take place the drug plus blood was incubated for 5 min at 37°C before addition of the aspirin substrate; the other solutions were also incubated at 37°C for 5 min before adding the aspirin.

The hydrolysis rates for the blood with and without added drug were compared and tested for significance using the modified Students' *t*-test for unpaired samples and small numbers (Hill, 1967).

Table 1 summarizes the results. Whether the drugs tested would have an effect on blood aspirin levels in clinical practice remains to be determined. Aspirin is absorbed and hydrolysed in the small intestine (Curry, 1977) as well as the stomach and at this stage the presence of an aspirin esterase inhibitor might play a significant part in allowing more unhydrolysed aspirin to be absorbed.

This work was supported by grants from the Arthritis and Rheumatism Council.

We would like to thank Mr R. Wilson of the Blood Transfusion Service, The Royal Infirmary of Edinburgh, for the supply of blood.

H.J. RYLANCE & RUTH C. WALLACE

*Rheumatic Diseases Unit, Northern General Hospital, Ferry Road, Edinburgh EH5 2DQ*

Received December 17, 1979

**References**

COTTY, V.F., STERBENZ, F.J., MUELLER, F., MELMAN, K., EDERMA, H., SKERPAC, J., HUNTER, D. & LEHR, M. (1977). Augmentation of human blood acetylsalicylate concentrations by the simultaneous administration of acetaminophen with aspirin. *Tox. appl. Pharmac.*, **41**, 7–13.

CURRY, S.H. (1977). *Drug Disposition and Pharmacokinetics.*, pp. 24, 65 and 74. Edinburgh: Blackwell Scientific Publications.

HILL, A.B. (1967). *Principles of Medical Statistics*, pp. 146–148. London: Lancet Ltd.

MORGAN, A.M. & TRUITT, E.B. (1965). Evaluation of acetylsalicylic acid esterase in aspirin metabolism. *J. pharm. Sci.*, **54**, 1640–1646.

## EFFECTS OF TRANYLCYPROMINE STEREOISOMERS ON MONOAMINE OXIDATION IN MAN

(±) Tranylcypromine (*trans*-2-phenylcyclo-propylamine, TCP, Parnate®) is an inhibitor of monoamine oxidase (MAO) which is an effective antidepressant drug. Whether its antidepressive effects are solely due to MAO inhibition is however unclear since, like several other antidepressants, it is also an inhibitor of neuronal uptake of catecholamines (Fuentes, Oleshansky & Neff, 1976). It has been shown that the (+) isomer is the more powerful inhibitor of MAO while (−) TCP may be more effective as an uptake blocker (Horn & Snyder 1972).

Here we report the effect of each TCP isomer on MAO in man, both by assay of the platelet enzyme and estimation of one of its substrates, phenylethylamine, in urine, and the results compared with plasma and urine levels of the drug. In addition these samples were also investigated for the presence of amphetamine, reported to be a metabolite of TCP in man (Youdim, Aronson, Blau, Green & Grahame-Smith 1979).

The investigation comprised of two separate experiments. One was a study in five depressed patients from whom blood was taken just before, and 3 h after, a single dose of 10 mg (+) TCP. This was repeated with the (−) isomer 1 week later by which time the platelet MAO activity had returned to normal. Secondly, three neurological patients received 5 mg (+) TCP twice daily for 2 days followed on the third day by 10 mg. A sample of blood was taken 2.5 h after this final dose. Urine was collected over the previous 24 h. The experiment was repeated 6 days later with (−) TCP and control samples were taken when the patients had been drug-free for 4 days.

TCP, phenylethylamine and amphetamine could all be determined by a single gas chromatographic procedure which for urine was similar to that of Blau, Claxton, Ismahan & Sandler (1979) and for plasma, which was prepared in the isolation of platelets for MAO assay, was a modification of the method of Reynolds, Sandler, Hardy & Bradford (1980). Briefly these involve solvent extraction of the amines with an internal standard followed by derivatisation to form the pentafluorobenzamides. These are then separated by capillary-column gas chromatography with electron capture detection and subsequently quantified.

MAO activity in platelets was measured using the method of Tipton & Youdim (1976) with dopamine as substrate.

From the results presented in tables 1 and 2 it can be seen that the (+) isomer of TCP is a substantially better inhibitor of human platelet MAO than is the

(−) isomer, confirming the results of Horn & Snyder (1972). This is reflected by the plasma concentration of phenylethylamine, a specific substrate for the MAO type B which is found in human platelets. Plasma phenylethylamine is only increased above control values after (+) TCP but not after the (−)-TCP administration, which would suggest from the data in Table 2 that a minimum inhibition of between 50 and 75% of platelet MAO B is required to bring about an increase in circulating phenylethylamine. This compares with the value of 85% which is found to be the amount of MAO inhibition in rat brain required to increase functional activity of transmitter amines (Green, Mitchell, Tordoff & Youdim 1977).

