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A COMPARISON OF THE EFFECTS OF SIX BARBITURATES AND A PLACEBO ON INSOMNIA AND MOTILITY IN PSYCHIATRIC PATIENTS

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Cyclobarbitone, hexobarbitone, quinalbarbitone sodium, pentobarbitone sodium, phenobarbitone sodium, nealbarbitone and a placebo have been compared in a controlled double-blind trial in twenty-four psychiatric patients with insomnia. Each of the barbiturates significantly prolonged sleep and hastened its onset. They also reduced the patients' motility, recorded by an electronic apparatus attached to the bed. There was no clear difference between these barbiturates in onset and duration of action during the 8 hr of recording; some effect upon sleep or motility was present throughout this period. Differences between compounds were of degree rather than of duration of action. Pentobarbitone, quinalbarbitone and phenobarbitone were most effective; cyclobarbitone and hexobarbitone were less effective; nealbarbitone had only a weak hypnotic action.

There is an increasing volume of evidence that the traditional division of barbiturates into those with short, intermediate and long actions is not borne out in clinical practice (Lasagna, 1956). An investigation of amylobarbitone sodium, butobarbitone and quinalbarbitone sodium (Hinton, 1961) showed no significant differences in their hypnotic action; even the "short-acting" compound reduced waking and restlessness for 8 hr. It seemed desirable to investigate a larger group of popular barbiturates, including a number of those alleged to act for only 2 to 4 hr. Cyclobarbitone, hexobarbitone and quinalbarbitone sodium were selected from the barbiturates described as short-acting in the Extra Pharmacopoeia (Martindale, 1958), quinalbarbitone has been recommended as a standard by Lasagna (1956) and was given in two dosages as in the previous barbiturate trial (Hinton, 1961). Pentobarbitone sodium was chosen for its intermediate action and phenobarbitone sodium for its long action. Nealbarbitone, the sixth barbiturate tested, has been introduced recently (Brandstrom, 1957; Ryde, 1959) and is said to be an effective sedative but to have only slight hypnotic action (Robin, Cronin & Scotton, 1961). Such a drug would be useful to patients requiring sedation without the disadvantages and dangers of impaired concentration or consciousness and it was opportune to test its hypnotic effect. Each barbiturate was given in its commonly used effective dose and compared with a placebo.

METHODS

Patients. The twenty-four subjects were psychiatric in-patients at the Maudsley Hospital. Some slept in a ward for ten moderately disturbed male patients with a night nurse always present; the others slept in a smaller room with two beds which could be observed through a window by the night nurse. The sleep of all patients was disturbed and they would usually have received an hypnotic drug. Their diagnoses were: depressive disorders, 18 (2 of whom were also addicted to alcohol); anxiety state, 3; hypomania, 1; schizophrenia, 1; and post-leucotomy state, 1. It was a condition of the trial that the patients were not given electro-convulsive therapy or medication other than the trial drugs. They had their last meal of the day by 6 p.m., although they might have a drink and a biscuit between 8 and 9 p.m. At 10 p.m. they got into bed and took the trial drug. The first three nights of recording, when the patients had butobarbitone (200 mg), were regarded as a preliminary period which allowed the patient to become familiar with the ward environment and trial procedure; the records of this period are not reported.

Drugs. The barbiturates and the placebo, each contained in identical gelatin capsules, were swallowed by the patient in the nurse's presence, neither knowing which drug was administered. The capsules were given on eight successive nights according to a Latin square sequence, the patients acting as their own controls and allotted at random to the rows of the square. Each patient had in turn cyclobarbitone (200 mg), hexobarbitone (500 mg), quinalbarbitone sodium (200 and 100 mg), pentobarbitone sodium (200 mg), phenobarbitone sodium (200 mg), nealbarbitone (200 mg) and a placebo.

Recording. Sleep was reported on by both nurse and patient, and the patient's motility was recorded by an electronic apparatus (Hinton, 1961) modified from the design of Cox & Marley (1959). The nurse observed the patient throughout the night and wrote on a form every 30 min from 10 p.m. to 6 a.m. the state of sleep or wakefulness, recording to the nearest 5 min the times of change in consciousness. The next morning the patient was asked to complete the following questionnaire:

Was your sleep: sound, fair, poor, very poor ?
Do you think there was a "hang-over" from the sedative ? Yes. No.
If there was a hang-over, how did it affect you ?

As soon as the patient was in bed and had taken the drug, the apparatus for recording movement was switched on for 8 hr. Two vertical rods were attached to the bedspring under the patient's hips and shoulders. When the patient changed position the rods were moved and this rotated two potentiometers. The potentiometers were connected to an electronic circuit in a side-ward, and the voltage changes induced were amplified to operate a pen-recorder. On the paper, which moved 1 in. every 2 min, a small movement of the body recorded 1 or 2 and a major change of position 6 or 8 arbitrary units.

