A CONTROLLED COMPARISON OF METHAMINODIAZEPOXIDE (CHLORDIAZEPOXIDE, "LIBRIUM") AND AMYLOBARBITONE IN THE TREATMENT OF ANXIETY IN NEUROTIC PATIENTS

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IN another paper, Jenner, Kerry and Parkin (1961) confirmed the views of earlier workers, Harris (1960) and Voelkel (1960) and others that methaminodiazepoxide is an effective agent in relieving anxiety in neurotic patients. That study was a blind controlled comparison of methaminodiazepoxide against lactose, but gave no indication of its value as compared with other drugs. The present paper is a comparison of methaminodiazepoxide (Librium, Roche) and amylobarbitone. The latter drug was felt to be one of the best known and most reliable drugs used in psychiatry for the treatment of anxiety. Raymond, Lucas, Beesley, O'Connell and Fraser-Roberts (1957) compared it very favourably with benactyzine, chlorpromazine, meprobamate, sedaltine and lactose. In that trial amylobarbitone was the only drug significantly better than lactose.

METHOD

The patients selected were the first 92 new or old cases attending the out-patient department suffering from neurotic anxiety. There was no selection for either age or sex. The nature of the trial was explained to each patient and they were asked to co-operate in finding which preparation was most helpful to them. It was decided to arrange the doses so that two capsules were to be taken three times a day throughout the trial. The dosage used was methaminodiazepoxide 20 mg. three times a day, and amylobarbitone 60 mg. (approximately 1 grain) three times a day. On the first visit the patient's condition was assessed and two weeks' supply of one type of capsule was prescribed. The second attendance was made two weeks later, when progress was recorded and two weeks' supply of the other capsules given. All the capsules used were identical in appearance. A third and last visit was made after another two weeks for a final assessment. The order in which the drugs were given was unknown to the doctor and the patient. On each visit the patient's impressions were recorded on a simple questionnaire and any other comments which the doctor felt relevant were written down. The only distinguishing feature between the capsules was their taste if they were opened—although both were bitter, methaminodiazepoxide was more bitter than amylobarbitone.

The patients were all given supportive psychotherapy in brief interviews with an emphasis on reassurance. Some of the patients had previously had group or more intensive individual psychotherapy but without material benefit. Most patients had had and were having other tranquillizers at the time of the initial interview. They were advised not to take any other

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drugs during the trial period. A few, however, were disinclined to give up nightly sedatives which they were taking. They were allowed to continue with these.

The questionnaire used to assess each patient's progress is shown in Table I. On the first visit the patient's symptoms were rated as absent, mild or severe. (The figures 0, 1 or 2 were used respectively to indicate this.) On subsequent visits the patient was questioned to indicate whether he had improved, got worse, or remained in the same condition since his last visit. (A minus sign indicated improvement and a plus sign that the symptoms had increased, the figures 0, 1 or 2 were used to indicate the degree of change.) The patient was finally asked to state his overall preference for one or the other of the preparations; this was rated as no preference, slight preference or strong preference. Table II is constructed from the answers given to this question.

TABLE I

Patient..... Dr..... Trial No.....

Age..... Sex..... M.S.W.D. Sep..... Hospital No.....

Diagnosis.....

Leading Symptoms (1) .....

(2) .....

Duration of Illness.....

Most striking features: Obsessional .....

Phobic .....

Hysterical .....

Previous or present treatment and opinion: LIBRIUM .....

BARBITURATES .....

Rating: Initial 0=absent, +1=mild, +2=severe, −1=slight opposite, −2=severe opposite. Follow-up 0=no change, −1=better, −2=much better, +1=worse, +2=much worse.

