THE INTERACTION OF TYRAMINE WITH A SINGLE DOSE OF TRANLYCYPROMINE IN HEALTHY VOLUNTEERS

It is well known clinically that antidepressant drugs of the monoamine oxidase inhibitor (MAOI) type may interact with the tyramine content of cheese and other foodstuffs to produce a hypertensive reaction. This interaction has been studied experimentally by measuring the effect of MAOIs on the pressor response to intravenous tyramine (Horwitz, Lovenberg, Engelman & Sjoerdsma, 1964; Leon, Abrams, Markowitz & Meisner, 1969; Palm, Fengler, Güllner, Planz, Quiring, May, Helmstaedt, Lemmer, Mood & Holler, 1971; Pettinger & Oates, 1968) and on the mydriatic effect of topical ocular tyramine (Bevan-Jones & Lind, 1971; Palm *et al.*, 1971). These studies have usually been carried out following repeated dosage with the MAOI. However, for reasons of safety and convenience it would be preferable for interaction with tyramine to be studied after a single dose of the MAOI, particularly if this is a new drug which is at an early stage of investigation in man. One previous attempt to demonstrate interaction between a single dose of a standard MAOI, phenelzine, and intravenous or topical ocular tyramine was unsuccessful (Trembath & Turner, 1979).

In the present study, we have investigated the interaction between topical ocular or intravenous tyramine and a single dose of another MAOI, tranlycypromine.

For the ocular interaction study, six healthy male volunteer ICI employees aged 20 to 36 years were included after giving their written informed consent. This was a randomised crossover study in which the subjects took a single 20 mg dose of tranlycypromine ('Parnate', Smith Kline & French) and a non-identical placebo, with 2 weeks between treatments. The tyramine eyedrops were prepared by making a 10-fold dilution of a commercially available 2.5% solution of tyramine ('Mydrial', Winzer, Germany). To elicit the pupillary response, 15 μ l of this solution, containing 47.5 μ g of tyramine, were instilled onto the right conjunctiva using a 'Pipetman' P20 micropipette with a sterilised disposable tip. This dose of tyramine was selected on the basis of a previous dose-finding study (Peet, Yates & Shields, 1980) as being most likely to be sensitive to MAO inhibition. The pupils were photographed as described previously (Peet *et al.*, 1980), prior to instilling tyramine and again at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6 and 24 h. This procedure was followed 24 h and 72 h after dosing with tranlycypromine and placebo for each subject. Pupil size was later measured with a ruler from the image of the photographic negative projected onto a screen at a fixed distance. The size of the treated pupil was expressed as a percentage of the control pupil in

order to estimate the degree of tyramine induced mydriasis.

For the intravenous study, four healthy male volunteer ICI employees aged 25 to 38 years were included after giving their written informed consent. Individuals with supine blood pressure greater than 130/90, or other relevant physical illness, were excluded. The tyramine pressor response was determined by a method based on that described by Ghose, Turner & Coppen (1975).

Two syringes were attached via a three-way tap to a butterfly cannula inserted into a forearm vein. One syringe contained tyramine 1 mg/ml and the other contained normal saline. After stable resting blood pressure recordings had been obtained, 0.5 mg of tyramine was administered and flushed through the cannula with saline. Blood pressure (BP) was monitored every half minute from the opposite arm by a second investigator using a standard sphygmomanometer. Subsequent larger doses of tyramine were given with increments of 0.5–1.5 mg, and the blood pressure monitored after each dose. Each increased dose was given only after the BP had been back to normal for at least 5 min after the previous dose. The aim was to identify the dose which would increase the systolic BP by 30 mm Hg. No further doses were given after this criterion had been reached. The electrocardiogram was monitored throughout the procedure. One hour after the final dose of tyramine, each subject was given a single 20 mg dose of tranlycypromine. 24 h later, the intravenous tyramine pressor test was repeated.

In both studies, the usual dietary restrictions associated with MAOIs were imposed for 24 h before and 7 days after the ingestion of tranlycypromine or placebo.

Blood was taken through a butterfly cannula from all subjects before and after treatment with tranlycypromine or placebo for estimation of platelet MAO activity by a method based on that of Wurtman & Axelrod (1963).

In the ocular study, platelet MAO was inhibited by $89.7 \pm 1.4\%$ (s.e. mean) at 24 h and $75.0 \pm 2.1\%$ at 72 h after 20 mg tranlycypromine. The degree and time-course of the tyramine-induced mydriasis did not differ significantly between tranlycypromine and placebo-treated subjects.

