Brit. J. Pharmacol. (1961), **16**, 82–89.

THE ACTIONS OF AMYLOBARBITONE SODIUM, BUTOBARBITONE AND QUINALBARBITONE SODIUM UPON INSOMNIA AND NOCTURNAL RESTLESSNESS COMPARED IN PSYCHIATRIC PATIENTS

BY

J. M. HINTON

From the Professorial Unit, the Maudsley Hospital, London

(*Received October* 5, 1960)

Amylobarbitone sodium, butobarbitone, quinalbarbitone sodium, and a placebo were compared in a controlled, double-blind trial in psychiatric patients with insomnia. An apparatus recording movement in bed is described, with sleep assessments by night nurses and patients. All three barbiturates significantly reduced movement and gave significantly longer, less broken and sounder sleep, without increased incidence of "hang-over." There was no follow-on effect from night to night. With effective doses there was no significant difference between these barbiturates in onset and duration of hypnotic action, although usually accepted as either short or intermediate acting.

The selection of a barbiturate from the large number available is, in clinical practice, often arbitrary or dependent upon local fashion. Those placed in the short-acting group are more often used with patients who cannot readily get to sleep, whilst the intermediate-acting barbiturates are prescribed for patients wakeful in the latter part of the night. Recently, the duration of action, by which these barbiturates are grouped, has been questioned. In order to evaluate the clinical hypnotic action of the widely-used amylobarbitone sodium it was compared with quinalbarbitone sodium and butobarbitone, accepted as having a short and an intermediate action respectively.

METHODS

Patients. The patients studied slept in a ward of 10 moderately disturbed men with a night nurse always present. They had insomnia due to their mental illness and would normally have received a hypnotic drug. The diagnoses in the 16 patients completing the trial were depression (9), schizophrenia (2), anxiety state (1), hypomania (1), alcohol addiction (1), personality disorder with depressive features (1) and hypochondriacal features (1). During the period of study no other medicinal or physical treatments, for example, electro-convulsive therapy, were given. For nine patients such treatment was indicated before the end of the trial period and so the trial was stopped and the records discarded, the next suitable patient being substituted. The patients had their last meal of the day by 6 p.m., with cocoa and biscuits between 8 and 9 p.m. At 10 p.m. they got into bed and took the trial drug contained in two gelatin capsules. On the first three nights of recording the capsules contained 0.2 g (3 grains) of pentobarbitone sodium. This preliminary period enabled the patient to become familiar with the ward environment and

the procedure of the trial; the records of this period were discarded. Considerable spontaneous improvement occurred in 10 patients during these three days and they were rejected at that point from the fully recorded trial. The final 16 subjects had their sleep recorded for eight nights each. The capsules containing the three barbiturates and the placebo could not be distinguished and their contents were not revealed to the patients and nurses assessing the results. The drugs were given on successive nights according to an 8×8 Latin square, the patients acting as their own controls. This square was designed (Williams, 1949) to enable one to calculate if there were a follow-on effect from any one night to another. The patients were allotted at random to the rows of the square and the square replicated for the second group of eight patients. Each patient had, in a different sequence, amylobarbitone sodium 0.2 g and 0.1 g, quinalbarbitone sodium 0.2 g and 0.1 g, butobarbitone 0.2 g and 0.1 g and,

