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The Protective Effect of Nimodipine, a Calcium Antagonist, and Its Influence on Soman Clearance in the Anaesthetized Rabbit

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Abstract—The effect of pretreatment with a vasoactive compound, nimodipine, on soman intoxication in peripheral organs of rabbits was studied by measuring changes in the cholinesterase and acetylcholinesterase activity and by measuring clearance of soman in blood using gas chromatography/high resolution mass spectrometry. In animals receiving soman only, initial blood concentrations were approximately 100 ng mL^{-1} and were still detectable after 5 min. The clearance rate of soman in blood markedly increased following nimodipine pretreatment such that soman was below the detection limit (0·002–0·003 ng mL^{-1}) in all samples. Soman injection caused a significant inhibition of the acetylcholinesterase activity in serum, and in brain. In rabbits pretreated with nimodipine, no significant inhibition of acetylcholinesterase activity occurred after soman injection. In view of the effects of nimodipine on soman clearance and on the acetylcholinesterase and cholinesterase inhibition during soman intoxication, we suggest that nimodipine has profound circulatory effects, which during soman intoxication, increase the vascular perfusion through the body and thereby increase the detoxifying capacity.

The toxic effects of organophosphates, such as soman, are mediated through a hyperactivity of the cholinergic nervous system. Soman also has effects on the circulation (Stewart & McKay 1961; Kentera et al 1982; Brezenoff et al 1984; Maxwell et al 1987; McGee & Brezenoff 1987; Scremin et al 1991). A soman-induced pressor response was elicited at 60–70% inhibition of acetylcholinesterase activity (AChE) in brain stem and hypothalamus, and was suggested to be centrally mediated (Brezenoff et al 1984; McGee & Brezenoff 1987).

The effect of soman on the blood flow, and on the detoxifying processes in different tissues was discussed by Maxwell et al (1987). A good correlation between changes in cholinesterase activity (ChE) and blood flow was found. Taken together, the soman-induced peripheral vasoconstriction (Stewart & McKay 1961; Kentera et al 1982), and the soman-induced reduction of blood flow in peripheral organs (Maxwell et al 1987), indicate that all existing endogenous capacities for detoxification of soman are not fully used during the soman intoxication.

Classical therapy after intoxication by organophosphates includes the muscarinic blocker, atropine and an oxime, reactivating the inhibited AChE. Focusing on the soman-distorted circulation, we investigated the effect of the calcium-channel blocker, nimodipine. 1,4-Dihydropyridine derivatives, such as nimodipine, prevent or reduce the intracellular loading of Ca^{2+} through potential-dependent and receptor-operated channels. Nimodipine appears to have a preferential action on cerebral vessels in rabbits (Haws et al 1983). In spite of this, several groups report its effect on vasodilation in other organs (Cain & Nicholson 1989; van der Giessen et al 1990). In a preliminary study, we reported that nimodipine, together with atropine and obidoxime, protected mice against soman intoxication (Karlsson & Sellström 1986).

The present study was performed to determine the mechanism whereby nimodipine increases survival following soman intoxication.

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Materials and Methods

Animals

Albino rabbits, Swedish Country Strain, 2·5–3·7 kg, were housed in individual cages (18–20°C, 50 ± 5% r.h.). They had restricted access to Ewos rabbit pellets K1 and tap water and were maintained on a 12-h alternating light/dark cycle, with artificial light provided between 1800 and 0600 h.

Materials

Soman (*O*-1,2,2-trimethylpropylmethylphosphonofluoridate), neopentyl sarin (*O*-2,2-dimethylpropylmethylphosphonofluoridate) and the internal standard, deuterated soman (CD_3P-soman), were prepared at this establishment according to standard procedures. The soman calibration standard solutions were prepared from the racemic mixture assuming a 55/45 ratio between the diastereoisomer pair (C+P−,C−P+)/(C+P+,C−P−) and equal amounts of enantiomers in each pair. Stock standard solutions (1 mg mL^{-1}) were prepared in hexane and stored at −20°C. Soman solutions for intravenous injection were prepared in deionized water immediately before each experiment.

