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The efficacy of bispyridinium derivatives in the treatment of organophosphonate poisoning in the guinea-pig

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The efficacy of a number of bispyridinium compounds, including both oxime and non-oxime derivatives, has been determined against poisoning by sarin, soman, tabun and VX in guinea-pigs receiving various supporting treatments. In conjunction with atropine therapy only, the oximes were effective against sarin and VX poisoning and of them only the 4-substituted oximes were beneficial against tabun poisoning. None of the compounds was effective against poisoning by soman. When the supporting drug treatment consisted of pyridostigmine pretreatment and therapy with atropine and diazepam (this treatment itself gave considerable protection against organophosphate poisoning) both the non-oxime and oxime derivatives increased the protection against all four agents although obidoxime and TMB-4 were not beneficial against soman poisoning. The results are discussed in relation to published studies in which these compounds have been found to be beneficial against soman poisoning in atropine-treated rats and mice. It is suggested that the guinea-pig is a better model for predicting the efficacy of treatments for organophosphate poisoning in primate species.

Pralidoxime mesylate (P2S, 1-methyl-2-hydroxyiminomethyl-pyridinium methanesulphonate) in combination with atropine, is effective against poisoning by many organophosphates (Davies et al 1959; Wilson & Sondheimer 1957) but is of little benefit in treating poisoning by soman (1,2,2-trimethylpropyl methylphosphonofluoridate) (Loomis & Salafsky 1963; Heilbronn & Tolagen 1965). This limitation in the efficacy of P2S (and related oximes) has led to the investigation of other approaches to the treatment of soman poisoning e.g., carbamate pretreatment (Berry & Davies 1970; Gordon et al 1978).

Over the past ten years Hagedorn and her colleagues (Oldiges & Schoene 1970) have synthesized a large number of bispyridinium dimethylether compounds containing both oxime and other substituents some of which have been reported to be beneficial in soman poisoning. However, the evidence for their efficacy has some limitations in that much of it is based on studies of the effects of these compounds on soman-inhibited acetylcholinesterase (Schoene 1968; Erdmann 1969; Domschke & Erdmann 1969; Harris et al 1978) or of their reversal of soman-induced neuromuscular blockade (Smith & Muir 1977; Smith et al 1981; Wolthuis et al 1981). The toxicological assessment of their efficacy has been mainly in mice and rats (Erdmann 1969; Boskovic & Stern 1970; Kepner & Wolthuis 1978; Boskovic 1979). Both these species are relatively resistant to organophosphate poisoning and do not respond well to post-poisoning treatment. In combination with atropine supported by benactyzine certain of these oximes will protect beagle dogs against poisoning by more than 5 × LD50 of soman (Schenk et al 1976; Weger & Szinicz 1981).

To facilitate an assessment of the potential value of these new compounds in the treatment of organophosphate anticholinesterase poisoning in man a representative number of them, including both oxime and non-oxime derivatives, (their structures are shown in Table 1) has been studied in the guinea-pig. This species was chosen as experience in this laboratory suggests that in its sensitivity to organophosphate poisoning and its response to post-poisoning therapy it is closer to the primates (rhesus monkey) than are the other commonly used laboratory animals. The efficacy of the compounds has been compared with that of P2S, TMB-4 and obidoxime against sarin (isopropyl methylphosphonofluoridate), soman, tabun (ethyl dimethylphosphoramidocyanidate) or VX (ethyl *S*-di-isopropylaminoethyl methylphosphonothiolate) poisoning in atropine-treated guinea-pigs. The comparison has been extended to the use of the compounds as adjuncts to therapy with atropine or atropine and diazepam (Lipp 1973; Johnson & Lowndes 1974; Vale & Scott 1974) in pyridostigmine pretreated guinea-pigs.

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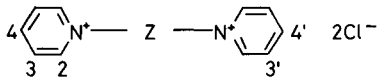
Table 1. The chemical structures of the bispyridinium compounds tested.



