PLASMA LEVELS AND CLINICAL RESPONSE WITH IMIPRAMINE IN A STUDY COMPARING EFFICACY WITH MIANSERIN AND NOMIFENSINE

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- 1 The comparative antidepressant efficacy of 150 mg imipramine, 60 mg mianserin and 150 mg nomifensine was studied in 45 depressed patients in a six week double-blind investigation.
- 2 In the efficacy analysis of 41 patients completing the study there was no overall significant difference in efficacy between the groups. Individual group comparisons showed no significant difference in response between mianserin and nomifensine, and mianserin and imipramine. There was a significant ($z=1.99$, $P<0.05$) improved response in the imipramine compared with the nomifensine treated group. The imipramine treated group were significantly older.
- 3 No significant plasma concentration/clinical response relationships were demonstrated with nomifensine, mianserin, imipramine or desipramine.
- 4 Plasma level monitoring of imipramine recommended by some investigators does not seem to be appropriate.

Introduction

The disadvantages of the traditional tricyclic antidepressants (TCA) in terms of their unwanted and even dangerous side-effects and latency of action are well known. Dissatisfaction with these compounds as a treatment of choice has provided the impetus for the search for new antidepressants which might be safer and more effective.

In a series of studies of the clinical effects of new antidepressants we compared two of the newer antidepressants, mianserin and nomifensine, which have different chemical structures and pharmacological profiles, with a standard TCA, imipramine.

Mianserin appears to antagonize cortical serotonin receptors and, unlike other antidepressants, appears to be selective for pre-synaptic α_2 -receptors. *In vitro* studies indicate that mianserin has no effect on serotonin or dopamine uptake in brain tissue. Although *in vitro* it inhibits the uptake of noradrenaline (NA) this does not appear to be the case *in vivo*. Increased NA turnover is seen with mianserin, possibly due to antagonism by mianserin at pre-synaptic α_2 -receptors. Nomifensine, a tetrahydroisoquinoline and chemically unrelated to the TCAs, has a pharmacological profile similar to that of imipramine but without the cardiovascular and anticholinergic effects seen with the older TCAs. It inhibits the uptake of dopamine (DA) and NA and has some effect on 5-hydroxytryptamine (5HT). Its most important difference from the older TCAs is its effect in inducing the release of DA and

blocking its re-uptake. These pharmacological actions have led to the suggestion that motor activity in depression might be selectively affected.

In the first part of the present study, older patients over the age of 50 were treated with a half standard dose because of a possible effect of age on the pharmacokinetics of the drugs. That study (Montgomery *et al.*, 1980) revealed significant advantages on some but not all measures for imipramine compared with nomifensine at three, four and six weeks and for mianserin compared with nomifensine at three and four weeks. We were interested to see if this pattern would also appear in a group of patients with a wider age range following the identical protocol but using a full standard dose.

Patients and methods

Patients referred to a psychiatric hospital suffering from primary affective disorder (Feighner *et al.*, 1972) who remained moderately to severely depressed [17 item Hamilton Rating Scale (HRS) score >17] following a placebo treatment period of five to 10 days were admitted to the trial. Patients with a history of organic illness, pregnancy, schizophrenia, depression secondary to any other illness, or who had received adequate antidepressant treatment during the previous month, were excluded. Following the placebo period, patients were randomly allocated double-blind to treatment with 50 mg imipramine, 50 mg nomifensine, or

20 mg mianserin three times daily in matching capsules. Patients were rated at the beginning of the placebo period, on entry to the trial and weekly for six weeks using the HRS (Hamilton, 1967), the Montgomery and Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979) and side-effects check list covering autonomic symptoms, CNS effects, gastrointestinal effects, drowsiness, headache, weakness/dizziness, excitability and dermatitis. Blood was drawn for drug plasma level determination weekly at 9.00 a.m. before the morning dose. Blood was stored at -20°C prior to analysis. Plasma concentrations of mianserin, imipramine and desipramine were measured by gas chromatography with nitrogen detection.