Solvents used were ethyl acetate (Merck, for residue analysis), 2-propanol, acetic acid (Merck, p.a.) and methanol (Merck HPLC grade). Solid phase extraction was performed using Bond Elut C_{18} columns (Analytichem International, CA, USA) connected to a vacuum manifold (Supelco Inc.).

To the buffer was added a 2-propranol solution containing the internal standard and neopentyl sarin. Calibration

standards were freshly prepared in ethyl acetate for each experiment.

Nimodipine was a generous gift from Bayer, Wuppertal, Germany, and was dissolved in dimethylsulphoxide (DMSO) (Fluka AB, p.a.).

Injection of drugs and antidotes

The rabbits were anaesthetized with intravenous methohexitone, 5 mg kg^{-1} (when measuring the AChE activities) or pentobarbitone, 30 mg kg^{-1} (when measuring soman clearance and ChE activities), approximately 5 min before soman treatment. Soman (10·8 μg kg^{-1} about 0·2 mL) was injected intravenously. This dose of soman corresponds to the dose causing death in 50% of all animals treated (Harris et al 1981). Nimodipine (10 mg kg^{-1} dissolved in DMSO) was injected intraperitoneally, 1 h before the anaesthetic. DMSO has been used by us in other biological systems where soman intoxication and nimodipine pretreatment was studied. DMSO had no influence on the soman toxicity in those experiments.

Mass spectrometric determination of soman

Extraction and sample preparation. Blood samples were taken from a femoral artery at the times indicated in Table 1, with a disposable syringe and immediately mixed with 3 mL ice-cold 0·2 M acetate buffer, pH 4·0, containing 1·5 mM aluminium nitrate, 0·1 mg mL^{-1} neopentyl sarin and CD_3P-soman internal standard (2 ng mL^{-1}). The samples were centrifuged at 1500 *g* for 10 min using a Beckman TJ-6 refrigerated centrifuge. Blood samples for blank and recovery experiments were taken immediately before the start of the experiments.

The supernatant was transferred to a C_{18} cartridge, preconditioned with 4 mL methanol and 4 mL deionized water. Vacuum was applied and the flow rate adjusted to approximately 4 mL min^{-1}.

Ethyl acetate (500 μL) was slowly passed through the C_{18} cartridge to extract soman. Extracts expected to have low concentrations of soman were concentrated on a SpeedVac sample concentrator (Savant Instruments Inc., NY, USA) to approximately 50 μL immediately before the analysis.

Gas chromatography/mass spectrometry. Blood samples were analysed using gas chromatography/high resolution mass spectrometry (GC/HRMS). A VG 70-SQ high resolution hybrid tandem mass spectrometer interfaced with a Hewlett-Packard 5890 gas chromatograph was used. Soman stereoisomers were separated on a 25 m (0·25 mm i.d.), Chirasil-L-Val fused silica capillary column with 0·12 μm film thickness. To the column a 4 m, 0·32 mm i.d. retention gap was connected with a press fit connector (Chrompack Inc., Middelburg, The Netherlands). To deactivate the column and make it useful below the nanogram level, the column was treated with Carbowax 1540 via the gas phase (Franken et al 1977).

Samples were introduced by splitless injection at a column temperature of 40°C. The column was programmed at 5°C min^{-1} to 120°C. The injector temperature was 150°C and the interface temperature was 160°C. The helium carrier gas pressure was 20 kPa giving an average carrier gas velocity of about 30 cm s^{-1}.

An electron impact (EI)-only source was used at 200°C with 40 eV energy, 500 mA trap current and a source pressure around 10^{-6} mbar. The mass spectrometer was tuned to a minimum resolution of 5000 and operated in the selective-ion recording mode. The perfluorokerosene ion at mass 118·9920 was used as a lockmass. Mass calibration using perfluorokerosene was performed daily or whenever the tuning was changed. The ions selected for the measurement of soman were m126·0246 and 99·0011. For CD_3P-soman m129·0434 and 102·0199 were used. The time at each channel was 80 ms with a 10 ms delay time between channels.

