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FAILURE OF BUPROPION TO AFFECT THE RESPONSE TO TYRAMINE IN MAN

Bupropion (dl-2-t-butylamino-3'-chloropropiophenone HCl) possesses antidepressant activity as shown by Fabre & McLendon (1978) in a double-blind placebo controlled trial. Potential antidepressant activity was suggested by its prevention of the effects of tetrabenazine in mice, as shown by Soroko, *et al.* (1977). In this respect the compound is similar to amitriptyline and imipramine but is much less potent (about 1/60th) in blocking the uptake of noradrenaline into rat hypothalamic synaptosomes. In view of this it appeared desirable to investigate possible blockade of the catecholamine uptake system in man by bupropion and also a reference tricyclic compound, and to do this using doses known to have clinical effects. The effects of orally administered bupropion and imipramine on the changes in systolic blood pressure produced by intravenous injections of tyramine in healthy volunteers are reported here.

Six healthy men, aged 24–32 years (mean 28 years), and weighing between 57 and 96 kg (mean 76 kg) each received the following treatments orally: bupropion hydrochloride 150 mg (3 × 50 mg tablets) plus imipramine dummy (2 tablets); imipramine hydro-

chloride 50 mg (2 × 25 mg tablets) plus 3 bupropion dummy tablets; imipramine dummy tablets (2 tablets) plus bupropion dummy tablets (3 tablets). Treatments were administered in the morning after an overnight fast and at intervals of at least 1 week. The order of administration was based on a 6 × 3 block ensuring that all possible orders of the three treatments occurred once only resulting in complete balance for both treatment and preceding treatments. The use of the double dummy design enabled double-blind conditions to be maintained despite the fact that the imipramine and bupropion tablets were completely different in appearance.

A polythene cannula was inserted in an antecubital vein in each subject. The subject then remained resting supine for the next 2 h when heart rate and blood pressure had stabilised. Beginning 2 h after ingestion of the tablets sensitivity of systolic blood pressure to tyramine was determined by the method of Ghose *et al.* (1976). Initial doses of tyramine sulphate were 400 µg in 1 ml saline, the dose being then increased until a rise in systolic blood pressure exceeded 30 mm Hg. The dose of tyramine required to produce a rise

Table 1 Effects of bupropion and imipramine on tyramine sensitivity expressed as the i.v. dose causing 30 mm Hg increment in systolic pressure

<i>Analysis of variance:</i>				
<i>Source</i>	<i>Sum of squares</i>	<i>df</i>	<i>Mean squares</i>	<i>F</i>
Subject	6.298	5	1.260	0.66 NS
Treatments	21.154	2	10.577	5.58 $P < 0.05$
Occasion	1.701	2	0.851	0.45 NS
Residual	15.171	8	1.896	

<i>Treatment</i>	<i>Dummy (L)</i>	<i>Bupropion (B)</i>	<i>Imipramine (I)</i>
Mean tyramine doses (mg)	3.48	4.12	6.03

Treatment comparisons
 $L \vee I P < 0.05$; $B \vee I P < 0.05$; $L \vee B$ NS

Friedman's analysis by ranks:

<i>Treatment</i>	<i>L</i>	<i>B</i>	<i>I</i>
Sum of ranks	9	11	16

($2P < 0.2$, > 0.1)

Duncan's test was used to examine the means for six subjects after the three treatments.

For the Friedman analysis ranks were assigned to the doses of tyramine required on different occasions for each subject, 1 for the lowest, 2 for the middle, and 3 for the highest dose.

Sums of ranks after the different treatments are shown.

of 30 mm Hg systolic pressure was then calculated after fitting lines by standard regression procedures of response against logarithm of dose.

Blood samples were taken at 2 h after oral treatment and at the end of assessment of tyramine responses. These were assayed for imipramine and bupropion, to check that the drugs had been adequately absorbed. The assessment of tyramine response took about one hour. Hence the second blood sample was taken approximately 3 h after treatment.

The results are summarised in Table 1. Parametric analysis of variance indicated that pretreatment with imipramine significantly ($P < 0.05$) increased the amount of tyramine required to raise the systolic blood pressure by 30 mm Hg when compared with the effects of both inert treatment and bupropion. The latter two treatments did not differ with respect to tyramine sensitivity.

Using a non-parametric method, Friedman's analysis by ranks, significance at the 0.05 level was not achieved but the trend for imipramine pretreatment to necessitate use of the higher doses of tyramine was clearly seen. The small number of subjects and conservative nature of the test gave a P value of less than 0.2 but greater than 0.1.

