Br. J. clin. Pharmac. (1978) **5**, 71S–76S

RELATIONSHIP BETWEEN MIANSERIN PLASMA LEVELS AND ANTIDEPRESSANT EFFECT IN A DOUBLE-BLIND TRIAL COMPARING A SINGLE NIGHT-TIME AND DIVIDED DAILY DOSE REGIMENS

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1 Twenty-six in-patients and 24 out-patients suffering from moderate or severe primary depressive illness were randomly allocated to either a single night-time dose of mianserin 60 mg or a three times daily regimen in a double-blind controlled trial.

2 There was no significant difference in antidepressant effect between the two dosage regimens in either patient group measured using Hamilton Rating Scale (HRS), the Beck Self-Rating Inventory (BSRI) and the new Montgomery and Åsberg Depression Scale (MADS).

3 A significant negative correlation (–0.36, $P<0.05$) was found between plasma levels and clinical response using the MADS. A trend for patients with low levels to do worse was also observed suggesting a curvilinear relationship. A highly significant poorer clinical response in patients with levels above 70 μg/l was observed using the MADS ($t = 3.33$, $P<0.005$). This was also seen with the HRS ($t = 2.42$, $P<0.02$).

4 A significant correlation ($r = 0.29$, $P<0.05$) with age is reported, and a highly significant increased variability ($F = 7.07$, $P<0.001$) of mianserin plasma levels in patients over 55 was demonstrated.

Introduction

THE relationship between plasma levels and clinical response has been the subject of several studies since Åsberg (1971) first suggested a curvilinear relationship with nortriptyline, the most commonly investigated tricyclic antidepressant. The curvilinear relationship with nortriptyline has been demonstrated by investigators in Denmark (Kragh-Sørensen *et al.*, 1973), the USA (Ziegler *et al.*, 1976, 1977), the UK (Montgomery, Braithwaite & Crammer, 1977; Montgomery *et al.*, 1978), but not in Australia (Burrows *et al.*, 1972).

It is important to determine the relationship between plasma level and response for a number of reasons. Firstly, a relationship is in itself a double-blind confirmation of the therapeutic action of a drug as distinct from a non-specific placebo effect. Secondly, the relationship provides important information in determining the appropriate dosage regimen. Thirdly, the kind of relationship shown reveals something of the mechanism of action of the drug.

A considerable amount of energy has been spent by several groups of investigators looking for the relationship between plasma level of antidepressants and therapeutic response. With a complex curvilinear relationship, this is sometimes difficult to detect and may require large numbers of patients. Detecting this depends on the variability of interindividual metabolism of tricyclic antidepressants which may by chance be small or large in any particular group studied.

Coppen *et al.* (1976) could find no relationship between mianserin plasma level and antidepressant effect. This may have been because their group of patients was fairly small.

One of the aims of the present study was to investigate the relationship in a larger group of patients who were receiving a single night-time dose or divided doses in a double-blind trial. The practice of prescribing tricyclic or tetracyclic antidepressants in a three times daily regimen is traditional. The assumption that a divided dose regimen conveys any clinical advantage

over the single night-time dose has not been tested for mianserin. With amitriptyline, Braithwaite *et al.* (1974) demonstrated that the single dose regimen would not produce any significant reduction in therapeutic efficacy and might be preferred, since a single dose at night is more reliably taken by patients. The extra advantage of giving a sedative tricyclic or tetracyclic antidepressant at night is that it avoids unwanted sedative effects in the day and may improve sleep. Because of the reported greater failure of out-patients to take tablets, we decided to test equal numbers of both in- and out-patients.

Methods

A group of 57 routine admissions in approximately equal groups of in-patients ($n = 29$) and out-patients ($n = 28$) were studied. They were diagnosed as suffering from primary depressive illness using the criteria of Feighner *et al.* (1972). Both reactive and endogenous depressive patients were included (Gurney *et al.*, 1972). As part of a larger cross-cultural study, these patients were shown to have very similar psychopathology to a sample of Swedish depressed in-patients (Montgomery, Åsberg *et al.*, 1977). Only patients who remained severely or moderately depressed after at least 1 week 'no treatment' period were admitted to the trial. This was assessed by a severity rating of 16 or more on the first 17 items of the HRS (Hamilton, 1967). Patients were all treated with mianserin 60 mg daily for 4 weeks. They were randomly allocated to one of two treatment regimens: two 10-mg mianserin tablets three times daily plus six tablets of matching placebo nightly, or two tablets placebo three times daily plus six 10-mg mianserin nightly.