The soman calibration standard solutions were prepared from the racemic mixture assuming a 55/45 ratio between the diastereoisomer pair (C+P−, C−P+)/(C+P+, C−P−) and equal amounts of enantiomers in each pair. The concentration of the individual soman stereoisomer was determined from a calibration curve prepared by plotting the area ratio of the individual isomer against the corresponding deuterated isomer of the standard solution.

Each time a set of samples was analysed, one to three calibration standard solutions were included. The results were corrected for recovery and blank values. During the experiments the recoveries at the 5 ng mL^{-1} level were normally in the 75–105% range.

Tissue preparation for ChE analysis

Following the withdrawal of the last blood sample for soman analysis, 5 min after soman intoxication, the rabbit was killed and the organs removed and frozen. For ChE analysis the organs were thawed, cut in small pieces and homogenized in a Potter-Elvehjelm homogenizer.

Tissue preparation for AChE analysis

Before perfusion of the heart with isotonic saline, 2 mL blood was withdrawn for determination of the serum AChE activity.

Immediately after perfusion, brains were removed, placed in ice-cold Ringer's solution containing 1% fraction V bovine serum albumin (BSA, Sigma, St Louis, MO) and small pieces of the fore-brain were removed and homogenized in a Potter-Elvehjelm homogenizer. Homogenates were centrifuged at 1000 *g* for 10 min and the resulting supernatant centrifuged at 20000 *g* for 10 min. The pellets resulting from each centrifugation were resuspended in 1·15% KCl.

Brain capillaries were prepared from rabbits by a modified method of Goldstein et al (1975) previously published (Algers et al 1986). The meninges, with the pial vessels, were removed and the brain chopped in small pieces, then pressed through nylon mesh. The resulting suspension was centrifuged using BSA-gradients and passed over a column of glass beads. The column retained the capillaries and the glass beads were gently agitated in ice-cold 1·15% potassium chloride. The supernatant with the suspended capillaries was finally centrifuged.

Measurements of ChE

The activity of ChE was determined according to Ellman et al (1961) in an automatic enzyme analyser, Clinicon Corona (Clinicon AB, Bromma, Sweden). Buffers and substrate concentrations were as given below, except for the use of