(this gives the change)

	Initial	2	3	4	5
How are you?	.....	.....	.....	.....	.....
Presenting symptom	.....	.....	.....	.....	.....
Fear (subjective)	.....	.....	.....	.....	.....
Depression	.....	.....	.....	.....	.....
Apathy	.....	.....	.....	.....	.....
Lack of concentration	.....	.....	.....	.....	.....
Irritability	.....	.....	.....	.....	.....
Sleep (rate type of disorder)	.....	.....	.....	.....	.....
Headache	.....	.....	.....	.....	.....
(note characteristic and change)	.....	.....	.....	.....	.....
Anorexia	.....	.....	.....	.....	.....
Ataxia	.....	.....	.....	.....	.....
Other symptoms (specify)	.....	.....	.....	.....	.....
	.....	.....	.....	.....	.....
	.....	.....	.....	.....	.....
	.....	.....	.....	.....	.....

Work 0=satisfactory, 1=with difficulty, 2=losing some time, 3=off work.

Working Ability	House	.....	.....	.....	.....	.....
	Job	.....	.....	.....	.....	.....

For statistical purposes χ^2 was calculated for the significance of the figures for drug preference shown in Table II. Slight preference in that Table was treated as no preference for statistical purposes. It is to be appreciated that the likely value of a drug to a patient depends upon the probability that he will have no preference. This is not taken into account when calculating the statistical significance from χ^2. In Table II a strong preference is reported by 70 per cent. of the patients. In Table III where symptoms are presented separately the number with no preference is of more relevance. In that Table χ^2 and p are presented for a whole series of related symptoms. Despite statistical objections to this the results are striking, but the difficulties of interpreting them are clinical as well as statistical.

TABLE II

The Table Shows the Numbers of Patients Expressing Strong, Slight or No Preference, for Amylobarbitone or Methaminodiazepoxide. χ^2 for the Strong Preference are as follows: Total 26, Male 13·2 and Female 12·6, all at One Degree of Freedom, are very Highly Significant. The Differences in Male and Female Responses are not Significant

Preference	No. of Patients	Male	Female
Strong preference for *Methaminodiazepoxide*	53	25	28
Slight preference for *Methaminodiazepoxide*	6	2	4
No preference	10	3	7
Slight preference for *Amylobarbitone* ..	6	3	3
Strong preference for *Amylobarbitone* ..	12	5	7
No result obtained	5	2	3
Total	92	40	52

TABLE III

The Table Shows the Number of Patients Suffering from Various Symptoms at the Beginning of the Trial, Their Preferences for One or Other of the Preparations for that Symptom, or Lack of Apparent Side-effect, and Their Statistical Evaluation. A Critical Appraisal of the Possible Interpretation is Made in the Text

Item	No. of Patients Initially Complaining of Symptom	No. Expressing Preference in Respect of the Symptoms and Side-effect for: Amylobarbitone	Methaminodiazepoxide	χ^2	p<
Drowsiness	24	20	27	1·04	0·5
Subjective fear	90	13	52	23·4	0·01
Depression	41	11	23	4·24	0·05
Apathy	28	2	15	9·94	0·01
Concentration	31	6	17	5·28	0·05
Irritability	48	9	28	9·75	0·01
Sleep:	50	9	29	10·55	0·01
Falling asleep	37	8	24	8·00	0·01
Duration of sleep ..	31	6	17	5·25	0·05
Broken sleep	27	6	8	0·29	0·70
Early waking	20	4	16	7·20	0·01
Headache:	47	9	31	12·10	0·01
Frequency of headache	—	2	17	11·82	0·01
Intensity of headache ..	—	4	17	8·05	0·01
Duration of headache ..	—	4	11	3·26	0·10
Difficulties with work ..	50	6	26	12·50	0·01
Anorexia	24	7	21	7·00	0·01
Ataxia	16	4	10	2·57	0·20
Vomiting	3	3	8	2·27	0·20

Results

The fact that more patients preferred methaminodiazepoxide to amylobarbitone is striking and this is shown in Table II where the preferences are rated as strong, slight or negligible.

As in the previous trial (Jenner *et al.*, 1961) it is difficult to assess the specificity of the drug for various symptoms. If a patient responded to the drug, he tended to show improvement in all his symptoms. It is possibly for this reason that methaminodiazepoxide is apparently preferred by more patients for every symptom. This is shown in Table III. In that Table these results are presented as numbers of patients showing a preference for amylobarbitone, or methaminodiazepoxide for each symptom. Experience with the type of patient treated suggests that patients who have a sense of well-being underestimate their symptoms and side-effects, whilst those who feel ill tend to overestimate them. Other drugs are also sometimes taken, often without the doctor knowing.

