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ELECTROENCEPHALOGRAM STUDY OF MIANSERIN IN DEPRESSED PATIENTS

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1 Electroencephalogram (EEG) recordings and blood level assessments were included in a clinical comparison of the effects of mianserin (GB-94), imipramine and placebo in depressed, hospitalized patients during a 3-week observation period.

2 Temporal changes in behavioural ratings were observed, but these failed to be distinguished among the active drugs and placebo. EEG measures also showed temporal changes, but these also failed to distinguish among the drug conditions, except at 2 h after administration of the first dose.

3 Plasma levels of mianserin were obtained with EEG recordings in a temporal relationship to the behavioural assessments. There were no correlations between the changes in EEG variables and plasma levels of mianserin, or between EEG and behavioural variables, except on acute administration. The lack of discrimination for the EEG variables may be related to the quality of the EEG recordings and the poor control of the temporal relationships of behavioural assessments to EEG recording and drug dosing.

Introduction

Following the demonstration that the EEG profile of mianserin was similar to that of amitriptyline (Itil *et al.*, 1972), a finding that seemed initially to be inconsistent with the available pharmacological information (Fell *et al.*, 1973), we carried out studies to define mianserin's profile in volunteers, using methods established in our laboratory (Fink, 1975; Fink *et al.*, 1975; Fink & Irwin, 1975). Our investigations supported the earlier finding: mianserin, at doses of 5, 10 and 15 mg, produced a systematic dose-related pattern of EEG change which was similar to that previously established for amitriptyline and imipramine.

When it became possible to estimate the plasma levels of mianserin, we carried out a pharmacodynamic study (Fink & Irwin, 1976; Fink *et al.*, 1978. Four normal adult male volunteers came to the laboratory on two occasions at least 10 d apart. On each occasion, after a 20-min EEG recording, the subjects received mianserin 15 mg orally. Blood samples and EEG recordings were repeated at 1, 2, 3, 5, 7 and 24 h after drug ingestion. This study showed the EEG profile to be an increase in frequencies below 6 Hz and above 18 Hz and a decrease in 7.5–15 Hz activity. The EEG changes were accompanied by changes in measures of vigilance, plasma drug levels, and critical flicker–fusion frequency (CFF). Peak drug levels and EEG effects occurred between the second and third hours. The amount of slow wave activity correlated directly with the drug levels, whereas the amount of alpha activity correlated inversely. CFF and self-ratings of vigilance also correlated inversely with the drug levels. The plasma (beta-phase) half-life of mianserin estimated from these data ranged from 7.7–19.2 hours. As the EEG changes and plasma levels of mianserin followed a similar time course, we inferred that mianserin is a drug possessing high effective penetrance to the brain.

We next compared the activity of another tetracyclic compound, GC-46, with that of mianserin, imipramine and placebo (Fink & Irwin, unpublished). In the dose-finding phase, we observed systematic EEG and behavioural effects of single doses of GC-46 at 10 and 15 mg. For the systematic study, we compared a single dose of GC-46 15 mg with mianserin 10 mg and imipramine 30 mg. The study was carried out using eleven normal male volunteers who came to the laboratory at weekly intervals for four consecutive 3-h sessions. Drugs and placebo were administered in a Latin-square design in double-blind conditions. Distinctive drug–placebo differences were defined for mianserin and GC-46, but not for imipramine. The profile for mianserin was the same as in the earlier study; that of GC-46 was similar to that of mianserin, but with a more rapid time of onset, a smaller decrease in total EEG power, an

increase in 8–9 Hz activity, and a decrease in frequencies above 17 Hz.

In 1975, a clinical assessment of mianserin, imipramine and placebo in depressed patients was begun at Mercy Hospital in New York. The study was carried out double-blind, with random assignment of patients to treatments. Initial doses were one or two capsules, three times per day. Capsules contained mianserin 10 mg, imipramine 25 mg, or lactose. Modifications in dosage were left to the physician's discretion during 3 weeks' treatment. Standard ward therapies continued concomitantly, and all patients received flurazepam hydrochloride (Dalmane) 30 mg at bed-time. In conjunction with the clinical assessments, we asked that EEG records and blood samples be taken at specified times to investigate whether the EEG profile of mianserin in these patients replicated our observations in normal volunteers; whether the relationships between EEG, plasma levels and behaviour observed in our volunteer study were replicated; and whether EEG measures and plasma levels had predictive value for therapeutic outcome in the treatment of these depressed patients.