Compound	4	3	2	Z	3′	4′
HS-6	H	H	-CHNOH	$-CH_2OCH_2-$	$-CONH_2$	H
HI-6	H	H	-CHNOH	$-CH_2OCH_2-$	H	$-CONH_2$
HGG-12	H	H	-CHNOH	$-CH_2OCH_2-$	$-COC_6H_5$	H
HGG-42	H	H	-CHNOH	$-CH_2OCH_2-$	$-COC_6H_{11}$	H
HS-14	H	H	-CHNOH	$-CH_2OCH_2-$	H	H
HS-8	H	$-CONH_2$	H	$-CH_2OCH_2-$	$-CONH_2$	H
SAD 128	$-C(CH_3)_3$	H	H	$-CH_2OCH_2-$	H	$-C(CH_3)_3$
P65	$-C(CH_3)_3$	H	H	$-(CH_2)_6-$	H	$-C(CH_3)_3$
BPE	H	H	H	$-CH_2OCH_2-$	H	H
Obidoxime	-CHNOH	H	H	$-CH_2OCH_2-$	H	-CHNOH
TMB-4	-CHNOH	H	H	$-(CH_2)_3-$	H	-CHNOH

MATERIALS AND METHODS

Animals

Porton strain (Dunkin-Hartley derived) female guinea-pigs (280–360 g) were used.

Compounds

Sarin, soman, tabun (all at least 95% pure), VX (at least 90% pure) and all the drugs used in the treatment were prepared within the Chemical Defence Establishment except for atropine sulphate, purchased from BDH Ltd, diazepam, donated by Berk Chemicals Ltd, and HGG-12 and HGG-42 obtained from Merck Ltd.

The organophosphorus compounds were dissolved in 0·9% NaCl (saline) immediately before use. The drugs were prepared in aqueous solution except for diazepam which was dissolved in propane-1,2-diol. Drugs were injected at a dose volume of 1 ml kg^{-1}.

Experimental procedure

Pyridostigmine iodide, 0·32 μmol kg^{-1} (i.m.) was injected into the right hind limb 30 min before the organophosphate was administered (s.c.) into the right groin. One minute after the organophosphate, or at signs of poisoning if these occurred sooner, atropine (50 μmol kg^{-1}) and the test compound were injected intramuscularly into the right hind limb followed immediately by diazepam (6·25 or 25 μmol kg^{-1}) (i.m.) into the left hind limb. In one series of experiments the dose of the test compound was divided, half being given 10 min before poisoning and half 1 min after poisoning. These experiments are clearly identified. Animals that did not receive a bispyridinium compound, were given the same adjuvant treatment as animals that were given a bispyridium compound.

LD50 values, based on 24 h mortalities in at least 4 groups of 6 animals, were estimated by probit analysis (Finney 1947). The data are expressed as Protective Ratios:

$$\text{Protective Ratio} = \frac{\text{LD50 organophosphate in treated animals}}{\text{LD50 organophosphate in untreated animals}}$$

The 95% confidence limits are given for each ratio.

Where toxic signs were observed when the test compound was injected into control animals at a dose of 130 μmol kg^{-1}, the maximum non-lethal dose was determined using groups of 3 guinea-pigs and a dose ratio of 3.

RESULTS

Therapeutic effectiveness in combination with atropine

To maximize their efficacy the oximes and related compounds were given in divided doses: one half 10 min before poisoning and the other half 1 min after poisoning in combination with atropine. The dose of the compounds was arbitrarily set at 130 μmol kg^{-1}, the dose of P2S used routinely in this Laboratory which is one tenth its LD50. The doses of TMB-4 and obidoxime were one third of the maximum non-lethal dose and for SAD 128 it was one half.