At the end of the wash-out period, baseline ratings were obtained on the Comprehensive Psychopathological Rating Scale (Åsberg *et al.*, 1977), the HRS, and the BSRI (Beck *et al.*, 1961). Patients were assessed weekly for 4 weeks using the HRS, the BSRI, and with the new MADS (Montgomery & Åsberg, unpublished), designed to be more sensitive to change, at 0 and 4 weeks. Ratings were carried out by two assessors blind to medication, who had been shown to have an adequate inter-rater reliability (HRS entry $r=0.89$, MADS entry $r=0.89$) (Montgomery, Åsberg, Jörnestedt *et al.*, 1977, and unpublished data). Reported side-effects were recorded on a standard form at the end of the wash-out period before treatment had started and weekly thereafter for 4 weeks. Blood was taken for plasma level determination after the wash-out period and weekly at the same time of the day (12 h after the night-time dose and before the morning dose). Blood was centrifuged and plasma stored at −20°C until measured using a gas liquid chromatographic method with nitrogen detection. No known enzyme-inducing or enzyme-inhibiting drugs were permitted during the trial. Only nitrazepam or diazepam were used for sedation where necessary.

Results

Fifty patients (37 female, 13 male, mean age 44.44, s.d. 14.99 yr) completed the trial; 26 were in-patients and 24 were out-patients. Of the seven who did not complete, two responded and stopped medication after 1 week; two complained of side-effects and were treated openly with the same dose of the drug with a different colour and responded; one developed mania at 3 weeks; and two developed physical illness (one developed a transient ischaemic attack, the other intestinal obstruction).

Table 1 shows the results from the patients who completed the trial. There was no significant difference between the single night-time and divided dose regimens in either the in-patient or the out-patient groups on the MADS, HRS or BSRI amelioration. As shown in Figure 1, the HRS and BSRI amelioration shows no apparent difference in treatment groups at weeks 1, 2, 3 or 4. We also examined differences using percentage change and final score on all scales used, and found no difference in therapeutic response between groups.

Figure 2 shows the course of side-effect-like symptoms for the two dosage groups. In both groups, 'side-effects' were higher before treatment with mianserin and decreased with treatment. There is no apparent difference between the groups.

Plasma levels were available for 47 patients. Mean plasma steady-state levels were 42.68 μg/l (s.e.m. 7.65) for the day-time dosage group and 56.36 μg/l (s.e.m. 6.28) for the night-time group. Mean levels for the total group were 50.06 μg/l (s.e.m. 4.92). These are in close accord, and analysis showed there was no significant difference in mean steady-state drug plasma levels in the two dose regimens. The slightly higher levels found in the single night-time dose group is in line with the shorter time inteval after the last dose. The plasma levels of mianserin revealed no difference in compliance between the treatment groups or, surprisingly, between in-patients and out-patients. The plasma levels at 3 weeks and 4 weeks correlated well ($r = 0.88$) but the drop in mean plasma levels between 3 and 4 weeks might indicate either compliance problems or possibly self-induction of enzyme systems. There was no relationship between plasma levels and reported side-effects.

The close similarity of all treatment groups allowed us to merge the data and examine the relationship between plasma levels of mianserin and clinical response. The relationship between clinical response shown in the final HRS and plasma level of mianserin is shown in Figure 3.