Methods

The clinical study has been described elsewhere (Perry *et al.*, 1978). EEG recordings of 15–20 min were scheduled before the first treatment dose; at 1 and 2 h after the first dose; and on days 4, 7, 14 and 21—the latter four samples to be in association with the behavioural evaluations. EEGs were recorded on strip-charts, and derivations O_1–Cz and O_1–F_3 were simultaneously recorded on FM magnetic tape through a Hewlett–Packard 3960A recorder. The O_1–Cz derivation was analyzed off-line at SUNY at Stony Brook, using our IBM system. The signal was prefiltered at 1.1 and 40 Hz band pass, digitized at 320 samples per second, and reduced by primary wave baseline cross analysis using established programmes (Fink, 1974). Epochs were 20 s long. Artefact rejection was accomplished by a technician who inspected the records without knowledge of the drug given. Quality of the recordings was scored on a scale of 0 to 6 (0 satisfactory, 2 mildly poor, 4 moderately poor, 6 unsatisfactory), using the number of artefact-free epochs, comments on the record, and technical difficulties as the criteria. EEG data for each session included means ± s.d. of the following variables: average epoch amplitude, amplitude deviation, average epoch frequency, frequency deviation; percentage time in primary wave frequency bands with upper limits of 3.5, 4.5, 6.0, 7.5, 9, 11, 13, 15, 18, 21, 24, 27, 30, 33, 40, and above 40 Hz; and Hjorth measures of activity, mobility and complexity (Hjorth, 1970).

Blood samples for mianserin assay were taken at the time of each EEG recording. Plasma was immediately extracted and frozen. Mianserin concentrations were determined by chemists at Organon International BV, Holland, using a mass fragmentographic method (de Ridder *et al.*, 1977).

At the end of the study, EEG means, plasma levels of mianserin, and the data and factors of the behavioural assessments (Hamilton Rating Scale (HRS) for depression, Clinical Global Impression (CGI) scale) were used in univariate and bivariate statistical analyses.

Results

Of 54 patients (8 male, 46 female; age range 18–70 yr) in the study, 19 received mianserin 30–60 mg daily, 16 imipramine 75–225 mg daily and 19 placebo.

EEG

Of 302 EEG recordings, 294 were recorded on tape in a manner suitable for computer processing. Of these, 199 were associated with concurrent behavioural assessments. Average EEG amplitudes ranged from 7.5–82.5 μV.

There were diverse problems in the EEG recordings which made analysis difficult, particularly the comparisons with behavioural ratings. Some EEG recordings were incomplete, and some did not have corresponding behavioural assessments. Of 199 paired EEG and behavioural assessments, 79 did not occur on the same day, and 76 of the EEGs had a quality rating worse than 2 (mildly poor). The relationship between the time of recording and the medication schedule could not be fixed; therefore, the interval between dosing and EEG recording was variable. Only 24 of the 54 patients have complete data up to day 21.

Analyses were carried out on the total data set, and on a subset selected on the basis of the quality of the EEG records. Analyses used: EEG means; differences in EEG means from the day before the first dose; and differences in standard score form ((mean − baseline mean)/baseline s.d.) following the method of Shapiro & Glasser (1974). For each variable in each data set, the mean value, s.d., and number of subjects in the mean were generated for each drug for each day of assessment. Mean values were plotted. Separate analyses of variance were carried out for each day, along with paired drug comparisons using Scheffé's method (Winer, 1971).

Acute dose effects EEG means at 1 and 2 h after the first dose were transformed to Z scores. The initial dose of mianserin was 10 or 20 mg, and of imipramine 25 or 50 mg. Analyses of variance and Scheffé comparisons of the second hour Z scores showed a systematic EEG profile for mianserin, but no

difference between the effects of placebo and imipramine. Mianserin increased EEG activity below 6 Hz; decreased average frequency relative to both placebo and imipramine; decreased 11–18 Hz activity relative to placebo; increased amplitude variability; and decreased activity above 18 Hz relative to imipramine (Table 1, Figure 1).

