Plasma concentrations of the oxime Pralidoxime Mesylate (P2S) after repeated oral and intramuscular administration

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Holland, P. and Parkes, D. C. (1976). *British Journal of Industrial Medicine*, 33, 43-46. **Plasma concentrations of the oxime Pralidoxime Mesylate (P2S) after repeated oral and intramuscular administration.** The use of the oxime P2S as intravenous therapy for organophosphorus anticholinesterase poisoning is well known. In emergency situations this route of administration may prove impractical due to severe symptoms of anticholinesterase poisoning and therefore the intramuscular route is to be preferred. The absolute intramuscular dose of P2S per man, recommended as necessary for adequate therapy of anticholinesterase poisoning, is 500 mg. In practical situations this dose may have to be repeated at intervals resulting in overdosage, and therefore the clinical side-effects which this regimen might have on normal subjects has been determined. It has also been suggested that where organophosphorus anticholinesterase compounds are handled continuously for many months in the year, for example, in crop spraying and in industry, P2S might be taken prophylactically. The effects that such a regimen might have when combined with therapeutic procedures in human subjects have therefore been evaluated. The absolute intramuscular P2S dose of 500 mg when repeated three times at 20-minute intervals in normal subjects produces no clinical side-effects. However, when this procedure is superimposed upon an oral P2S prophylactic regimen, up to 60% of the individuals complain of visual side-effects which may prove a hazard in cases of mild anticholinesterase poisoning. It is suggested that these visual side-effects are caused by an accumulation of P2S in the eye during prolonged oral administration.

The use of the oxime 2 hydroxyiminomethyl-N-methyl pyridinium methane sulphonate (Pralidoxime Mesylate; P2S) given by slow intravenous infusion, as an adjunct to atropine sulphate is accepted therapy for poisoning by some organophosphorus (O-P) anticholinesterase compounds (Martindale, 1972). In emergency situations or where no medical aid is immediately available, its use in this manner might be impractical and therefore immediate administration intramuscularly, possibly by means of self-injection devices (Barkman, Edgren, and

Sundwall, 1963; Barkman, 1973) would be more desirable. Measurement of changes in P2S plasma concentration with time following intramuscular administration of a single dose of P2S expressed in terms of body weight, has been carried out by various workers (Sundwall, 1960; Calesnick, Christensen, and Richter, 1967). Holland, Parkes, and Shakespeare (1972) have shown that administration of absolute intramuscular doses of 500 mg P2S per man is needed to achieve plasma P2S levels of 3.0 µg/ml to 4.0 µg/ml recommended as

necessary for adequate therapy of O-P anticholinesterase poisoning (Crook *et al.*, 1962; Sundwall, 1961). It has also been suggested that P2S might be of benefit if given orally as prophylactic in situations where the more potent O-P anticholinesterases are handled and used continuously (Quinby, 1968; Taylor, Llewellyn-Thomas, and Sellers, 1965; Coleman, Little, and Grant, 1961). Doses of greater than 1.0 g per man (Sundwall, 1960) and 2.0 g to 4.0 g per man (Sidell, Groff, and Kaminskis, 1972) have been shown to be necessary for adequate prophylactic therapy.

In military situations where there is a risk of poisoning by the more potent O-P anticholinesterase nerve gases it is recommended that P2S be taken prophylactically and if poisoning occurs then 2.0 mg atropine sulphate be administered intramuscularly by a self-injection device on up to three occasions, if necessary, at 20 min intervals (*Medical Manual of Defence against Chemical Agents*, 1972). In Sweden, collaboration between Astra Pharmaceuticals and the Swedish military authorities has resulted in a self-injection device being produced containing a mixture of the oxime toxogonin and atropine. If the oxime P2S is to be used in this way then it can be envisaged that up to three intramuscular injections of P2S would be administered. In such circumstances P2S may be given in excess particularly in military situations where self aid therapy is employed. Therefore this study was carried out to determine what clinical effects might be produced by the simple repeated intramuscular administration of therapeutic doses of P2S, and when given to individuals already taking P2S as a prophylactic.