The urine phenylethylamine results presented here do not, however, show such a clear-cut relationship with either blood MAO activity or plasma concentrations of the amine. While the sampling differences between a single blood sample and a time-integrated urine collection may contribute to this, it seems metabolic effects in the kidney may well be important, particularly considering the close relationship of urinary TCP and phenylethylamine concentrations.

It is notable that while in the single dose experiment (−)TCP plasma levels are higher than those of the (+)isomer, the reverse effect is apparent after the longer treatment. Since after several doses the rate of removal would determine the circulating concentrations, this observation presumably reflects differencies in the uptake and disposition of the two amines, (−)TCP being both absorbed and removed faster. Fuentes *et al.* (1976) have observed just such an effect in TCP isomer concentrations in rat brain after single parenteral doses of the inhibitors.

Youdim *et al.* (1979) have reported the detection of amphetamine in the plasma of a patient taking an overdose of (±)TCP. This prompted us to search for amphetamine in the plasma and urine samples investigated here. However, no chromatographic peak could be detected corresponding to this amine in either fluid, down to a sensitivity, in urine, of less than 0.01% of the ingested TCP dose. Thus amphetamine does not appear to be an important metabolite at therapeutic doses of TCP in man.

We have, however, noted the presence of an unidentified amine present in plasma during treatment with the (+), but not the (−) isomer.

The lack of an effective MAO inhibition after (−)TCP treatment may be of clinical importance. If as is generally assumed, TCP therapeutic efficiency derives from its MAO inhibition, then the (−)isomer is an unneccessary adduct to the functionally effective (+)form. On the other hand, as Snyder (1974) has suggested, the uptake inhibition characteristics of the (−)isomer may be responsible for its antidepressant action, in which case MAO inhibition due to the (+)TCP is a drastic effect to be avoided. Nevertheless it is conceivable that a synergistic action of the two drugs is responsible for the therapeutic efficacy of the racemic mixture.

Escobar, Schiele & Zimmermann (1974) compared the clinical effect of the two isomers in a small study and concluded that the (−) form is of greater benefit to depressed patients. It would seem relevant to expand these studies into a careful clinical comparison of the efficacy of both isomers and the

**Table 1** Platelet MAO inhibition and plasma tranylcypromine concentration after a single dose of (+) or (−) tranylcypromine

| | *MAO inhibition* (%) | *TCP concentration* (*ng/ml*) |
|---|---|---|
| (+) isomer | 53.2 ± 17.7 | 2.8 ± 0.7 |
| (−) isomer | 27.4 ± 16.9 | 15.8 ± 8.2 |

Results expressed as mean ± s.d.
Values from five patients.

**Table 2** Effects of monoamine oxidase inhibition by tranylcypromine isomers in man

| *Regime* | *Patient* | *Platelet MAO inhibition* (%) | *Plasma PE** (*ng/ml*) | *Plasma TCP* (*ng/ml*) | *Urinary PE* (*μg/g creatinine*) | *Urinary TCP* (*μg/g creatinine*) |
|---|---|---|---|---|---|---|
| Control | 1 | 0 | 0.15 | 0 | 6.2 | 0 |
| | 2 | 0 | 0.21 | 0 | 3.8 | 0 |
| | 3 | 0 | — | 0 | 1.9 | 0 |
| (+) TCP | 1 | 89.6 | 0.35 | 51 | 14.7 | 29.8 |
| | 2 | 90.5 | 0.50 | 70 | 30.5 | 71.1 |
| | 3 | 74.4 | 0.54 | 48 | 5.9 | 6.9 |
| (−) TCP | 1 | 37.3 | 0.23 | 30 | 11.4 | 44.1 |
| | 2 | 32.0 | 0.19 | 22 | 14.1 | 152.4 |
| | 3 | 50.0 | 0.20 | 11 | 6.5 | 28.9 |

*Normal mean value (±s.d.) 0.21 (±0.04) ng/ml. $n = 5$.

racemic form with, in addition, a biochemical investigation of monoamine oxidation to correlate with clinical effects.

We thank Prim. Dr D. Seemann for clinical aspects of this study, which was supported in part by Röhm Pharma, F.R.G. We are indebted to Mrs V. Schay for excellent technical assistance and Mrs M. Fuchs for secretarial work.