Chronic dose effect EEG data were combined and reduced to means of eleven variables for each session: average epoch amplitude, average epoch frequency, complexity, and percentage time in frequency bands to 24 Hz in 1.5–6 Hz bands. Data were then grouped by day using the date of measurement nearest to the design days (0, 4, 7, 14 and 21). Analyses of variance and Scheffé comparisons were carried out. The only consistent change was an increase in 4.5–7.5 Hz activity with mianserin relative to placebo on day 4. No other EEG difference between treatments was found in the total data set, and this was corroborated in the subset of better quality records.

Behavioural assessments

The behavioural data exhibited changes in time, but not differences due to drugs, for a number of the variables including the CGI scale, the HRS factors for anxiety/somatization, cognitive disturbance, diurnal variation and retardation, and the HRS total score. These scores reflect the improvement in symptoms in all patients during the study, irrespective of the drug administered.

More side-effects were observed with mianserin than with imipramine or placebo on day 4. No other behavioural difference between the treatments was observed on this or later days in the study (Perry *et al.*, 1978).

Plasma levels of mianserin

Ninety-eight blood samples were available from 15 of the patients who received mianserin. Mean plasma levels at one and 2 hours after the first dose were 8.2 and 16.9 μg/l. Mean plasma levels on days 4, 7, 14 and 21 were 26.0, 35.5, 42.7 and 45.7 μg/l, respectively. For individual data, see Perry *et al.* (1978).

Mianserin levels were plotted for each patient, together with corresponding measures of EEG change (percentage time 4.5–7.5 Hz). To assess whether plasma mianserin contributed to EEG changes, product–moment correlation coefficients were calculated. When the good quality EEGs alone are used, a direct relationship was observed between plasma mianserin concentration and 4.5–6 Hz standard scores at 2 h after the first dose. No significant relationships to EEG were found on later days (Figure 2).

Table 1 Mean ± s.d. of EEG Z scores

Time	*Day 1 (2 h after first dose)*					
Drug	*Mianserin*		*Placebo*		*Imipramine*	
n	*13*		*14*		*14*	
EEG variable	*Mean*	*s.d.*	*Mean*	*s.d.*	*Mean*	*s.d.*
Upper band limits:						
3.5 Hz	2.8*†	4.8	−0.1	1.0	−0.1	1.2
4.5 Hz	1.3*†	1.8	−0.1	0.8	−0.2	0.9
6.0 Hz	2.1**‡	2.4	−0.1	1.0	−0.0	0.9
7.5 Hz	1.0	3.6	−0.1	0.9	−0.2	0.7
9 Hz	−0.3	3.2	0.0	1.0	−0.3	1.0
11 Hz	−0.1	2.8	0.2	1.6	−0.3	1.0
13 Hz	−1.3*	1.8	0.5	1.6	−0.3	0.9
15 Hz	−1.3*	2.4	0.6	1.3	−0.1	0.7
18 Hz	−1.2*	2.6	0.6	0.9	0.3	0.5
21 Hz	−0.9†	2.0	0.5	1.2	0.9	1.1
2.4 Hz	−0.8†	2.2	0.4	1.4	1.0	1.2
27 Hz	−0.5†	2.0	0.1	1.1	1.1	1.2
30 Hz	−0.4	1.9	−0.1	1.1	0.8	1.0
33 Hz	−0.5†	1.7	−0.1	0.8	0.7	0.9
40 Hz	−0.5†	2.0	−0.1	1.1	0.9	0.8
>40 Hz	−0.7	2.2	−0.3	1.2	0.8	1.0
Activity	2.2	3.8	0.5	2.6	0.1	1.8
Amplitude average	1.6	3.7	0.2	2.4	−0.2	1.7
Amplitude deviation	1.7†	2.1	0.4	1.5	0.1	0.8
Frequency average	−3.0**‡	3.9	0.3	1.7	1.2	1.3
Complexity	−1.7	3.8	−0.5	1.5	0.4	1.6

Anova and Scheffé paired comparisons: with placebo *$P<0.05$; **$P<0.01$; with imipramine †$P<0.05$; ‡$P<0.01$.