Materials

Oxime (P2S) injections 1.0 g were formulated by Koch Light Laboratories in water to give final doses of 200 mg, 500 mg, and 750 mg in 2.0 ml. P2S tablets (1.0 g) were obtained from Glaxo Laboratories Ltd.

Subjects were healthy male service volunteers aged between 18 and 26 years, normal on medical examination and with normal blood biochemistry.

Procedure

Altogether 28 volunteers were the subjects of an experiment to determine the plasma P2S levels and clinical effects produced by more than one intramuscular injection. They were divided into three groups so that 9, 10, and 9 volunteers respectively received one, two, and three intramuscular injections of 500 mg P2S. The injections were given at 20 min intervals into the upper outer aspect of the thigh. Blood samples for assay of P2S content (Creasey and Green, 1959) were obtained by venepuncture from the median cubital vein. Subjects receiving two and three P2S injections donated blood samples immediately before each injection and at 10, 20, 30, and 60 min after the final injection.

A total of 49 volunteers took part in an experiment

involving both oral and intramuscular administration of P2S in the same individual, one, two, or three injections being given. After oral administration of the drug (see below), 11 received 1×500 mg P2S, 16 received 2×500 mg P2S, and 22 received 3×500 mg P2S, each injection being given at 20 min intervals, intramuscularly. Each man took four oral P2S doses each of 4.0 g (as 4×1.0 g tablets) at 6 hr intervals during the 24 hr before the first injection. The first oral P2S dose was given at 19.00 hr, the final dose being at 07.00 hr and the first P2S intramuscular injection at 10.00 hr at which time from previous experience in this laboratory, P2S plasma levels from the oral regimen were known to be at or near their maximum. The injection procedure, blood sampling procedure, and P2S assay were as described above. Blood samples were taken 5 min before the first injection and at 18, 30, 40, 50, and 80 min from those receiving two P2S injections, and at 18, 38, 50, 60, 70, and 180 min from those receiving three P2S injections.

During both experiments note was taken of any side-effects complained of by the volunteers. The subjects were allowed complete freedom during the experiments providing their activities did not interfere with the trial procedure. However they remained in the ward complex until all procedures were complete.

Results

Changes in mean P2S plasma levels after 1, 2, and 3 intramuscular injections of 500 mg P2S together with standard deviations are shown in Table 1. Mean peak P2S plasma levels of $7.9 \mu\text{g/ml}$ were attained 10 min after a single 500 mg intramuscular dose of P2S. The percentages of subjects with plasma levels of $4.0 \mu\text{g/ml}$ or more at 10, 20, 30, and 60 min were 100%, 100%, 89%, and 56% respectively, and they all had plasma levels of $3.0 \mu\text{g/ml}$ or more 60 min after injection. Two intramuscular injections of 500 mg P2S produced mean peak plasma levels of $13.9 \mu\text{g/ml}$ at 30 min and three injections of the same dose produced mean peak plasma levels of $18.4 \mu\text{g/ml}$ at 50 min. Peak plasma levels were always obtained 10 min after the final injection and levels of $4.0 \mu\text{g/ml}$ or above were maintained for periods of 2 hr to 3 hr.

Mean P2S plasma levels after one, two, and three intramuscular injections of P2S following an earlier oral P2S are given in Table 2. One, two, and three intramuscular injections produced mean peak plasma levels at 10 min of $15.4 \mu\text{g/ml}$, $15.6 \mu\text{g/ml}$, and $23.9 \mu\text{g/ml}$ respectively after the final injection. Mean plasma P2S levels at 3 hr after the final oral P2S dose in the second group of subjects were lower than those of the other two groups. Plasma P2S levels of $3.0 \mu\text{g/ml}$ – $4.0 \mu\text{g/ml}$ were maintained for 2 hr to 3 hr after these multiple injections.