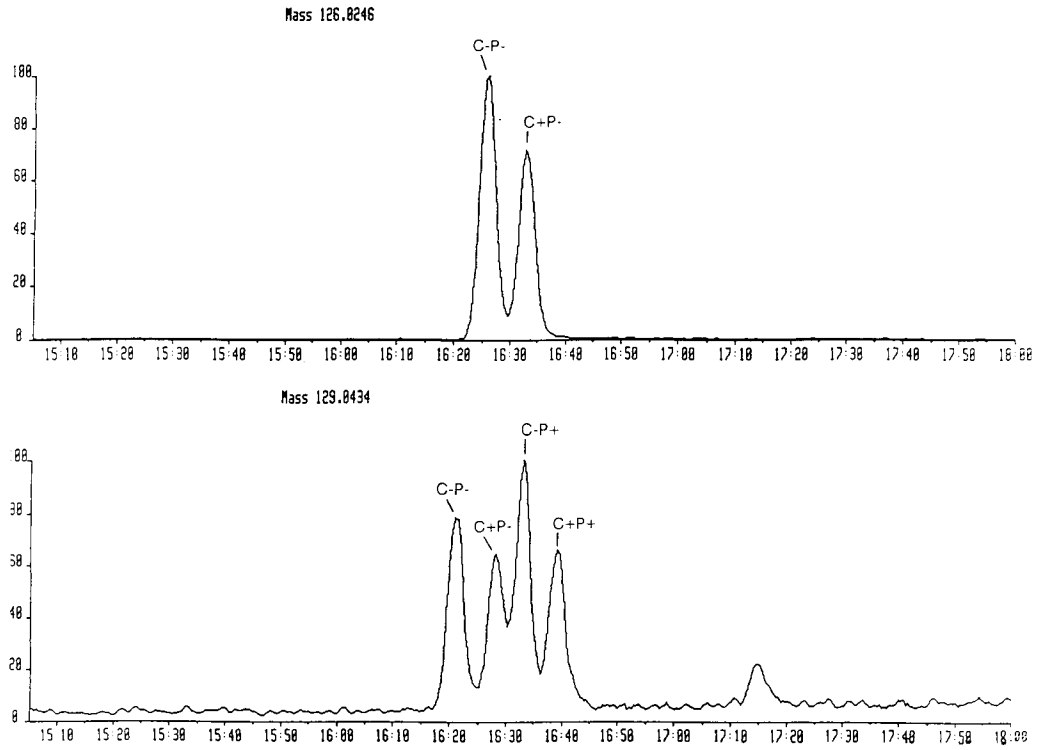

FIG. 1. GC/HRMS analysis of a blood sample taken 30 s after intravenous administration of 10·8 μg kg^{-1} soman. In the soman channel (upper trace, m126·0246) the C−P− and C+P− stereoisomers are present at 107 and 63 ng mL^{-1}, respectively. In the internal standard channel (lower trace, m129·0434) all four isomers are present indicating little or no decomposition of soman during sample preparation.

tetra-isopropyl pyrophosphoramide (iso-OMPA, Sigma, St Louis, MO) as butyrylcholinesterase inhibitor. Activity was expressed as specific activity (mol mg^{-1} s^{-1}).

Measurements of AChE

To assess AChE activity, the butyrylcholinesterase activity was inhibited by iso-OMPA 2·5 mM. The reaction mixture added to the cuvette for 10 min consisted of 2·3 mL phosphate buffer 0·1 M, pH 8·0, 80 μL 5,5′-dithiobis-2-nitrobenzoate (DTNB, Sigma, St Louis, MO) 0·01 M and 100 μL sample. The addition of 20 μL substrate, acetylthiocholine iodide (Sigma, St Louis, MO), 75 mM in phosphate buffer 0·1 M pH 7·4, started the reaction and the absorbance was recorded at 412 nm in a Perkin Elmer 557 spectrophotometer. Proteins were determined according to the method of Lowry et al (1951) and the activity of AChE expressed as mol (mg protein)$^{-1}$ s^{-1}.

Statistical evaluation

For each experiment, mean ± s.d. was calculated. In some experiments comparisons amongst different groups were made by the non-parametric Neuman-Keul test (Dunnett 1970).

Results

Mass spectrometric determination of soman in serum

A chromatogram from an authentic blood sample is shown in Fig. 1. Two peaks can be seen in the soman channel (m126). These peaks are the C+P− and C−P− stereoisomers. In the internal standard channel, m129 amu, the presence of the four stereoisomers indicate that little or no decomposition of the P+ isomers had occurred during sample preparation. After the initial rapid decline in the concentration of the C+P− and C−P− isomers, they could be followed for a few minutes (Fig. 2). No P+ isomer could be detected in any of the samples. In rabbits pretreated with nimodipine, the concentration of soman was not detectable (< 0·003 ng mL^{-1}) (Table 1).

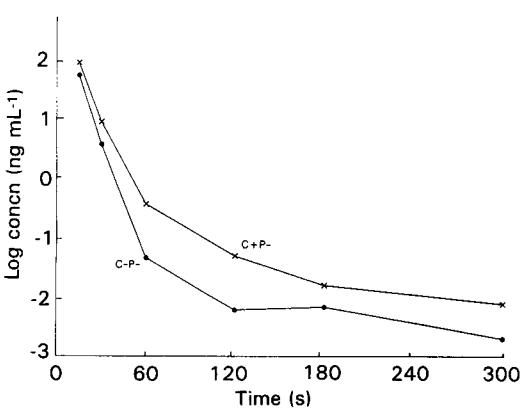

FIG. 2. An example of the clearance of soman in rabbit blood, after intravenous injection of 10·8 μg kg^{-1} soman.

ChE activity in different organs (Table 2)

There was no significant difference between the ChE activity observed in the liver, brain, heart or kidney of rabbits pretreated with nimodipine and of rabbits given soman only. Decreased activities were recorded in lung, muscle, skin,

Table 1. The concentration (ng mL^{-1}) of soman stereoisomers C+P− and C−P− in rabbit blood. Rabbits 1–3 were exposed to soman only (10·8 $\mu g\ kg^{-1}$, i.v.) whereas rabbits 4–7 were pre-treated with nimodipine (10 mg kg^{-1}, i.p.) 1 h before soman for 5 min.