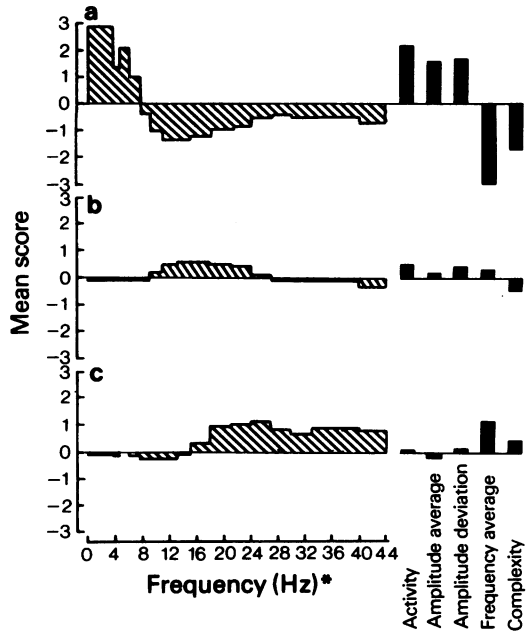

Figure 1 Mean EEG changes from baseline at 2 h after the first dose. a, Mianserin ($n=13$); b, placebo ($n=14$); c, imipramine ($n=14$). *Primary wave baseline cross.

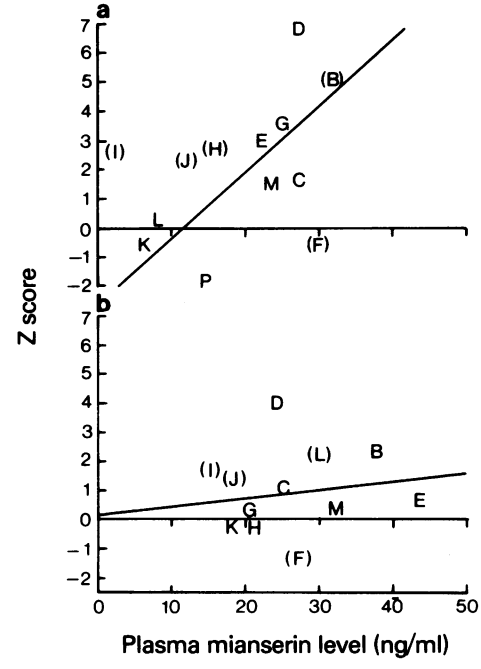

Figure 2 Linear regression of EEG (4.5–6.0 H_2) on plasma levels of mianserin. a, Day 1, $Y=0.23X-2.6$, $r=0.73$, $P\leqslant 0.05$; b, day 4, $Y=0.03X-0.1$, $r=0.22$, NS. Parenthesized patients not included in regression because EEG records of poor quality.

Discussion

In the patient sample, we found that acute EEG changes after mianserin parallelled changes found in volunteers 2 h after dosing. There were also characteristic EEG effects on day 4, but not in later measurements. As the behavioural changes showed improvement in time regardless of drug, we were unable to identify a behavioural–EEG association.

In part, the lack of association between EEG variables and other measures at other times may be related to the problems in obtaining reliable EEG data. We failed to control the time of recording, particularly in relation to the times of dosing and behaviour assessment. Many of the EEG records were recorded poorly, and the amount of data which we rejected was so great that we probably had unrepresentative estimates of the EEG means.

The failure to find EEG differentiations among the drugs may also reflect the failure to develop distinctive behavioural effects. It has become an axiom of EEG studies that the correlations between behavioural and EEG variables after psychoactive drugs remain strong whenever distinctive behavioural effects are recorded. In the present study, the patients exhibited behavioural improvement independent of specific pharmacological effects, suggesting that environmental factors were more important than cerebral pharmacological effects.

Other scientists have attempted clinical and EEG correlations, with varying results. Some have found correlations between behavioural changes and quantitative EEG measures (Itil, 1974; Robinson, 1974; Dasberg *et al.*, 1974), whereas other have failed to make these associations (Serafetinides *et al.*, 1972; Hollister & Barthel, 1959). Perhaps the difficulty is related to the sensitivity of the quantitative EEG. If recordings are not directly related in time to behavioural assessments, or samples are not carefully collected with attention to the degree of alertness, time of day, and other variables that affect the EEG, then the association of EEG with behavioural variables may be obscured. Further, the quantitative EEG reflects brain function in short periods of time (minutes), whereas behavioural assessments in clinical studies reflect large segments of time (hours or days).

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