Effect of a single oral dose of phenelzine on the tyramine pressor and ocular responses in man

P. W. TREMBATH, P. TURNER*, *Department of Clinical Pharmacology, St. Bartholomew's Hospital, London, EC1A 7BE, U.K.*

The pressor and ocular responses to sympathomimetic amines such as tyramine and phenylephrine are useful for studying drugs active at the sympathetic neuro-effector junction. The effect of repeated doses of monoamine oxidase (MAO) inhibitors on the pressor response to sympathomimetic amines has been established. For example, Boakes et al (1973) observed that phenelzine produced a marked potentiation of the pressor effect of phenylephrine in man and Bevan-Jones & Lind (1971) found that the mydriatic response to tyramine was potentiated in patients treated with iproniazid, isocarboxazid and clorgyline.

However, the effects of a *single* dose of a MAO inhibitor on the pressor or ocular responses to sympathomimetic agents has not been established. If there was a potentiation it would be of practical use in the early evaluation of potential MAO inhibitors in single dose sudies in volunteers. The present study was undertaken with a view to assessing the ability of such single dose studies to evaluate a new drug found to have MAO inhibiting properties in animals.

Three male and three female healthy volunteers age 21 to 28 years participated with their informed consent. All were free of renal, cardiovascular and hepatic disease, had a supine blood pressure of less than 140/90 after 10 min rest, and the following preliminary tests were within normal limits: e.c.g., serum Na^+, K^+, Cl^-, HCO_3^-, urea, GOT, alkaline phosphatase, bilirubin, albumin and total protein. The subjects took a low tyramine diet for one day before and four days after taking phenelzine (Nardil, Warner) either in mid-morning or mid-afternoon, depending on the subsequent planned testing times. Two subjects initially received 15 mg, then three subjects received 30 mg, and finally four subjects received 45 mg of phenelzine orally.

Pre-phenelzine pressor responses were determined at the same time of day as the planned post-phenelzine responses were to be measured. The tyramine pressor responses were measured according to Ghose et al (1975) except that the initial intravenous tyramine dose used was 2 mg. Further increments, usually 0·5 or 1 mg greater than the preceding dose were given, depending on the magnitude of the previous blood pressure response. After each tyramine injection the maximum systolic response was noted every 30 s. A further injection of tyramine was given only after the blood pressure had returned to baseline for at least 5 min. When the systolic pressure had increased by 30 mm Hg or more no further injections were given. The dose of tyramine producing a 30 mm Hg increase in systolic pressure was determined from the dose response curve and used as a basal standard for comparison.

Following phenelzine administration, the amounts of tyramine required to produce 30 mm Hg rise were determined at the times shown in Table 1. The effect of phenelzine was measured by subtracting the basal value from each post-phenelzine value for tyramine, such that a negative value represented a potentiation of the tyramine pressor response, and a shift to the left in the dose-response curve.

The ocular response to tyramine was determined before and approximately 20 and 44 h after phenelzine. Pupil diameters (mm) were measured from X8 enlargements of photographs taken initially and 30 and 60 min after instilling 2% tyramine solution into the right conjunctival sac, the left pupil serving as a control (Sneddon & Turner, 1967). The initial pupil diameter difference ($R-L_0$) was subtracted from the maximal pupil diameter difference (either $R-L_{30}$ or $R-L_{60}$) to obtain the maximal observed mydriatic response to tyramine (MMRT). The effect of phenelzine on the MMRT was determined by subtracting the pre-phenelzine MMRT from the MMRT one and two days after the single dose of phenelzine. These measurements were all made by an independent observer unaware of the treatment protocol or the expected results.

The mean basal dose of tyramine producing a 30 mm Hg rise was 4·64 mg (s.d. 0·95 mg). In five subjects, there was no significant difference between basal values obtained in the morning or afternoon (mean difference = 0·04 mg, s.e. difference = 0·28 mg). The differences in tyramine dose (post-phenelzine dose—basal dose) producing the 30 mm rise are shown in Table 1. Paired *t*-tests on the results for 30 and 45 mg phenelzine at 18, 23 and 42 h showed that the tendency for the post-phenelzine dose to be lower at 23 and 42 h was not statistically significant and the differences were of a similar order of magnitude to those found on comparison of repeated basal values.