Time (min)	Rabbit 1		Rabbit 2		Rabbit 3		Rabbits 4–7	
	C+P−	C−P−	C+P−	C−P−	C+P−	C−P−	C+P−	C−P−
0·25	63·0	107·0	61·3	76·5	—	—	<0·002	<0·003
0·50	4·14	10·1	1·64	3·87	180·0	161·0	—	—
1·00	0·05	0·41	0·029	0·157	3·99	2·67	—	—
1·50	—	—	0·011	0·043	0·784	0·985	—	—
2·00	0·006	0·054	—	—	0·230	0·194	—	—
3·00	0·007	0·017	0·003	0·008	0·052	0·046	—	—
5·00	0·002	0·008	0·003	0·002	0·006	0·001	—	—

Table 2. The ChE activities in different organs and AChE activity in serum.

	ChE activity (10^{-9} mol $mg^{-1}\ s^{-1}$)	
	Soman	Soman + nimodipine
Liver	21·9±4·6	29·7±3·6
Lung	2·5±1·7	1·5±0·2
Muscle	6·3±0·9	4·1±0·6
Heart	2·6±0·9	2·1±0·3
Skin	0·7±0·4	0·3±0·1
Diaphragm	5·0±2·3	3·0±0·8
Kidney	4·2±0·8	4·3±1·0
Intestine	34·8±15·6	19·9±6·4
Brain	11·0±5·6	22·2±17·1

	AChE activity (10^{-11} mol $mg^{-1}\ s^{-1}$)		
	Soman	Soman + nimodipine	Control
Serum	2·7±0·8	*7·2±1·4	*8·5±1·7

Nimodipine pretreatment (10 mg kg^{-1}, i.p.) 1 h before soman (10·8 $\mu g\ kg^{-1}$, i.v.) for 5 min and soman only (5 min). The control value for AChE activity in serum was 8·5±1·7 mol $mg^{-1}\ s^{-1}$. Values represent mean±s.d. from 4–6 rabbits. *$P<0·05$.

intestine and diaphragm as a result of nimodipine pre-treatment.

AChE activity in serum

The AChE in serum was significantly reduced after soman treatment but this reduction was prevented by pre-treatment with nimodipine (Table 2).

AChE activity in the brain

In the 1000 *g* fraction, containing whole cells and cell debris, AChE activity was reduced in the soman-treated animals (control, 1·04±0·13 nmol $mg^{-1}\ s^{-1}$; soman, 0·28±0·06 nmol $mg^{-1}\ s^{-1}$; $P<0·05$). In soman-treated animals pre-treated with nimodipine, the AChE activity in this fraction was not significantly different from control (0·92±0·13).

In the 20000 *g* fraction, the results were similar (control, 1·50±0·26 nmol $mg^{-1}\ s^{-1}$; soman 0·74±0·10 nmol $mg^{-1}\ s^{-1}$, $P<0·05$; pre-treated with nimodipine, 1·45±0·18 nmol $mg^{-1}\ s^{-1}$).

Soman-treatment reduced the AChE activity of microvessel preparations (control, 0·62±0·11 nmol $mg^{-1}s^{-1}$, soman, 0·26±0·07, $P<0·05$), but the activity of preparations from animals pre-treated with nimodipine was not significantly different from either controls or soman-treated animals (0·47±0·07).

Discussion

Soman is a molecule with two asymmetric centres, one at its carbon atom (C+ or C−) and one at its phosphorus atom (P+ or P−). The P+ isomers are more rapidly detoxified in-vivo than the P− isomers (Maxwell et al 1988), which may explain their greater toxicity.

The method for analysing soman, previously developed by Benschop et al (1985), was adapted for high resolution mass spectrometry. In Fig. 1 the separation of the isomers is demonstrated. Using the corresponding deuterated internal standard isomer, each individual stereoisomer can be quantitated by mass spectrometry although they are not separated by the chromatographic system. We have used an internal standard with the same stability as the analyte to compensate for eventual losses of the analyte during sample preparation or storage before analysis.

