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.

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