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Lethal plasma concentrations of pralidoxime methane sulphonate (P2S) given parenterally

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Pralidoxime methane sulphonate (P2S), given by i.m. or i.v. injection, is standard therapy for oxime-sensitive organophosphorus poisoning. Plasma concentrations of at least 4 μg/ml are required for optimum therapeutic effects (Sundwall, 1961), and can be achieved in man within 5 min of receiving 500 mg i.m. (Holland, Parkes & Shakespeare, 1972). In the rabbit we found the acute LD_{50} of P2S to be 258 mg/kg i.m. and 118 mg/kg i.v. Others quote 356 mg/kg i.m. for monkeys, 145 mg/kg i.v. for rabbits (Davis & Willey, 1958), and 125 mg/kg i.p. for mice (Barkman, Edgren & Sundwall, 1963). The variation between these values, and the necessity to determine the ratio of therapeutically effective to toxic plasma concentrations, lead us to investigate what constitutes a lethal plasma level of the drug.

Plasma P2S concentrations were measured (Creasey & Green, 1959) sequentially in female rabbits for up to 2 h after receiving the LD_{50} of P2S by i.m. (258 mg/kg) or i.v. (118 mg/kg) injection.

Typical results are shown in Figure 1. Following the i.m. LD_{50} there may occur: (a) a progressive rise in plasma concentration with early death at levels >200 μg/ml; (b) a rapid rise to 100-150 μg/ml which is maintained for 30-40 min, then an abrupt increase with death at concentrations >200 μg/ml; (c) a rise to peak concentrations <100 μg/ml followed by a slow decline with survival. After the acute i.v. LD_{50} there occurs either a rapid rise in concentration with death at levels >200 μg/ml, or an increase to 100-200 μg/ml and then a prompt and continuous fall with survival.

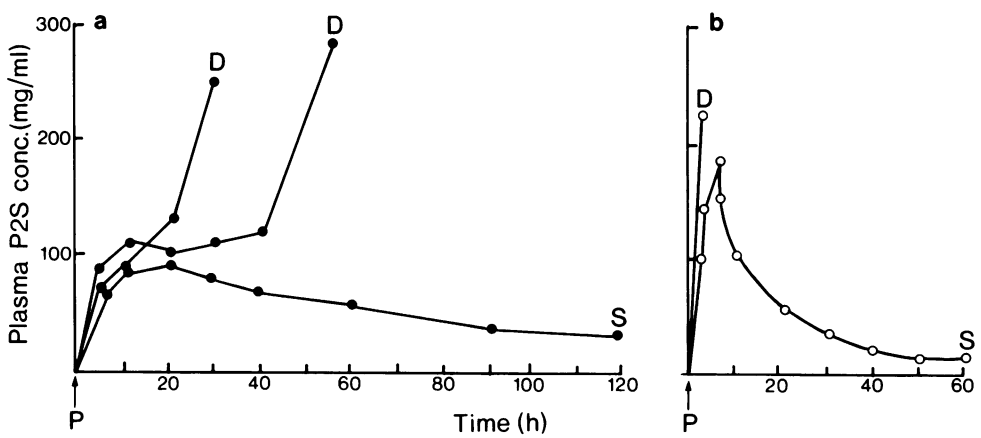

Fig. 1 Typical changes in plasma P2S concentrations in rabbits that survived (S) or died (D) following an injection (P) of the acute i.m. LD_{50} (●) or i.v. LD_{50} (○) of P2S.

The results suggest:

(a) Plasma P2S concentrations at death are >200 μg/ml;

(b) Plasma concentrations of 100-200 μg/ml may be tolerated for a few minutes, but if maintained an abrupt rise may occur with death at concentrations >200 μg/ml;
(c) Sustained plasma concentrations <100 μg/ml are not lethal.

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Effect of the (−)- and (+)-isomers of fenfluramine and norfenfluramine on glucose uptake by the isolated rat hemidiaphragm

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We have previously shown that fenfluramine and its main metabolite norfenfluramine cause an increase in glucose uptake by the rat hemidiaphragm preparation (Kirby & Turner, 1974). We have now studied the effects of the (−)- and (+)-isomers of fenfluramine and norfenfluramine on this preparation. The method used was as described by Frayn & Adnitt (1972). In all experiments 100 μU/ml of insulin were included in the incubation medium, as it had been shown previously by us that no significant increase in glucose uptake occurred with either fenfluramine or norfenfluramine in the absence of insulin.

From the results shown in Table 1 it can be seen that the (−)-isomer of fenfluramine has significantly greater activity than the (+)-isomer over the therapeutic range of 50-100 ng/ml (Campbell, 1971). However, no significant difference is seen between the activity of the two isomers of norfenfluramine, both causing a similar increase in glucose uptake in therapeutic concentrations. No change in glycogen content could be detected following treatment with the isomers of either compound. We also studied the effect of 10,

Table 1 Effect of fenfluramine and norfenfluramine isomers on glucose uptake by the isolated rat hemidiaphragm (with 100 μU/ml insulin)

Fenfluramine (+) ng/ml	10	50	100	1000
Mean % change ± s.e.*	+1.4 ± 3.8	+4.2 ± 8.3	+9.6 ± 8.9	+8.2 ± 6.7
t	0.36	0.51	1.08	1.22
Significance (*P*)	NS	NS	NS	NS
Fenfluramine (−) ng/ml	10	50	100	1000
Mean % change ± s.e.*	+15.8 ± 3.2	+25.0 ± 5.1	+33.9 ± 8.7	+19.3 ± 6.1
t	4.02	4.90	3.90	3.16
Significance (*P*)	$0.001 > p$	$0.001 > p$	$0.01 > p > 0.001$	$0.02 > P > 0.01$
Norfenfluramine (+) ng/ml	10	50	100	1000
Mean % change ± s.e.*	−0.3 ± 4.6	+12.9 ± 7.7	+12.1 ± 6.4	+13.9 ± 5.9
t	0.07	1.68	1.89	2.36
Significance (*P*)	NS	NS	NS	$0.05 > P > 0.02$
Norfenfluramine (−) ng/ml	10	50	100	1000
Mean % change ± s.e.*	+12.1 ± 8.4	+12.1 ± 6.2	+16.9 ± 5.6	+13.1 ± 5.0
t	1.44	1.90	3.02	2.62
Significance (*P*)	NS	NS	$0.02 > P > 0.01$	$0.05 > P > 0.02$

* All comparisons are made on a 'within rat' basis $n = 10$.
NS = not significant.