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Brief Reports

Minaprine: An Anticholinergic-Free Antidepressant?
Results of a Controlled Trial of Mianserin

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Minaprine is an amino-phenylpyridazine antidepressant reported to be relatively free of anticholinergic effects, cardiotoxicity, drowsiness, and weight gain. Minaprine (100 mg t.d.s. and 100 mg b.d.) was compared with mianserin (20 mg t.d.s.) in 117 depressed patients, and all three regimes produced significant reductions in scores on the HRSD at the end of six weeks' treatment. There were no anticholinergic effects, but there was a significantly greater incidence of drowsiness with mianserin than with minaprine.

The introduction of a new antidepressant is justified if it has advantages over those already in use, but so far no new drug has proved to be more efficacious than its forerunners (Paykel, 1985). However, new compounds may bestow 'fringe benefits' in relation to side-effects and, in particular, anticholinergic effects, cardiotoxicity, drowsiness, and weight gain may cause problems with established drugs.

Minaprine is an amino-phenylpyridazine compound which facilitates serotonergic, dopaminergic, and cholinergic transmission. The chemical configuration is shown in Fig. 1. The compound has been shown to exert antidepressant effects in experimental studies (Biziere *et al*, 1982) and in clinical trials against placebo (Jouvent *et al*, 1984), imipramine and maprotiline (Radmayr *et al*, 1984) and nomifensine (Mikus *et al*, 1984). These studies have demonstrated freedom from all the adverse effects mentioned above. Mianserin is relatively free from anticholinergic effects and cardiotoxicity, but often causes drowsiness and weight gain, and so was chosen as the comparative drug for this study.

The trial

European studies have indicated the effective dose range to be 200–300 mg daily, such side-effects as occurred being dose-related (Biziere *et al*, 1985). Since adverse events may affect patient compliance in general practice (Wheatley, 1987), a parallel group, randomly assigned double-blind trial was undertaken to compare minaprine (100 mg t.d.s. and 100 mg b.d.) with mianserin (20 mg t.d.s.) (10 mg t.d.s. for patients aged 65 years and over). The drugs were supplied in matching capsules, one week's supply at a time, and capsules were counted at the end of each assessment period, to check patient compliance. The trial was undertaken by 13 general practitioner members of the group, who treated 117 depressed patients for six weeks; DSM-III criteria (American Psychiatric Association, 1980) were used, with a minimum score on the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1967) of 19 or more. Those taking part had previously attended training sessions to validate inter-rater reliability in completing the HRSD.

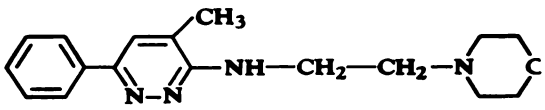

FIG. 1 *Formula of minaprine: 3 – (2N morpholino) ethylamino, 4–methyl, 6–phenyl pyridazine, dihydrochloride.*

Patients were excluded if they were suffering from schizophrenia, chronic brain syndrome, senile dementia, epilepsy, cardiac, renal or hepatic failure, or peptic ulcer, as were women who might be pregnant or breast feeding. Furthermore, patients were excluded if they were being treated with lithium, had an abnormal EEG or ECG, or were suicidal. Written informed consent was obtained from all patients before the start of the trial.

Predictably, females outnumbered males; the sex ratios for the three groups were minaprine (t.d.s.) 3 : 1, minaprine (b.d.) 5.5 : 1, and mianserin 3.2 : 1. In the three groups respectively, the mean ages were 57.0, 51.7 and 55.9 years, the mean durations of the present depressive episode 19.4, 10.1, and 18.8 weeks, and incidence of previous attacks 45%, 59% and 55%.

Results

The full six-week trial was completed by 34 patients in the minaprine (t.d.s.) group, 28 in the minaprine (b.d.) group, and 32 in the mianserin group. The 'last visit carried forward' (LVCF) method was used for another eight patients who completed at least three weeks (two in the minaprine (t.d.s.) group, four in the minaprine (b.d.) group, and two in the mianserin group), and these were included in the analysis. Otherwise, there were five drop-outs in the minaprine (t.d.s.) group, nine in the minaprine (b.d.) group, and four in the mianserin group, leaving 99 patients for analysis. The paired *t*-test was used to test for pre–post differences, and the *t*-test for

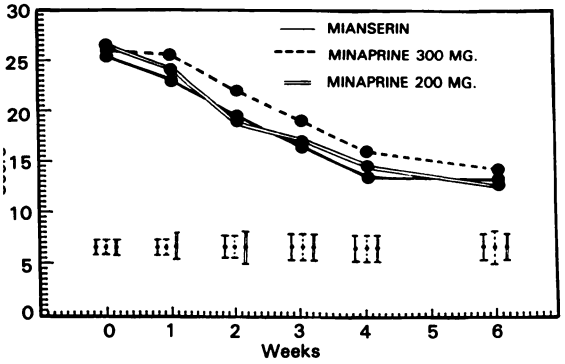

FIG. 2. *Reduction in mean HRSD scores during the trial* (——, mianserin; – – –, minaprine (100 mg t.d.s.); ═══, minaprine (100 mg b.d.)). Error bars indicate s.e.m.s.

between-group differences. The results are shown graphically in Fig. 2.

There was a highly significant reduction in mean HRSD scores at all periods ($P<0.01$) except from week 0 to 1 in the minaprine (t.d.s.) group only.

However, mean scores do not necessarily represent the true picture of antidepressant drug effects, and different categories of response should also be considered. According to Hamilton (1987, personal communication) a final score of 6 or less on the HRSD can be considered as 'symptom-free', while end-points between 7 and 18 (minimum score for entry was 19) would represent 'improvement', and a final score of 19 or more, 'no change or worse'. Using these criteria, at the end of the trial the proportions of 'symptom-free' were: minaprine (t.d.s.) 4 (11%), minaprine (b.d.) 8 (27%), and mianserin (10) (29%); 'improved': 22 (63%), 17 (57%), and 17 (50%) respectively; and 'failures' 9 (26%), 5 (17%), and 7 (21%) respectively.

Side-effects

The only side-effect of any importance was drowsiness or tiredness which, allowing for baseline incidence, occurred in no patients on minaprine (t.d.s.), 4 (10%) on minaprine (b.d.), and 6 (16%) on mianserin ($P<0.05$, χ^2). The only anticholinergic effects recorded were two cases of dry mouth on minaprine (b.d.), and one on mianserin. Otherwise, there were only two cases of 'irritability' in the minaprine (t.d.s.) group, with no other side-effects of any importance.

Discussion

Relief of depression was virtually identical between both doses of minaprine and the control drug mianserin, with the usual delayed onset of therapeutic effect and proportion of poor responders in all three groups. Although the proportion of patients rendered 'symptom-free' was lower in the minaprine (t.d.s.) group than in either of the other two groups, the differences are not statistically significant (χ^2). Although the occurrence of anticholinergic effects was negligible with either minaprine or mianserin, there was a significantly increased incidence of drowsiness with the control drug. Furthermore, a disadvantage of mianserin is the necessity to undertake a monthly haematological screening which, in the present climate of public opinion concerning psychotropic drugs, may have an adverse effect on patient compliance. Although we did not measure weight during the trial, weight gain can be a troublesome side-effect with most antidepressant drugs, and can sometimes nullify the improvement in depressive symptoms, particularly in female patients, who can experience a return of depression as their girth increases (personal observations).

This is a relatively small sample, but if the freedom from unwanted effects with minaprine is confirmed in further trials, then it should prove to be a useful addition to the antidepressant drug spectrum.

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