Results

Forty-five patients entered the study. Forty-one patients, seven male and 34 female, mean age 44 years, completed four weeks treatment and 37 completed six weeks treatment. There were four drop-outs (two male and two female) in the first three weeks of the study. Two in the imipramine treated group complained of side-effects, one in the nomifensine treated group deteriorated and was withdrawn and one in the mianserin treated group was withdrawn because of non-compliance with treatment. These patients were excluded from the analysis.

Table 1 shows the entry data of patients completing the trial. The age of the imipramine

treated group is higher compared to the nomifensine and mianserin treated groups. The imipramine treated group were significantly older than the nomifensine treated group ($z=1.77$, $P<0.05$). Because of a possible differential response with age, the analysis was carried out with age as a covariant.

Analysis of clinical efficacy was carried out using ranking procedures (Meddis, 1980). The scores of the four patients who completed four weeks treatment but not six weeks were included in the six week analysis. There was no significant difference in outcome measured on the HRS or MADRS between the three treatment groups in the overall analysis (Figure 1, Table 2). Comparing individual treatment groups, there was no significant difference in outcome between the mianserin and the imipramine treated groups. There was a significant difference between the nomifensine and imipramine treated groups at six weeks measured by the HRS final score ($z=1.99$, $P<0.05$; Figure 2).

Side-effects were analysed, by subtracting the side-effects whilst on placebo before active therapy was started, from the side-effects reported during active treatment. There was no significant difference in corrected side-effects measured either as patients reporting mild or moderate side-effects (Figure 3). In all treatment groups side-effects were less at the end of the treatment period than at the start of active treatment. Table 3 shows the range of steady state plasma concentrations achieved. There was no significant relationship between clinical response and steady state plasma concentrations of imipramine, desipramine, mianserin or nomifensine.

Table 1 Entry data of patients completing trial

	<i>Mianserin</i> (<i>n</i> = 14)	<i>Nomifensine</i> (<i>n</i> = 14)	<i>Imipramine</i> (<i>n</i> = 13)
Sex	13 F 1 M	11 F 3 M	10 F 3 M
Mean age	42	40 ^a	50 ^a
Range	27–69	27–72	28–76
Mean HRS entry	22.5 (1.16)	21.79(1.04)	22.39(5.26)
Mean MADRS entry	31.57(1.75)	30.57(1.38)	31.15(1.38)
^a $z=1.77$, $P<0.05$			

Table 2 Mean HRS and MADRS scores at weeks 2, 4 and 6

	<i>Mianserin</i>	<i>Imipramine</i>	<i>Nomifensine</i>
MADRS			
Week 2	22.64 (8.34)	21.85(13.10)	21.64(14.53)
Week 4	21.14 (9.98)	19.46(13.49)	23.36(11.42)
Week 6	18.21(12.63)	11.69(13.16)	17.86 (8.57)
HRS			
Week 2	16.86 (6.59)	16.92 (7.8)	16.43 (8.09)
Week 4	15.86 (7.09)	14.31(10.10)	16.64 (7.47)
Week 6	13.86 (2.02)	8.15 (9.32)	13.57 (7.20)

Figure 1 Mean MADRS scores weeks 0–6. ■ Nomifensine ($n=14$), □ mianserin ($n=14$), ◆ imipramine ($n=13$).

Figure 2 Mean HRS scores week 0–6. Symbols as in Figure 1. * $P<0.05$.

Figure 3 Percentage of patients with corrected side-effects of mild or greater severity. □ Nomifensine, ▨ mianserin, ■ imipramine.

Table 3 Mean plasma concentrations of mianserin, nomifensine, imipramine and desipramine

<i>Drug</i>	<i>Mean plasma concentration (ng/ml)</i>	<i>Range</i>
Nomifensine	95	34–290
Mianserin	33	15–67
Imipramine	93	25–271
Desipramine	139	31–391

Discussion

With all new antidepressants it is important to establish whether there is a clinical response and plasma concentration relationship. With established antidepressants such a relationship is of interest for the light it may throw on the mechanism of action of the compound. With new compounds a relationship would serve as confirmation of a pharmacological effect independent of placebo response, and can provide a rational basis for suggested dosage.

