J. Pharm. Pharmac., 1968, **20**, *Suppl.*, 122S–125S Received April 29, 1968

SHORT COMMUNICATION

Effect of pretreatment with monoamine oxidase inhibitors or (+)-amphetamine on leptazol convulsions in mice and rats

T. A. R. TURNER AND P. S. J. SPENCER

IT has been claimed that monoamine oxidase inhibitors inhibit the actions of leptazol in experimental animals (Chow & Hendley, 1959; Prockop, Shore & Brodie, 1959; Yen, Salvatore & others, 1962). But other workers have failed to confirm this anticonvulsant action (Kobinger, 1958; Lessin & Parkes, 1959) and some have claimed a proconvulsant effect (Sansome & Dell'Omodarme, 1963; Spoerlein & Ellman, 1961). Reports of the effect of (+)-amphetamine on leptazol convulsions are equally conflicting. Small doses capable of antagonizing electroshock convulsions are described as ineffective against leptazol according to Wolff & Stock (1966), whilst Friebel & Klatt (1959) demonstrated a pro-convulsant action. Reserpine enhances the effect of leptazol in animals, the greatest effect appearing to coincide with maximal depletion of tissue amines. If the animals are pretreated with a monoamine oxidase inhibitor before receiving reserpine, however, the subsequent sensitivity of the animal to leptazol is reduced (Pfeifer & Galambos, 1967) or is unaffected (Chen & Bohner, 1961; Spoerlein & Ellman, 1961).

We report initial observations during a re-examination of the interaction between leptazol and five representative monoamine oxidase inhibitors.

EXPERIMENTAL

Animals. Adult male TO albino mice, weighing 18–25 g, and adult male Wistar albino rats, weighing 150–200 g, were used. They were maintained on a 41 B cube diet and water until 2 hr before experiment. Twenty-four hr before experiment, all animals were transferred to a temperature controlled room at 20 ± 0·5°, relative humidity 60%, where the experiments were made.

Leptazol convulsions. Convulsions were produced in groups of 10 mice by intraperitoneal injection of leptazol (80 mg/kg) in 0·9% saline (0·2 ml/20 g weight). In groups of 10 rats convulsions were produced by the intraperitoneal injection of leptazol (55 mg/kg) dissolved in 0·9% saline (0·5 ml/100 g weight). Saline injection of the same volumes were used as controls in both species. The *mortality ratio* was the proportion of mice dead in the test group divided by the proportion dead in the control group, 15 min after the leptazol injection. The *convulsive ratio* was the number of convulsive episodes in a group of test rats divided by the number of episodes in a control group of equal size, during the 15 min period after leptazol injection. Mortality or convulsive ratios

From the Department of Pharmacy, University of Aston, Birmingham, 4, England.

greater than one indicate a pro-convulsant effect, and ratios less than one indicate an anti-convulsant effect. The results in Figs 1 and 3 are the means from at least three duplicate experiments; significance of difference was calculated by Student's *t*-test.

Locomotor activity. Groups of 4 mice received intraperitoneal injections of (+)-amphetamine, 5 mg/kg, or its vehicle, 0·9% saline. Locomotor activity was determined for successive 30 min intervals during the next 6 hr, using a Faraday Animal Activity Recorder (Hawkesley & Sons, Lancing, Sussex). By previously acclimatizing the mice to the procedure of intraperitoneal injection, and making activity counts in their home cages, the contributions of fear and exploration to the total activity counts were reduced to a minimum.

Body temperature. Using the method of Brittain & Spencer (1964), the oesophageal temperatures of groups of ten mice were determined at 30 min intervals after the intraperitoneal injection of (+)-amphetamine, 5 mg/kg, or its vehicle, 0·9% saline (0·2 ml/20g).

Administration of drugs. The six compounds studied were: iproniazid phosphate, phenelzine hydrogen sulphate, nialamide, tranylcypromine sulphate, pargyline hydrochloride and (+)-amphetamine sulphate. Each drug was dissolved in 0·9% saline and administered intraperitoneally. All doses in the text have been expressed in terms of the free base.

