REFERENCES

ANDÉN, N.-E. (1966). On the function of the nigrostriatal pathway. In: *Mechanisms of Release of Biogenic Amines*, ed von Euler, U. S., Rosell, S. & Uvnas, B., pp. 357–359. Oxford: Pergamon Press.

CHRISTIE, J. E. & CROW, T. J. (1971). Central actions of amphetamines and ephedrines after unilateral lesions of the dopamine neurones. *Br. J. Pharmac.*, **41**, 405*P*.

CONSOLO, S., DOLFINI, E., GARATTINI, S. & VALZELLI, L. (1967). Desipramine and amphetamine metabolism. *J. Pharm. Pharmac.*, **19**, 253–256.

ROSS, S. B. & RENYI, A. L. (1967). Inhibition of the uptake of tritiated catecholamines by antidepressant and related agents. *Eur. J. Pharmac.*, **2**, 181–186.

UNGERSTEDT, U. (1969). Behavioural registration of dopamine synaptic activity in the brain after 6-hydroxy-dopamine lesions. *Acta physiol. scand.*, **77**, Suppl. 330, 117.

Atropine sulphate absorption in humans after intramuscular injection of a mixture of the oxime-P2S and atropine

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The accepted therapy for poisoning by anticholinesterase compounds is atropine sulphate and pralidoxime mesylate (P2S). The former, depending on the severity of poisoning, can be given in repeated intramuscular doses of 2·0 mg and the oxime as 1·0 g given either by slow intravenous infusion or intramuscularly. The feasibility of administering this combined therapy as a single intramuscular injection has been studied in human subjects with particular reference to the effects which such a combination would have on the absorption rate of atropine.

The minimum intramuscular dose of P2S required to produce adequate therapeutic plasma P2S levels is 500 mg per man and this dose plus a higher one, 750 mg, has been used, in combination with 2·0 mg atropine sulphate, in these studies.

Subjects were twenty-two healthy volunteers. The uptake of atropine after injection was measured in terms of the change in heart rate as revealed in a continuous recording of a single chest lead electrocardiogram (e.c.g.).

For 1 h before commencement of the experiment, subjects lay quietly on a bed with minimal disturbance, and a continuous e.c.g. record was made for the last 5 min of this period. The intramuscular injections were then given into the outer aspect of the thigh and the e.c.g. then continuously recorded for 2 hours.

The influence on heart rate of the following was determined:

(a) Water for Injection B.P.	subjects 1–5
(b) 500 mg P2S in 2·0 ml Water for Injection B.P.	
(c) 750 mg P2S in 2·5 ml Water for Injection B.P.	subjects 1–5
(d) 2·0 mg atropine sulphate	subjects 1–22
(e) Combination of (b) and (d)	subjects 13–22
(f) Combination of (c) and (d)	subjects 1–12.

At least 5 days elapsed between intramuscular injections of atropine alone and combined with P2S.

From the e.c.g. records, measurements were made of the times to reach (a) peak bradycardia, (b) return to control and (c) peak tachycardia. For each individual, values obtained for mixed injections were subtracted from those for the atropine alone

injection and a mean difference obtained. From this the standard error and t values were calculated and levels of significant difference obtained from Student's t test tables.

It was found that for each P2S dose level, no significant difference occurred in the rate of absorption of atropine from either the single or combined injections. However, when all twenty-two subjects are treated as one group a significant difference ($P=<0{\cdot}01$) exists in the time to reach peak bradycardia such that the rate of absorption of atropine from the combined injection is enhanced by 4–5 minutes.

Role of brain monoamines in the fatal hyperthermia induced by pethidine or imipramine in rabbits pretreated with pargyline

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In patients undergoing long-term treatment with monoamine oxidase (MAO) inhibitors, therapeutic doses of pethidine or tricyclic antidepressants have caused severe toxic ractions characterized by symptoms which include excitement and hyperthermia. Similar effects are produced by pethidine or tricyclic antidepressants in rabbits pretreated with MAO inhibitors (Nymark & Nielsen, 1963; Loveless & Maxwell, 1965). This drug–drug interaction has been investigated in rabbits pretreated with drugs which selectively alter the concentrations of brain monoamines.

The intravenous infusion of pethidine hydrochloride (5 mg/kg) or imipramine hydrochloride (5 mg/kg) caused fatal hyperthermia in rabbits premedicated with pargyline hydrochloride (two daily doses of 25 mg/kg s.c.). The pargyline treatment increased the concentrations of cerebral noradrenaline, dopamine and 5-hydroxytryptamine (5-HT) by 91%, 81% and 129%, respectively.

The drug interaction was not antagonized with either reserpine (two daily doses of 0·5 mg/kg) or α-methyl-p-tyrosine methylester (four doses of 80 mg/kg at 12 hourly intervals) were administered in conjunction with the pargyline premedication. In these animals the concentration of cerebral 5-HT was again substantially increased, whereas the catecholamine concentrations were either unchanged or reduced.

The development of fatal hyperthermia was completely prevented when the rabbits were pretreated with p-chloro-phenylalanine (125 mg/kg daily for 3 days) in conjunction with the pargyline premedication. p-Chloro-phenylalanine prevented the increase in brain 5-HT normally produced by pargyline without affecting the ability of pargyline to increase the brain catecholamine content.

The results indicate that the excitement and hyperthermia evoked by pethidine or imipramine in combination with MAO inhibitors can take place only in the presence of raised levels of cerebral 5-HT.

REFERENCES

LOVELESS, A. H. & MAXWELL, D. R. (1965). A comparison of the effects of imipramine, trimipramine and some other drugs in rabbits treated with a monoamine oxidase inhibitor. *Br. J. Pharmac. Chemother.*, **25**, 158–170.

NYMARK, M. & NIELSEN, I. M. (1963). Reactions due to the combination of monoamine oxidase inhibitors with thymoleptics, pethidine or methylamphetamine. *Lancet*, **2**, 524–525.