Valid results are more likely to be obtained, and differences between antidepressants demonstrated, in well conducted hospital based studies where the random variance affecting treatment is reduced. In this study, which was hospital based, all patients were treated initially for a period of five to 10 days with placebo and patients responding were omitted from the study. This would have the effect of reducing the response rate due to placebo or random factors in the remaining patients who entered the study, in whom the response seen was approximately 54%. This is in line with rates of response to antidepressant treatment reported by other investigators and may be taken to indicate an antidepressant effect of the drugs.

From the overall analysis of the three treatment groups in this study it appeared that there was no significant difference in response. Comparing the individual treatment groups the two newer antidepressants, nomifensine and mianserin, appeared to have the same order of antidepressant efficacy. Although imipramine appeared to have a better response this did not reach significance compared with mianserin. At six weeks there was, however, a significantly improved response in the imipramine treated group compared with the nomifensine treated group. This result may however have been affected by the difference in age between the groups. When patients are randomly allocated to treatment there is a risk that the treatment groups may not be balanced in every respect. In this study, although the groups were well matched on other variables such as initial severity and sex distribution, the imipramine treated group were by

chance significantly older. The relationship of age with likely response to antidepressant treatment is not fully understood but there is evidence of a differential effect with different age groups. For example, in a study of a large number of depressed patients it has been reported that there was a significantly better response to antidepressant therapy in the age group over 55 years than in the younger group (Montgomery, 1982).

In the first part of this series of studies investigating older patients treated with a half standard dose, a deterioration in response was observed between two and three weeks in the nomifensine treated group. Such a reversal of antidepressant effect, which is unusual in the response curve to antidepressants, can be seen in several of the studies of nomifensine including the placebo controlled investigation of Kröger (1976). This may be taken as evidence of some neuronal effect and an explanation in terms of receptor sensitivity has been suggested (Montgomery 1980). In this study, which investigated the full dose of 150 mg of nomifensine, the reversal of effect is not seen. It is possible that there are different active pharmacological effects of nomifensine at low doses compared with high doses.

The presence of a relationship between clinical response and plasma concentrations has been reported with several of the TCAs but not with all antidepressants. The most consistent finding has been the demonstration of an association between poorer response and higher plasma levels of nortriptyline. There is less agreement concerning the relationship with amitriptyline, with some investigators finding no relationship, others a positive correlation between response and levels, and others a curvilinear relationship. Where an association has been found between poorer response and high plasma concentrations it appears to be the levels of the metabolite nortriptyline which are associated with a poorer response (Montgomery, 1980).

In this study we did not find a significant relationship between plasma concentrations of nomifensine and clinical response. This is in accord with the earlier study (Montgomery, 1980) which also did not find a significant relationship. The findings from other investigations of nomifensine are in accord and it therefore seems likely that a relationship between response and plasma concentrations such as is seen with nortriptyline does not exist with nomifensine.

Our finding of no significant relationship between plasma concentrations of mianserin and response differs from the findings in our earlier study (Montgomery *et al.*, 1978). In 49 patients treated with 60 mg mianserin, patients developing

plasma concentrations $>70\mu\text{g/l}$ were associated with a poorer response. Other investigators, for example Coppen *et al.* (1976), did not find a significant relationship. There is considerable inter-individual variability of plasma levels and in any particular group the range of levels developed may be large or small. In the present study there were no patients developing high plasma concentrations so the association between high concentrations and poorer response could not be tested. It seems that with mianserin, only a small number of patients develop high concentrations which are therefore not a significant clinical problem as with some of the TCAs, where a third or more patients have been reported to develop high plasma levels associated with a poor response.

We did not observe a significant relationship between plasma concentrations of imipramine or its metabolite desipramine and clinical response in this study. It therefore seems that the association between higher levels and better response which has been reported (Glassman & Perel, 1973; Gram *et al.*, 1976; Reisby *et al.*, 1977) is still open to question. Some of these studies have methodological flaws, for example, the use of flexible dosages which confuses the relationship between levels and response, and in the study of Glassman & Perel (1973), the retrospective exclusion of severely depressed psychotic patients. In the recent study of Simpson *et al.* (1982) a standard dose was used and they reported that the previously published cut-offs failed to discriminate responders and non-responders on all of the measures of response used except one.

