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MIANSERIN, MAPROTILINE AND THE ELECTROENCEPHALOGRAM

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1 EEGs were recorded from patients with depressive illness before and after four weeks of treatment with mianserin, maprotiline or placebo.

2 Visual analysis of the records showed a small but statistically significant increase in frequency of beta activity in the mianserin group.

3 One subject taking maprotiline developed spike and wave discharges but had no convulsive seizures.

4 The findings do not support those of previous studies. It seems that changes seen in the EEG early after treatment are not sustained for four weeks.

Introduction

There have been many studies of the effects of drugs on the electroencephalogram (EEG) and in recent years several have involved computer analysis of the data. These automatic methods can be misleading as they miss transient abnormalities, and analyse artefact as well as cerebral activity. They may fail to detect trends and physiologically determined features of the EEG are not recognized by signal analysis programmes. In this study a visual examination of 16 or 20 channel EEGs was undertaken in patients with primary depressive illness who were treated with mianserin, maprotiline or placebo. EEGs were taken before and after one month of treatment. The patients were randomly selected from a larger sample in whom the clinical effectiveness of the drugs and cardiac changes related to therapy were assessed (Edwards & Goldie, 1983, this issue).

This is the first asystematic study of drug effects after four weeks of treatment, and plasma levels of the drugs at the time of the EEG recording are reported. Visual analysis was carried out with the aid of a transcription sheet by one of us (E.M.S.) who was blind to the patient, treatment and timing of the recording. The results support a trend expressed in the literature, namely the longer the duration of treatment, the less the effects of these drugs on the EEG.

Method

EEGs were recorded from 31 patients before treatment and again after four weeks treatment during the course of a placebo controlled trial of mianserin and maprotiline in the treatment of primary depressive illness. When the code was broken at the end of the study it was found that nine patients, five of whom were female, had received mianserin, nine (five female) maprotiline, and 13 (eight female) placebo. The imbalance was due to patients being dropped from the trial or being unable to attend for their EEG initially or after four weeks of treatment. The age range of the patients was 18 to 60 years. The mean ages, sex and plasma drug levels after four weeks treatment are given in Table 1.

Before commencing the trial all patients gave their informed consent and the trial had the approval of the Hospital Ethical Committee. There was an initial washout period of six to eight days except in three patients, one in the maprotiline group and two in the placebo group, where the washout periods were five, five and four days, respectively. None of the patients had undergone electroconvulsive therapy in the preceding six months. Treatment was with capsules containing either 30 mg mianserin, 75 mg maprotiline or placebo; all medication being taken at night. By 28 days all patients in the mianserin group were taking 90 mg at night while in the maprotiline group all but two patients were on 225 mg at night; these two were taking 150 mg at night. No other medication was allowed except 5 mg of nitrazepam as a hypnotic at night when absolutely necessary. Two patients in the active treatment groups and five in the placebo group received nitrazepam but only three of these (one on maprotiline and two on placebo) had received the drug during the 10 day period leading up to the second EEG.

The second EEG was recorded 12–18 h after the previous dose of drug and blood was taken within 1 h of this recording to assess drug levels. The plasma was separated and stored at −20°C until estimated by gas-liquid chromatography in the case of mianserin and a double radio-isotope derivative technique in the case of maprotiline (Riess, 1974). Silver–silver chloride electrodes were placed

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Table 1 Age and sex of patients in each treatment group with plasma level of drug

Mianserin			*Maprotiline*			*Placebo*	
Sex	*Age*	*Plasma level (ng/ml)*	*Sex*	*Age*	*Plasma level (ng/ml)*	*Sex*	*Age*
F	55	103	F	60	328	F	24
F	34	31	M	44	236	M	50
M	25	30	M	60	329	F	52
F	36	60	F	18	205	F	38
F	45	25	F	38	99	F	50
F	33	31	M	37	230	F	22
M	52	121	F	55	305	M	36
M	56	99	F	19	294	M	34
F	42	—	M	52	158	M	25
						M	54
						F	46
						F	64
						F	49
6F	42±11	63±40	5F	43±16	243±80	8F	42±13
3M			4M			5M	

according to the international 10–20 system and impedances checked to be 5 kΩ or less. Recordings were taken using standard bipolar montages with amplifier time constants at 0.3 s and a high frequency cut at 70 Hz or above. The recording included periods with the eyes open and closed, 3 min of hyperventilation and photic stimulation.

Analysis was visual by one observer using the London Hospital EEG standard transcription sheet (Scott & Prior, 1981). The records were coded before analysis so that the observer was blind to the patient and drug and whether the record had been taken before or after treatment. After analysis of all the records the code was broken and the results collated with special reference to clinical abnormalities in the records, changes in rhythms or other features which may have been related to treatment.