None of the compounds was effective against soman poisoning in that the protection achieved was not greater than by atropine alone (Table 2). All of the oximes gave good protection against sarin and VX poisoning but against tabun poisoning only the 4-substituted oximes, TMB-4 and obidoxime, were effective. SAD 128, which does not have an oxime

Table 2. Effectiveness of oximes and bispyridinium compounds against organophosphate poisoning in atropine-treated guinea-pigs. The animals received half the dose of the test compound (i.m.) 10 min before challenge (s.c.) with the organophosphate and the rest of the compound together with 50 μmol kg^{-1} atropine (i.m.) 1 min after.

Compound	Total dose (μmol kg^{-1})	Protective Ratio (95% Confidence Limits) Tabun	Sarin	Soman	VX
—	—	1·3 (0·9–1·9)	<3	1·5 (1·2–1·9)	<3
P2S	130	2·5 (1·7–3·4)	38* (27–52)	1·3 (1·1–1·5)	25 (14–44)
HS-6	130	2·6 (2·0–3·4)	35 (19–65)	1·8 (1·6–2·2)	9·6 (7·9–12)
HI-6	130	2·2 (1·8–2·8)	76 (44–130)	2·6 (2·1–3·1)	66 (32–140)
HGG-12	130	3·7 (2·8–4·9)	12 (7·1–20)	2·4 (1·9–3·1)	5 1 (3·8–6·9)
Obidoxime	40	19 (13–28)	59 (37–94)	1·8 (1·4–2·3)	58 (23–150)
TMB-4	13	13 (8·4–22)	46 (28–76)	1·0 (0·8–1·2)	40 (14–120)
SAD 128	21	1·4 (1·0–1·9)	<3	1·5 (1·3–1·7)	—

* Data from Davies et al (1959). The whole of the P2S was given 1 min after poisoning.

substituent, was ineffective against poisoning by any of the organophosphates.

Efficacy in combination with enhanced therapy

Supplementing atropine therapy with diazepam and pyridostigmine pretreatment increased the protection achieved against soman poisoning (Table 3). None of the compounds tested gave any marked improvement in the efficacy of the drug treatment until the full combination of pyridostigmine pretreatment supported by post-poisoning therapy with atropine and diazepam was used: all of the drugs, except P2S, significantly raised the level of protection but no compound was significantly better than any other.

The dose of diazepam used in these experiments was 25 μmol kg^{-1} but this was not critical in that the same protection was achieved at 6·25 μmol kg^{-1}. However the protection was reduced by lowering the dose of diazepam to 3·12 μmol kg^{-1}.

Efficacy against organophosphate poisoning in pyridostigmine pretreated guinea-pigs

All the bispyridinium compounds were tested against poisoning by sarin, soman, tabun or VX, in guinea-pigs receiving pyridostigmine pretreatment and therapy with atropine and diazepam (Table 4). The standard dose of 130 μmol kg^{-1} was used except for SAD 128 and P65: the dose of SAD 128 was half the maximum non-lethal dose whereas P65 was used at the maximum non-lethal dose. 130 μmol kg^{-1} is about the LD50 for obidoxime.

The pyridostigmine, atropine and diazepam combination gave good protection against all four organophosphates. Inclusion of P2S or the bispyridinium compounds into the treatment raised the levels of protection achieved which were higher than when atropine alone was the supporting therapy (Table 2). The 2-substituted oximes and the non-oxime substituted bispyridinium compounds were effective against tabun poisoning. All the oximes gave better protection against poisoning by sarin, tabun or VX than by soman whereas the non-oxime compounds gave similar levels of protection against all four agents. Obidoxime and TMB-4 although used at doses which were lethal or near lethal to control animals were the most effective compounds in the treatment of sarin or VX poisoning but were the least effective against soman; TMB-4 reduced the protection achieved by pyridostigmine, atropine and diazepam.

The dose of the bispyridinium compounds was varied to determine the optimal protective dose against soman poisoning. Except for obidoxime and TMB-4, none of the doses tested gave a significant improvement on that reported in Table 4.