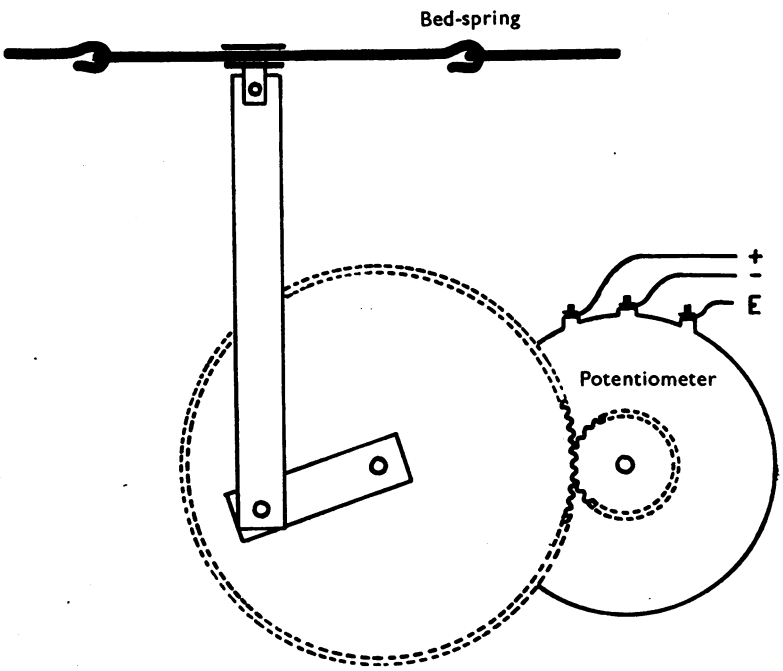

Fig. 1. Diagram of the apparatus which was attached to the bed so that the movements of the patient, which displaced the bed-spring, rotated the potentiometer.

twice, a placebo, lactose, as a comparison. The effects of these drugs were recorded in three ways: firstly, an electronic device to measure movement in bed; secondly, the night nurses' estimate of sleep or wakefulness; and, thirdly, some subjective estimates by the patient.

Movement record. The apparatus used to record the motility of the patient has been slightly modified from that described by Cox & Marley (1959) and used to assess the hypnotic value of two drugs (Hinton & Marley, 1959). Two upright rods were attached to the centre of the bed-spring under the patient's hips and shoulders and they were displaced vertically when the patient moved (see Fig. 1). By means of a crank these vertical movements were modified to rotate a potentiometer, the rotary excursion being increased through two gear-wheels. The voltage differences produced by turning the potentiometer were fed into the circuit described by Cox & Marley (1959) and amplified to provide enough power to work a counter and a pen recorder, which were kept in a side-ward. The counter gave the total motility score and provided a check when counting the score recorded on the paper, which

moved through the pen recorder at 1 inch/2 min throughout the night. A small movement of the trunk usually scored 1 or 2, whereas a vigorous complete change of position would score 6 or 8.

Nurses' record. The night nurse recorded every half-hour if the patient appeared asleep or awake. She also noted the time of getting to sleep or waking and any periods of wakefulness during the night.

Patients' record. The following morning the patient was asked to mark on a simple questionnaire his own estimate of the quality of his sleep (sound, fair, poor, or very poor), whether or not he had a "hang-over," and, if he did, how it affected him.

RESULTS

Movement record. The movements scored by the pen recorder were counted and subjected to analysis of variance. Table 1 gives an example of the method applied to the total motility score for the night. Table 2 shows the application

TABLE 1

TOTAL MOTILITY SCORE FOR THE NIGHT

Analysis of variance showing highly significant difference between drugs and between patients

	Degrees of freedom	Sums of squares	Mean square	Variance ratio	Probability
Between squares	1	3,528	3,528	6·5	<0·05
Between occasions	14	4,446	318	0·6	—
Between patients	14	90,444	6,460	11·9	<0·001
Between drugs	7	20,607	2,994	5·4	<0·001
Interaction of drugs and squares	7	2,326	332	0·6	—
Residual	84	45,690	544		
Total	127	167,041			

TABLE 2

MEAN TOTAL MOTILITY SCORES FOR THE NIGHT

t test applied to comparison of barbiturates separately with each placebo night

	0·2 g			0·1 g			Placebo	
	Buto-barb.	Quinal-barb. sod.	Amylo-barb. sod.	Buto-barb.	Quinal-barb. sod.	Amylo-barb. sod.		
Mean score	18·5	26·9	29·8	49·1	38·8	36·9	52·7	56·9
t	4·15	3·13	2·7	0·44	1·69	1·93	—	—
Probability	<0·01	<0·01	<0·01	>0·05	>0·05	>0·05	—	—

of the *t* test to the mean total motility score for each drug as compared with the placebo nights; it was thought to be a stricter test of significance to compare the barbiturate with both placebo nights separately. If it was different from only one placebo night it has not been considered further. Using the methods outlined by Williams (1949) possible carry-over or residual effects of one drug on another were tested in the case of the total motility score for the night, but, as this gave no indication that such effects were present, it was not considered necessary to carry out this more elaborate analysis for the other scores.

