A study of pre-operative sedatives

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Summary

A state-registered nurse acted as a whole-time investigator following patients through the pre-operative night in hospital and questioning them in the morning, to assess the relative merits of different medications. Two new sedatives were compared with a standard barbiturate and a placebo, and information was collected from patients who elected to have no medication to help them sleep. Subjective assessment enabled the placebo to be distinguished from the active medications, although there was little difference between these. The importance of psychological factors is discussed in relation to those patients who had no medication.

Introduction

This study was an attempt to compare the merits of certain drugs used to help patients sleep on the night before surgery. The investigation was carried out between the end of July and the middle of December 1966; during this time one of the authors (J.M.) worked at night, following the progress of patients during the time of action of the drugs in question. The medications used were nitrazepam ('Mogadon') 10 mg (drug A); a mixture of methaqualone 250 mg and diphenhydramine hydrochloride 25 mg (drug B); butobarbitone 200 mg (drug C) and a placebo (drug D). Additional information was collected from patients who received no medication.

Method

The intention was, as far as possible, to study patients who had been admitted to hospital for an operation the following day. Such patients are spending their first night in hospital, in circumstances likely to produce anxiety and sleeplessness. The trial was conducted on a single-dose basis, each patient being studied for one night only, and receiving only one of the four medications. In practice, some patients were included in the trial who were not spending their first night in hospital, although having an opera-

tion the following day, and some were studied on a night other than the pre-operative night.

All information was recorded on a standardized card (Parkhouse, 1967). This included the age, sex and weight of the patient, previous history of insomnia or the taking of sedatives, tranquillizers, analgesics, mood-elevators, stimulants or other drugs likely to influence the effect of the pre-operative hypnotic. Previous or concurrent conditions which might influence the ease of getting to sleep were also recorded, e.g. pain or discomfort, mechanical interference with sleep from drips, splints, tubes, etc., nausea or vomiting, frequency of micturition, excessive noise in the ward and so forth. The number of nights spent in hospital prior to the test night was recorded, in all cases where the patient had not been admitted the same day, and the previous administration of sedatives while in hospital was of course noted.

All patients were seen by the nurse-investigator at 21.00-21.30 hours before any sedative drugs were administered. The initial approach to the patient was as follows: 'I am from the anaesthetics department and we are studying how good various sleeping tablets are. We will give you something to help you sleep and see how you get along, but first of all all I would like to ask you one or two questions. We don't want to force you to have a sleeping tablet; some people manage perfectly well without them, but if you are doubtful about getting off to sleep in this ward it is better to have something now than later on in the night.' The investigator then scored her impression of the patient at this time, according to the scheme 1 = already feeling sleepy; 2 = awake but unusually placid; 3 = normal; 4 = apprehensive; 5 = very apprehensive. Tablets were then given to all patients who decided to have them; medications were made up in identical form and dispensed in random order according to a predetermined code. The nurse-investigator did not know which drugs, or how many drugs, were included in the study.

The investigator returned to visit each patient, regardless of whether or not he had received medication, at intervals during the night. These visits were made $\frac{1}{2}$ hr after sleeping tablets were given (or after the time when they would normally have been given), $1\frac{1}{2}$ hr later, and thereafter at 2-hr intervals from midnight until 06.00 hours. It was found that the time of drug administration varied from ward to ward and from patient to patient; five or six assessments were available in the majority of cases. Some patients who had decided not to have sleeping tablets changed their minds at midnight or 01.00 hours when still awake; these patients were scored during the rest of the night, and naturally a smaller number of assessments was available.

At each visit, the investigator assessed the patient according to three criteria:

'Variable 1': the state of consciousness was assessed as: 1 = sound sleep; 2 = sleeping fitfully or doubtfully (i.e. at the first approach the investigator was not sure whether or not the patient was asleep); 3 = drowsy; 4 = fully awake 5 = excited and unable to sleep.