The relation between protection and dose for obidoxime and TMB-4

In view of the apparently anomalous effects of obidoxime and TMB-4 against soman poisoning in pyridostigmine-pretreated guinea-pigs the experiments were repeated using lower, non-toxic doses of these oximes (Table 5). The results confirmed that a

Table 3. Effectiveness of oximes and bispyridinium compounds against soman poisoning in guinea-pigs receiving various supporting drug treatments. Pyridostigmine (0·32 μmol kg^{-1} i.m.) was injected 30 min before challenge with soman (s.c.). One min after poisoning P2S (130 μmol kg^{-1}) HS-6 (130 μmol kg^{-1}), SAD 128 (21 μmol kg^{-1}) or BPE (130 μmol kg^{-1}) was injected i.m. with atropine (50 μmol kg^{-1}). Diazepam (25 μmol kg^{-1}) was given by a separate i.m. injection.

Compound	Protective Ratio (95% Confidence Limits) Supporting treatment: Atropine	Atropine diazepam	Pyridostigmine atropine	Pyridostigmine atropine diazepam
—	1·5 (1·2–1·9)	2·2 (1·8–2·7)	5·2 (4·1–6·6)	8·7 (5·7–14)
P2S	1·7 (1·5–1·9)	2·5 (1·9–3 1)	6·8 (5·4–8·5)	14 (10–19)
HS-6	1·8* (1·6–2·2)	3·5 (2·8–4·3)	6·6 (4·8–9·2)	19 (16–23)
SAD 128	1·5* (1·3–1·7)	1·8 (1·4–2·2)	3·8 (2·4–5·9)	27 (20–36)
BPE	—	3·1 (2·1)–4·6)	5·5 (3·9–7·7)	25 (17–35)

* Half the dose of compound was given 10 min before poisoning, as in Table 2.

dose of 130 μmol kg^{-1} TMB-4, which is greater than its LD50 in control animals gave considerable protection against poisoning by sarin or VX but was deleterious against soman poisoning. Lowering the dose of TMB-4 decreased its deleterious action in the treatment of soman poisoning and reduced its efficacy against poisoning by sarin or VX. At none of the doses tested was obidoxime of any benefit in treating soman poisoning. The dose of diazepam used in these series of experiments was 6·25 μmol kg^{-1} and the results were consistent with the previous experiments (Table 4) in which 25 μmol kg^{-1} diazepam was used.

Table 4. Effectiveness of oximes and bispyridinium compounds against organophosphate poisoning in pyridostigmine-pretreated guinea-pigs. Pyridostigmine (0·32 μmol kg^{-1} i.m.) was injected 30 min before challenge with organophosphate (s.c.). One min after poisoning the test compound was injected (i.m.) with 50 μmol kg^{-1} atropine. Diazepam (25 μmol kg^{-1} or 6·25 μmol kg^{-1}*) was injected (i.m.) separately.

		Protective Ratio (95% Confidence Limits)			
Compound	μmol kg^{-1}	Tabun	Sarin	Soman	VX
—	—	11 (7·7–16)	11 (10–13)	8·7 (5·7–14)	15 (7·2–33)
P2S	130	34 (28–40)	45 (25–81)	14 (9·8–20)	69 (38–120)
HS-6	130	73 (52–100)	57 (37–89)	19 (16–23)	82 (50–130)
HI-6	130	34 (18–63)	110 (62–190)	15 (9·6–25)	68 (39–120)
HGG-12	130	68 (46–99)	54 (30–95)	20 (16–26)	55 (42–74)
HGG-42	130	12 (7·4–19)	40 (19–82)	12 (9·1–17)	31 (25–39)
HS-14	130	—	—	17 (11–26)	—
TMB-4	130	76 (46–120)	220 (120–400)	2·0 (1·4–2·8)	310 (190–520)
Obidoxime	130	—	380* (220–630)	9·7 (6·7–14)	410* (320–530)
SAD 128	21	38 (27–53)	19 (11–32)	27 (20–36)	60 (45–80)
P65	4·7	—	—	19 (13–26)	—
HS-8	130	—	—	11 (7·6–16)	—
BPE	130	27 (20–38)	24 (12–48)	25 (17–35)	47 (37–59)