Similarly, there was no significant potentiation of the tyramine ocular response by a single dose of phenelzine (15–45 mg in 5 subjects). The pupil diameters in one subject could not be measured because the iris was so dark that the pupil margin could not be readily distinguished.

* Correspondence.

Table 1. Effect of single doses of phenelzine (15–45 mg) on the tyramine pressor response in six normal subjects. The dose of tyramine (mg) required to produce a 30 mm Hg increase in systolic blood pressure was determined before and after the administration of phenelzine. The pre-treatment dose was subtracted from the post-treatment doses at the times specified to obtain the tyramine dose difference.

		Tyramine dose difference (mg)							
		Time (h) after oral phenelzine							
Subject	Phen. dose	3	6–8	18	23	30	42	66	90
I	15	0·00	−0·15			−0·30			
II	15	−0·30	0·30			0·15			
III	30			−0·25	−0·65		−0·40		
IV	30			2·10	−0·30		−0·23		
V	30			0·65	−1·00		1·20		
III	45		−0·5	−0·43	0·08		−0·98		
IV	45			−1·60	0·10		−0·50		
II	45			−0·68			0·05	0·30	
VI	45		0·75	0·10			0·10	−0·30	−0·25
		Mean difference		−0·02	−0·35		−0·11		
		s.e. difference		0·44	0·21		0·26		
		t		0·05	1·65		0·43		
		P		NS	NS		NS		

It is possible that while MAO inhibition after a single dose of phenelzine may have been found by using a much higher dose of phenelzine, or by choosing different times for testing the tyramine pressor and ocular responses, the use of a higher single dose of phenelzine was not considered justifiable ethically. Also, in the context of evaluating a method for use in single-dose clinical trials, the use of a high dose of a new potential MAO inhbitor would not be acceptable.

The choice of times after phenelzine administration for testing the pressor and ocular responses to tyramine was based on animal experiments. Rand & Trinker (1968) found a potentiation of tyramine pressor responses in rats pre-treated with phenelzine (20 mg kg^{-1}) 18–22 h earlier. Botting et al (1977) studied the interaction between phenelzine (100 mg kg^{-1}) and pethidine in mice. They found a potentiation of the analgesic and hypothermic effects of pethidine in mice pre-treated with phenelzine 18 h earlier, which they attributed to MAO inhibition. They observed that brain 5-hydroxytryptamine concentrations increased shortly after phenelzine administration and were still elevated 24 h later.

In the present study, the pressor and ocular responses to tyramine were studied particularly between 18 and 42 h. The maximum (but statistically insignificant) reduction in the amount of tyramine needed to produce the 30 mm rise was 0·35 mg, and occurred 23 h after phenelzine administration. Given the between-patient variation, it would be necessary for the reduction to be at least 1 mg for the tyramine pressor response to be a useful indicator of MAO inhibition. It appears unlikely that the choice of other testing times for either the ocular or pressor responses to tyramine would have produced more favourable results.

This work was partly supported by the Pharmaceuticals Division of I.C.I. Limited. Dr P. Trembath is a Clinical Sciences Fellow of the National Health and Medical Research Council of Australia.

April 26, 1978

REFERENCES

Bevan-Jones, B., Lind, N. A. (1971) Br. J. Pharmacol. 41: 428P

Boakes, A. J., Laurence, D. R., Teoh, P. C., Barar, F. S. K., Benedikter, L. T., Prichard, B. N. C. (1973) Br. Med. J. 1: 311–315

Botting, R., Bower, S., Eason, C. T., Hutson, P. H., Wells, L. (1977) J. Pharm. Pharmacol. 30: 36–40

Ghose, K., Turner, P., Coppen, A. (1975) Lancet 1: 1317–1318

Rand, M. J., Trinker, F. R. (1968) Br. J. Pharmacol. Chemother. 33: 287–303

Sneddon, J. M., Turner, P. (1967) J. Physiol. (London) 189: 20–22