Effect of Flurazepam on Sleep in the Laboratory

M.W. Johns and J.P. Masterton[1]

Sleep Laboratory, Department of Surgery, Monash University, Alfred Hospital,
Melbourne

Abstract. A new hypnotic drug, flurazepam, was given to six healthy young men in a blind trial involving sleep on four consecutive nights in the laboratory. Continuous recordings of the electroencephalogram, electro-oculogram and electrical resistance of palmar skin made throughout the

Key Words
Continuous electroencephalography
Electrical skin resistance
Flurazepam
Sleep

night enabled sleep to be analyzed objectively in terms of the usual stages. Sleep on the third night, when flurazepam 15 mg was taken, was compared with that on the second and fourth nights, when a placebo was taken. Flurazepam permitted sleep which was objectively better and subjectively as good as the best sleep without the drug. There was no inhibition either of REM-sleep or of δ-wave sleep as occurs with many other hypnotics.

Although there are some uncertainties about the criteria by which to judge the efficacy of hypnotic drugs (6), it is generally agreed that they should initiate sleep rapidly, maintain it for several hours with few awakenings and leave no deleterious hangover effects next day. They should also have the lowest possible toxicity in overdose and minimal capacity for inducing tolerance and dependence. In recent years, an additional criterion has been added: hypnotics should not affect the usual pattern of sleep stages, particularly REM or dreaming sleep and stage 4 sleep.

Most hypnotics, which are used commonly, fail to meet at least one and usually several of these criteria. In particular, it has been a matter of concern in recent years that most reduce the amount of REM sleep during the first few nights of their administration and then cause a rebound, with excess REM sleep,

and perhaps nightmares, and disturbed sleep after drug withdrawal (15). Although early fears that an absence of REM sleep for a few nights would lead to major psychiatric disturbances have proved to be exaggerated (2), much emphasis has been placed on finding an effective hypnotic drug which does not interfere with dreaming sleep.

Flurazepam is a relatively new hypnotic which is structurally similar to other benzodiazepine drugs, including nitrazepam and diazepam. It is widely used in the USA, and in the few clinical trials in which it has been studied in sleep laboratories, it has been found to be effective in reducing the latency before sleep onset and the number of awakenings during the night. Flurazepam is also said to increase the total duration of sleep without decreasing the proportion of REM sleep (4) but it may reduce the proportion of stage 4 sleep (10, 12). Of particular importance is the observation that flurazepam continues to be effective after continued use for many nights by insomniac patients. By contrast, some other hypnotics, such as glutethimide and chloral hydrate given in the usual therapeutic doses, become ineffective after being used for only a few nights (11).

An experiment was carried out among healthy young adults who took flurazepam 15 mg in a blind trial which involved four consecutive nights' sleep in the laboratory. The aim of this experiment, was not so much to confirm that flurazepam decreases the latency before falling asleep and reduces the number of awakenings during the night — none of the subjects suffered from insomnia — but was to determine also whether flurazepam, unlike most other hypnotics, permits undisturbed sleep, with the normal distribution of stages both on the night of its administration and later on the first night without the drug.

Methods

Six male medical students (ages 21–24) who were in the clinical years of their course at Monash University Medical School volunteered for the experiment. They were offered a small financial reward for spending four consecutive nights (Monday to Thursday) in the sleep laboratory. They were told that they would be involved in a trial of a new hypnotic drug. Only one subject had slept in the laboratory before this experiment began. The subjects were free from physical and psychiatric illness at the time, as judged by brief questioning and their responses to the Cornell Medical Index Health Questionnaire. None had used hypnotic drugs in the past. Responses to a detailed Sleep Questionnaire indicated that their sleep habits when at home were comparable to the average reported by two large groups of similar students (7).