RESULTS AND DISCUSSION

The intraperitoneal injection of 0·9% saline alone, or the intraperitoneal injection of any of the five monoamine oxidase inhibitors or (+)-amphetamine alone (at the doses in Fig. 1), did not induce convulsions or cause death in mice. The results of the pretreatment at varying times before leptazol are shown in Fig. 1.

A transient but significant proconvulsant effect was observed in mice pretreated with iproniazid and phenelzine (substituted hydrazines), and also with tranylcypromine which does not belong to this chemical group. By contrast, the hydrazine monoamine oxidase inhibitor nialamide, and the non-hydrazine monoamine oxidase inhibitor pargyline were devoid of this proconvulsant effect. A definite anticonvulsant action was not observed with any of the five monoamine oxidase inhibitors at the doses used.

The doses quoted in Fig. 1 all produce effective inhibition of monoamine oxidase activity. This was verified using the method of Corne, Pickering & Warner (1963). Groups of 10 mice were pretreated with a monoamine oxidase inhibitor for 1½ or 4 hr before the intraperitoneal injection of 5-hydroxytryptophan at 50 mg/kg. The proportion of control mice eliciting the characteristic head-twitch response varied between 0 and 10% when examined 25 min later. In contrast, the proportion of mice giving this response after pretreatment with a monoamine oxidase inhibitor was consistently 60% or greater. This potentiation of the head-twitch response is considered to indicate an effective inhibition of monoamine oxidase activity by these doses of inhibitor drugs.

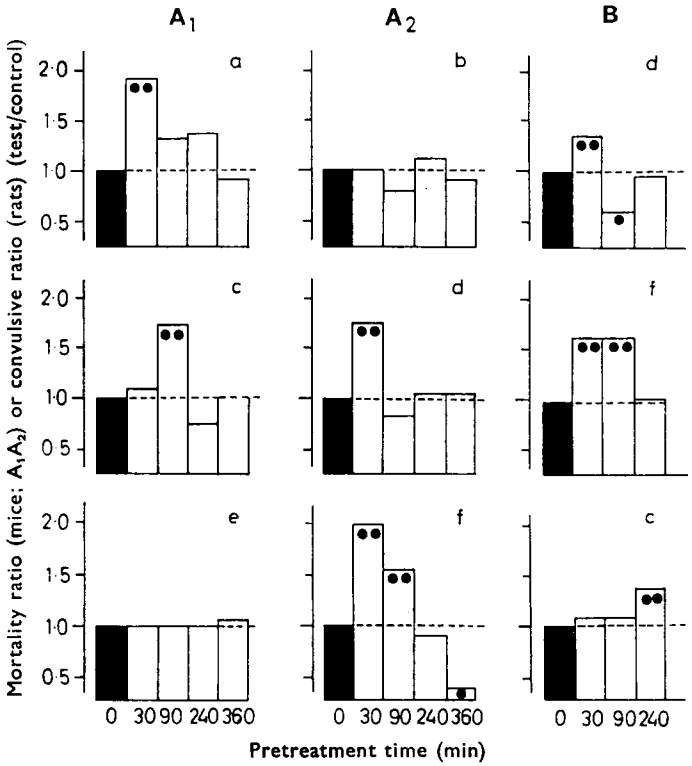

FIG. 1A. Effects of (a) iproniazid (65 mg/kg), (b) nialamide (10), (c) phenelzine (6), (d) tranylcypromine (2), (e) pargyline (50) and (f) (+)-amphetamine (5) on leptazol-induced mortality in mice. Each drug was injected at various times before administration of leptazol; group mortality was assessed 15 min later. (● ● indicates significant proconvulsant effect, and ● indicates significant anticonvulsant effect $P = <0{\cdot}05$).

B. Effects of phenelzine, tranylcypromine and (+)-amphetamine on leptazol-induced convulsions in rats. Pargyline was also tested but did not differ from the control. Each drug was injected at various times before administration of leptazol; the number of convulsive episodes in test and control groups was counted during the next 15 min (● ● indicates significant proconvulsant effect, and ● indicates significant anticonvulsant effect, $P = <0{\cdot}05$).