From the point of view of the treatment of out-patients it is interesting that the greatest similarity is shown in response to questions about drowsiness. It can be seen in Table III that there is little to choose between the two drugs at these doses if one is concerned about producing drowsiness. This is a particularly undesirable side-effect in drivers, machine workers, etc.

Headache was complained of by 47 patients at the first visit. Of these 44 described them as tense, dull, a feeling of tightness, or indescribable. The other 3 patients described them as throbbing. Thirty-one patients thought methaminodiazepoxide preferable for their headaches, 9 preferred amylobarbitone. Six patients felt that both drugs were equally effective and of definite value.

Eleven were not helped by either drug. Ten patients complained of headache for the first time during the course of the trial—6 whilst receiving amylobarbitone and 4 whilst receiving methaminodiazepoxide. When headache was relieved it was reported to be less frequent, less intense and of shorter duration.

The effect on sleep is assessed for sleep at night as distinct from the side-effect of drowsiness by day. Although the capsules were taken by day, patients had changes in their sleep at night. It should be remembered that some patients continued their customary night sedation (usually a barbiturate) throughout the study. It is not suggested that methaminodiazepoxide is suitable for night sedation when compared with the established drugs (e.g. barbiturates) used for this purpose. Table III shows the number of patients who would choose methaminodiazepoxide or amylobarbitone taken during the day for its effects on their sleep at night. More reported ease in falling asleep, increased duration of sleep, reduction of the number of times sleep was disturbed and loss of early waking on methaminodiazepoxide. A similar consistent improvement in all aspects of sleep was reported by patients who slept better at night on amylobarbitone given during the day.

The symptom of apathy showed that 15 patients preferred methaminodiazepoxide and only 2 amylobarbitone. It is probable that the decreased apathy whilst on methaminodiazepoxide is also reflected in improved working ability.

Severe ataxia did not appear in any patient on methaminodiazepoxide nor was it produced by amylobarbitone. In a previous study severe ataxia was found and seemed to be produced by methaminodiazepoxide. Sixteen patients reported subjective unsteadiness of gait at the first interview classified in Table III as ataxic; of these 10 were improved by methaminodiazepoxide and 4 by amylobarbitone. Our total experience with methaminodiazepoxide by now probably includes over 300 patients. Drowsiness and ataxia are the

important side-effects produced. Severe ataxia is more common in elderly patients, and its absence as a side-effect in this trial may be due to only two patients being over sixty years of age. Looking back on our previous trial we note that some of the younger patients who appeared to have ataxia also had marked hysterical features. In some, this complaint may have been suggested by the doctor discussing this in order to complete the rating scale. The fact that it occurred in two patients whilst they were receiving lactose supports this view. Previous work gave the impression that patients with conversion symptoms did less well. In Table IV an attempt is made to separate some of the patients

TABLE IV

The Numbers of Patients Whom it was felt could be Classified According to Whether They had Obsessional, Hysterical or Phobic Features as the Most Prominent Accompaniment of Their Anxiety, and Their Overall Preferences for the Two Drugs Being Tested

Prominent Features	No. Patients Showing a Preference for: Methamino-diazepoxide Strong	Methamino-diazepoxide Slight	Amylobarbitone Strong	Amylobarbitone Slight	No. with No Preference	Total
Hysterical ..	8	1	1	0	3	13
Phobic	24	4	8	3	4	43
Obsessional ..	13	0	1	0	2	16

into those showing predominantly hysterical, phobic or obsessional features. Hysterical features included aphonias, pains and globus. The phobias included claustrophobia, fear of travelling, fear of crowds, fear of being alone and other morbid fears. Obsessional features included re-checking, hand washing and other repetitive behaviour. The preferences for each drug are given under these headings. The preference for methaminodiazepoxide is marked in each type of patient. The difference in the results for phobic, hysterical and obsessional symptoms is not striking. This result does not confirm our previous impression. It does, however, show that even when the results are split in this way the overall result is the same.