'Variable 2': spontaneous activity was recorded as: 0 = completely still (in common parlance, 'flat out'); 1 = slightly restless; 2 = markedly restless; 3 = confused and disorientated.

'Variable 3': the response was noted to whispering the patient's name or lightly feeling his pulse, as: 0 = no response; 1 = slight response; 2 = more-or-less full arousal.

Before leaving the hospital in the morning, the investigator visited all patients and questioned them about various aspects of the night's sleep. The questions and responses were arranged as follows:

(1) Did you have a good or a bad night?: 1 = good; 2 = indifferent; 3 = bad.

(2) Was it a restful night or a restless night?: 1 = restful; 2 = indifferent; 3 = restless.

(3) Do you think the night was better or worse than it would have been without a sleeping tablet—that is, looking back, would you have preferred to do without one (or, alternatively, to have had one)? : 1 = better the way it was; 2 = don't know; 3 = would have been better the other way.

(4) Did you wake during the night, and if so did you have difficulty in getting to sleep again?: 1 = didn't wake up; 2 = woke up and went to sleep again with no trouble; 3 = woke up and had difficulty getting to sleep again.

(5) Did you dream?: 1 = no dreams; 2 = pleasant dreams; 3 = unpleasant or disturbing dreams.

(6) Do you remember me coming to see you during the night, and if so, how often?: 0 = no memory; 1 = one visit remembered; 2 = two visits remembered, etc.

Finally, the occurrence of any of the following side-effects was scored as: 1 = slight, 2 = moderate, 3 = severe: sweating, undue depression (too heavily asleep), frequency of micturition, tachycardia, twitching, tremor, 'hangover', headache, visual disturbance, dry mouth, nausea or vomiting, residual drowsiness, muscular incoordination, dizziness, faintness, mental excitation, gastro-intestinal disturbance, skin rash.

Results

Rather more than half the patients elected to have sleeping tablets. At the pre-medication visit all patients were classified as grade 2, 3 or 4 and there was no significant difference between the drug groups.

In the analysis of results, patients with a history of taking sedatives or tranquillizers were excluded. There were nine patients who were given sleeping tablets during the later part of the night, and for whom less than five assessments were available; these patients were also excluded from the analyses presented below. Of the patients who received tablets, there were eight not having an operation the following day; these patients were not included in the analyses, although in fact their inclusion would have made little difference to the findings. With these exclusions, there were 131 cases available for comparison.

Table 1 summarizes the investigator's assessments in each group of patients:

Variable 1: this is simply an index of the cumulative total score, assessed as described above. A higher figure represents less sound sleep during the night. There was no statistically significant difference between the active drugs, although numerically the score for drug A was highest and that for drug B lowest. Patients who received no medication had a mean score slightly lower than the placebo group. The difference between drug B and drug D (placebo) was significant at the 2% level, and that between drug A and drug D at the 5% level, using Student's 't-test'.

Variable 2: there was very little objective restlessness with either drug A or drug B, rather more with drug D (placebo) and most of all with drug C (the barbiturate). Patients receiving no medication scored better than the placebo or barbiturate groups. None of these differences was statistically significant.

TABLE 1

Mean scores with standard errors for information collected by nurse-investigators during night of study (see text)

	Variable 1	Variable 2	Variable 3	Asleep at $\frac{1}{2}$ hr	Asleep at $1\frac{1}{2}$ hr
Drug A	11.2 $\pm$ 0.50 (20)	0.15 (20)	4.5 $\pm$ 0.41 (20)	25.0% (20)	85.0% (20)
Drug B	10.7 $\pm$ 0.53 (14)	0.29 (14)	4.2 $\pm$ 0.48 (14)	71.5% (14)	85.8% (14)
Drug C	10.9 $\pm$ 0.61 (20)	0.45 (20)	4.4 $\pm$ 0.51 (20)	45.0% (20)	100% (20)
Drug D (Placebo)	13.1 $\pm$ 0.69 (17)	0.41 (17)	5.82 $\pm$ 0.47 (17)	35.2% (17)	64.7% (17)
No tablet	12.4 $\pm$ 0.34 (60)	0.22 (60)	5.30 $\pm$ 0.23 (59)	33.3% (60)	81.7% (60)

Figures in parentheses are numbers of patients.

