 6 was least effective in reactivating paraoxon inhibited human erythrocyte AChE (Fig. 2). It produced a slow and dose dependent increase in AChE activity, but the data remained significantly lower compared to the other oximes.

Comparable data (obidoxime > HLö 7 > 2-PAM > HI 6) were obtained with the other organophosphates (chlorfenvinphos, dichlorvos, dicrotophos, heptenophos, mevinphos, monocrotophos, phosphamidon), with the organophosphonate trichlorphon or with *s*-substituted phosphorothioates (malaoxon, omethoate, oxydemeton-methyl, Figs 3, 4). In general, the maximum reactivation was obtained with 10 or 30 µmol/l obidoxime or HLö 7, while for 2-PAM and HI 6 in most cases a further increase in reactivation was obtained in the presence of 100 µmol/l oxime.

Obidoxime and 2-PAM were almost comparably effective against the *s*-substituted organophosphoroamidothioate methamidophos and both (30 and 100 µmol/l) were superior to HLö 7 and HI 6 (Figs 3, 4).

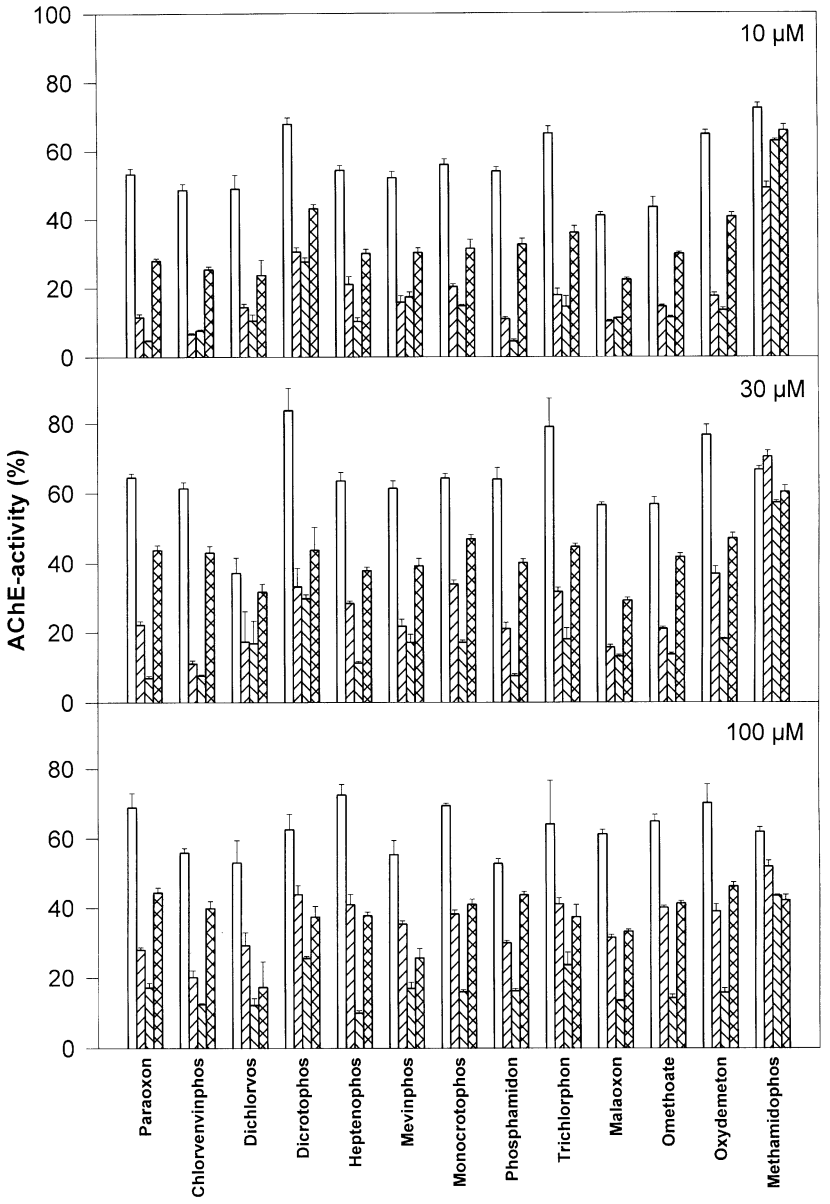


**Fig. 3** Reactivation of organophosphate inhibited human AChE by obidoxime (*blank column*), 2-PAM (*right-hatched column*), HI 6 (*left-hatched column*) or HLö 7 (*cross-hatched column*). The oxime dose was 10 (*top*), 30 (*center*) or 100 µmol/l (*bottom*). The data, 5 min after the addition of the oxime, are shown as % of the control activity in means ± SE ($n = 6$, each)