Each subject came to the laboratory at approximately 30 min before the time at which he usually went to bed on week nights when at home. Electrodes were attached to record a single channel of the electroencephalogram (right parieto-temporal region referred to the left mastoid process), horizontal eye movements, and electrical resistance of skin measured from the palmar surfaces of the index and middle fingers (8). These three channels of information were recorded continuously on a FM magnetic tape recorder until approxi-

mately 07.45 h each morning. Each subject slept alone in a warm room with the recording equipment in an adjacent room. An analyzer which automatically counted the number of δ-waves with an amplitude exceeding 40 microvolts during each 20 sec of the EEG enabled each night's sleep to be analyzed objectively in terms of wakefulness and stages, 1, 2, 3, 4 and REM sleep, as defined by *Rechtschaffen and Kales* (16). Statistical differences between the characteristics of sleep on each night were tested by the Student's t-test for paired observations, accepting as significant a probability of < 0.05 in two-tailed tests.

A capsule containing flurazepam 15 mg was taken approximately 15 min before the lights were put out on the third night in the laboratory. Identical-looking and tasting placebo capsules were taken at comparable times on the first, second and fourth nights. Thus, the experimenters knew when the active drug was administered, but the subjects did not. In addition to the objective analysis of sleep each night, subjects recorded their own estimates of the times at which they slept, the number and duration of any awakenings during the night and the overall quality of the night's sleep.

Results

Of the 24 nights of recording, two (the fourth nights in two subjects) were technically unsatisfactory from the point of view of scoring individual sleep stages. Nevertheless, in all six subjects, it was possible to compare sleep on the first two nights in the laboratory, when placebo was taken, with that on the third night, when flurazepam was taken. In four subjects, comparisons could also be made with sleep on the night after drug administration.

Often, when sleep is recorded for the first time in the laboratory, there are more frequent awakenings, less REM sleep and longer delay before the start of the first REM period than on subsequent nights. This disturbance to sleep, called 'the first-night effect' (1), leads many investigators to discard results from their first-night recordings. Although only some of the differences between the first and second nights' sleep in the present investigation were statistically significant (table I), the overall pattern of changes was consistent with this 'first-night effect': on the first night, sleep was shorter and more disturbed; the amount of REM sleep was less (p < 0.05) and the delay before the first REM period was longer (p < 0.05) than on the second night. It is noteworthy that the amounts of δ-wave sleep (stages 3 and 4) were not affected. However, adaptation to the recording situation in the laboratory may not be complete by the second night. Therefore, in this investigation, the effects of flurazepam taken on the third night, were determined from the results of that night's recordings, in comparison with both the second and the fourth nights when placebos were taken. Thereby, any variations in sleep which were not caused by the drug could be identified more readily. In addition, any tendency for flurazepam to modify the amount of sleep obtained in each stage, might be manifested not only as a change in one direction from the second to the third nights, but also as a rebound phenomenon in the opposite direction on the fourth night. An example of the latter would be

Table I. The average characteristics of sleep for four nights measured objectively in healthy subjects taking either flurazepam 15 mg or placebo

	Average for night ± SD			
	first (placebo)	second (placebo)	third (flurazepam)	fourth (placebo)
Delay before falling asleep, min	16.8 ± 9.2	22.5 ± 25.5	12.7 ± 6.3	14.2 ± 8.0
Delay before first REM period, min	179.0 ± 94.5[1]	89.7 ± 30.1	109.0 ± 40.6	99.8 ± 23.6
Number of arousals to wakefulness in first 6 hours' sleep	8.3 ± 2.9	7.0 ± 3.6[2]	2.3 ± 2.0[1]	3.7 ± 1.2[1,2]
Total duration of wakefulness during night, min	64.0 ± 72.6	31.5 ± 26.8	17.7 ± 9.9	10.2 ± 5.2
Total duration of sleep, min	390.0 ± 55.0	421.8 ± 27.3[2]	471.8[1] ± 27.0	473.6 ± 23.1[1]
Minutes of stage 1	15.7 ± 8.8	12.5 ± 3.7	11.3 ± 5.5	11.0 ± 2.5
Minutes of stage 2	193.7 ± 57.7	201.2 ± 31.0	244.7 ± 43.7	248.8 ± 28.3
Minutes of stage 3	44.0 ± 20.6	48.2 ± 13.2	55.8 ± 24.6	39.8 ± 24.7
Minutes of stage 4	54.0 ± 24.7	51.2 ± 27.0	52.5 ± 23.8	64.3 ± 28.9
Minutes of REM	82.8 ± 18.6[1]	108.8 ± 10.4	107.5 ± 15.3	108.3 ± 6.9

There were results from six subjects for nights 1, 2 and 3, but from only four subjects on night 4.