RESULTS

Arranging the results as histograms allows a general comparison of the effects of the six barbiturates and the placebo. The sleep distribution for the twenty-four nights with any one drug has been obtained by calculating the mean amount of sleep for each of the hours between 10 p.m. and 6 a.m. Similarly the mean motility score per hour has been calculated for each drug to show the pattern of restlessness throughout the night. In Fig. 1 the mean sleep and motility distributions for each barbiturate are shown as a hatched block and compared with the line of the placebo mean. With a placebo the patients showed impairment of sleep throughout the night (they had a mean of 5.26 hr of sleep, whereas in similar circumstances recovered patients usually slept for more than 7 hr). They were more restless than recovered

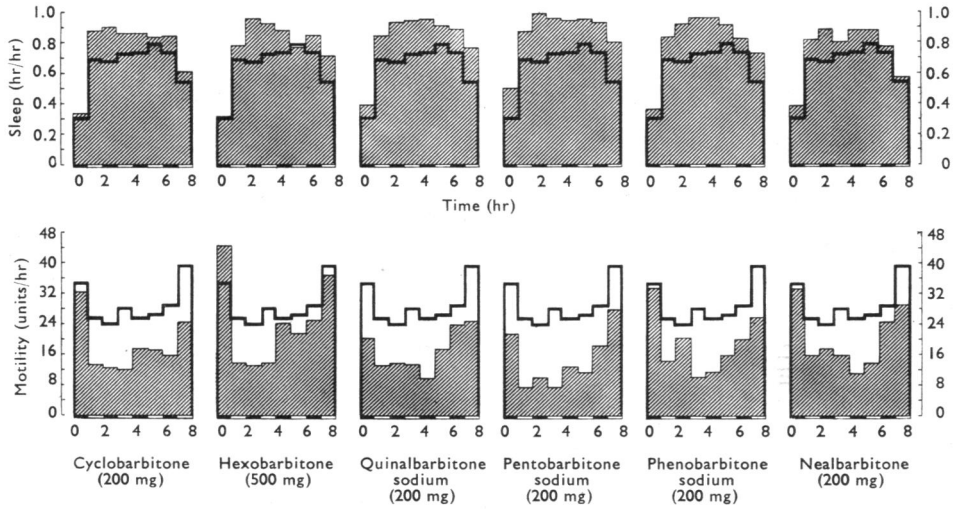

Fig. 1. Mean distributions of sleep (upper histograms, hr of sleep per hr) and of motility (lower histograms, arbitrary units/hr) of twenty-four patients given barbiturates (hatched blocks) compared with the mean responses to a placebo (lines).

patients who have been similarly observed, and they did not show the usual drop in motility which occurs in the early hours of sleep (Hinton, 1962).

Each of the barbiturates increased the time slept and there was a parallel reduction of movement. It is clear that quinalbarbitone, pentobarbitone and phenobarbitone were effective hypnotics and the action of all three persisted throughout the night. Hexobarbitone (500 mg) and cyclobarbitone (200 mg) appear from the histogram to be less powerful hypnotics in the doses used, but they still had some effect even in the 8th hr after ingestion. With nealbarbitone (200 mg) the patients obtained a little more sleep than with the placebo and were considerably less restless.

To determine the statistical significance of the differences observed, the results with each drug and the placebo have been compared after the first hour and for the four 2 hr periods of the night (10 p.m. to 12, 12 to 2, 2 to 4, 4 to 6 a.m.) as shown in Table 1. Similar comparisons have been made in respect of the time taken to get to sleep, the number of interruptions of sleep, and the patients' assessment of the quality of their sleep, taking as numerical values sound = 1, fair = 2, poor = 3, and very poor = 4. For each set of results the statistical significances of the differences have been assessed by analysis of variance and, if significant, the *t* test has been used to compare a drug with the placebo or with another drug. In the analysis of variance the differences between patients were nearly always significant at the 0.1% level and were usually greater than the differences between drugs. This emphasizes the need to use the patient as his own control when comparing hypnotic drugs. There was a just-significant difference in the total amounts of sleep obtained in different nights in the trial series. On the last two nights of the trial the patients tended to get a little more (0.4 hr) sleep than before. This spontaneous improvement underlined the importance of the random order of the drug sequence.