There are of course other reasons for avoiding very high plasma concentrations. For example the possibility of increased subjective side-effects, cardiotoxicity, etc. Because of the variability in patients' tolerance of unwanted effects, a correlation between plasma concentrations and subjectively experienced side-effects is not easy to establish. However a relationship with at least some side-effects is likely to exist. For example a study by Rudorfer & Young (1980) demonstrated that high plasma concentrations of desimipramine were associated with a greater suppression of salivation than low levels in depressed patients.

Side-effects were not an important problem in this investigation and there were no significant differences between the treatment groups, although there were two patients in the imipramine group who withdrew because of unacceptable side-effects. The side-effects in all treatment groups were less at the end than at the beginning of the study and this probably reflects the fact that subjectively experienced side-effects are frequently confounded with depressive symptoms which mimic side-effects.

The numbers in the present study were too small to adequately test the hypothesis that high levels of imipramine are associated with better response than low levels. We therefore took the opportunity of analysing the data from patients treated with imipramine in both parts of the present series studies. In these 25 patients the correlation between plasma levels and clinical response was -0.16 with imipramine and -0.09 with desipramine, which is too low to suggest that high levels may be associated with better response. The absence of a significant correlation is in line with the findings of Simpson *et al.* (1982) rather than with those of Glassman & Perel (1973) and Gram *et al.* (1976).

Using the cut-offs suggested by Glassman & Perel (1973) and Reisby *et al.* (1977) no significant relationship could be seen. A good response was seen in patients developing levels both above and below the recommended cut-offs. For example at a cut-off of 240ng/ml imipramine plus desipramine there were six responders ($\text{HRS} \leq 8$) and three non-responders with levels above the cut-off compared with nine responders and seven non-responders below. At the lower cut-off of 180ng/ml there were six responders and five non-responders with levels above the cut-off compared with nine responders and five non-responders below. We conclude that the association between high levels and improved response is so weak and accounts for so little of the variance that plasma level monitoring for clinical improvement would be inappropriate, although it can of course be useful for checking on compliance.

It is worth stressing that 36% of the patients treated with 75 mg imipramine developed levels of imipramine above the cut-off suggested by Gram *et al.* (1976). In the second study using a dose of 150 mg imipramine, 73% of patients developed levels above the cut-off. Comparing these two studies there is no improvement in response associated with the higher dose. Therefore from our results we find no support for the practice of using high doses of imipramine.

It seems unnecessary to raise the dose of imipramine to the heroic levels reported by some investigators. Doses at very high levels may be expected to be associated with increased side-effects, confusional states, cardiotoxicity, etc., and we would recommend with a traditional TCA such as imipramine, clinicians use the minimum dose indicated from the studies to be associated with adequate clinical response. Giving patients unnecessary quantities of toxic drugs is clearly inadvisable.

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Discussion

J. Feighner

We have not found nomifensine to be a broad spectrum antidepressant but it appears quite effective in patients with psychomotor retardation. Has Dr Montgomery analysed his data according to psychomotor retardation pattern?

S.A. Montgomery

We have not completed a per item analysis on the second study but in the first study I reported we found that the lassitude item did not predict response.

B. Leonard

Dr Montgomery, have any other trials reported this deterioration with nomifensine? It is biologically a very interesting phenomenon.

S.A. Montgomery

The original two week placebo controlled study of Kröger does not show it so clearly. However, at the end of the two week period when the drug was stopped there was a deterioration in the following week. That is not strictly comparable but the phenomenon appears to be present because when the placebo was stopped no deterioration was seen. In a number of studies there is a flattening in response between the second and the third week.

S.R. Hirsch

Dr Montgomery, would comment on the fact that the mianserin and nomifensine group had an average mean score above 15 when they finished the six weeks which effectively meant that on average they were still almost sufficiently depressed to qualify to enter a depression study.