Combination of oximes and non-oxime bispyridinium compounds

The non-oxime bispyridinium compounds have been reported to delay the ageing of soman-inhibited acetylcholinesterase (Harris et al 1978) and HS-6 and related compounds have been shown to reactivate the unaged soman-inhibited enzyme (Harris et al 1981; Hauser et al 1981; Clement 1981). To determine whether the reported actions of the non-oxime bispyridinium compounds and of the oximes were synergistic in-vivo combinations of the two were evaluated in the treatment of soman poisoning in pyridostigmine pretreated guinea-pigs. The compounds were all tested at one half of the maximum non-lethal dose, except for P2S which was used at about one sixth of that dose.

Table 5. Dose related protection of TMB-4 and obidoxime against organophosphate poisoning in pyridostigmine pretreated guinea-pigs. Pyridostigmine (0·32 μmol kg^{-1} i.m.) was injected 30 min before challenge with organophosphate (s.c.). After poisoning the oxime was injected (i.m.) with atropine (50 μmol kg^{-1}). Diazepam (6·25 μmol kg^{-1}) was injected (i.m.) separately.

		Protective Ratio (95% Confidence Limits)		
Oxime	μmol kg^{-1}	Sarin	Soman	VX
—	—	8·3 (6·5–11)	11 (8·9–14)	6·9 (4·9–9·6)
TMB-4	4	—	8·6 (6·4–11)	—
	13	32 (16–66)	9·3 (6·9–12)	38 (25–58)
	40	—	7·1 (5·6–9·0)	190 (130–280)
	130	54 (14–210)	<4	69 (27–180)
Obidoxime	13	52 (41–66)	14 (11–18)	67 (34–130)
	26	54 (32–92)	9·2 (5·8–15)	69 (47–100)
	40	—	9·3 (7·8–11)	—
	130	380 (220–630)	11 (8·3–14)	410 (320–530)

LD50 TMB-4 was 94 μmol kg^{-1} (i.m.).
LD50 Obidoxime was 260 μmol kg^{-1} (i.m.).

None of the combinations tested produced toxic signs in control groups of guinea-pigs. The results (Table 6) showed no evidence of synergism between the non-oximes and oximes and no combination gave significantly better protection than its individual components (Table 4). Combinations of non-oxime compounds (SAD 128, P65 and BPE) and combinations of oximes (P2S, HS-6 and TMB-4) were tested but none showed any increased protection against soman poisoning. Combinations including TMB-4 gave lower levels of protection than the other oximes. It is conceivable that the soman-inhibited acetylcholinesterase aged before the non-oxime compounds could exert their delaying action, therefore in a further series of experiments, SAD 128, BPE or P65 was administered with pyridostigmine, 30 min before poisoning by soman in guinea-pigs receiving atropine, P2S, diazepam therapy. In no case was the Protective Ratio of the treatment

improved by the presence of the bispyridinium compound.

DISCUSSION

Neither P2S nor any of the bispyridinium compounds was effective against soman poisoning in the guinea-pig when atropine was the sole supporting therapy. This is not inconsistent with the findings of Boskovic & Stern (1970) who reported that in mice given various combinations of cholinolytics, HS-6 and obidoxime (100 μmol kg^{-1}) raised the LD50 (s.c.) of soman by a factor of less than 2. However, in a more recent paper Boskovic (1979) showed that a higher dose of HI-6 (140 μmol kg^{-1}) in combination with atropine (28 μmol kg^{-1}) gave a protective factor of 4·2 against s.c. soman poisoning in mice whereas HS-6 gave a factor of only 1·2. Neither oxime was effective against intraperitoneally injected soman.