## Discussion

The data presented demonstrate that at equimolar doses the bispyridinium oxime obidoxime is superior to 2-PAM, HI 6 and HLö 7 in reactivating organophosphate pesticide inhibited human erythrocyte AChE. Concerning the comparison between obidoxime and 2-PAM these findings agree with literature data (Schoene and Strake 1971; Bismuth et al. 1992). Various clinical and experimental studies demonstrated a considerable therapeutic effect of obidoxime in poisoning with different organophosphorus compounds (Erdmann 1968; Hahn and Henschler 1969; Xue et al. 1985; De Kort et al. 1988; Quadri and Malacrida 1990). Numerous studies have been undertaken to evaluate the ability of 2-PAM to reactivate organophosphate inhibited AChE and to improve the clinical status of pesticide poisoned patients (for review see Bismuth et al. 1992; Marrs 1993). The efficacy of this oxime seems to be much more dependent on the organophosphorus compound incorporated compared to obidoxime. Willems and coworkers (1993) recorded a reasonable AChE reactivation with 2-PAM in human parathion poisoning, while this oxime was ineffective against dimethoate. Karalliedde and Senanayake (1989) suggested that the efficacy of 2-PAM is lower in poisoning with dimethyl organophosphates compared to diethyl compounds. Recently, the usefulness of 2-PAM for treatment of pesticide poisoning was doubted at all, since the authors observed no differences in outcome between oxime treated and non-treated patients (De Silva et al. 1992), but the late onset of oxime