The motility scores after the first hr, the first 2 hr and the first 4 hr were compared between the barbiturates and the placebos to see how long it took for a significant difference to appear. Table 3 shows that after 1 hr 0.2 g butobarbi-

TABLE 3

MEAN SCORES OF MOVEMENT; OF ONSET, DURATION, AND INTERRUPTIONS OF SLEEP; AND OF QUALITY OF SLEEP AND "HANG-OVER"

Over-all significance of difference between drugs assessed by analysis of variance (probability column): difference between pairs of means by *t* test (*=$P<0.05$, †=$P<0.01$ when compared with placebos)

	0·2 g			0·1 g					
	Buto-barb.	Quinal-barb. sod.	Amylo-barb. sod.	Buto-barb.	Quinal-barb. sod.	Amylo-barb. sod.	Placebo		Proba-bility
Movement score									
After 1st hr	3·5*	7·0	8·5	10·6	8·6	9·8	11·0	13·5	<0·05
After 1st 2 hr	5·4†	7·9*	11·4	15·9	11·6	13·7	14·9	18·8	<0·01
After 1st 4 hr	8·1†	12·5†	17·6*	31·1	19·6	18·0*	30·8	29·4	<0·001
After 2nd 4 hr	10·4*	14·4	12·3*	18·1	14·3	18·9	21·9	27·5	<0·01
After 8 hr	18·5†	26·9†	29·8†	49·1	38·8	36·9	52·7	56·9	<0·001
Total sleep in hours	7·09*	7·06*	7·06*	6·22	6·63	6·28	5·66	5·88	<0·05
Time to get to sleep, in min	35·6	29·1	30·3	52·5	41·3	51·6	57·5	41·3	>0·05
Breaks in sleep	0·56*	0·44*	0·69	0·75	1·19	1·06	1·75	1·31	<0·01
Quality of sleep (sound=1 to 4)	1·81	1·56†	1·69*	1·94	1·88	2·19	2·31	2·81	<0·001
"Hang-over" (total incidence)	4	3	3	3	2	3	2	4	—

tone had significantly reduced restlessness as compared with both placebo nights. After 2 hr quinalbarbitone 0.2 g also showed statistically significant effect. After 4 hr all three barbiturates in their 0.2 g doses were significantly better than the placebo, with 0.1 g amylobarbitone sodium also reaching a significant level. Although the barbiturates became significantly different from the placebo at different times, at no time was there a significant difference between the 0.2 g doses of any two barbiturates.

Comparison of scores for the second 4 hr of the night would show if any of the barbiturates had a more sustained effect. Butobarbitone 0.2 g and amylobarbitone sodium 0.2 g maintain their significant effect; quinalbarbitone sodium 0.2 g just fails to reach the level of significance when compared with both placebo nights, but it is not significantly different from the other two barbiturates tested.

The total 8-hr movement score (Tables 1 and 2) is, as expected, reduced by the barbiturates; the difference between the 0.2 g doses and the placebo easily reaches the 1% level of significance. Throughout the night the 0.1 g doses give results intermediate between 0.2 g and placebo, rarely achieving a statistically significant difference from placebo.

Nurses' record. Although the nurses did not know which, if any, barbiturate was in the capsules, they assessed the patients' length of sleep such that the mean was 7.09 hr for butobarbitone 0.2 g and 7.06 hr for both amylobarbitone and quinalbarbitone sodium 0.2 g. The means for the two placebo nights were 5.66 and 5.88 hr, significantly different when subjected to the same statistical tests as the movement score. These results (Table 3) parallel the results for the motility score in that patients who are asleep move less. It may be noted that levels of statistical significance are less readily reached by comparison of sleep estimations,

the probability of the difference between placebo and 0.2 g barbiturate being a chance one is between 5% and 1%, whereas the movement score shows a probability of less than 1%.

Sleep was broken less frequently when the patient received a barbiturate than when he took the placebo, the larger dose being more effective (see Table 3). The difference was statistically significant ($P<0.05$) between placebo and 0.2 g of butobarbitone and quinalbarbitone sodium.