Figure 4 shows groups of plasma levels against

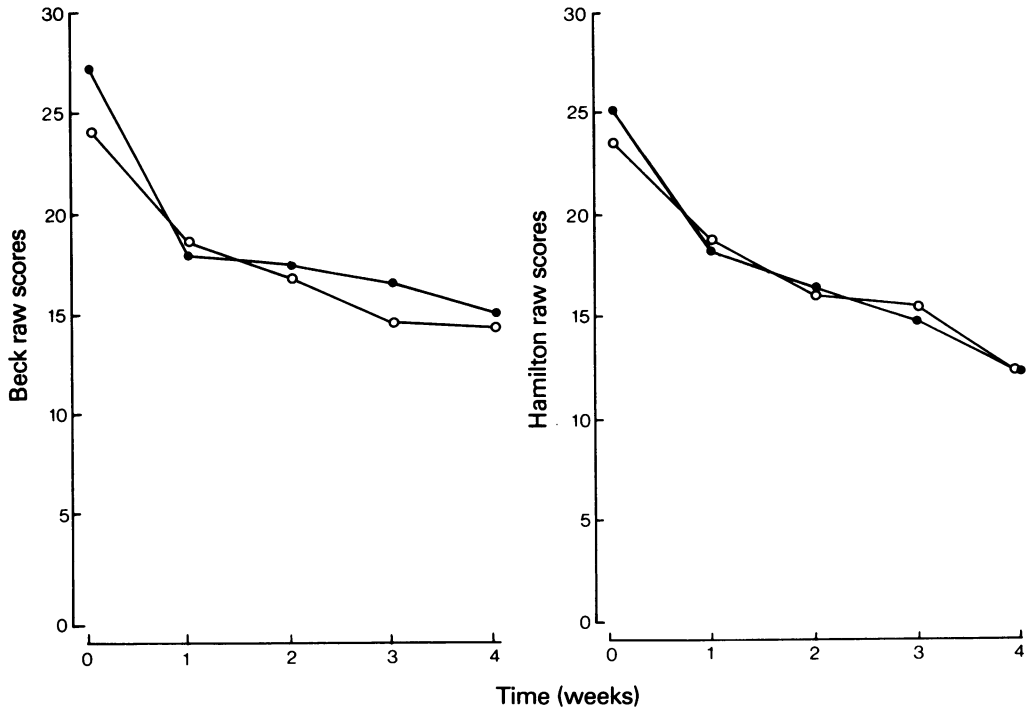

Figure 1 Amelioration of HRS and Beck scores on a single night-time dose (●) and a divided dose regimen (○).

response measured using the HRS and MADS amelioration. Plasma levels above 70 μg/l are associated with a poorer clinical outcome. There is a significant difference in the amelioration of the HRS between those above and below 70 μg/l (t = 2.42, $P<0.02$), with patients with the higher levels having a poor response. With the more sensitive MADS, this difference is highly significant (t = 3.33, $P<0.005$). The two patients with levels below 15 μg/l have a slightly poorer outcome but this difference is not significant. The correlation between the HRS amelioration and plasma level is negative and not significant (r = −0.22), but that with the MADS is significant (r = −0.36, $P<0.05$), the lower response being associated with high plasma levels.

There was no relationship between plasma level and

Table 1 Results (raw and scale scores ± s.e.m.) from patients who completed the trial

	Single night-time dose					
	In-patients (n=14)		*Out-patients (n=12)*		*Total (n=26)*	
	Entry	*Amelioration*	*Entry*	*Amelioration*	*Entry*	*Amelioration*
HRS	27.1 (1.23)	15.1 (1.98)	23.6 (1.42)	11.3 (1.23)	25.5 (4.99)	13.3 (1.25)
MADS	19.6 (0.9)	9.4 (1.96)	16.7 (0.92)	6.6 (1.76)	18.2 (0.69)	8.1 (1.33)
BSRI	31.8 (3.1)	12.6 (3.96)	23.3 (3.34)	10.7 (3.17)	27.8 (2.38)	12.3 (2.37)
	Divided dose					
	In-patients (n=12)		*Outpatients (n=12)*		*Total (n=24)*	
	Entry	*Amelioration*	*Entry*	*Amelioration*	*Entry*	*Amelioration*
HRS	23.2 (2.18)	11.3 (2.93)	24.3 (1.33)	12 (3.27)	23.7 (1.26)	12.1 (1.86)
MAD	16.8 (1.62)	8.0 (2.39)	17.6 (1.14)	7.9 (2.41)	17.2 (0.97)	7.9 (2.36)
BSRI	26.3 (3.6)	12.1 (4.55)	22.8 (3.41)	7.5 (2.82)	24.6 (2.45)	9.8 (2.66)

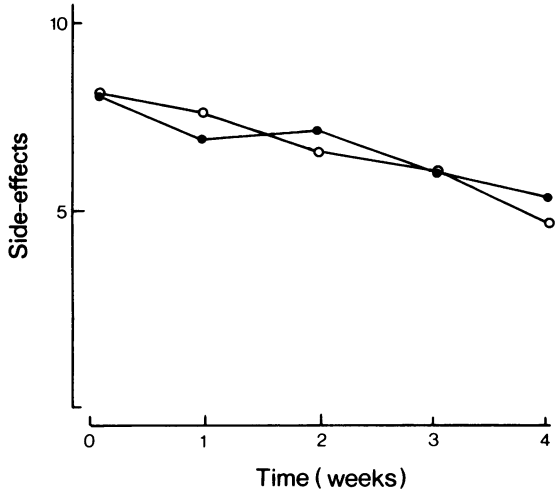

Figure 2 Course of side-effects during treatment with mianserin 60 mg, single night-time dose (●) or divided dose regimen (○).

