Timing of therapy in experimental poisoning with organophosphorus compounds

SIR,—In previous studies on experimental therapy of acute poisoning with organophosphorus compounds in rats using pralidoxime and atropine (Sanderson & Edson, 1959; Sanderson, 1961), some of the results suggested that intraperitoneal injection of pralidoxime and atropine together immediately after oral administration of some organophosphorus compounds gave less benefit than either drug separately. With certain of the compounds, notably morphothion, this treatment brought about a worsening and acceleration of anticholinesterase effects and mortality, during the first half hour only, which exceeded the effects produced by the organophosphorus compound alone. These effects did not occur when morphothion was given intraperitoneally, or when treatment was with atropine or pralidoxime alone.

As this observation could have important implications in therapy for organophosphorus poisoning in man, these findings have now been re-examined. In the present experiments, therapy in rats was delayed in some animals until the onset of toxic effects, thus confirming organophosphorus poisoning, otherwise the methods were unchanged (Sanderson, 1961). The results of these experiments are summarised in Table 1. As previously found, a combination of pralidoxime and atropine given immediately caused accelerated anticholinesterase effects which were usually lethal, while treatment with atropine alone, or in combination with pralidoxime, delayed till onset of effects, was beneficial.

Thus while harmful effects can arise with the combined pralidoxime-atropine therapy for poisoning if this therapy is begun before the onset of symptoms, these

TABLE 1. EFFECT OF ATROPINE AND ATROPINE/PRALIDOXIME THERAPY ON MALE RATS GIVEN ORAL MORPHOTHION

Treatment group		First injection	Deaths in test period	Time of onset	Time of deaths	Observations
I None (control)		—	5/6	30 min	8–23 hr	Normal slow anticholinesterase action
II Atropine	A	Immediately after morphothion	2/6	35 min	8½–23 hr	Good control of secretions; general condition improved.
	B	After onset of of poisoning	1/6	30 min	9–23 hr	Similar to previous group
III Pralidoxime +atropine	A	Immediately after morphothion	5/6	5–8 min	15 min –4½ hr	Rapid development of severe anticholinesterase effects, with 4 deaths in first 20 min, then recovery apparently complete after 45 min and recurrence as treatment wore off
	B	After onset of poisoning	2/6	35 min	9–23 hr	Recovery apparently complete in 60 min, then recurrence as treatment wore off, becoming marginally better than Group IIB

Doses: morphothion, 300 mg/kg orally; atropine sulphate, 17·4 mg/kg, and pralidoxime iodide, 100 mg/kg, i.p. repeated after 4 hr, then given s.c. at 8 and 24 hr.

effects are not seen when treatment with the combination is delayed until the onset of symptoms.

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Ethanolamine and anaphylactic shock

SIR,—As is well known, mepyramine and other antihistamines protect guinea-pigs against anaphylactic shock. Smith (1961) has reported that ethanolamine alone has no protective effect but potentiates the protective effect of mepyramine. In addition, he made experiments with guinea-pig ileum and suggested that ethanolamine inhibits the SRS-A liberation in anaphylaxis. Because of the fundamental interest of his observations we have repeated the protection experiments with the same method (Herxheimer, 1952), giving mepyramine and ethanolamine intramuscularly before the animals were shocked. The results were calculated according to the method of Armitage, Herxheimer & Rosa (1952) which differs somewhat from the calculation of Smith in the mathematical expression of the protection but leads to comparable conclusions. The Table shows that the combination of ethanolamine and mepyramine has no greater protective effect than mepyramine alone. It even appears that the combination of 1·0 and 0·05 mg mepyramine with 20 mg of ethanolamine protected less than mepyramine alone. The animals were fed with pellet food containing additional ascorbic acid supplemented with hay.

We therefore are unable to confirm the results reported by Smith.

TABLE 1. EFFECTS OF ETHANOLAMINE AND MEPYRAMINE IN PROTECTING GUINEA-PIGS FROM ANAPHYLATIC SHOCK

Ethanolamine 20 mg/kg Mepyramine 0·01 mg/kg		Mepyramine 0·01 mg/kg
$\bar{x}$ = 30 n = 14 s.e. = 4·9	← P > 0·35 →	$\bar{x}$ = 32·5 n = 44 s.e. = 4·5
Ethanolamine 20 mg/kg Mepyramine 0·05 mg/kg		Mepyramine 0·05 mg/kg
$\bar{x}$ = 34·2 n = 42 s.e. = 4·2	← P < 0·001 →	$\bar{x}$ = 54·9 n = 35 s.e. = 2·9
Ethanolamine 20 mg/kg Mepyramine 1·0 mg/kg		Mepyramine 1·0 mg/kg
$\bar{x}$ = 68 n = 9 s.e. = 3·9	← P < 0·01 →	$\bar{x}$ = 79·5 n = 24 s.e. = 2·4

$\bar{x}$ = mean antianaphylactic protection in % (ranging from 0–100%)
n = number of experiments
s.e. = standard error
P = level of significance of difference between two results

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