Variable 3: the scores for the three active drugs were almost identical; the difference between drug B and placebo was significant at the 5% level. Patients receiving no medication were close to the placebo group, but slightly better.

The last two columns of Table 1 show the percentage of patients in each treatment group who were asleep $\frac{1}{2}$ hr and $1\frac{1}{2}$ hr after medication (or after the time when medication would have been given, in the case of those patients who received nothing).

At $\frac{1}{2}$ hr, the proportion of patients asleep after drug B was higher than after placebo, although the difference was not statistically significant. After drug C, 45% of patients were asleep at $\frac{1}{2}$ hr and after drug A only 25%. The difference between drug B and drug A was statistically significant at the 2% level.

At $1\frac{1}{2}$ hr, over 85% of patients were asleep after each of the three active drugs; there was little difference between these scores, although the barbiturate appeared best since all patients were asleep. After placebo, 65% of patients were asleep after $1\frac{1}{2}$ hr; the difference between this and the barbiturate group was significant at the 2% level, but the χ^2 analysis in this case was based on small 'expected' numbers.

Of the patients who received no medication of any kind, 33% were asleep at $\frac{1}{2}$ hr (compared to 35% after placebo) and 82% were asleep at $1\frac{1}{2}$ hr.

The only side-effects noted were hangover, residual drowsiness, dizziness and headache. Hangover was reported once after drug A (moderate), once after drug B (moderate), three times after drug C (twice mild and once moderate), and

four times after placebo (twice mild and twice moderate). Residual drowsiness was noted six times after drug A (four times mild and twice moderate), four times after drug B (twice mild and twice moderate), four times after drug C (twice mild and twice moderate), and once after placebo (mild). Headache was reported once after drug A (moderate), once after drug B (moderate) and once after drug C (mild). Moderate dizziness was reported twice after drug A.

Fig. 1 summarizes the patients' responses to questioning on the morning after study. In response to all questions asked, the highest incidence of favourable replies came from the barbiturate group (drug C), and the lowest from the placebo group and the group who received no medication. There was almost no difference between drug A and drug B. Some representative χ^2 values were calculated, by comparing the favourable responses with the combined number of unfavourable and undecided responses. For the answers to the question 'Did you have a good or a bad night?' (Row 1) the difference between drug A and drug D (placebo) was significant at the 5% level, and that between drug C and drug D at the 1% level. In response to the question 'was it a restful night?' (Row 2) the difference between drug C and drug D was significant at the 5% level and that between drug A and drug D was not significant. For the question 'Do you think the night was better or worse than it would have been without a sleeping tablet?' (Row 3) the difference between drug A and drug D and between drug B and drug D were significant at the 5% level and that between drug C and drug D at the 1% level. For Row 4,

FIG. 1. Responses to questions asked the morning after study. Rows represent questions (see text) and columns represent medications (see text). The number above each bar is the actual number of patients, but the heights of bars have been scaled to a common percentage level, as indicated on the left.

the question about waking during the night, the number of patients who found difficulty in getting to sleep again was compared with the combined number of those who didn't wake up and those who woke up and went to sleep again easily; the difference between drug C and drug D was significant at the 5% level. Surprisingly few patients, however, managed, reported that they had not woken at all during the night. A further surprise was the low incidence of dreams (Row 5). Only four patients reported dreams; two of these claimed to have had unpleasant or disturbing dreams, one after placebo and one with no treatment.

Discussion

It is a common experience in hospital that patients will sometimes protest that they were unable to sleep at all during the night although in the opinion of the nursing staff they were soundly asleep whenever visited. Discrepancies of this kind were occasionally evident in the present study, but were insufficiently frequent to influ-

ence the final analysis of results. Of more interest is a general comparison between the value of the assessments made by the investigator during the night and the opinions reported by the patient in the morning.