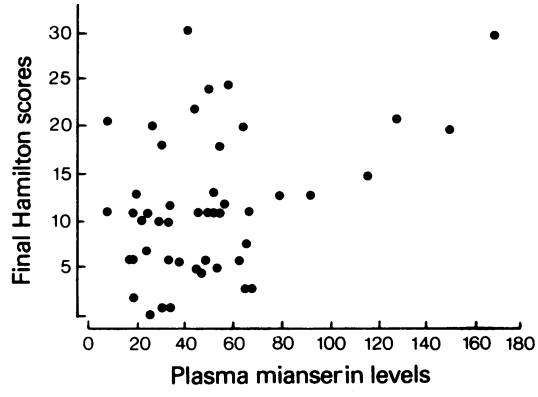

Figure 3 Relationship between plasma mianserin levels and clinical response measured by the final HRS score.

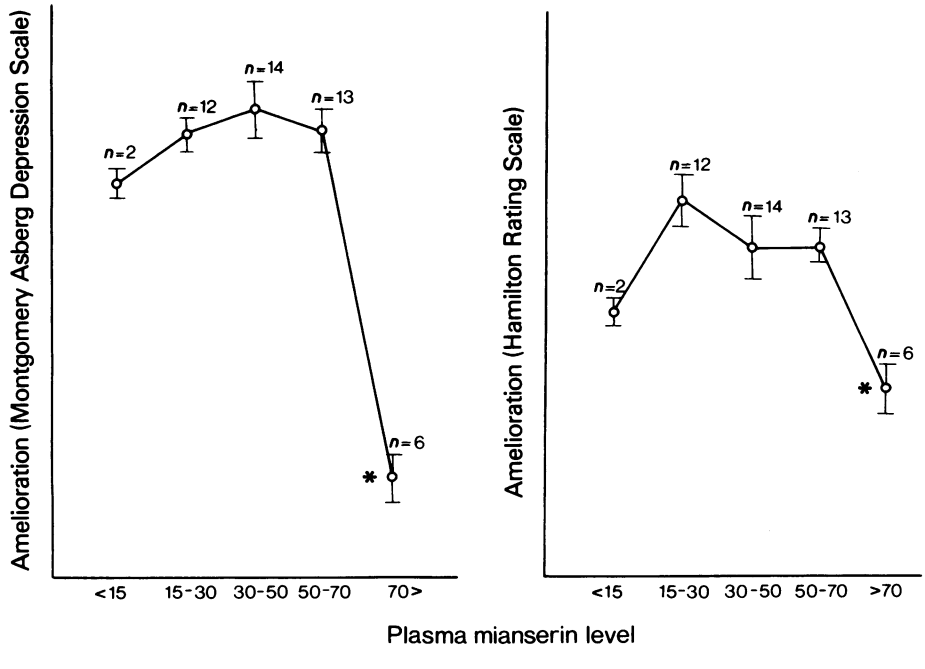

Figure 4 Relationship between plasma mianserin levels and clinical response measured using the HRS and MADS amelioration. $^{**}P < 0.005$; $^{*}P < 0.02$.

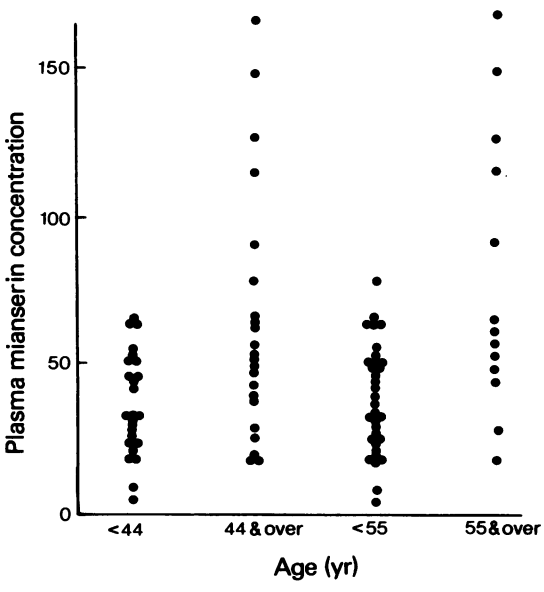

Figure 5 Variability of mianserin plasma levels with age.

weight ($r = -0.05$). The relationship between plasma level and age is interesting. Simple linear correlation ($r = 0.29$, $P<0.05$) demonstrates a significant relationship. Plasma levels of patients above and below the median age (44 yr) were compared and there was a highly significant ($F = 5.5$, $P<0.001$) increased variability in the older group.

