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Some Pharmacological Observations on Tranylcypromine (SKF *trans*-385); A Potent Inhibitor of Monoamine Oxidase.* (25256)

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Zeller *et al.*(1) have demonstrated iproniazid (1-isonicotinyl-2-isopropylhydrazine) to be an inhibitor of monoamine oxidase. Shore and Brodie(2) and Brodie and Shore(3) have reported on the pyrexia, central nervous system (CNS) stimulation and sympathomimetic effects produced in rabbits pretreated with iproniazid followed by reserpine. These effects included increased motor activity and alertness, dilation of the pupil, increased heart rate and piloerection, and were attributed to the action of iproniazid as an *in vivo* inhibitor of monoamine oxidase. We have studied the effects produced by a new and potent *in vivo* inhibitor of monoamine oxidase, (tranylcypromine; 2-phenylcyclopropylamine hydrochloride); and compared its activity with both iproniazid phosphate and *d*-amphetamine sulfate.

Method. The test procedure employed was similar to that described by Brodie and Shore (3), and Horita(4). Several groups of rabbits were pretreated with a range of doses of either iproniazid (25 to 100 mg/kg), tranylcypromine (0.1 to 2 mg/kg), or *d*-amphetamine (1 to 5 mg/kg). Reserpine was administered at various intervals *thereafter* and rectal temperature recorded in an attempt to measure pyrexia at the time of *peak* drug action. The animals were also observed for signs of CNS stimulation. The potency of tranylcypromine relative to that of iproniazid was determined in 3 groups of 6 rabbits each. Groups of rabbits were treated with various doses of either compound. Reserpine was then administered at the time of peak drug action as previously determined. A regression line was obtained by plotting the per cent of rabbits exhibiting rectal temperatures of 42°C or higher against log dose. The dose which caused a rise of rectal temperature of 42°C or higher in 50% of rabbits (ED_{50}) and 95% fiducial limits were determined by the method of Litchfield and Wilcoxon(5). The durations of action of both tranylcypromine and iproniazid were determined by administering ED_{50}s of these compounds to groups of 6 rabbits. This was followed by administration of reserpine at various intervals thereafter. All compounds were investigated in rabbits by the intravenous route of administration. The dose of reserpine employed in all cases was 6 mg/kg. Rectal temperatures were determined with a thermistor thermometer. A converse series of experiments was also performed in which rabbits were first treated with reserpine and 2 hours later, when the animals were deeply sedated, either iproniazid, tranylcypromine or *d*-amphetamine was tested for its ability to arouse the rabbits from their reserpine stupor.

Results. Tranylcypromine produced maximum pyretogenic effects when it was administered 6 hours prior to reserpine. Time of peak effect for iproniazid was 20 hours.

High doses of *d*-amphetamine administered 1 to 6 hours prior to reserpine failed to produce the typical syndrome of symptoms consisting of pyrexia and central excitement. Tranylcypromine was found to be approximately 250 times more potent than iproniazid in this test procedure. The regression lines obtained by plotting the per cent of rabbits

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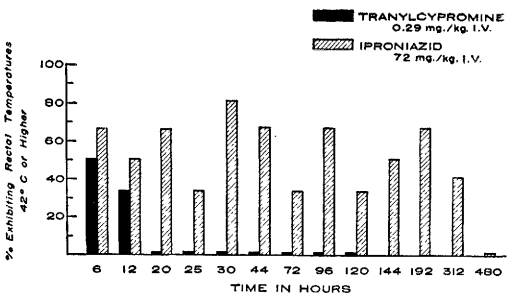

FIG. 1. Duration of action of both tranylcypromine and iproniazid in rabbits.

exhibiting rectal temperatures of 42°C or higher against log dose did not deviate from parallelism significantly. The duration of action of tranylcypromine and iproniazid is shown in Fig. 1. Observe that the duration of action of tranylcypromine is considerably shorter than that of iproniazid. The effects had subsided within 20 hours following its administration. In contrast, an equieffective dose of iproniazid was of extremely long duration lasting for as long as 13 days, although the effects were no longer apparent after 20 days. It should be emphasized that iproniazid *per se* at a dose of 100 mg/kg failed to produce any overt side effects, and tranylcypromine in doses as high as 5 mg/kg produced only moderate mydriasis in nonreserpinized rabbits. None of the compounds produced a significant rise in rectal temperature when given alone.

In the converse experiments in which either tranylcypromine, iproniazid, or *d*-amphetamine sulfate was studied for ability to arouse rabbits from their reserpine stupor, iproniazid was ineffective in doses up to 100 mg/kg(3). d-Amphetamine sulfate was effective as an analeptic against reserpine only in doses (2 mg/kg or higher) which produced central nervous system stimulation. Tranylcypromine effectively antagonized the reserpine-induced stupor at a dose of 5 mg/kg. Furthermore, this analeptic effect of tranylcypromine lasted for as long as 24 to 48 hours.

Discussion. Tranylcypromine appears to have a dual component of action. When administered to rabbits *before* reserpine it produced central excitation and pyrexia, and this effect is assumed to reflect the action of this compound as an inhibitor of monoamine oxidase. The results obtained in these experiments suggest that tranylcypromine is a relatively short-acting inhibitor of monoamine oxidase. Furthermore, our results support the findings of Hess and co-workers(6) who reported on the extremely long duration of action of iproniazid as an inhibitor of monoamine oxidase. It was of particular interest that these same workers suggested the possibility that iproniazid may act by destroying the enzyme monoamine oxidase. In this connection, it is tempting to speculate from our data that it takes at least 13 days for the resynthesis of monoamine oxidase to reach pre-iproniazid levels. Both tranylcypromine and d-amphetamine produced an analeptic effect in rabbits deeply sedated with reserpine. However, there were significant differences between these two compounds. The analeptic action of tranylcypromine was of much longer duration than that of *d*-amphetamine; in addition, tranylcypromine antagonized the reserpine-induced depression in doses which produced no overt signs of CNS stimulation.

Summary. Treatment of rabbits with tranylcypromine followed by the injection of reserpine produces central nervous system stimulation and a marked rise in rectal temperature. The effects produced by tranylcypromine are assumed to reflect the activity of this agent as an inhibitor of monoamine oxidase.

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