A COMPARISON OF DICLOFENSINE AND DESMETHYLIMIPRAMINE USING TYRAMINE PRESSOR TESTS IN NORMAL SUBJECTS

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Eight male volunteers received placebo, diclofenine 25 mg, diclofenine 50 mg and desmethylinipramine (DMI) 50 mg at least a week apart. Using tyramine pressor tests, no statistically significant differences between the noradrenaline reuptake blocking effects of the three active treatments could be demonstrated. Visual analogue rating scales showed an increase in dryness of the mouth at 3 h after DMI but no similar effect after either dose of diclofenine.

Keywords diclofenine desmethylinipramine tyramine pressor test

Introduction

Phase I studies of antidepressant drugs cannot assess their desired therapeutic effects, that is elevation of a depressed mood. Regardless of the central mechanisms of action the evaluation of peripheral pharmacodynamic actions (whether in the assessment of adverse effects or other actions such as noradrenaline reuptake blockade) provides a method of investigating new compounds in normal volunteers.

Diclofenine is a new isoquinoline derivative antidepressant which is structurally very similar to nortriptyline but from which it differs in some central and peripheral pharmacological actions (Keller *et al.*, 1982). Diclofenine is an equipotent inhibitor *in vitro* and *in vivo* of 5-hydroxytryptamine, dopamine and noradrenaline uptake (Keller *et al.*, 1982).

Animal work has shown that the drug has both central and peripheral noradrenaline reuptake blocking effects (unpublished data, F. Hoffman La Roche, Basle). The aim of this study was to assess the peripheral noradrenaline reuptake blocking properties of single doses of diclofenine using tyramine pressor tests in normal subjects.

Methods

Eight healthy volunteers aged 19 to 23 years, all normal on physical examination, electrocardiogram, biochemical and haematological screening were randomised to receive each of four treatments in a Latin square design. The treatments were placebo, des-

methylinipramine (DMI) 50 mg, diclofenine 25 mg and diclofenine 50 mg. Each treatment was given in the form of a single dose of matching tablets and capsules. The treatments were given 1 week apart. Volunteers were given a list of tyramine containing foods and asked to avoid them totally for 48 h prior to and during each study day as well as alcohol and cigarettes. None of the volunteers was a regular cigarette smoker.

Informed written consent was obtained from each subject and the study was approved by the ethical committee of St Bartholomew's Hospital.

After a light breakfast subjects underwent a tyramine pressor test and completed visual analogue scales for mood, energy (vitality), sedation, appetite and dryness of the mouth before receiving treatment. These scales were constructed in a standard manner with a 10 cm line marked at each end with opposing extreme subjective descriptions, e.g. for mood 'I have never felt so sad' and 'I have never felt so elated.' Volunteers were asked to divide the line at a point reflecting their feelings at that time. These assessments were repeated at 1, 3 and 6 h after dosing.

The tyramine pressor tests were performed using the method of Ghose *et al.* (1975) with two modifications: heart rate was not measured and systolic blood pressure (SBP) was measured using an Infrasonde electronic sphygmomanometer to improve precision when measuring blood pressures every 30 s. The Infrasonde was calibrated against a Hawksley random zero machine and good agreement for SBP

found between the two in 11 volunteers (unpublished observations).

Analysis

At each time point the dose of tyramine needed to produce a 30 mm Hg rise in SBP (T30) was noted. Where necessary T30 was calculated by interpolating between two points on a graph of SBP plotted against dose of tyramine assuming a linear relationship. Tyramine ratio was calculated as the ratio of T30 after treatment to T30 at baseline for each time point after each treatment (Figure 1).

Comparisons between treatments at each time point were made using a $\log_{10}$ transformation of T30 (LT30) to normalise the distribution of residuals. Two way analysis of covariance was performed (using baseline values as the covariate) to take account of differences between subjects and treatments simultaneously.

Visual analogue scale data were analysed in a similar way using the distance (in mm) from the left hand end of the 10 cm line.

Transformation did not have a significant effect on the distribution of residuals and was not employed.

For both LT30 and visual analogue scale ratings 95% confidence intervals were calculated.

Results

The visual analogue scales showed a reduction in appetite between 3 and 6 h coinciding with lunch during all treatments. There were no differences between the treatments. There were also no differences between the treatments for ratings of sedation or mood. Differences were seen for energy ratings reaching statistical significance only at 1 h ($F(3,21) = 3.95$, $P < 0.025$). This difference was contributed largely by DMI which appeared to increase energy compared with both placebo and the other treatments. Dryness of the mouth at 3 h differed significantly between treatments ($F(3,21) = 5.01$, $P < 0.01$).

Again this was due to increased dryness caused by DMI. Diclofenac at either dose did not differ from placebo in this respect.

There were no changes in tyramine ratio following placebo but all the active treatments caused the ratio to rise (Figure 1). There were virtually no differences between the active treatments at 1 h but at 3 h and 6 h diclofenac 50 mg produced a greater change in ratio than the other active treatments. When both baseline and placebo values were taken into account using analysis of covariance, significant differences were seen between subjects at all times and between treatments from 1 h onwards ($F(3,21) = 3.97$, $P < 0.025$; 20.53, $P < 0.001$; 31.79, $P < 0.001$ for 1 h, 3 h and 6 h respectively). When the three active treatments were compared the differences did not reach statistical significance (Figure 2).

Discussion

For those tricyclic antidepressants that have been studied there is a good correlation between the

Figure 2 Percentage change in T30 (dose of tyramine needed to produce a 30 mm Hg rise in systolic blood pressure) compared with placebo for D25, D50 and DMI at 1 h, 3 h and 6 h $\pm$ 95% confidence intervals.

Figure 1 Tyramine ratio following placebo (P), desmethyylimipramine 50 mg (DMI), diclofenac 25 mg (D25) and diclofenac 50 mg (D50) at 1 h, 3 h and 6 h for each subject (●) with mean (—).

tyramine pressor response and plasma level of the drug (Freyschuss *et al.*, 1970; Ghose *et al.*, 1976). In this respect, however, there may be marked differences in the potency of different antidepressants (Mulgirigama *et al.*, 1977). In order to compare our results for diclofenine with those of other workers for other drugs, we included an active control drug—DMI—as well as placebo. This also served to validate our methodology.

As has previously been reported (Ghose *et al.*, 1976) we saw a rapid onset of effect after a single oral dose of all three active treatments. The mean LT30 for the larger dose of diclofenine was consistently higher than that for both the lower dose and DMI 50 mg although the differences did not reach statistical significance. This suggests that diclofenine is a more potent inhibitor of monoamine reuptake than DMI in the adrenergic neurone of healthy males after a single

dose. In contrast McEwen (1977) found nomifensine to be less potent than DMI in this respect in three volunteers.

The interpretation of the rating scale scores for energy is difficult. Biologically antidepressants would not be expected to increase vitality in volunteers. Whilst energy was significantly increased 1 h after DMI the direction of the effect was not consistent at other times and for other treatments. It is thus unlikely that this observation is anything other than a chance finding.

The lack of anticholinergic effects of diclofenine at both doses is an important observation and is in keeping with the findings of Culig *et al.* (1983). The expected finding of increased dryness of the mouth following DMI 50 mg demonstrated the ability of the rating scale to identify this pharmacological effect.

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