The London Hospital transcription sheet calls for examination of 16 features in the EEG including alpha rhythm, spikes and the effect of hyperventilation. The user identifies the presence of each feature together with its characteristics, for example amplitude of alpha rhythm, symmetry and responsiveness. By transcription of repeat records one can reliably identify changes which may be quite subtle.

Results

The EEG in patients with primary depressive illness is normal and therefore not used clinically unless neurological disease enters into the differential diagnosis. All patients in our study were free from neurological illness and have remained so in the follow-up period.

EEG frequency

In view of the reported effects of mianserin and maprotiline on the basic EEG rhythms, the records were analysed with respect to the frequency of the alpha and beta bandwidths. The presence or absence of theta activity unrelated to drowsiness was also noted. There were no significant differences in the frequencies of the drug and placebo groups before treatment. Table 2 summarizes the changes in rhythms. There was no change in the alpha or theta rhythms but the mianserin group had a small increase in beta frequency from 20.5 to 22.1 Hz during treatment which was statistically significant at the 5% level (paired *t*-test).

Epileptiform activity

Records were examined for features relating to epilepsy. One 19-year-old female subject, whose initial record was normal, showed generalized polyspike and wave activity in frequent bursts lasting up to 1.5 s (Figure 1), when she was taking maprotiline. There was no focal disturbance and no photoconvulsive response. The discharges were still present but less marked four weeks later when she was no longer taking the drug. We could not follow up these changes as the patient refused to attend for further EEG recordings. She had no family or past history of epilepsy and has never had a seizure disorder.

One other subject, in the mianserin group, had some right temporal sharp waves in both records but there was no history of epilepsy and this abnormality did not change over the 28 day period.

Table 2 Mean frequency of alpha and beta activity and presence of theta waves before and during treatment with placebo, mianserin and maprotiline. Significance by paired *t*-test

		Mianserin	*Maprotiline*	*Placebo*
Subjects				
n (female)		9(6)	9(5)	13(8)
Age (years)		42±12	43±16	42±13
EEG frequency				
Alpha	Before treatment	9.3±0.9	9.3±0.9	10.1±1.1
	During treatment	9.4±1.0	9.2±0.6	10.4±1.7
		NS	NS	NS
Beta	Before treatment	22.5±2.0	19.25±2.1	21.8±3.5
	During treatment	22.1±2.2	21.25±2.1	21.0±4.7
		$P=0.05$[a]	NS	NS
Theta present	Before	3	4	3
	During	3	4	4
Plasma drug level (ng/ml)		63±40	243±80	—