The time taken to get to sleep was, as expected, less with barbiturates than without. However, the individual variation and scatter was so wide in this group of disturbed patients (the times ranged from 5 min to 3¾ hr) that in the analysis of variance the difference was not significant. Table 4 shows the proportion of

TABLE 4

PERCENTAGE OF PATIENTS ASLEEP 15, 30, 45 AND 60 MIN AFTER 0·2 G BARBITURATE COMPARED WITH PLACEBO

(*=$P<0.02$ using arc sin transformation)

	Butobarb.	Quinalbarb. sod.	Amylobarb. sod.	Placebo
After 15 min	25%	31%	25%	22%
After 30 min	44%	68%*	50%	32%
After 45 min	94%*	81%	94%*	56%
After 1 hr	94%*	94%*	94%*	72%

subjects asleep at the end of each quarter-hour for the first hour; the arc sin transformation of the square roots of the proportions (Davies, 1954) was used to assess the significance of differences. Compared with the placebo, this proportion becomes significantly greater for quinalbarbitone sodium after 30 min (C.R.=2.34, $P<0.02$) and amylobarbitone sodium and butobarbitone after 45 min (C.R=2.45, $P<0.02$).

Patients' record. The patients thought their sleep sounder when the capsules contained a barbiturate. Rating "sound" as 1, "fair" as 2, "poor" as 3, and "very poor" as 4, the results were again found to be significant when subjected to analysis of variance. The difference from placebo was significant with quinalbarbitone sodium 0.2 g ($P<0.01$) and amylobarbitone sodium 0.2 g ($P<0.05$), but with butobarbitone it just failed to reach the 5% level.

The patients who said that they had a "hang-over" usually described it as a feeling of heaviness, tiredness, slight giddiness or a headache. Inspection of Table 3 shows that this "hang-over" was reported 2 to 4 times with each barbiturate in both doses and also with placebo, and it is apparent that its incidence was not significantly related to barbiturates in this trial.

The pattern of sleep. The motility score per hour, illustrated as a histogram in Fig. 2, indicates the distribution of restlessness throughout the night. Without the barbiturate (broken line in histogram) this group of patients with insomnia moved most in the first hour whilst seeking sleep; in the next few hours they moved considerably less with variation from hour to hour and towards 6 a.m. movement increased again. With the barbiturates the pattern is similar, although quantitatively different. It is apparent that butobarbitone 0.2 g is effective throughout the 8 hr and, notably, the first 1 hr, although what little effect the 0.1 g

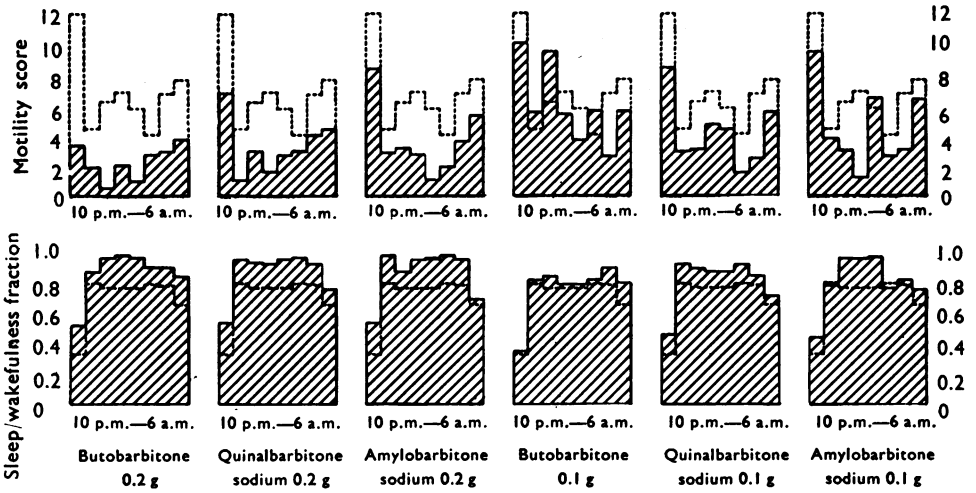

Fig. 2. The alteration of movement and recorded sleep produced by the three barbiturates (hatched) in 0·2 g and 0·1 g doses as compared with placebo (broken line). Upper histograms; mean motility score for each hour between 10 p.m. and 6 a.m. Lower histograms: mean sleep/wakefulness fraction for each hour (a score of 1·0 indicates that all the patients slept throughout that hour).

dose has is in the latter part of the night. The action of quinalbarbitone and amylobarbitone sodium is soon discerned and again persists until morning. The record of the patients' sleep made by the nurses provides a corresponding pattern if it is illustrated as a sleep/wakefulness fraction per hour, such that a score of 1.0 is attained if all 16 patients slept the whole hour. The barbiturates increased the amount of sleeping at the same time as they decreased the movement, although the alteration of motility is greater.