Analysis of the responses in relation to the patient's age shows no significant correlation. The ages varied from 19 years to 63 years and the average age was 37 years (38 years for females and 36 years for males). Most of the patients were between the ages of 20 and 50 years.

The length of time the patient had been ill seemed to have no bearing on the drug preferred. When the sex of the patient was considered, males showed a slightly but not statistically significant, greater preference for methamino-diazepoxide than females (see Table II). This differs from the more significant results in the previous trial (Jenner *et al.*, 1961).

The present trial included 49 people who had previously received methaminodiazepoxide, of whom 31 had given a report favourable to this drug. The possibility that we had selected people who respond favourably to methaminodiazepoxide has therefore to be considered. As the results from the remaining 43 patients are equally convincing we feel that the conclusions from this trial have not been biased in this way.

One of us (J.) seems to have questioned the patients more closely in regard to vomiting and nausea. He recorded the fact that 7 patients complained

of this only while taking amylobarbitone and one patient only while taking methaminodiazepoxide. Three patients initially complained of vomiting and 2 seemed to have been helped by amylobarbitone and 1 by methaminodiazepoxide. Another one of the authors (P.) recorded one case in which nausea occurred only when the patient was taking amylobarbitone. Nausea and vomiting in neurotics taking barbiturates is also reported by Goodman and Gilman (1955).

Discussion

The results suggest that methaminodiazepoxide is likely to be superior to amylobarbitone for the symptomatic relief in a neurotic patient. It is possible that the dose of methaminodiazepoxide used in this study was too high and that of amylobarbitone too low for a fair comparison. Our impression from uncontrolled studies is that 10 mg. three times a day of methaminodiazepoxide is adequate and little is gained from higher doses. Larger doses of amylobarbitone would, however, be more effective but always at the price of increasing drowsiness. Raymond *et al.* (1957) used 100 mg. of amylobarbitone three times a day, but they do not discuss the drowsiness this produces. We feel that amylobarbitone would not be as suitable for prolonged treatment as methaminodiazepoxide, even if it were more effective in higher doses. Nevertheless, it can only be concluded from this trial that in the doses used methaminodiazepoxide is more likely to be effective than amylobarbitone.

The safety of methaminodiazepoxide is in its favour, particularly for prolonged out-patient or general practice use. Large doses have been taken without lethal effect. Hines (1960) reports a schizophrenic female aged 47 who took 1,150 mg. methaminodiazepoxide in 20 minutes, and a male patient aged 22 who took 1,600 mg. of methaminodiazepoxide in 24 hours. In neither case was gastric lavage used and no long-term physical impairment caused. In contrast barbiturates are one of the commonest suicidal agents.

One of the major limitations of this trial is the short period of two weeks spent on each drug. Both drugs are, however, fairly quickly effective, especially amylobarbitone. Their relative merits have not been tested over longer periods. Our impression of these drugs in prolonged treatment is that both lose their efficacy in some cases. It is known that barbiturates lead to habituation, but not if this occurs with methaminodiazepoxide. Prolonged trials to decide this and other matters would be difficult, and choice may have to be left to clinical experience. Most clinicians would agree that in acute attacks of anxiety, very high doses of amylobarbitone (or another barbiturate) with the patient in bed is of exceptional value. It is not to be suggested that methaminodiazepoxide in this role is in any way the equal of amylobarbitone. The results in this trial only show the relative values of the two drugs in out-patient practice with anxious patients who are attempting to lead a comparatively normal life. It must be pointed out that the results of any clinical trial are always in question until confirmed by similar studies in many centres. Further controlled studies of methaminodiazepoxide are still required and their results awaited with interest.

Summary

A controlled trial of methaminodiazepoxide 20 mg. three times a day against amylobarbitone 60 mg. three times a day has been performed in neurotic patients complaining of anxiety. The results show highly significantly that patients usually prefer methaminodiazepoxide. Other factors are also discussed.

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