Table 6. Effectiveness of oxime and bispyridinium combinations in the treatment of soman poisoning in pyridostigmine-pretreated guinea-pigs. Pyridostigmine (0·32 μmol kg^{-1} i.m.) was given 30 min before poisoning with soman (s.c.). Atropine (50 μmol kg^{-1}) was given with the test combination (i.m.) 1 min after poisoning. Diazepam (6·25 μmol kg^{-1} i.m.) was given separately.

Compounds	Dose μmol kg^{-1}	Protection ratio (95% confidence limits)
SAD 128 + P2S	20 + 200	18 (11–28)
SAD 128 + HS-6	20 + 200	26 (17–37)
SAD 128 + TMB-4	20 + 20	14 (7·7–24)
BPE + P2S	200 + 200	18 (11–28)
BPE + HS-6	200 + 200	16 (10–26)
BPE + TMB-4	200 + 20	16 (9·3–27)
P65 + P2S	2 + 200	18 (11–30)
P65 + HS-6	2 + 200	16 (11–22)
P65 + TMB-4	2 + 20	11 (7·3–17)
BPE + SAD 128	200 + 20	23 (14–36)
BPE + P65	200 + 2	18 (12–25)
P2S + HS-6	200 + 200	14 (11–19)
P2S + TMB-4	200 + 20	11 (7·3–17)
—	— —	11 (8·9–14)

Kepner & Wolthuis (1978) reported that in rats treated with atropine (108 μmol kg^{-1} i.p.) HI-6 (278 μmol kg^{-1} i.p.) raised the LD50 (s.c.) of soman by a factor of 8 whereas HS-6 was somewhat less effective (protective factor 4). In rabbits, therapy with HS-6 (84 μmol kg^{-1}) and atropine (25 μmol kg^{-1}) has been shown (Harris et al 1981) to have a protective ratio of 10 against soman (i.v.) poisoning. Weger & Szinicz (1981) have evaluated some of these H-oximes (at doses of approximately 80 μmol kg^{-1}) in beagles receiving supporting treatment with both atropine and benactyzine poisoned by 5LD50 (s.c.) soman: more than 50% of the dogs treated with HI-6, HGG-12 or HGG-42 survived but only 17% survived of those treated with HS-6.

Because of the differing experimental protocols employed there are great difficulties in establishing a pattern of species variation in the efficacy of the bispyridinium oximes against poisoning by soman. However, the published data suggest that these compounds may be more effective in the mouse, rat, rabbit and dog than in the guinea-pig. Unfortunately there are no reported studies of the efficacy of these compounds in primates. Unpublished, preliminary data in this Laboratory have shown that the rhesus monkey, treated with atropine, is not protected against soman poisoning by P2S (Protective Ratio <2), by a combination of HGG-12 and obidoxime (<2) or by HI-6 (<2·5). These data are more consistent with the guinea-pig results than those reported for other species.

Evidence to support the suggestion of species variation in the effectiveness of bispyridinium oxime treatment against soman poisoning is available from in-vitro studies of their restoration of soman-induced neuromuscular blockade in intercostal muscles from human biopsies, dogs (Wolthuis et al 1981) rats and guinea-pigs (Smith et al 1981). The ability of HS-6, HI-6 and HGG-42 to restore function varied with species: rat > dog > guinea-pig > human.

Against poisoning by sarin and VX in the guinea-pig the bispyridinium oximes gave good protection similar to that provided by P2S. As expected the 2-substituted oximes were less effective than obidoxime or TMB-4 against tabun poisoning (Heilbronn & Tolagen 1965). Boskovic (1979) reported that HS-3 [(2,4′-dihydroxyiminomethyl)-bispyridinium dimethylether] gave good protection to atropine treated mice against poisoning by sarin (Protective Ratio 13·6) or VX (47) but not against tabun (3·4). Weger & Szinicz (1981) have demonstrated that HI-6, HGG-12 and HGG-42, supported by atropine and benactyzine, are effective against sarin and VX poisoning in the dog.