DISCUSSION

The measurement of movement during the night is a practicable method of obtaining an indication of the hypnotic effect of drugs and correlates with the evaluation of sleep by the nurses and patients. Although a more direct method of measuring sleep would be welcome, this at least avoids disturbing the patients' rest, gives a reliable score and does not ask for too much co-operation from disturbed psychiatric patients, in comparison with other methods discussed in previous papers (Cox & Marley, 1959; Hinton & Marley, 1959). As expected, the trial confirmed that 0.2 g of these three barbiturates were efficient hypnotic agents, inducing sleep earlier, increasing the amount of sleep obtained between 10 p.m. and 6 a.m., reducing restlessness and the interruptions of sleep; whilst the patient feels that he has slept more soundly without any increase in unwelcome bodily sensations on waking.

The main purpose of the trial was to compare the action of these three barbiturates as there are surprisingly few controlled studies on the production of sleep by barbiturates in human subjects. Animal experimentation inducing anaesthesia is not a satisfactory substitute, nor is the estimation of blood or plasma barbiturate

level, as there may be considerable differences between the comparative rates of metabolism of different barbiturates in man and animals (Brodie, Burns, Mark, Lief, Bernstein & Papper, 1953); moreover the relationship between blood levels of barbiturates and anaesthesia is not very exact (Raventós, 1954). Tatum (1939), when discussing the now traditional method of classifying barbiturates according to the duration of action, wrote, "Experimentalists are forced to depend upon symptoms such as incoordination and various stages of anaesthesia rather than hypnosis or sleep." In the *Extra Pharmacopœia* (1958), amylobarbitone sodium and butobarbitone are placed in the intermediate group, acting within 30 min and having a duration of 5 to 6 hr, whilst quinalbarbitone sodium is said to be short-acting with its action apparent in 15 to 20 min and lasting 2 to 4 hr. Goodman & Gilman (1955) write that the short-acting barbiturates produce less than 3 hr hypnosis. Differing emphasis is placed upon the reputedly slower onset of action of the intermediate-acting derivatives, but Tatum (1939) had said of the barbiturates, "It so happens that, with the exception of barbital and phenobarbital, practically all of them have a short induction period." In the last decade doubts have been expressed concerning the claimed periods of action of the various barbiturates. In 1951 Goodnow, Beecher, Brazier, Mosteller & Tagiuri, in testing for impaired physiological performance in man after 0.1 g of pentobarbitone sodium, found this trend still present after 14 hr. In 1956 Lasagna, noting the absence of clinical data bearing on the accepted classification of the barbiturates, showed clearly that in a group of chronically ill patients quinalbarbitone (secobarbital) sodium and pentobarbitone sodium had a similar onset and duration of effect.

The results of this trial show that there is little clinical difference between the effects of the one short-acting and the two intermediate-acting barbiturates. With 0.2 g of each barbiturate a decrease in restlessness becomes apparent in the first hour, notably with butobarbitone, one of the intermediate group. All three drugs have an effect throughout the night; at no time is there a significant difference between the 0.2 g doses, although sometimes one and sometimes another barbiturate reaches a different level of statistical significance. This also applies to the length of sleep, the number of times it was broken and the patients' estimate of its soundness. It might be said that the 0.2 g dose was so large as to obscure the finer differences between the three barbiturates, but 0.1 g was in most cases insufficient to produce a significant difference from placebo in these disturbed patients. Amylobarbitone and quinalbarbitone sodium 0.1 g produced a qualitatively similar sleep and movement pattern to the 0.2 g dose, and all that can be said of butobarbitone 0.1 g is that, in marked contrast to 0.2 g, it was not as ineffective in the latter part of the night as in the first part. In many of the assessments 0.2 g of butobarbitone had the greatest effect, but it is to be remembered that it contains almost 10% more of the barbiturate base than 0.2 g of the sodium salts of amylobarbitone and quinalbarbitone. It would be justifiable to say that variation in the severity of disturbance in psychiatric patients hides the differences between the drugs. This factor, randomized by the design of the trial, played a part in the failure to reach a statistically significant difference in the times taken to get to sleep. Stewart (1956) had a similar finding in a clinical trial using buto-