The use of a whole-time trained nurse in this investigation has some parallels with studies of mild analgesics recently reported (Parkhouse, Collie & Wood, 1967; Parkhouse & Hallinon, 1967) and represents in some respects an extension of the work of le Riche & Belle (1963) and le Riche & Csima (1964). In the clinical assessment of phenomena such as pain and drowsiness there are always differences, but not always very clearly defined differences, between subjective and objective appraisal (Parkhouse & Holmes, 1963). In the present study, the only form of assessment available during the time of drug action was the investigator's opinion, since it was of little use to expect a subjective opinion from the patient while he was asleep! The response to questioning the following morning represented a retrospective judgment on the part of the patient, which may be called subjective. It should be pointed out, though, that this patient's opinion was still elicited by a single trained investigator, rather than by various members of the ward nursing staff. It should further be remembered that these questions were asked by the same investigator who had followed each patient through the night; it would, therefore, be expected that whenever some doubt arose as to the categorization of a patient's answer the tendency would be for the score put down to correlate with the nocturnal opinion. In future studies it would be interesting to see how a questionnaire handed to the patient for completion in the morning would compare with questioning by an investigator.

Experience in the clinical evaluation of analgesic drugs suggests that the opinion of a single, trained investigator is more sensitive than that of the ward staff. Likewise, Hinton (1961) found that it was easier to show differences between drugs from the measurement of nocturnal restlessness than from nurses' reports. In the present study it proved possible to distinguish between active drugs and a placebo, in quite small groups of patients, on the basis both of observation during the night and questioning the following day. There would seem to have been little difference in sensitivity between these two methods of assessment in the present case, but certain questions remain to be answered: one wonders, for instance, whether the answers to morning questions recorded by the investigator would have been as meaningful if she had not

been observing the patients throughout the night.

In assessing the clinical effects of a hypnotic drug the final court of appeal is the patient's opinion. It might well be argued, for example, that restlessness noted by an observer during the night is of little consequence if completely unremembered by the patient. In the present study the incidence of restlessness as observed objectively during the night was higher with butobarbitone than with any other form of management, yet when patients were asked the following morning 'Did you have a restful or a restless night?' there were no patients who admitted to restlessness, and the percentage who claimed to have had a restful night was higher than with any other form of management. Patients were not questioned in the morning about the speed of onset of sleep, so that only the investigator's nocturnal assessment was available. It would appear that a mixture of methaqualone and diphenhydramine hydrochloride was notably more effective than other forms of management in securing rapid sleep.

A study such as this throws interesting light on the response to placebo and the relative importance of psychological and pharmacological factors in securing sleep. Patients who elect to have no sleeping tablets are a self-selected group; although they may prove to be wrong in their judgment they expect to sleep with little difficulty, so that it may be assumed that psychological factors are very strongly in their favour. The placebo group was also self-selected, in the sense that these patients presumably felt that they were unlikely to get to sleep without the aid of a drug. As would perhaps be expected from these considerations, the scores for those patients who elected to have no medication were, on most of the criteria examined, better than the scores for the placebo group but not as good as the scores for the active drug groups. It would seem that receiving a placebo was not as effective in inducing sleep as having confidence in

one's own ability to sleep, and neither was as effective as receiving an active drug.

The results presented here are relevant only to the situation under discussion, the use of a single dose of a hypnotic drug to facilitate sleep on the night before an operation. The same results would not necessarily be expected from the repeated use of the same drugs in other circumstances, in mentally disturbed patients or in patients with chronic insomnia. The use of repeated doses raises the question of habituation, cumulative effect and the danger of overdosage. The present study is not relevant to these problems. Although the main conclusion from this investigation is that a standard barbiturate was rather better than either nitrazepam or a mixture of methaqualone and diphenhydramine hydrochloride it may well be that the non-barbiturate hypnotics would show up to more advantage in long-term administration.

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