G.P. REYNOLDS, W.-D. RAUSCH & P. RIEDERER

*Ludwig Boltzmann Institute for Clinical Neurobiology (Head: Prof. Dr. K. Jellinger), Lainz Hospital, Wolkersbergenstr. 1, A-1130 Vienna, Austria*

Received October 8, 1979

**References**

BLAU, K., CLAXTON, I.M., ISMAHAN, G. & SANDLER, M. (1979). Urinary phenylethylamine excretion: gas chromatographic assay with electron capture detection of the pentafluorobenzoyl derivative. *J. Chromatogr.*, **163**, 135–142.

ESCOBAR, J.L., SCHIELE, B.C. & ZIMMERMANN, R. (1974). The tranylcypromine isomers: A controlled clinical trial. *Am. J. Psychiat.*, **131**, 1025–1026.

FUENTES, J.A., OLESHANSKY, M.A. & NEFF, N.H. (1976). Comparison of the apparent antidepressant activity of (−) and (+) tranylcypromine in an animal model. *Biochem. Pharmac.*, **25**, 801–804.

GREEN, A.R., MITCHELL, B.D., TORDOFF, A.F.C. & YOUDIM, M.B.H. (1977). Evidence for dopamine deamination by both Type-A and Type B monoamine oxidase in rat brain *in vivo* and for the degree of inhibition of enzyme necessary for increased functional activity of dopamine and 5-hydroxytryptamine. *Br. J. Pharmac.*, **60**, 343–349.

HORN, A.S. & SNYDERS, S.H. (1972). Steric requirements for catecholamine uptake by rat brain synaptosomes: studies with rigid analogs of amphetamine. *J. Pharmac. exp. Ther.*, **180**, 523–530.

REYNOLDS, G.P., SANDLER, M., HARDY, J. & BRADFORD, H. (1980). The determination and distribution of 2-phenylethylamine in sheep brain. *J. Neurochem.*, **34**, 1133–1138.

SNYDER, S.H. (1974). Mechanism of antidepressant efficacy of monoamine oxidase inhibitors: Inhibition of monoamine oxidase or of catecholamine reuptake. *J. Psychiat. Res.*, **10**, 153.

TIPTON. K. & YOUDIM, M.B.H. (1976). Assay of monoamine oxidase. In. *Monoamine oxidase and its inhibition*, Wolstenholme, G.E.W. & Knight, J., pp. 393–403. Amsterdam: Elsevier.

YOUDIM, M.B.H., ARONSON, J.K., BLAU, K., GREEN, A.R. & GRAHAME-SMITH, D.G. (1979). Tranylcypromine (Parnate) over-dose: Measurement of tranylcypromine concentrations and MAO inhibitory activity and identification. *Psychol. Med.*, **9**, 377–382.

## DRUG METABOLISM IN WHITE VEGETARIANS

Asian vegetarians metabolize antipyrine more slowly than Asians or Europeans who eat meat regularly (Mucklow, Caraher, Henderson & Rawlins, 1979; Fraser, Mucklow, Bulpitt, Kahn, Moulds & Dollery, 1978; Wilmana, Brodie, Mucklow, Fraser, Toverud, Davies, Dollery, Hillyard, McIntyre & Park, 1979). The dietary factors responsible for this effect have not been fully elucidated. We now wish to report a study of hepatic drug metabolism in white vegetarians, using antipyrine, paracetamol and phenacetin as probes of oxidation, conjugation and metabolism at first pass.

Nine white vegetarians (six males, three females; 23–40 years) agreed to participate. Seven were lactovegetarians and two were vegans. They had been vegetarians for a mean of 5.1 years (0.5–14 years). None had any clinical evidence of hepatic, haematological or renal disease and baseline haemoglobin, urea and electrolytes and liver function tests were all normal. None smoked cigarettes or were on regular medication. All were informed about the aims of the study and gave their written informed consent. The study had the approval of the Research Ethics Committee.

Each subject listed and weighed all food consumed in 1 week. Calculation of daily consumption of calories, fat, carbohydrate and protein was based on McCance & Widdowson's Composition of Foods (1978). The volunteers were studied on two occasions. On the first, antipyrine 600 mg and paracetamol 1.5 g were taken together and on the second, phenacetin 900 mg was ingested, both following an overnight fast. Unstimulated salivary samples were taken at 0, 2, 3, 5, 8, 12, 24 and 32 h for antipyrine and paracetamol measurements. In the phenacetin study, plasma was obtained for analysis at 0, 0.5, 1, 2, 3, 4 and 5 h after ingestion of the drug. Antipyrine and paracetamol were measured using specific gas chromatographic methods (Fraser, Mucklow, Murray & Davies, 1976; Prescott, 1971). Phenacetin