TABLE 1

MEAN ASSESSMENTS OF SLEEP AND MOTILITY OF TWENTY-FOUR PATIENTS GIVEN BARBITURATES AND A PLACEBO

Significances of difference between responses to drugs assessed by analysis of variance (column F); differences between drugs and placebo by *t* test (*=$P<0.05$, †=$P<0.01$, ‡=$P<0.001$)

	Cyclo-barbitone (200 mg)	Hexo-barbitone (500 mg)	Quinalbarbitone sodium (200 mg)	Quinalbarbitone sodium (100 mg)	Pento-barbitone sodium (200 mg)	Pheno-barbitone sodium (200 mg)	Neal-barbitone (200 mg)	Placebo	F	*P*
Sleep (hr)										
1st hr	0·34	0·33	0·40	0·43	0·50	0·38	0·39	0·31	1·49	—
1st 2 hr	1·23	1·12	1·24	1·28	1·38	1·22	1·20	1·01	1·92	—
2nd 2 hr	1·76†	1·90‡	1·89‡	1·78‡	1·95‡	1·87‡	1·70*	1·42	4·83	<0·001
3rd 2 hr	1·70	1·67	1·87*	1·75	1·91*	1·87*	1·77*	1·54	2·46	<0·05
4th 2 hr	1·46	1·56*	1·66†	1·48	1·73‡	1·56*	1·35	1·29	5·77	<0·001
Total	6·16†	6·24†	6·65‡	6·29†	6·96‡	6·51‡	6·02*	5·26	5·16	<0·001
Motility score										
1st hr	32	44	20*	24	21*	34	33	35	2·58	<0·05
1st 2 hr	45	58	33†	35†	29‡	48	49	61	3·62	<0·001
2nd 2 hr	25*	27*	27*	28*	18*	30*	33*	53	2·18	<0·05
3rd 2 hr	35*	46	27‡	33*	24‡	27‡	24‡	53	3·98	<0·001
4th 2 hr	40	62	49	54	46	45	53	69	1·28	—
Total	145‡	193	136‡	150‡	116‡	151‡	159†	235	4·76	<0·001
Time before sleep (min)	57*	50*	54*	50*	41*	56*	64*	95	2·88	<0·05
Breaks in sleep	1·13	1·13	0·42*	1·50	0·50*	1·46	0·96	1·67	2·76	<0·05
Quality of sleep Sound=1 Very poor=4	1·79‡	2·17	1·75‡	1·96†	1·38‡	1·88†	2·04*	2·58	5·47	<0·001
Incidence of hang-over	8	6	7	7	8	7	8	7	—	—

Cyclobarbitone, hexobarbitone and quinalbarbitone sodium

Of these " short-acting " drugs, quinalbarbitone sodium seemed the most effective. In a dose of 200 mg it increased the mean amount of sleep from 5.26 hr with placebo to 6.65 hr and reduced the mean total motility from 235 to 136; a dose of 100 mg had a significant but smaller effect. The larger dose reduced the mean time taken to fall asleep from 95 to 54 min. Its effect in increasing sleep was significant in the second, third and fourth 2 hr periods of the night. The effect on motility became statistically significant before that on the observed sleep, being apparent in the first hour and remaining significantly different from the effect of the placebo for 6 hr. The motility scores for the last 2 hr periods of the night showed no statistically significant difference, probably because of the wide range of scores towards morning. Quinalbarbitone sodium (200 mg) significantly reduced the number of interruptions of sleep and the patients said it improved the quality of their sleep.

Hexobarbitone, although given in a recommended dose of 500 mg, did least well as an hypnotic, apart from nealbarbitone (200 mg). It was the only drug that failed to reduce the patients' total motility or to improve the subjective quality of sleep to a significant extent. It did increase their observed time of sleep, statistical significance being reached in the second and fourth 2 hr periods. Hexobarbitone (500 mg) was significantly less effective than pentobarbitone sodium (200 mg) in increasing sleep ($t=2.29$, $P<0.05$) and was associated with greater total restlessness than pentobarbitone (200 mg) or quinalbarbitone sodium (100 and 200 mg), especially in the first and third 2 hr periods ($P<0.05$).

Cyclobarbitone (200 mg) showed a greater effect than hexobarbitone (500 mg) in some of the comparisons and a lesser effect than 200 mg of quinalbarbitone sodium ($P<0.05$); its action resembled that of 100 mg of quinalbarbitone sodium. It increased the length of sleep, improved its subjective quality and reduced restlessness.

In general when these three " short-acting " barbiturates were given in effective doses, their actions were apparent for at least 8 hr. As with other hypnotic drugs, it was often easier to detect statistically significant changes in sleep and motility in the middle portion of the night, but their actions were not confined to this time. In the Extra Pharmacopoeia (Martindale, 1958) " short-acting " barbiturates are said to act for 2 to 3 hr. This was clearly not so with 200 mg or even 100 mg of quinalbarbitone sodium, nor with hexobarbitone (500 mg) or cyclobarbitone (200 mg), for some of their effects were statistically significant up to the sixth or eighth hour.

