THE EFFECTS OF MEPROBAMATE AND PENTOBARBITONE SODIUM ON SLEEP AND MOTILITY DURING SLEEP: A CONTROLLED TRIAL WITH PSYCHIATRIC PATIENTS

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Meprobamate (2-methyl-2-n-propyl-1, 3-propanediol dicarbamate) was synthesized by Ludwig and Piech (1951). It is an interneuronal blocking agent capable of producing muscular relaxation without affecting respiration or other vital activities (Berger, 1954). The drug produces restful sleep and generalized muscular relaxation (Borrus, 1955). It was decided to test its effect, compared with that of a placebo and pentobarbitone sodium, on motility measured on a bed providing quantified estimates of movement during sleep or recumbency.

Method

Eleven male patients aged 22 to 70 years, suffering from hypsomnia of a degree to require a night hypnotic, were studied. They slept in a ward of 10 moderately disturbed psychiatric patients. Of the 11, eight were depressed, two were schizophrenic, and one was a chronic alcoholic withdrawn from alcohol for four weeks. The trial was of the self-controlled, double-blind variety. Each patient was in the trial for 18 days, the drugs being given in random order at 9.30 p.m. For the first nine days (Series 1) the patient received on three nights each placebo alternating with meprobamate at two dose levels (400 and 800 mg.). For the second nine days (Series 2) the effect of 800 mg. meprobamate was compared with that of a conventional hypnotic (200 mg. pentobarbitone sodium) and placebo. Meprobamate and placebo were in identical tablet form and the pentobarbitone ("nembutal") in neutral-coloured capsules. The drugs were crushed and given in fluid to the patient. No additional treatment or medication was provided during the trial.

As in the method for validating the bed (Cox and Marley, 1959) the patient's motility scores were recorded hourly from the Veeder-Root counter during the period 10 p.m. to 6 a.m. by one nurse, an independent rating (as in the previous paper) of the patient's sleep being given by another. Eight patients completed a questionnaire (see previous paper) each morning relating to their night's sleep, the other three subjects being unable to comply satisfactorily on account of their mental state.

The results were dealt with by analysis of variance. A one-tail test of significance was employed if the placebo scores were to be compared with a drug score, and a

two-tail test of significance if the two drug scores were to be compared.

Results

The mean and standard error of the mean scores for all results are shown in Table I.

Comparison of Effects of Placebo, Meprobamate, and Pentobarbitone Sodium on Motility.—The total motility scores between 10 p.m. and 6 a.m. for Series 1 and 2 were subjected to analysis of variance. For Series 1, the variance ratio between drugs ($F = 5.76$, $P < 0.01$) proving significant, the differences between mean motility scores were tested. Only 800 mg. significantly reduced movement (Table II). For Series 2, the variance ratio between drugs ($F = 4.39$, $P < 0.05$) was significant, so the differences between mean motility scores for the drugs were examined. Both 800 mg. meprobamate and 200 mg. pentobarbitone sodium significantly reduced movement as compared with placebo (Table II).

Time of Onset of Action of Drugs.—The mean motility scores at 11 p.m., 12 p.m., 1 a.m., and 2 a.m. were subjected to analysis of variance to ascertain the earliest moment the effect of the drug became significant. For both series this was at 12 p.m. The significant differences between the 12 p.m. mean motility scores was due in Series 1 to the effect of 800 mg. meprobamate ($t = 2.19$, $P < 0.02$) and in Series 2 to the significant difference between the action of placebo and 200 mg. pentobarbitone sodium ($t = 2.6$, $P < 0.01$). A significant effect of 800 mg. meprobamate was not evident until 1 a.m. in Series 2.

Nurses' and Patients' Ratings of Motility Scores.—There was a significant correlation in Series 1 between the nurses' ratings and the total night motility scores ($r = +0.47$, $P < 0.01$) but not between the patients' rating and the total motility scores ($r = +0.22$, $P > 0.05$). In Series 2, there was a significant correlation between both the nurses' rating and total night

TABLE I
MEAN AND STANDARD ERROR OF MEAN FOR MOTILITY SCORES, NURSES', AND PATIENTS' RATINGS DERIVED FROM PATIENTS RECEIVING PLACEBO, MEPROBAMATE, AND PENTOBARBITONE SODIUM

Scores or Ratings	No. of Patients	Indices (Units)	Series 1								
			Placebo			400 mg. Meprobamate			800 mg. Meprobamate		
			Night 1	Night 2	Night 3	Night 1	Night 2	Night 3	Night 1	Night 2	Night 3
Total motility scores (bed)	11	Mean S.E. of Mean	77.1 19.64	80.1 20.09	67.5 13.82	69.3 18.94	70.8 18.64	62.9 16.25	40.3 8.18	54.4 14.43	49.1 12.89
Nurses' total ratings	11	Mean S.E. of Mean	13.5 0.89	12.6 0.75	10.5 0.78	10.4 0.63	10.1 0.64	9.9 0.52	9.9 0.72	10.3 0.39	9.8 0.56
Patients' total ratings	8	Mean S.E. of Mean	13.6 0.98	13.8 0.25	13.6 0.55	13.8 0.83	12.5 0.66	11.8 0.75	12.0 0.69	11.1 0.97	11.5 1.09