barbitone and amylobarbitone sodium in ward patients. The variation between these mentally ill individuals was great, always more than that between the drugs, and having 2 patients who moved little in the second group of 8 patients produced some variance between the two groups, hence the significant difference between squares in Table 1. Nevertheless, in Lasagna's (1956) trial with chronically ill patients, where the individual's insomnia was presumably more constant, similar conclusions were reached.

The possibility was considered that, once a barbiturate had induced sleep, the patient stayed asleep and the drug with a short action could not be distinguished from one with intermediate action. If the hypnotic action were short, a patient taking quinalbarbitone sodium 0.2 g and waking in the first part of the night would be more restless in the second half of the night than the mean of all the patients receiving this drug. In fact, 6 such patients awoke between midnight and 2.30 a.m., and their mean motility score for the first half of the night was 15 (mean for all those taking quinalbarbitone sodium was 12.5). The mean for these 6 in the second four hours of the night was 14.2, compared with 14.4 for the whole group (placebo group 24.7). This trend indicates that quinalbarbitone sodium was still effectively inducing sleep again once the patient had woken.

It is clear that the accepted grouping of the short-acting and intermediate-acting barbiturates is, as yet, not borne out by controlled studies of their hypnotic action in man.

I wish to thank Dr. D. L. Davies, whose help and encouragement made this investigation possible; also Dr. A. E. Maxwell for his advice on statistics; Mr. G. H. Cox for his technical assistance, including the construction of the recording apparatus; Sister Kvass and the nursing staff of Ward 4 for their careful recording; and May & Baker for supplying the barbiturates.

REFERENCES

BRODIE, B. B., BURNS, J. J., MARK, L. C., LIEF, P. A., BERNSTEIN, E. & PAPPER, E. M. (1953). The fate of pentobarbital in man and dog and a method for its estimation in biological material. *J. Pharmacol. exp. Ther.*, **109**, 26–34.

COX, G. H. & MARLEY, E. (1959). The estimation of motility during rest or sleep. *J. Neurol. Neurosurg. Psychiat.*, **22**, 57–60.

DAVIES, O. L. (1954). *The Design and Analysis of Industrial Experiments*, p. 26. London: Oliver & Boyd.

GOODMAN, L. S. & GILMAN, A. (1955). *The Pharmacological Basis of Therapeutics*, 2nd ed., p. 138. New York: Macmillan.

GOODNOW, R. E., BEECHER, H. K., BRAZIER, M. A. B., MOSTELLER, F. & TAGIURI, R. (1951). Physiological performance following a hypnotic dose of a barbiturate. *J. Pharmacol. exp. Ther.*, **102**, 55–61.

HINTON, J. M. & MARLEY, E. (1959). The effects of meprobamate and pentobarbitone sodium on sleep and motility during sleep: a controlled trial with psychiatric patients. *J. Neurol. Neurosurg. Psychiat.*, **22**, 137–140.

LASAGNA, L. (1956). A study of hypnotic drugs in patients with chronic diseases, comparative efficacy of placebo; methyprylon (noludar); meprobamate (miltown, equanil); pentobarbital; phenobarbital; secobarbital. *J. chron. Dis.*, **3**, 122–133.

MARTINDALE (1958). *The Extra Pharmacopœia*, 24th ed., p. 238. London: Pharmaceutical Press.

RAVENTÓS, J. (1954). The distribution in the body and metabolic fate of barbiturates. *J. Pharm. (Lond.)*, **6**, 217–235.

STEWART, J. S. (1956). Clinical trial of methyprylone, a piperidine hypnotic. *Brit. med. J.*, **2**, 1465–1467.

TATUM, A. L. (1939). The present status of the barbiturate problem. *Physiol. Rev.*, **19**, 472–495.

WILLIAMS, E. J. (1949). Experimental designs balanced for the estimation of residual effects of treatments. *Aust. J. sci. Res.*, *(A)***2**, 149–168.