Concentrations of imipramine of 5.83 ± 3.82 (s.d.) ng/ml and bupropion of 147 ± 21 (s.d.) ng/ml at 2 h

after ingestion confirm absorption of the drugs. The respective values at approximately 3 h were 6.67 ± 2.50 (s.d.) ng/ml and 127 ± 41 (s.d.) ng/ml.

The initial demonstration that a tricyclic antidepressant drug (nortriptyline) could reduce the blood pressure response to tyramine employed a group of depressed patients receiving nortriptyline chronically over a period of 3–4 weeks (Freyschuss, Sjoqvist & Tuck, 1970). That the effect could be shown very much more rapidly was demonstrated by Ghose *et al.* (1976) using a single oral dose of 50 mg desmethylinipramine, and assessing the effects on tyramine 3 h after administration of the antidepressant. In the present study it was decided to begin testing tyramine sensitivity 2 h after oral administration of the antidepressants, because peak concentrations of bupropion in male subjects receiving the tablet preparation occur on average after 1.5 h (unpublished observations). The drug is also more rapidly metabolised than imipramine having a $T_{1/2}$ of 11 h (unpublished observations). It was hoped that adequate amounts of both drugs would be absorbed between 2 and 3 h after administration and both the pharmacodynamic effects and the blood level measurements confirm this. The dosages of the two antidepressants were chosen because Ghose *et al.* (1976) had demonstrated that tyramine blockade could occur after a 50 mg dose of desipramine, and

150 mg daily of this compound would be an average therapeutic dose. In the case of bupropion the therapeutic dose is usually 100–150 mg three times daily.

Imipramine, like desipramine, quite clearly decreases the sensitivity to intravenous tyramine. Bupropion, by contrast, produced no significant change. These effects were clearly apparent using the parametric analysis of variance, but a similar trend appeared using non-parametric statistics even in this small group of subjects. In view of this it seems un-

likely that the antidepressant effect of bupropion results from blockade of noradrenaline uptake.

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PRELIMINARY STUDIES ON THE DISPOSITION OF MEPTAZINOL IN THE NEONATE

At present the most widely used pre-partum analgesic in the United Kingdom is pethidine even though it is appreciated that this may cause significant respiratory depression. Furthermore pethidine readily crosses the placenta and yet the neonate is less well able to dispose of the drug than is the mother (Cooper, Stephen & Aggett, 1977). The average neonatal elimination half-life has been estimated to be 22 h which is approximately 7 times longer than that of healthy adults (Caldwell *et al.*, 1978). This delayed excretion is likely to exacerbate any respiratory complications seen in the infant.

Meptazinol is a new major analgesic which has recently been shown to be useful in alleviating labour pain (Jackson & Robson, 1980). In contrast to pethidine it has been shown to produce minimal effects on respiration (Jordan *et al.*, 1978). Furthermore the drug has a relatively short half-life, 2.2 ± 0.05 h (mean $\pm$ s.e. mean) (Rosseel *et al.*, 1975), which could be advantageous to its use as a pre-partum analgesic. While previous studies have shown meptazinol to cross the placenta freely (Jackson & Robson, 1980) no investigations have been reported on the disposition in the neonate. This communication describes preliminary results from such a study.

Thirteen women participated in this trial. Their weights ranged from 55–91 kg (72 ± 3.4 kg, mean $\pm$

s.e. mean). They were given meptazinol 100–150 mg i.m. Ten received a single injection approximately 3 h prior to delivery, while the remaining three patients had one or two earlier doses separated by 3 h intervals. Heparinized blood samples were taken at birth from both mother and infant from a cephalic or femoral vein. Subsequently samples were taken from the infant at various times selected from 4, 8, 12, 18 and 24 h after birth.

Plasma concentrations of meptazinol were determined using an HPLC method with fluorescence detection. Briefly, 0.5 ml plasma was extracted with 3 ml ethyl acetate after the addition of 0.1 ml pH 9.5 1 M bicarbonate buffer and 100 ng of internal standard, Wy 23128 (the *N*-cyclopropyl analogue of meptazinol). After vortex mixing for 2 min followed by centrifugation, the ethyl acetate layer was removed and reduced to dryness under a stream of nitrogen at 50°C. The residue was reconstituted in 150 μ l 66% aqueous methanol and 100 μ l injected onto a Spherisorb CN column (Phase Separations Ltd, Queensferry, Clwyd, U.K.). The column was eluted with 45% methanol in 0.5% aqueous ammonium acetate at a flow rate of 2 ml min⁻¹. Meptazinol was detected by means of its natural fluorescence (282 nm excitation, and 300 nm emission). The approximate retention times of the drug and internal standard were 4.3 and 5.5 min