Scores or Ratings	No. of Patients	Indices (Units)	Series 2								
			Placebo			200 mg. Pentobarbitone Sodium			800 mg. Meprobamate		
			Night 1	Night 2	Night 3	Night 1	Night 2	Night 3	Night 1	Night 2	Night 3
Total motility scores (bed)	11	Mean S.E. of Mean	65.6 12.39	62.5 14.00	67.2 12.21	29.7 8.01	42.6 7.19	44.6 8.97	40.1 9.67	63.1 11.53	48.1 8.01
Nurses' total ratings	11	Mean S.E. of Mean	11.1 0.93	10.9 0.73	11.8 0.85	9.0 0.37	9.5 0.20	9.6 0.44	9.3 0.55	10.3 0.61	9.6 0.47
Patients' total ratings	8	Mean S.E. of Mean	11.9 0.34	13.1 0.70	13.6 0.74	10.6 0.72	11.0 0.70	11.1 1.06	10.6 1.14	12.1 1.00	11.6 0.94

TABLE II
SYNOPSIS OF FINDINGS FOR DRUG TRIAL

	Series 1		Series 2	
	Placebo and 400 mg. Meprobamate	Placebo and 800 mg. Meprobamate	Placebo and 800 mg. Meprobamate	Placebo and 200 mg. Pentobarbitone Sodium
Total motility scores	P > 0.20	P < 0.001	P < 0.05	P < 0.001
Nurses' total ratings	P < 0.001	P < 0.001	P < 0.01	P < 0.001
Patients' total ratings	P < 0.001	P < 0.001	P > 0.05	P < 0.001
Patients' individual ratings	Duration of sleep	P < 0.05	P < 0.05	P < 0.001
	Soundness of sleep	P > 0.05	P < 0.01	P < 0.001
		—	+	+

+ = significant difference between mean scores for placebo and drug; — = no significant difference between mean scores for placebo and drug.

motility scores ($r = +0.45$, $P < 0.01$) and between the patients' rating and total motility scores ($r = +0.41$, $P < 0.01$).

Analysis of Nurses' Ratings.—As the variance ratio between drugs for Series 1 ($F = 12.95$, $P < 0.001$) was significant, the mean ratings for the drugs were compared. From the nurses' ratings, it appeared that both 400 and 800 mg. meprobamate significantly reduced restlessness (Table II). For Series 2, as the variance ratio between drugs was significant ($F = 4.91$, $P < 0.05$), the mean ratings were compared. From the nurses' ratings both 800 mg. meprobamate and 200 mg. pentobarbitone sodium significantly reduced restlessness (Table II).

Analysis of Patients' Rating.—The patients' total rating for their own sleep were subjected to analysis

of variance. For Series 1, as the variance ratio between drugs ($F = 12.95$, $P < 0.001$) was significant, the mean ratings were tested. From the patients' ratings, both 400 and 800 mg. meprobamate significantly improved sleep (Table II). For Series 2, the variance ratio between drugs ($F = 10.16$, $P < 0.001$) was significant. In this instance, 200 mg. pentobarbitone sodium but not 800 mg. meprobamate was deemed to have improved sleep significantly.

The totals for the patients' ratings were also split into the individual scores for each of the items on the questionnaire, and then subjected to analysis of variance. In Series 1, the patients stated that they slept longer both with 400 and 800 mg. meprobamate as compared with placebo (question 2 on the questionnaire) and that sleep was sounder (question 3) with the 800 mg. does as compared with placebo

SERIES 1

SERIES 2

FIG. 1.—Mean motility scores at 11 and 12 p.m. and at 1, 2, and 6 a.m. for 11 patients. (Series 1: □ = placebo; ○ = 400 mg. meprobamate; ● = 800 mg. meprobamate. Series 2: □ = placebo; ● = 800 mg. meprobamate; ⊙ = 200 mg. pentobarbitone sodium.)

(Table II). For Series 2, patients stated that they slept longer after 200 mg. pentobarbitone sodium and 800 mg. meprobamate as compared with placebo (question 2), sleep also being sounder (question 3) with these two than with placebo (Table II).

Discussion

The perfect solution to the problem of measuring depth of sleep remains elusive, and although observations by nurses of the wide-awake or snoring patient are reliable, intervening sleep levels are difficult to determine. Techniques such as shining a light on the patient (Straus, Eisenberg, and Gennis, 1955) have disadvantages, while subjective ratings by the patient may or may not agree with the nurses' evaluation of his sleep (Hare, 1955; Imboden and Lasagna, 1956). In the group of patients we studied, a subjective appraisal alone might have been misleading, for the patients with more severe mental illness were unable to complete the sleep questionnaire. Least weight should be attached to data derived from the questionnaire, as Glaser (1953 1954) and Glaser and Whittow (1953) have shown that repeated completion of questionnaires may

diminish the number of responses scored on them giving a false impression in such a case of habituation to the drug. Moreover, in the previous investigation, no correlation was found between the motility scores and the patients' own estimate of sleep (Cox and Marley, 1959).