1 Significantly different from corresponding results on the second night.
2 Significantly different from corresponding results on the third night.

an increase in the percentage of REM sleep above normal levels when the drug was withdrawn (14).

When flurazepam was taken on the third night, the total duration of sleep was significantly increased ($p < 0.05$) and the number of arousals to wakefulness during the first 6 h was decreased compared with the second night ($p < 0.01$). The increase in the total duration of sleep was almost entirely attributable to an increase in stage 2 — there was no change in either REM sleep or δ-wave sleep. The delay before falling asleep and the total duration of awakenings during the night were both decreased on the third night, but neither change was statistically *significant*.

On the fourth night, when placebo was taken again, the total duration of sleep did not change, but the number of arousals to wakefulness increased from the third night ($p < 0.05$). Once again, there was no significant change in the amount of REM sleep or of δ-wave sleep from the third (drug) night to the fourth (drug-withdrawal) night. Thus, there was a total of approximately 108 min of REM sleep and 100 min of δ-wave sleep on each of the second, third and fourth nights.

Compared with the second night, the total duration of sleep on the fourth night was increased ($p < 0.01$) and the number of arousals to wakefulness reduced ($p < 0.05$) — a difference which suggests that adaptation to the laboratory continued throughout the experiment. Nevertheless, flurazepam significantly reduced the number of awakenings during the night, when compared with the night before and the night after, and did not change the amount of REM sleep or δ-wave sleep obtained. The absolute amounts and percentages of time spent in each stage of sleep on both the third and fourth nights were virtually identical to the 'normal' figures reported for young adults by other investigators (9, 18).

The subjective quality of sleep after taking flurazepam was judged by each subject to be as good or better than that on any of the other nights. No side effects were noted apart from the comment of one student saying that he felt a little more listless than usual on the day after taking the drug.

Discussion

The results of this small-scale trial of flurazepam in the sleep laboratory are in agreement with many of the findings of other investigations. The lowest therapeutic dose of flurazepam recommended for use as an hypnotic (the dose in the treatment of severe insomnia would be 30 mg) permitted sleep in healthy young adults which was objectively better and subjectively as good as their best sleep without the drug. Unlike several other hypnotics, flurazepam has been found also to be an effective drug when used for prolonged periods by insomniacs (12). In double-blind trials involving subjective reports, patients with insomnia have preferred flurazepam to placebo (19) or to corresponding doses of either chloral hydrate or glutethimide (5).

Several investigators have shown that another benzodiazepine drug, nitrazepam, tends to inhibit REM sleep, at least for the first few nights, and may cause a rebound of REM sleep, and nightmares, after drug withdrawal (3, 15). There appears to be general agreement that flurazepam in the usual therapeutic dose does not do this (4, 10, 12). In contrast to the findings of the present investigation, *Kales et al.* (10, 12) reported that flurazepam inhibited stage 4 sleep. It may be that a more prolonged or higher dosage than that used here

would have that effect. However, *Kales et al.* observed this effect on the first night when flurazepam was administered.

Sambrooks et al. (17) have shown that flurazepam does not produce any significant decrement in visuo-motor performance when tested 1 h after ingestion of the drug, whereas nitrazepam does. This suggests that flurazepam may be preferable from the point of view of its effect, for example, on a patient's ability to drive a car.

Another important characteristic of this and, indeed, of any hypnotic, is its toxicity and tendency to produce difficult problems of medical management after being taken in overdose. There seems to be little doubt that nitrazepam presents few serious problems from this point of view (13). Whether or not this is true also of flurazepam has not yet been established, but if the latter proves to be relatively non-toxic when taken in overdose, it will be a useful hypnotic.