Braithwaite *et al.* (1978) found a significant increased variability of plasma levels of nortriptyline and amitriptyline above and below the age of 55 yr, the approximate mean age for hospital admission for depression. We compared the patients in our group above and below 55 yr and found an increased and highly significant variability in patients of 55 yr and over ($F = 7.07$, $P<0.001$) (Figure 5).

Discussion

The close similarity between the clinical response measured using the HRS, BSRI and MADS for the 60-mg divided dose group and the 60-mg single night-time dose group, shows that the single night-time dose is equally effective in both out-patients and in-patients. The advantages of a single night-time dose in terms of clinical simplicity and better compliance are discussed by Braithwaite *et al.* (1974). Our study confirms the apparent lack of reported side-effects demonstrated by Coppen *et al.* (1976), with maximum side-effects occurring before treatment started and a steady decline through treatment. This lends further support to the idea that 'side-effects' relate more closely to depressive symptomatology than drug-effects. The lack of any difference in side-effects in both treatment groups and the absence of a relationship between side-effects and plasma levels is in contrast to the findings with nortriptyline (Åsberg *et al.* 1971). This provides further evidence of the relative lack of side-effects from mianserin. The small number of drop-outs in our study provides further support for the view that mianserin is generally well tolerated. The demonstration of a relationship between plasma level of mianserin and clinical response is of considerable interest. The significant negative correlation of levels and clinical response on the MADS is largely accounted for by the poorer response observed in the high levellers. The demonstration of the upper end of a range for maximum therapeutic response at about 70 μg/l, is highly significant.

The patients with the two lowest levels appear to have a poorer response than those with intermediate levels but some caution is needed in interpreting this finding in a small group of patients with low levels. This study suggests, however, that there is a range of plasma levels for optimum therapeutic response for mianserin as has been shown for nortriptyline by Åsberg *et al.* (1971), Kragh-Sørensen *et al.* (1973), Ziegler *et al.* (1976) and Montgomery, Braithwaite & Crammer (1977). The poor response of the high level group is similar to that reported by Kragh-Sørensen *et al.* (1973) and Montgomery *et al.* (1978) for nortriptyline, and indicates that high levels of mianserin may inhibit spontanous recovery. This suggests there may be a reversal of action at the synapse with high levels of mianserin. Further supporting evidence is available from retrospective analysis of the subsequent outcome on these six high levellers. One stopped taking the drug at 4 weeks and responded in 2 weeks. The other five remained depressed at 6 weeks and had their drug stopped before alternative treatment. Four out of these five responded within 1 week and the fifth did not. Curvilinear relationships are difficult to demonstrate and depend on patients with faster or slower clearance of the antidepressant. The earlier study of Coppen *et al.* (1976) was smaller, with only 17 patients on mianserin, and was therefore unlikely to produce sufficient patients outside the range to demonstrate the relationship. The increased variability with age which we have demonstrated for the first time with mianserin is in line with that shown for nortriptyline and for amitriptyline by our group (Braithwaite *et al.*, 1978). The correlation of plasma levels with age and the increased variability with age suggests that a lower dose may be more appropriate for the older group.

The presence of a therapeutic window of plasma levels of mianserin for optimum response is indicated in this study, with a highly significant clinical disadvantage associated with high levels. The fact that we demonstrated the relationship with high levels indicates that the dose of 60 mg daily may be higher than necessary.

We could find no clinical advantage for the divided dose regimen or disadvantage for the single night-time dosage in terms of therapeutic outcome or side-effects. We recommend the single night-time dosage of mianserin in the treatment of depression.

We thank Organon Laboratories Limited, for arranging matching tablets and the plasma level mianserin determinations; the medical and nursing staff in Preston Hall Hospital for their help and cooperation; Mrs Hughes for secretarial assistance; and John Pearson for his courtesy and help.

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