Symptoms

Intramuscular injection of a 25% concentration of P2S (500 mg in 2.0 ml) produced in 50% of subjects

TABLE 1
MEAN P2S PLASMA LEVELS ($\mu\text{g/ml}$) AFTER MULTIPLE INJECTIONS OF 500 mg P2S

Dose (mg) of P2S	Analysis	Time (min)								
		10	20	30	40	50	60	70	80	100
500 mg	Mean	7.9	6.9	5.6			3.7			
6.0 mg/kg to	Range	5.6-10.7	5.9-9.9	3.1-8.4			3.0-6.0			
8.2 mg/kg	SD $\pm$	1.7	1.6	1.8			1.0			
500 mg $\times$ 2	Mean		7.5	13.9	12.6	10.4			6.0	
12.6 mg/kg to	Range		5.9-9.8	11.8-19.2	11.2-14.6	8.4-12.9			4.0-7.8	
17.3 mg/kg	SD $\pm$		1.5	2.0	1.5	1.4			1.4	
500 mg $\times$ 3	Mean		7.9		12.9	18.4	17.1	13.9		8.8
13.1 mg/kg to	Range		4.4-11.5		8.9-19.0	13.0-28.9	12.0-24.9	10.3-17.2		7.0-10.6
23.5 mg/kg	SD $\pm$		2.3		3.5	5.0	3.9	2.4		1.6

TABLE 2
MEAN P2S PLASMA LEVELS ($\mu\text{g/ml}$) AFTER MULTIPLE P2S INJECTIONS IN THE PRESENCE OF ORAL P2S

Dose of P2S	Analysis	Time (min)									
		0 (3 hr)	10	20	30	40	50	60	70	80	180
500 mg	Mean	8.4	15.4	14.8	13.7			11.3			
6.1 mg/kg to	Range	6.4-9.7	11.1-18.9	9.7-19.8	9.2-18.8			9.1-16.6			
8.7 mg/kg	SD $\pm$	1.8	2.8	2.7	2.7			2.6			
500 mg $\times$ 2	Mean	6.8		10.8	15.6	15.1	13.7			7.4	
11.8 mg/kg to	Range	2.9-11.4		5.7-15.5	8.8-23.1	9.2-19.6	9.9-18.7			4.6-11.0	
16.6 mg/kg	SD $\pm$	2.3		2.9	4.2	3.2	2.6			2.0	
500 mg $\times$ 3	Mean	8.2		13.8		18.5	23.9	21.3	19.3		8.9
13.4 mg/kg to	Range	4.3-14.3		10.0-20.3		12.7-26.2	16.2-33.9	15.9-31.7	12.3-25.8		4.9-13.0
27.0 mg/kg	SD $\pm$	3.6		3.1		3.4	3.9	3.9	4.0		2.4

a stinging sensation at the injection site followed by a dull ache which soon disappeared.

Looseness of the stools was complained of by three subjects after the fourth oral dose of P2S but was not of sufficient severity to interfere with their normal activities.

One out of 11 subjects receiving 1×500 mg P2S, two out of the 16 subjects receiving 2×500 mg P2S, and 15 of the 22 subjects receiving 3×500 mg P2S complained of visual disturbances. These were evident only when the injections were given intramuscularly after the P2S oral regimen. Three of the ten subjects receiving 2×500 mg P2S intramuscularly alone were doubtful about the transitory presence of misty vision, but no complaints of similar effects were made from subjects receiving 3×500 mg P2S intramuscularly alone. Symptoms complained of were heaviness of the eyes, blurred vision when reading small print, and difficulty in accommodation after a sudden head movement. Symptoms lasted from a few minutes to 2 hr to 3 hr and in some instances occurred on more than one occasion.

