ETHINAMATE AND METHYPRYLONE AS HYPNOTICS: A COMPARATIVE TRIAL

By

I. C. LODGE PATCH, M.D., M.R.C.P., D.P.M.

M. D. EILENBERG, M.B., M.R.C.P., D.P.M.

Senior Registrars

and

E. H. HARE, M.D., D.P.M.

Physician

Bethlem Royal and The Maudsley Hospitals

THE use of barbiturates in the treatment of insomnia carries a constant risk of habituation and of fatal poisoning from suicidal or accidental overdose. For these reasons, new non-barbiturate hypnotics deserve the closest attention. Ethinamate ("Valmidate") and methyprylone ("Noludar") are two such drugs. No trial comparing the hypnotic efficacy of ethinamate with a barbiturate has yet been reported, though Gruber *et al.* (1954) found the day-time sedative effect of 500 mg. ethinamate to be less (in duration of action) than 100 mg. of quinalbarbitone sodium. Methyprylone has been compared with barbiturate by Stewart (1956) who found 200 mg. equivalent to 100 mg. of amylo- or butobarbitone, by Lasagna (1956) who found 250 mg. equivalent to 100 mg. of pento- or quinal-barbitone, and by Thomson (1958) who found 400 mg. equivalent to 100 mg. of quinalbarbitone.

The present paper reports a clinical trial designed to compare the hypnotic efficacy of ethinamate and methyprylone against each other and against butobarbitone and a placebo. The method used has yielded consistent and therefore probably reliable results in previous trials (Hare, 1955; Salter *et al.*, 1959).

METHOD

Subjects. The subjects were 47 patients suffering from neurotic or recent psychotic illness, all in good physical health and all complaining of some degree of insomnia. Seven patients failed to complete the minimum of twelve nights on the trial. Of the remaining 40 patients, 18 (11 male, 7 female) were in the Maudsley Hospital and 22 (8 male, 14 female) in Bethlem. Their ages ranged from 17 to 70 years, with a mean of 38.

Drugs. The comparison was made between butobarbitone 200 mg., methyprylone 200 mg., ethinamate 500 mg. and a lactose placebo (to which quinine was added to simulate the taste of barbiturate). The drugs were put up in identically-appearing capsules and administered in a randomized order (different in the two hospitals) over a nearly consecutive series of nights. The randomization was so designed that each patient received each drug four times during a series of 16 nights and on any one night the different drugs were, as far as possible, equally distributed among the patients. In the Maudsley Hospital the patients swallowed the capsules whole but in Bethlem the capsules

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were emptied into water and taken as a draught. The four drugs were identified by letters and the code known only to the pharmacists until the conclusion of the trial.

Records. The drugs were given at the same hour (9.30 p.m.) each night. At half-hourly intervals until 6.30 a.m. the night nurse visited each patient and recorded whether he was awake or asleep. The nurse also recorded whether the patient's sleep had been quiet or restless and noted any spontaneous comments by the patients on the quality of his sleep or his condition on waking. If a patient was awake between periods of sleep, this was counted as a night of "interrupted sleep".

A total of 976 nights were recorded, the average number of nights per patient being 24, with a range of 13 to 44.

Results

For comparative purposes, the principal measure of a patient's response to a drug was taken as the mean number of times per night on which he was recorded as being awake. This number, multiplied by 30, will approximately represent the time in minutes for which he was awake during the nine hours recorded. The time taken to fall asleep may be represented in a similar way. Table I shows the combined results for the 40 patients. Correlated t-tests

Table I

Sleep Record on Different Drugs, 40 Patients

Sleep Index	Drugs: Buto-barbitone 200 mg.	Methy-prylone 200 mg.	Ethin-amate 500 mg.	Lactose
Mean time awake (minutes per patient per night)	95	110	120	128
Mean time to fall asleep (minutes per patient per night)	44	51	50	51
Interrupted sleep (number of nights when this occurred)	54	81	80	86
Restless sleep (number of nights so reported)	26	36	36	32

between the mean times awake on the different drugs give the following results. Butobarbitone is significantly better, i.e. is associated with a shorter time awake, than each of the other drugs ($P<1$ per cent.); methyprylone is significantly better than the placebo ($P<1$ per cent.); the differences between methyprylone and ethinamate and between ethinamate and the placebo do not quite reach the 5 per cent. level of significance. The butobarbitone scores are also significantly better than the other drugs for the mean time to fall asleep and for the number of nights of interrupted sleep ($P<5$ per cent.).

Table II shows the effect of different factors on the comparative scores for the mean time awake. It can be seen that none of the four factors examined had any appreciable influence on the relative efficacy of the drugs.

No adverse comments or complaints of hangover were recorded during the trial.

TABLE II

Mean Time Awake on Different Drugs (Lactose Expressed as 100) by Various Factors

Factor	Number of Patients	Drugs: Buto-barbitone 200 mg.	Methy-prylone 200 mg.	Ethin-amate 500 mg.	Lactose
Hospital:					
Maudsley	18	76	85	89	100
Bethlem	22	74	87	98	100
Sex:					
Male	19	75	84	91	100
Female	21	72	87	97	100
Age:					
Under 35	20	72	82	88	100
Over 35	20	78	91	102	100
Diagnosis:					
Depression	24	82	94	102	100
Not depression ..	16	65	77	85	100
All patients	40	74	86	94	100

DISCUSSION

In terms of the indices used, the results indicate that butobarbitone 200 mg. is a more effective hypnotic than either methylprylone 200 mg. or ethinamate 500 mg. This is in line with the findings of Stewart (1956) that methyprylone 200 mg. is about as effective as butobarbitone 100 mg. In contrast, Thomson (1958), using the method of sequential analysis, found no significant difference between methyprylone 200 mg. and placebo, although 400 mg. produced a significantly better result. It may be, however, that his method, based on the patients' subjective preferences, provides a less clear distinction between the actions of weak hypnotics and placebos.

Ethinamate, in the present study, showed a hypnotic action no better than the placebo, a finding which is in agreement with Gruber *et al.*

It is of interest that butobarbitone caused a significantly more rapid onset of sleep than did the other drugs, for ethinamate and methyprylone are marketed as rapidly acting hypnotics, whereas butobarbitone is classed as a hypnotic of "medium duration". The work of Lasagna (1956) has already thrown doubt on the common supposition that, for clinical purposes, the barbiturate hypnotics can be classed into short-, medium- and long-acting.

Our finding that the comparative efficacy of the drugs was uninfluenced by age or sex is in accordance with that of Drew (1958), who found no relation between these factors and the response to alcohol as measured by driving-test errors.

The differences we observed between the active drugs and the placebo cannot be expressed in absolute terms. The patients received the placebo on only one night in four and it seems likely that the rhythm of satisfactory sleep established by three nights on active drugs would be to some extent carried over to the fourth night, thus increasing the apparent efficacy of the placebo. Indeed, the use of a placebo in this type of comparative trial is probably unnecessary.

Summary

1. By a controlled clinical trial, the hypnotic efficacy of ethinamate ("Valmidate") and methyprylone ("Noludar") were compared with each other and with butobarbitone and a placebo. The subjects were 40 psychiatric patients and an average of 24 nights sleep per patient was objectively recorded.

2. The trial was divided between two hospitals, with consistent results.

3. Butobarbitone 200 mg. was significantly more effective than the other drugs on most of the criteria used, and this comparative efficacy was uninfluenced by factors of age, sex or diagnosis.

4. Methyprylone 200 mg. was more effective than the placebo, but did not differ significantly from ethinamate 500 mg. Ethinamate 500 mg. was not significantly more effective than the placebo.

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