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Mianserin Hydrochloride: A Novel Antidepressant

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Summary. The antidepressant activities of mianserin hydrochloride were investigated and compared with those of amitriptyline. The therapeutic efficacy of the two drugs appeared similar, but the incidence of side-effects was significantly higher with amitriptyline. Plasma levels of mianserin were determined during the trial and were not related to the therapeutic activity of the drug.

Introduction

We report here an investigation of the antidepressant properties of mianserin hydrochloride,* a piperazino-azepine compound. Although classical animal pharmacological tests failed to predict any antidepressant activity for the compound, it was found that mianserin produces changes in the human electroencephalogram similar to those produced by the tricyclic antidepressants (Itil, 1973).

The evaluation of any antidepressant therapy requires the assessment not only of the benefits of the compound as demonstrated in a controlled trial but also of the unwanted or side-effects. A further need in the evaluation of a new drug is the necessity to measure the concentration of the drug in the plasma of the patients. Apart from this being a good indication of whether the patient is receiving the prescribed medication, it is also recognized that patients metabolize drugs at different rates. This produces varying plasma concentrations and presumably different concentrations at their site of action. This has been well documented with tricyclic antidepressant drugs, such as amitriptyline (Braithwaite *et al*, 1972) and nortriptyline (Sjöqvist, 1971). The varying response to a standardized dose of a drug has led to many investigations of the relationship of the steady-state plasma concentrations to the therapeutic effect and side-effects. For example, it has been claimed that, on a standard dose of nortriptyline, patients with excessively high and low plasma steady-state concentrations fail to respond satisfactorily to treatment (Kragh-Sørensen, 1973. It has been reported that patients with higher steady-state plasma concentrations of amitriptyline respond better than those with a lower plasma concentration of the drug (Braithwaite *et al*, 1972). The serial measurement of plasma concentrations of a drug should show (a) if a steady state is achieved, (b) the range of variation from patient to patient, (c) the relationship between plasma concentration of the drug, therapeutic outcome and side-effects.

During the present trial and mianserin, adrenergic and cholinergic interactions of the compound were investigated. These will be described in detail in a further report, but their relevance to the clinical results will be discussed here.

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Patients and Methods

A group of 39 in-patients suffering from primary depressive illness were studied. None of the patients had a past history of mania. The patients were given either mianserin (20 mg thrice daily) or amitriptyline (150 mg at night). They were told that they were being given antidepressant medication, but were not told which antidepressant they were to receive.

The patients were assessed for severity of depression by the first sixteen items of the Hamilton Rating Scale (HRS) (Hamilton, 1960) by assessors who were unaware of the patient's medication. Only patients with a HRS of 16 or more were included in the trial. The majority of ratings were performed by two assessors who showed a high concordance in their ratings. The patients were classified into endogenous

and reactive depression by a system based on the Newcastle Rating Scale (Gurney *et al*, 1972).

The trial was designed to last six weeks. After an initial assessment of one week or more on placebo tablets, patients were allocated randomly to receive either mianserin or amitriptyline. Before commencing the trial the patient was asked to complete a standardized side-effects inventory. Subsequently, the patient was assessed by the HRS and was asked to complete the side-effects inventory at two, four and six weeks after commencing active medication. At the same time, blood samples were taken at 9 am (that is about 13 hours after the last dose of the drug), for estimation of the plasma concentration of the compound.

Determination of drug concentration in plasma

15 ml heparinized blood samples were taken after two, four and six weeks of treatment, on the same day that the patients' clinical state was assessed. The samples were withdrawn 13–13·5 h after the last drug intake, just before the early morning dose.

The blood was centrifuged for 5 minutes at 2,000 rev/min, and the plasma was transferred into separate tubes containing 50 μg of a saturated sodium citrate solution. Awaiting despatch to Oss for analysis, the samples were stored at −15 °C.

Mianserin plasma levels were determined by mass fragmentography (Hammar *et al*, 1968) using deuteriated mianserin as internal standard and a novel high pressure liquid chromatographic (HPLC) clean-up procedure (de Ridder, in press).

For 1 ml samples, the lower limit of detection for reliable measurements is 1 ng. At this level, the assay precision was determined to be 6–7 per cent and the accuracy better than 10 per cent, both measured in a ten-fold experiment.

The samples were randomly analysed, without any knowledge of patients clinical state. Depending on the amount of plasma available, samples were analysed two to four times. The deviations of separate measurements were within the assay specifications.

Results

Therapeutic effect of mianserin

Thirty-nine patients completed the trial. The details of the patients are in Table I, and the results are shown in Table II, and Fig 1. It will be seen that the improvement in the two treatment groups is remarkably similar and that there was no significant difference between them. Reactive and endogenous patients responded similarly to mianserin.