The dose-response curves before and after tranlycypromine and the degree of MAO inhibition after tranlycypromine for the four subjects in the intravenous study are shown in Figure 1. The pressor effects of tyramine were consistently potentiated by tranlycypromine, markedly in two subjects and slightly in the other two. The doses of tyramine

required to raise systolic BP by 30 mm Hg, calculated to the nearest 0.5 mg from the dose-response curves, are significantly lower after tranylcypromine than before ($P < 0.05$, one-tailed t -test).

In our studies, the high level of MAO inhibition achieved with a single 20 mg dose of tranylcypromine was similar to that previously reported by Gentil, Alevizos & Lader (1978). In spite of this high level of inhibition of platelet MAO, and the refinement of methodology, we were unable to show an interaction between tranylcypromine and topical ocular tyramine. It is possible that the level of platelet MAO inhibition does not reflect the degree of inhibition of MAO in the iris and that repeated dosing with an MAOI is needed to inhibit ocular MAO sufficiently for an interaction with tyramine to be detected in the iris.

The failure of Trembath & Turner (1979) to show an interaction between intravenous tyramine and a single dose of phenelzine was probably due to the relative lack of potency in man of phenelzine in comparison to tranylcypromine (Kobayashi, 1966; Robinson, Lovenberg, Keiser & Sjoerdsma 1968). Trembath & Turner (1979) did not measure the actual level of MAO inhibition following phenelzine. In order to be clinically meaningful, tyramine interaction studies should be performed only when the

level of MAO inhibition is greater than 80%, since this level of inhibition is necessary for antidepressant efficacy (Robinson, Nies, Ravaris, Ives & Bartlett, 1978).

In this study we have confirmed that a single 20 mg dose of tranylcypromine produces a more than 80% inhibition of platelet MAO and demonstrated that this significantly potentiates the pressor effects of intravenous tyramine. We have thus been able to demonstrate the potentially dangerous interaction between tyramine and a monoamine oxidase inhibitor after a single dose of the latter in normal volunteers.

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M. PEET, R.A. YATES, J.A. CARROLL¹ & D.N. MIDDLEMISS¹

CNS Clinical Pharmacology Unit, Clinical Research Department, and Bioscience Department¹, Imperial Chemical Industries Limited, Pharmaceuticals Division, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG

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Figure 1 Dose-response curves showing the rise in blood pressure produced by intravenous tyramine before (●) and after (○) administration of tranylcypromine. The % inhibition of MAO for each individual is shown in the boxes.

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COMPARATIVE EFFECTS OF ICI 125,211 AND CIMETIDINE ON ANTIPYRINE KINETICS

Cimetidine, at usual dosage, has been shown to inhibit the metabolism of antipyrine, diazepam and oral anticoagulants (Klotz, Antilla & Reimann, 1979; Serlin, Sibeon, Mossman, Breckenridge, Williams, Atwood & Willoughby, 1979). In the latter case the effect is to prolong prothrombin times of patients on anticoagulant therapy. This undesirable effect has been attributed to the imidazole moiety of the cimetidine molecule.

The new H₂-receptor antagonist ICI 125,211 contains a thiazole ring and has proven to be about 6-8

times more potent as inhibitor of human gastric acid secretion than cimetidine (Richardson, Feldman & Fordtran, 1980; Strekker, Valenzuela & Douglas, 1980). Preliminary clinical studies showed that 200 mg twice daily of this H₂ receptor antagonist is sufficient to reduce effectively acid secretion for about 24 h.

To elucidate the influence of ICI 125,211 on hepatic drug metabolizing enzymes we investigated the antipyrine pharmacokinetics before and after the end of 1 week's treatment (200 mg twice daily) in six

Table 1 Antipyrine kinetics (mean $\pm$ s.d.) before and after 1 week's treatment with H₂-receptor antagonists

	ICI 125,211 (2 $\times$ 200 mg) (n=6)		Cimetidine (5 $\times$ 200 mg) (n=6)	
	Before	After	Before	After
V _d (l)	44.4 $\pm$ 7.1	45.2 $\pm$ 5.3	42.7 $\pm$ 7.0	43.1 $\pm$ 2.0
T _{1/2} (h)	13.8 $\pm$ 4.1	12.8 $\pm$ 4.1	12.4 $\pm$ 4.9	15.0 $\pm$ 4.5*
Cl (ml/min)	40.3 $\pm$ 14.3	41.8 $\pm$ 14.8	46.0 $\pm$ 19.6	35.8 $\pm$ 10.5*

* $P < 0.05$