Only one non-oxime bispyridinium compound, SAD 128, was tested in the guinea-pig as an adjunct to atropine therapy. It was of no benefit against poisoning by sarin, soman or tabun, indicating that the oxime group is essential for any protective activity.

Although only a relatively small number of compounds has been evaluated in this study they are typical of the H-series and it may be concluded that

in combination with atropine therapy the H-compounds are not effective against soman poisoning in the guinea-pig.

Supplementing atropine therapy with pyridostigmine pretreatment and diazepam increased the protection achieved against poisoning by all four organophosphates tested, giving Protective Ratios greater than 8. The mechanism by which this protection is achieved is not clear but must be related to the protection of acetylcholinesterase in the peripheral system by pyridostigmine (Berry & Davies 1970), the antimuscarinic action of atropine and the anticonvulsant property of diazepam (Lipp 1973; Johnson & Lowndes 1974; Vale & Scott 1974; Johnson & Wilcox 1975).

It was only in combination with this augmented treatment that the bispyridinium compounds and P2S gave any benefit against soman poisoning. The non-oxime derivatives were the most effective adjuncts against soman poisoning and gave similar levels of protection against poisoning by sarin, tabun and VX. The beneficial action was a property of the unsubstituted bispyridinium skeleton since BPE was as effective as SAD 128. The oxime substituted compounds were, if anything, less effective than the non-oxime derivatives against soman poisoning but they were more effective against sarin, VX or tabun poisoning. This is in contrast to the lack of protection against tabun poisoning achieved by the 2-oximes as adjuncts to treatment consisting solely of atropine.

The properties of the compounds which are responsible for the enhanced protection against soman poisoning in pyridostigmine pretreated animals remain to be identified. It is unlikely to be reactivation of the soman inhibited acetylcholinesterase since combinations of bispyridinium compounds which have been shown to delay the ageing of the inhibited enzyme in-vitro (Harris et al 1978) with oximes reported to reactivate the unaged soman inhibited acetylcholinesterase (Harris et al 1981; Hauser et al 1981; Clement 1981) gave no additional benefit. Although in-vivo studies with the sciatic nerve—gastrocnemius preparation (Smith & Muir 1977; Kepner & Wolthuis 1978) have shown that HS-6 and HI-6 can restore neuromuscular function blocked by soman when given up to 64 min after poisoning in both the rat and the guinea-pig the restoration in the guinea-pig is due to a direct pharmacological action of the oximes rather than to reactivation of inhibited acetylcholinesterase as in the rat. The bispyridinium compounds have a number of pharmacological properties (Smith & Muir 1977; Lundy & Tremblay 1979; Clement 1981) including ganglion blocking ('hexamethonium-like') and post-junctional non-depolarizing ('curare-like') actions which could be beneficial against organophosphate poisoning. However Boskovic & Stern (1970) found that neither hexamethonium nor tubocurarine was beneficial against soman poisoning in mice.

In pyridostigmine-pretreated guinea-pigs obidoxime was the most effective oxime against sarin or VX poisoning but it was ineffective against poisoning by soman. TMB-4 was similarly effective against sarin and VX (and tabun) poisoning but had an adverse effect against poisoning by soman. Both the oximes were used at doses which were super-lethal or near lethal in control guinea-pigs. Lowering the dose of obidoxime reduced its beneficial effects whereas lowering the dose of TMB-4 reduced both its beneficial actions (against sarin and VX poisoning) and its adverse action against soman poisoning. As there is no evidence that soman has a qualitatively different mechanism of acute lethality from those of sarin, tabun or VX the different response to the two oximes cannot be explained. These effects were peculiar to the 4-oximes: similar results were not observed with the 2-oximes.

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