Discussion

Plasma P2S levels after single intramuscular and intravenous P2S injections to humans have been determined by various workers. Administration of 30 mg/kg P2S intramuscularly and intravenously resulted in no adverse clinical effects despite plasma P2S levels of 20 $\mu\text{g/ml}$ and 50 $\mu\text{g/ml}$ from intramuscular and intravenous administration respectively (Sundwall, 1960). Plasma P2S levels of 12.0 $\mu\text{g/ml}$ following 45 mg/kg intramuscularly also produced no clinical effects (Calesnick *et al.*, 1967). Two doses of 750 mg P2S intramuscularly produced no clinical effects but when 750 mg P2S intramuscularly was followed by 2.0 g P2S orally one subject out of nine complained of diplopia (Barkman *et al.*, 1963). In civilian situations where no medical aid is immediately available and in military situations where nerve agent poisoning might occur, the self-administration of P2S and atropine sulphate by means of a self-injection device (Barkman, 1973; Barkman *et al.*, 1963) has been suggested.

The study described here has shown that 500 mg

P2S intramuscularly per man provides rapidly a P2S plasma level of greater than the 4.0 $\mu\text{g/ml}$ which is recommended as necessary for effective therapy. This dose in a 25% solution is acceptable to humans and can be given in a volume capable of inclusion in the currently available self-injection device. As a therapy P2S would be used as an adjunct to atropine sulphate so enhancing the therapeutic effect of the latter (Davies, Green, and Willey, 1959). It is important therefore to know that liberal use of P2S itself carries no unacceptable risks.

If used as a prophylaxis (Sundwall, 1960; Quinby, 1968; Taylor *et al.*, 1965; Coleman *et al.*, 1961) P2S cannot be expected to prevent the symptoms of cholinesterase inhibition occurring and it is logical to assume that in many instances the drug will still have to be given intramuscularly with atropine. It has been shown that up to three intramuscular doses of 500 mg P2S can be tolerated by humans despite earlier oral P2S administration but ocular disturbances may occur. In subjects complaining of these effects plasma levels were above 20.0 $\mu\text{g/ml}$ although other subjects with plasma levels of this order were free of symptoms.

Two of the 16 subjects receiving two intramuscular doses of 500 mg P2S had peak plasma levels of 23.1 $\mu\text{g/ml}$ (16.6 mg/kg) and 22.9 $\mu\text{g/ml}$ (14.5 mg/kg), and 15 of the 22 subjects receiving three intramuscular doses of P2S had a range of peak P2S plasma levels of 19.9 $\mu\text{g/ml}$ to 33.9 $\mu\text{g/ml}$ (18.8 mg/kg to 26.0 mg/kg).

Intramuscular P2S given alone did not produce any ocular side-effects despite plasma P2S levels of 21.4 $\mu\text{g/ml}$ (23.5 mg/kg) and 28.9 $\mu\text{g/ml}$ (24.6 mg/kg) in two out of nine subjects receiving 3×500 mg intramuscular P2S doses. When administered intramuscularly in higher doses in terms of body weight than employed in the study described, no visual effects have been reported despite plasma P2S levels in excess of 20 $\mu\text{g/ml}$ (Sundwall, 1960; Calesnick *et al.*, 1967; Barkman *et al.*, 1963) whereas when intramuscular and oral P2S are combined ocular disturbances are reported (Barkman *et al.*, 1963).

The mechanism of production of ocular effects has not yet been elucidated. Prolonged oral P2S administration might lead to accumulation of P2S in tissues including the eye which, with the added effect of intramuscular P2S, is sufficient to precipitate these unwelcome effects.

It appears that multiple intramuscular injections of 500 mg P2S can be tolerated by humans, but in the presence of an oral prophylactic regimen, side-effects may occur. Anticholinesterase poisoning and

the use of atropine sulphate plus oxime as a therapy might modify these side-effects. These factors are currently being investigated.

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