Side-effects of mianserin

At two, four and six weeks a corrected side-effects score was calculated by subtracting the

Table I

Details of patients treated by mianserin and amitriptyline

Medication	N	Sex		Age (years)		Baseline HRS	
		M	F	Mean	SE	Mean	SE
Mianserin HCl ..	17	2	15	48·5	3·9	24·2	1·8
Amitriptyline ..	22	5	17	61·6	2·0	25·4	1·3

Table II

Results of treatment (HRS percentage improvement at 6 weeks)

Medication	Endogenous			Reactive			All patients		
	N	Mean	SE	N	Mean	SE	N	Mean	SE
Mianserin	8	62·6	10·1	9	61·0	12·1	17	61·8	7·7
Amitriptyline ..	19	57·3	9·4	3	77·0	6·1	22	60·0	8·3

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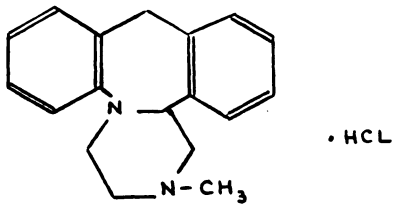

FIG 1.—Chemical structure of mianserin hydrochloride.

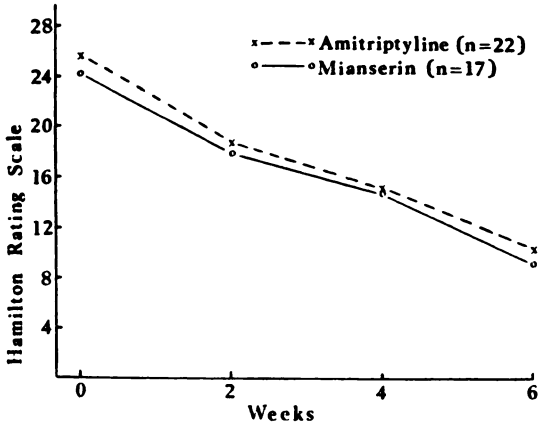

FIG 2.—Mean Hamilton depression rating scores during treatment with mianserin and amitriptyline.

baseline score (while on placebo) from the subsequent score. An increase in the score is therefore reflected in a positive corrected side-effects score.

The results are summarized in Table III. A remarkable feature is that the side-effects in the mianserin group decreased, whereas the amitriptyline group showed an increase. This difference between the two groups was significant at two, four and six weeks.

Plasma concentrations of mianserin, therapeutic outcome and side-effects

The average concentration of mianserin on each of the three occasions for each patient was calculated. The means of this average when calculated for the group as a whole, was 36·2 ng/ml (range 18·3 to 72·7 ng/ml). The correlation between two week and six week plasma concentration was highly significant ($r = 0·87$, $P < 0·01$); the correlation between four week and six week plasma concentration was even higher ($r = 0·97$, $P < 0·01$).

There appeared to be no relationship between the plasma concentration of mianserin and therapeutic outcome. Therapeutic effect was expressed: (a) as percentage improvement over baseline HRS scores of the six week rating; (b) as the 'raw' six week score on the HRS; (c) as the reduction (amelioration score) from baseline HRS to six week HRS. Using each variate, there was no correlation (calculated as either product moment or as a rank correlation), between the average plasma level for each patient and the therapeutic outcome. Similar calculations were made for the two and four weeks' HRS. Correlations between plasma level and corrected side-effects scores were also calculated at the two, four and six weeks' period and were found not to be significant.

DISCUSSION

The effects of mianserin and amitriptyline (in doses of 150 mg daily, an established antidepressant), were remarkably similar in the two treatment groups, which consisted of patients who had failed to respond to one week's

TABLE III
Side-effects of Mianserin and Amitriptyline

Medication	Corrected side-effects score					
	At 2 weeks		At 4 weeks		At 6 weeks	
	Mean	SE	Mean	SE	Mean	SE
Mianserin	−2·88	2·2	−3·93	2·6	−6·39*	1·9
Amitriptyline	2·80	1·7	3·00	1·8	2·38	1·7

* Significantly different from baseline ($P < 0·01$).
Mianserin vs amitriptyline: At 2 weeks 't' = 2·07; $P < 0·05$.
At 4 weeks 't' = 2·20; $P < 0·05$.
At 6 weeks 't' = 3·40; $P < 0·01$.

placebo treatment. Mianserin appeared to be equally effective in treating patients classified as either reactive or endogenous. The number of reactive amitriptyline patients was too small to be significant. However, there was a striking difference in the corrected side-effects between mianserin and amitriptyline. The side-effects of patients receiving placebo consist of the symptoms of the illness—such as a decrease in salivary secretion (Palmai *et al*, 1967)—together with the psychological effects induced by taking a tablet. Mianserin decreases the reported side-effects, which may indicate not only an absence of significant side-effects but also an improvement in those symptoms of the illness which themselves are side-effects. In this respect mianserin was clearly superior to amitriptyline. In another paper, we report the effects of mianserin and amitriptyline in patients on the tyramine pressor test, salivary flow and other tests of adrenergic interaction and anticholinergic activity. It was found that mianserin appears to be devoid of the effects that amitriptyline has on these tests (Ghose *et al*, 1975).

Mianserin produces constant plasma levels in the individual patients after two, four and six weeks of treatment. Although the highest plasma concentration was four times the lowest, this did not affect the therapeutic outcome or side-effects of the drug.

The mode of action of mianserin is obscure, but in the dose we used the drug does not influence the reuptake of amines (as do the tricyclics), nor is it a monoamine oxidase inhibitor, as it did not alter the tyramine pressor response. The apparent lack of effect on amines is difficult to reconcile with the biogenic amine theory of affective disorders. It may well be that the mode of action of the drug will throw fresh light on the chemical pathology of affective disorders.

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