Pentobarbitone sodium, phenobarbitone sodium and nealbarbitone

Pentobarbitone sodium (200 mg) was the most effective compound against insomnia and restlessness. In all the objective and subjective measures of sleep and movement except the last 2 hr motility score, it differed significantly from the placebo, often at the 0.1% level of probability. The difference from quinalbarbitone or phenobarbitone sodium (200 mg) was not statistically significant but the drug was often superior (significantly at 5% or 1% level) to the other barbiturates tested.

Its effective action exceeded the 5 to 6 hr period usually expected of an intermediate-acting barbiturate.

Phenobarbitone sodium (200 mg) was very effective both by objective and subjective assessments. Although quinalbarbitone and pentobarbitone achieved a significant difference from the placebo earlier than phenobarbitone, these barbiturates did not differ significantly in direct comparison of effectiveness. In the second 2 hr period and onwards phenobarbitone clearly demonstrated its effect; its continued action in the seventh and eighth hours was anticipated.

Nealbarbitone (200 mg) did not increase sleep as much as any of the other drugs tested, although it did differ significantly from the placebo. What hypnotic action it had was most significant (on statistical evaluation) from the third to sixth hour, and it reduced motility over a similar period. It reduced the time taken to get to sleep and the patients rated their sleep more sound with this drug than with the placebo.

Hang-over

As shown in Table 1 the total incidence of hang-over reported was remarkably uniform with each of the barbiturates and even the placebo. The numbers involved, an incidence of six to eight in twenty-four nights, were unsuitable for detailed statistical analysis. When the description of the hang-over was considered, there did appear to be a relationship between drug and symptom. The commonest complaint was of headache or of feeling heavy-headed. This was reported only once with the placebo; three times with hexobarbitone, pentobarbitone, phenobarbitone and quinalbarbitone (100 mg); four times with quinalbarbitone (200 mg); six times with cyclobarbitone; and seven times with nealbarbitone. The next most common symptom of hang-over was to feel sleepy, dazed or confused. This was reported four times with the placebo and was less frequent, occurring from one to three times, with the various barbiturates. Giddiness or unsteadiness was reported once or twice in the twenty-four mornings after the placebo and after each barbiturate except pentobarbitone, for which it occurred four times. Nausea was fairly evenly distributed, occurring once or twice with most treatments. Not surprisingly, the incidence of hang-over seemed to be more closely related to the patient than to the treatment; eight patients never reported a hang-over, three never failed to.

DISCUSSION

The results of this clinical investigation are in keeping with the growing opinion that the barbiturate hypnotic drugs do not conform to their traditional division into short-, intermediate- and long-acting compounds. Lasagna (1956) clearly demonstrated the similarity of hypnotic action of quinalbarbitone, pentobarbitone and phenobarbitone and the view that such barbiturates are not so very dissimilar in action is now being more widely disseminated. Previous views on the hypnotic action of barbiturates in man were largely based upon extrapolations from work on animal anaesthesia, drug metabolism and blood levels. This work, and the problems of clinical evaluation of hypnotic drugs, were discussed briefly in an earlier paper (Hinton, 1961).

From the present study it is not possible to say of any of the barbiturates in the doses tested that their action was restricted to 4 hr or less. Each of those that had an effect in the first 4 hr had some significant action after that period. This was so even with hexobarbitone, cyclobarbitone and nealbarbitone which were the least powerful compounds in the doses used. The present investigation gives no information about the effects of these barbiturates either after 8 hr or with repeated doses. Phenobarbitone, for instance, is cumulative (Butler, Mahaffee & Waddell, 1954) and the clinical results of the balance between cumulation and tolerance of any barbiturate may well alter after repeated administrations.

The clinical inference from this trial would be to prefer pentobarbitone, quinalbarbitone and phenobarbitone sodium as effective hypnotic drugs by the criteria of induction and prolongation of sleep, which is less broken, more sound and accompanied by less restlessness. The " short " and " intermediate " acting barbiturates appear to act longer than is usually supposed ; in the previous similar trial (Hinton, 1961), which showed the same response to quinalbarbitone sodium, there were remarkably parallel findings for butobarbitone and amylobarbitone sodium. Nealbarbitone may differ qualitatively in that its hypnotic action is weak. If other studies confirm the investigation of Robin *et al.* (1961) which showed comparable relief of anxiety by nealbarbitone and amylobarbitone sodium, nealbarbitone might have advantages as a day-time sedative.

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