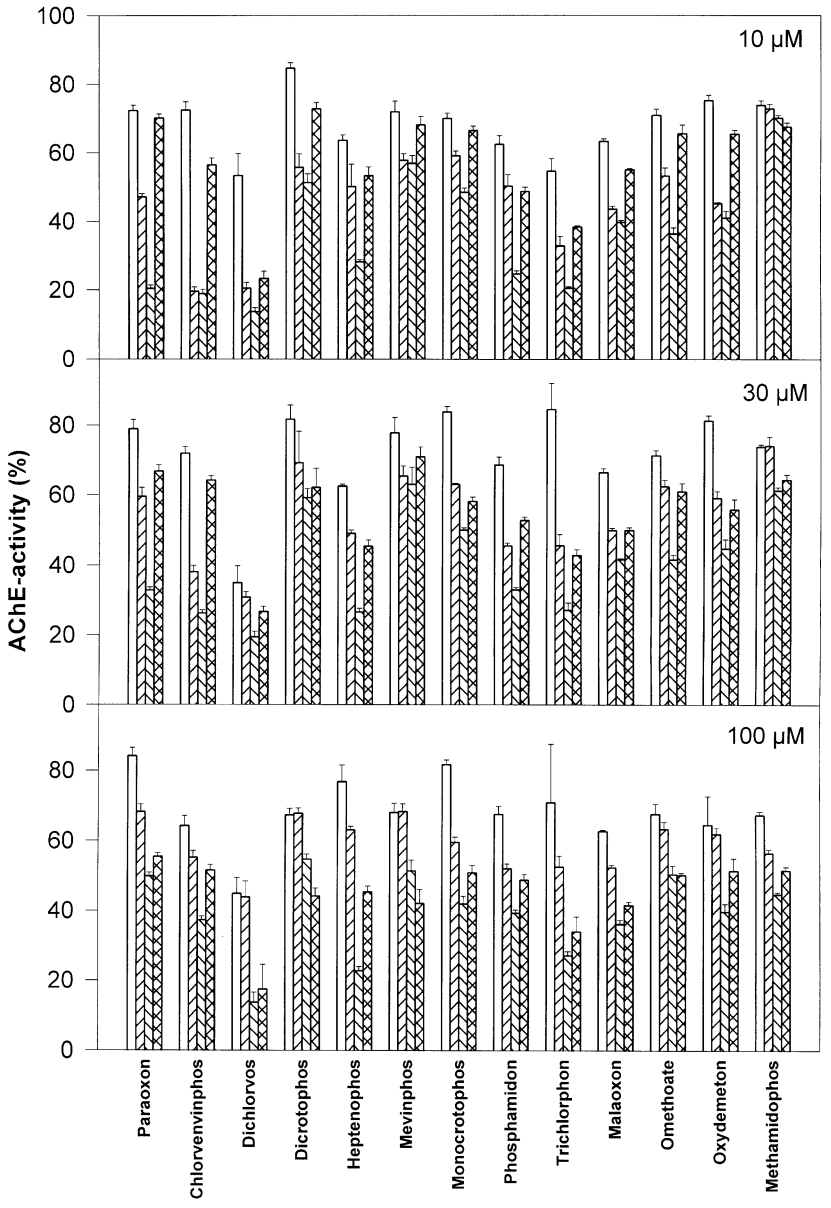


**Fig. 4** Reactivation of organophosphate inhibited human AChE by obidoxime (*blank column*), 2-PAM (*right-hatched column*), HI 6 (*left-hatched column*) or HLö 7 (*cross-hatched column*). The oxime dose was 10 (*top*), 30 (*center*) or 100 µmol/l (*bottom*). The data, 60 min after the addition of the oxime, are shown as % of the control activity in means ± SE ($n = 6$, each)

treatment and a high portion of organophosphorus compounds with rapid ageing make the interpretation of the data difficult.

HI 6 was extensively tested for its effects against nerve agents regarding AChE reactivation and treatment of experimental poisoning (for review, see Bismuth et al. 1992), however, until now, only little information has been available on the reactivation of pesticide inhibited AChE by this oxime. In vitro tests showed that HI 6 was less potent in reactivating electric eel AChE inhibited by different phosphoramidates compared to obidoxime (Langenberg et al. 1988). HI 6 was comparable to 2-PAM in reactivation of methamidophos inhibited electric eel AChE and failed (like 2-PAM) to reactivate profenofos-inhibited AChE (Glickman et al. 1984). In organophosphate insecticide poisoned patients the repetitive administration of high doses of HI 6 (500 mg) resulted in a fairly rapid reactivation of dichlorvos inhibited erythrocyte AChE, but the reactivation was slow after malathion and HI 6 was almost ineffective against dimethoate and phosphamidon (Kusic et al. 1991).

HLö 7 was shown to be an effective antidote in nerve agent poisoning (Eyer et al. 1992), but until now the information on its efficacy against pesticides is scarce. In agreement with the present study, HLö 7 was less effective than obidoxime but superior to 2-PAM and HI 6 in reactivating paraoxon inhibited human AChE from intact erythrocytes in vitro (Irmhof-Britt 1993).

Besides the extent, the velocity of AChE reactivation is another important parameter for the assessment of oxime effects. With obidoxime the reactivation

occurred more rapidly with almost all organophosphates tested (with the exception of methamidophos, data not shown) compared to HLö 7, 2-PAM or HI 6. Fast reactivation could be of importance in severe poisoning, where a rapid AChE reactivation is necessary for the improvement of neuromuscular transmission especially of the diaphragm.

There is a persistent discussion on the oxime plasma level necessary for AChE reactivation in organophosphate poisoned patients (Karalliedde and Senanayake 1989; Kusic et al. 1991; Willems et al. 1992, 1993). Most authors refer to a therapeutic plasma level of 4 μg/ml defined for pralidoxime methanesulfonate (Sundwall 1961), which would correspond to approximately 15 μmol/l 2-PAM, 11 μmol/l obidoxime or HI 6 and 8 μmol/l HLö 7. In the present study the optimum dose was between 10 and 30 μmol/l for obidoxime, whereas with 2-PAM the reactivation dose-dependently increased from 10 to 100 μmol/l. Thus it has to be concluded that the recommended plasma level of 4 μg/ml may be sufficient for obidoxime (and HLö 7; Eyer 1995) but is far too low for 2-PAM (or HI 6). In the presence of organophosphates, the therapeutic effect of oximes declines by reinhibition and even higher oxime doses will become necessary for sufficient AChE reactivation (Willems et al. 1993).

In addition, the formation of an "aged" enzyme-organophosphate complex may be responsible for the inability of oximes to reactivate AChE, since aged enzyme is resistant to reactivation by the presently available oximes (Berends et al. 1959). This fact may be of importance in poisoning by dimethyl compounds because the *O*,*O*-dimethyl-phosphoryl-AChE complexes are considered to undergo very rapid ageing (Bismuth et al. 1992).

In conclusion, the data of the present study demonstrate that obidoxime, 2-PAM, HI 6 and HLö 7 are effective in reactivation of human erythrocyte AChE inhibited by various organophosphorus compounds in vitro after a short period of inhibition and in the absence of the poison. Furthermore, it was shown that obidoxime is superior to the other oximes concerning velocity and extent of reactivation.

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