[a]Paired *t*-test

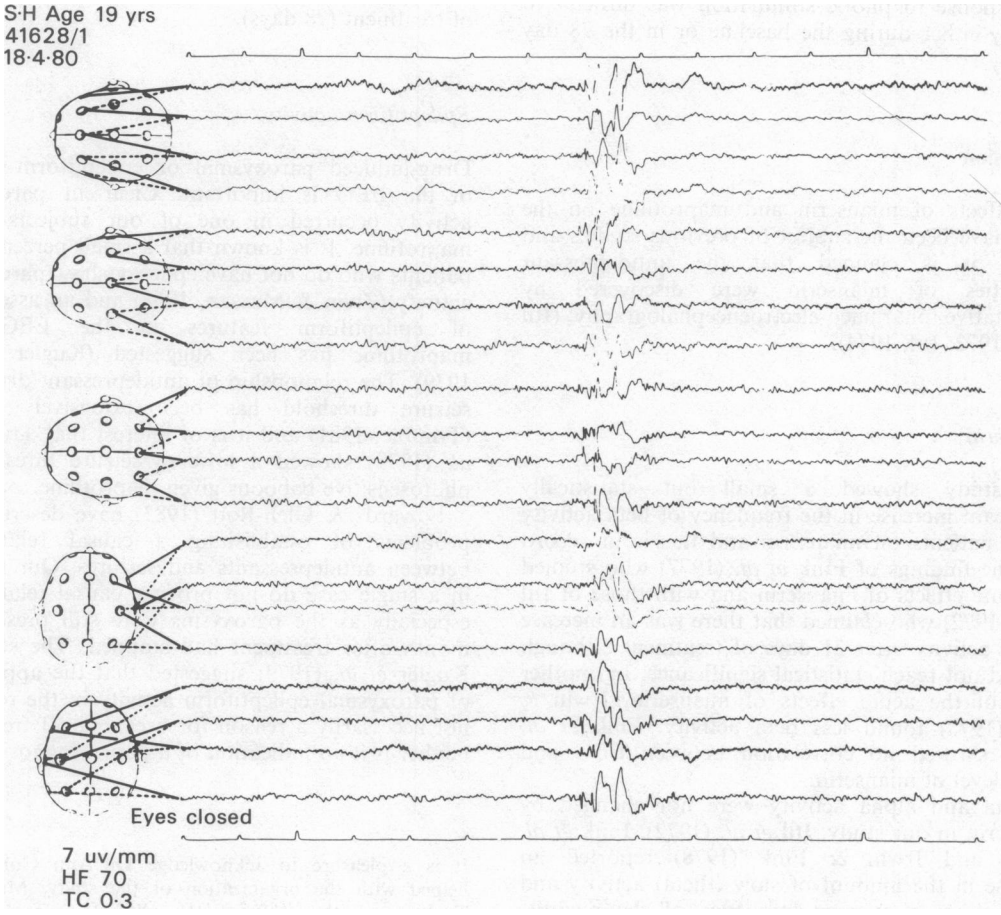

Figure 1 The EEG of a 19-year-old woman taking maprotiline shows generalized short bursts of polyspike and wave activity.

Minor changes in EEG

The records were next analysed for changes in features such as the appearance of lambda waves and development of a mu rhythm. These changes are physiological and are not important clinically but nonetheless represent changes in cerebral function.

Analysis showed an average of 1.7 changes per subject in the mianserin group, 1.8 per subject in the maprotiline group and 2.6 per subject in the placebo group. The nature of these changes was variable and no consistent pattern emerged. Comparison showed that the second record (during treatment) was the more 'normal' of the two as often as the converse. Changes due to drowsiness were not a feature. The most commonly recorded changes were in response to hyperventilation which were often a little more or a little less marked at the time of the second recording. In some patients the response to photic stimulation was difficult to identify either during the baseline or in the 28 day EEG.

Discussion

The effects of mianserin and maprotiline on the EEG have been the subject of previous studies and indeed it is claimed that the antidepressant properties of mianserin were discovered by quantitative pharmaco-electroencephalography (Itil *et al.*, 1972; Itil, 1974).

Mianserin

Our study showed a small but statistically significant increase in the frequency of beta activity in the patients on mianserin and this is in accord with the findings of Fink *et al.* (1977) who studied the acute effects of mianserin and with those of Itil *et al.* (1972) who claimed that there was an increase in fast activity after 21 days of treatment although this did not reach statistical significance. In another study of the acute effects of mianserin, Irwin & Fink (1978) found less beta activity. Fink *et al.* (1977) showed no correlation between EEG and blood level of mianserin.

Theta and alpha activity were not changed by mianserin in our study. Itil *et al.* (1972), Fink *et al.* (1977) and Irwin & Fink (1978) reported an increase in the amount of slow (theta) activity and a reduction in average frequency of the records. These investigators stated that the effects of mianserin on the EEG decrease with time. Our results suggest that by 28 days the enhancing effects of mianserin on slow activity have abated.

Maprotiline

In contrast with mianserin there have been many studies of the EEG effect of maprotiline. Some use computer processing but many were visual analyses. Several groups of workers have indicated no change in the EEG (Singh *et al.*, 1976; Bergener *et al.*, 1978; Logue *et al.*, 1979; Henderson, 1980). However, acute studies have shown an increase in the amount of slow activity with an increase or synchronization of the alpha activity and less beta activity (Jovanovic & Tan-eli, 1970; Deniker *et al.*, 1972; Jovanovic *et al.*, 1972; Mizurec *et al.*, 1973; Lemperiére *et al.*, 1975; Hanus *et al.*, 1981).

Our findings show no change in the EEG which may in part be due to the relatively long duration of treatment (28 days).

Epileptiform activity

Drug-induced paroxysmal or epileptiform activity in the EEG is important. Clear-cut paroxysmal activity occurred in one of our subjects taking maprotiline. It is known that a small percentage of patients who do not have epilepsy show paroxysmal activity (Zivin & Marsan, 1968) and an association of epileptiform features in the EEG with maprotiline has been suggested (Kugler *et al.*, 1979). The relationship of antidepressant drugs and seizure threshold has been extensively studied (Trimble, 1981) and it is of interest that Trimble *et al.* (1978) showed a lowered seizure threshold in photosensitive baboons given maprotiline.

Edwards & Glen-Bott (1983) have described the problems of establishing a causal relationship between antidepressants and seizures. Our findings in a single case do not prove a causal relationship especially as the paroxysms were still present one month after treatment had stopped. The study by Kugler *et al.* (1979) suggested that the appearance of paroxysmal epileptiform activity in the record is not necessarily a reason for breaking off treatment, neither is it an indication of a poor prognosis.

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