Following the intravenous injection of soman, only the P− isomers of soman were detected during the first few minutes after dosing. This is in accordance with previous findings and is a result of the rapid enzymatic hydrolysis of the P+ isomers (Benschop et al 1985).

Soman is a potent ChE and AChE inhibitor. This is illustrated by the decrease in AChE activity observed in serum and brain. Inhibition of the ChE and AChE activity by soman, in other organs, could be expected and has also been demonstrated by Maxwell et al (1987). Soman intoxication causes an increase in the peripheral vascular resistance. Kentera et al (1982) and Maxwell et al (1987) found that blood flow was affected in some tissues even though cardiac output and heart rate were normal. Maxwell et al (1987) also pointed out a correlation between changes in peripheral bloodflow and changes in the ChE activity of tissues in soman-intoxicated animals.

Nimodipine pretreatment resulted in an apparent reactivation of the AChE activity of serum and brain; results for microvessels were equivocal. Nimodipine did not, however, reactivate porcine AChE, in-vitro (Puu, unpublished results), and a mechanism other than a direct influence of nimodipine on the esterase seems to be involved. Nimodipine is known to inhibit the influx of extracellular Ca^{2+} into vascular smooth muscle cells, to decrease the blood pressure and systemic vascular resistance (Duncker et al 1986, 1987).

Following the injection of soman to rabbits anaesthetized with methohexitone, the AChE activity in serum and brain was significantly inhibited; pretreatment with nimodipine made the AChE inhibition less pronounced. We also found

that the clearance rate of soman from blood was considerably increased after pretreatment with nimodipine (Table 1). Our hypothesis is that the previously reported peripheral vasoconstriction induced by soman (Maxwell et al 1987) was counteracted by nimodipine and that soman-intoxicated animals given nimodipine have their circulation normalized. A decreased blood flow has been reported to occur in muscle and kidney as a result of a 50–60% inhibition of ChE activity (Maxwell et al 1987). Nimodipine pretreatment further decreased ChE activity in muscle, whereas the ChE activity in kidney was unaffected. This decrease of AChE activity in muscle may reflect an increased blood flow. Soman-intoxicated rats had an increased blood flow in the heart, whereas it was unchanged in liver (Maxwell et al 1987). Likewise, we observed small changes in ChE activity in the heart, but in the liver we found a small increase in ChE activity following the nimodipine pretreatment.

Blood flow in rat brain was increased after soman exposure (Maxwell et al 1987; Scremin et al 1991), with a parallel decrease in the AChE activity (Maxwell et al 1987). In rabbits pretreated with nimodipine the AChE and ChE activity was almost normalized.

To achieve a higher resolution and to confirm the cerebral circulatory effects of nimodipine on the soman intoxication, we compared the effect of soman on the AChE activity in isolated microvessels with that of brain homogenates, and serum. The rapid disappearance of soman and the increased cerebral AChE activities observed during nimodipine treatment, indicate that the use of nimodipine may have increased the endogenous capacity for soman detoxification. We suggest that nimodipine causes an increase in the vascular perfusion allowing a large volume of the body to contribute with detoxifying reactions. Our results on the circulatory changes induced by soman, in principle, support those of Maxwell et al (1987). In this paper we, accordingly, retract our previous theory that a pre-capillary vasospasm in the brain is a result of an organophosphate intoxication (Sellström et al 1985).

If, as suggested, nimodipine normalizes the soman-induced circulatory disturbances, the circulation through more peripheral organs, like skin and intestine, is no longer reduced. The organophosphates thus have access to ChE and carboxylesterases in these organs, which will contribute to the faster clearance of soman and the better retained AChE activity observed when rabbits were pretreated with nimodipine before soman was given. Our results suggest that a hitherto overlooked aspect of the intoxication by anticholinesterases may deserve further investigation. The cholinergic crisis evoked by organophosphates will affect the circulation in a way that jeopardizes the body's endogenous capacity for detoxification. Whether nimodipine induces circulatory changes that facilitate the soman detoxification, prevent or restore the circulation disturbed by soman, is not clear. We suggest that a carbamate, oxime and anti-muscarinic treatment protocol should be expanded to include a non-specific vasodilating compound such as nimodipine.

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