These results indicate that a proconvulsant action by a monoamine oxidase inhibitor is not related to its ability to inhibit this enzyme, nor to the presence or absence of the hydrazine moiety.

A feature common to the three compounds showing proconvulsant activity is their inherent sympathomimetic activity (Goldberg, 1964) and therefore, (+)-amphetamine should also exert a proconvulsant action with leptazol, and this was investigated (see Fig. 1). At a dose of 5 mg/kg, this produced a marked and slightly more prolonged potentiation of the convulsant and lethal effects of leptazol than was observed with iproniazid, phenelzine or tranylcypramine, yet, 6 hr after its administration, a definite anticonvulsant effect was observed which may be a true

postictal effect related to the earlier intense central adrenergic stimulation produced by (+)-amphetamine.

(+)-Amphetamine (5 mg/kg) did not increase the body temperature of mice but it did cause an elevation of motor activity, 30 min counts being $\approx 3 \times 10^3$ from 0–3 hr while controls were $< 0{\cdot}25 \times 10^3$.

The effects of phenelzine, tranylcypromine and (+)-amphetamine on leptazol convulsions in rats (see Fig. 1B) support the conclusions from the mice experiment, that monoamine oxidase inhibition *per se* was not associated with a potentiation of the convulsive effects of leptazol. But like (+)-amphetamine, inhibition of monoamine oxidase by inhibitors with inherent sympathomimetic activity potentiated the effects of leptazol in rats.

It is concluded that leptazol convulsions and deaths due to leptazol may be potentiated in rats and mice by pretreatment with (+)-amphetamine or monoamine oxidase inhibitors possessing inherent sympathomimetic activity. The effect is transient; for (+)-amphetamine it appears to coincide roughly with the elevation of motor activity by the drug and thus may be due to an effect on the central rather than the peripheral adrenergic nervous system. Nevertheless, an effect on the animals' ability to inactivate leptazol cannot be excluded. Drugs which simply inhibit monoamine oxidase, whether of the hydrazine group or not, possess neither proconvulsant nor anticonvulsant activity.

Acknowledgement. One of us (T.A.R.T.) is grateful to the Medical Research Council for a training scholarship.

References

Brittain, R. T. & Spencer, P. S. J. (1964). *J. Pharm. Pharmac.*, **16**, 497–499.
Chen, G. & Bohner, B. (1961). *J. Pharmac. exp. Ther.*, **131**, 179–184.
Chow, May-I. & Hendley, C. D. (1959). *Fedn Proc. Fedn Am. Socs exp. Biol.*, **18**, 376.
Corne, S. J., Pickering, R. W. & Warner, B. T. (1963). *Br. J. Pharmac. Chemother.*, **20**, 106–120.
Friebel, H. von & Klatt, I. (1959). *Arzneimittel-Forsch.*, **9**, 245–247.
Goldberg, K. I. (1964). *J. Am. med. Ass.*, **190**, 456–462.
Kobinger, W. (1958). *Arch. exp. Path. Pharmak.*, **233**, 559–566.
Lessin, A. W. & Parkes, M. W. (1959). *Br. J. Pharmac. Chemother.*, **14**, 108–111.
Pfeifer, A. K. & Galambos, E. (1967). *Archs int. Pharmacodyn. Thér.*, **165**, 201–211.
Prockop, D. J., Shore, P. A. & Brodie, B. B (1959). *Ann. N.Y. Acad. Sci.*, **80**, 643–651.
Sansome, M. & Dell'Omodarme, G. (1963). *Archs int. Pharmacodyn. Thér.*, **144**, 392–398.
Spoerlein, M. T. & Ellmann, A. M. (1961). *Ibid.*, **133**, 193–199.
Wolff, H. H. & Stock, G. A. (1966). *J. pharm. Sci.*, **55**, 1455–1457.
Yen, H. C. Y., Salvatore, A. T., Silverman, A. J. & Kline, T. O. (1962). *Archs int. Pharmacodyn. Thér.*, **140**, 631–645.