The objective findings in Series 1 of the drug trial are that 800 mg. but not 400 mg. meprobamate significantly reduces motility during sleep or recumbency. The subjective findings, on the other hand (nurses' and patients' ratings), suggest that meprobamate at both dose levels is superior to placebo in reducing restlessness and as a hypnotic. Lasagna (1956) noted that of various agents for promoting sleep in chronically ill patients, 400 mg. meprobamate was almost as effective as 800 mg. of the drug.

In Series 2, the objective findings are that both 200 mg. pentobarbitone sodium and 800 mg. meprobamate have a definite depressant action on motility, pentobarbitone being superior to meprobamate. The first part of the subjective results (nurses' ratings) are in agreement. However, from the patients' total ratings, pentobarbitone sodium but not 800 mg. meprobamate appeared to have

significant action, although paradoxically analysis of the patients' ratings for individual items on the questionnaire suggests that both drugs are superior to placebo in enhancing duration and soundness of sleep. Lasagna demonstrated that either 400 mg. or 800 mg. meprobamate was as effective as 100 mg. or 200 mg. phenobarbitone as a hypnotic, but less effective than either 100 mg. or 200 mg. quinalbarbitone sodium.

In both series, no significant effect of the drug on motility was detected until 150 minutes (12 p.m.) after administration, that for Series 1 being due to 800 mg. meprobamate and for Series 2 attributable to pentobarbitone sodium.

Inasmuch that motility during sleep and depth of sleep are at least partially correlated (and in this investigation there was a significant correlation between motility scores and the nurses' rating in both Series and between motility scores and patients' ratings of sleep in Series 2) the results are consistent with the notion that 800 mg. meprobamate possesses weak hypnotic action and reduces restlessness during sleep, although in both respects it is much less effective than 200 mg. pentobarbitone sodium. The smaller dose (400 mg.) of meprobamate seems also to possess a mild hypnotic effect but had no significant action on restlessness during sleep. Our results were obtained from patients with severe sleep disturbance, and it may be that both 400 mg. and 800 mg. meprobamate would exert a more pronounced hypnotic effect in subjects with milder insomnia.

Summary

Eleven psychiatric patients with marked insomnia were prescribed in random order 400 mg., 800 mg. meprobamate, and placebo (Series 1), and 200 mg. pentobarbitone sodium, 800 mg. meprobamate, and placebo (Series 2).

Measurements of motility during sleep were obtained from an electronic recording unit attached

to the bed. The patients' sleep was rated also by the nurses and the patients themselves.

Meprobamate, 800 mg., but not 400 mg., significantly reduced motility scores in Series 1. In Series 2, both 200 mg. pentobarbitone sodium and 800 mg. meprobamate significantly diminished restlessness during sleep.

From the nurses' ratings, 200 mg. pentobarbitone sodium and 400 mg. and 800 mg. meprobamate exerted a significant hypnotic action as compared with placebo.

As judged by the patients' total ratings, 400 mg. and 800 mg. meprobamate improved sleep in Series 1 but only pentobarbitone in Series 2. Analysis of individual items from the sleep questionnaire indicated that all drugs used prolonged sleep as compared with placebo, but that sleep was only sounder after 800 mg. meprobamate or 200 mg. pentobarbitone sodium.

It is contended that both 400 mg. and 800 mg. meprobamate possess weak hypnotic activity, that 800 mg. reduces restlessness, but that in both respects 200 mg. pentobarbitone sodium is superior.

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REFERENCES

- Berger, F. M. (1954). *J. Pharmacol.*, **112**, 413.
 Borrus, J. C. (1955). *J. Amer. med. Ass.*, **157**, 1596.
 Cox, G. H., and Marley, E. (1959). *J. Neurol. Neurosurg. Psychiat.*, **22**, 57.
 Glaser, E. M. (1953). *Brit. J. Pharmacol.*, **8**, 187.
 — (1954). *Clin. Sci.*, **13**, 199.
 — and Whittow, G. C. (1953). *J. Physiol (Lond)*, **122**, 43P.
 Hare, E. H. (1955). *Brit. J. prev. soc. Med.*, **9**, 140.
 Imboden, J., and Lasagna, L. (1956). *Bull. Johns Hopk. Hosp.*, **99**, 91.
 Lasagna, L. (1956). *J. chron. Dis.*, **3**, 122.
 Ludwig, B. J., and Piech, E. C. (1951). *J. Amer. chem. Soc.*, **73**, 5779.
 Straus, B., Eisenberg, J., and Gennis, J. (1955). *Ann. intern. Med.*, **42**, 574.