References

1 *Agnew, H.W.; Webb, W.B., and Williams, R.L.:* The first night effect: an EEG study of sleep. Psychophysiology 2: 263–266 (1966).

2 *Dement, W.C.:* The biological role of REM sleep (ca. 1968); in Sleep: physiology and pathology, pp. 245–265 (Lippincott, Philadelphia 1969).

3 *Haider, I. and Oswald, I.:* Effects of amylobarbitone and nitrazepam on the electrodermogram and other features of sleep. Brit. J. Psychiat. 118: 519–522 (1971).

4 *Hartmann, E.:* The effect of four drugs on sleep patterns in man. Psychopharmacologia 12: 346–353 (1968).

5 *Jick, H.:* Comparative studies with a hypnotic (RO5-6901) under current investigation. Curr. ther. Res. 9: 355–357 (1967).

6 *Johns, M.W.; Hepburn, M., and Goodyear, M.D.E.:* Use of hypnotic drugs by hospital patients. Med. J. Austr. 2: 1323–1327 (1971a).

7 *Johns, M.W.; Gay, T.J.A.; Goodyear, M.D.E., and Masterton, J.P.:* Sleep habits of healthy young adults: use of a sleep questionnaire. Brit. J. prev. soc. Med. 25: 236–241 (1971b).

8 *Johns, M.W.:* Methods for assessing human sleep. Arch. intern. Med. 127: 484–492 (1971).

9 *Kales, A.; Jacobson, A.; Kales, J.D.; Kun, T., and Weissbuch, R.:* All-night EEG sleep measurements in young adults. Psychon. Sci. 7: 67–68 (1967).

10 *Kales, A.; Kales, J.D.; Scharf, M.B., and Tan, T.L.:* Hypnotics and altered sleep-dream patterns. II. All-night EEG studies of chloral hydrate, flurazepam and methaqualone. Arch. gen. Psychiat. 23: 219–225 (1970a).

11 *Kales, A.; Allen, C.; Scharf, M.B., and Kales, J.D.:* Hypnotic drugs and their effectiveness. All-night EEG studies of insomniac subjects. Arch. gen. Psychiat. 23: 226–232 (1970b).

12 *Kales, J.D.; Kales, A.; Bixler, E.O., and Slye, E.S.:* Effects of placebo and flurazepam on sleep patterns in insomniac subjects. Clin. Pharmacol. Ther. 12: 691–697 (1971).

13 *Mathew, H.; Proudfoot, A.T.; Aitken, R.C.B.; Raeburn, J.A., and Wright, N.:* Nitrazepam – a safe hypnotic. Brit. med. J. iii: 23–25 (1969).

14 *Oswald, I. and Priest, R.G.:* Five weeks to escape the sleeping-pill habit. Brit. med. J. *ii:* 1093–1095 (1965).

15 *Oswald, I.:* Drugs and sleep. Pharmacol. Rev. *20:* 273–303 (1968).

16 *Rechtschaffen, A. and Kales, A.* (ed.): A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. US Nat. Inst. Hlth Publ. No. 204 (1968).

17 *Sambrooks, J.E.; MacCulloch, M.J.; Birtles, C.J., and Smallman, C.:* Assessment of the effects of flurazepam and nitrazepam on visuo-motor performance using an automated assessment technique. Acta Psychiatr. scand. *48:* 443–454 (1972).

18 *Williams, R.L.; Agnew, H.W., jr., and Webb, W.W.:* Sleep patterns in young adults: an EEG study. EEG Clic. Neurophysiol. *17:* 376–381 (1964).

19 *Zimmerman, M.A.:* Comparative effects of flurazepam hydrochloride (Dalmane) and placebo in patients with insomnia. Curr. ther. Res. *13:* 18–22.

Request reprints from: Dr. *M.W. Johns,* Department of Surgery, Monash University Medical School, Alfred Hospital, *Prahran, Victoria 3181* (Australia)