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ANXIETY AND SLEEP AFTER FOSAZEPAM

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1 Six volunteers of mean age 59 years received placebo for a week, then fosazepam (60 mg) nightly for 3 weeks, then placebo for 3 weeks. Subjective ratings and all-night electrophysiological recordings were made.

2 Fosazepam administration improved subjective sleep quality but impaired feelings of morning vitality. Its withdrawal was associated with anxiety, impaired concentration and continuing impairment of morning vitality. Measured sleep duration increased on fosazepam, sleep was less broken, slow wave sleep stages 3 and 4 diminished in duration and so did REM sleep.

3 Despite the short half-life of fosazepam some drug effects persisted for several days after withdrawal, suggesting action of a long half-life metabolite.

Introduction

Fosazepam is a new benzodiazepine and serum concentrations after intravenous injection in man reveal that it has a short half-life of about two hours (Hoechst AG, internal report). Its formula is shown in Figure 1.

The major metabolite is 3-hydroxyfosazepam, which has a half-life of under 4 hours. The second known metabolite is desmethyldiazepam, originally believed to account for 8% of the breakdown products (Hoechst AG, internal report) but, as will be mentioned later, this may be an underestimate. The compound is water-soluble and has sedative, muscle-relaxing and anti-convulsant properties in mice, while trials in humans indicate that a dose of 60-80 mg may be useful in clinical practice (Hoechst AG, internal report).

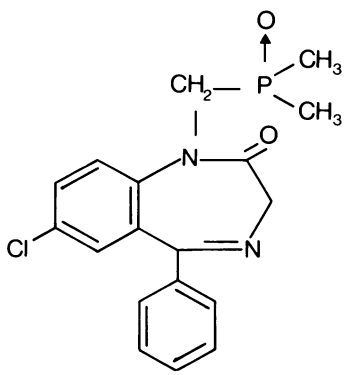

Figure 1 The structural formula of fosazepam.

Methods

Six volunteers who regarded themselves as poor or rather poor sleepers, two men and four women aged 55-63 (mean 59 years), participated during a 7 week period. Each day they completed 100 mm visual analogue self-ratings of (a) daytime anxiety and (b) daytime powers of concentration, making these ratings each evening, (c) sleep quality (d) feelings of zest and freshness, these being rated each morning about 20 min after rising. Ultimately the point at which the individual had made the mark was measured in mm from the left hand end of the line. The subjects attended the sleep laboratory for all-night electrophysiological recording during the first 5 weeks. In the first week they took placebos at bedtime and there were an initial two nights under full laboratory conditions for adaptation, followed by three more nights for baseline data. In the next week, the first, second and fifth nights on fosazepam (60 mg) nightly were recorded in the laboratory. Fosazepam continued to be taken nightly and in the third week subjects attended the laboratory once for adaptation and then in the fourth week were recorded on the fifteenth, sixteenth and nineteenth drug nights. In the fifth week they resumed placebos and slept in the laboratory on the first, second and fifth nights of the placebo pills, which were continued for three withdrawal weeks in all.

When the experiment was complete the simultaneous records of electroencephalogram (EEG). electromyogram and electro-oculogram

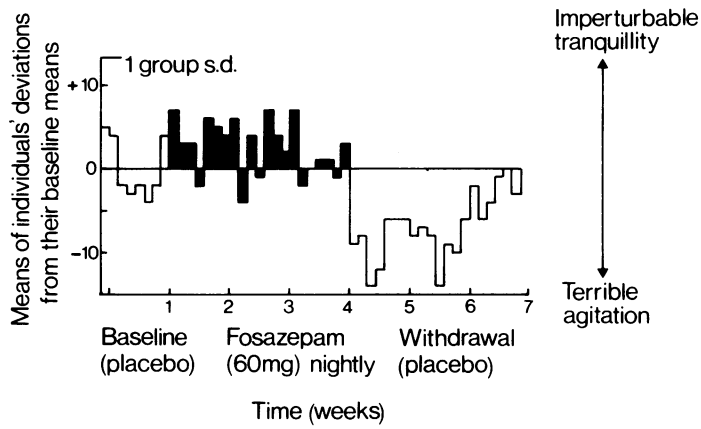

Figure 2 The effect of fosazepam and fosazepam withdrawal on anxiety. Withdrawal of fosazepam was associated with an increase in anxiety and this was significant ($P < 0.01$) when the three withdrawal weeks were compared with the baseline week.

were coded and scored 'blind' in 20 s epochs for the stages of sleep (Rechtschaffen & Kales, 1968). The raw data were then analysed by computer.

A one-way analysis of variance for repeated measures in unequal samples was used for the sleep data (Winer, 1962) and planned comparisons were made between treatment means and baseline means. For the subjective data one-way anovar was used to evaluate overall differences between treatment conditions, followed by Tukey's test to compare treatments with baseline (Bond & Lader, 1974). Some of the sleep data presented are for the first 6 h of accumulated sleep. On some nights some subjects did not achieve 6 h of sleep and here figures have been obtained by taking the mean for the first hour, the mean for the second hour and so on. The mean for the first 6 h could then be derived from the hourly means even though the fifth and sixth hour means had sometimes been derived from fewer than six subjects.

Results

Subjective feelings

Analysis of variance of the anxiety data demonstrated that significant differences were present ($F = 36.7$, d.f. = 1,46; $P < 0.01$). Figure 2 suggests a reduction of daytime anxiety during intake of fosazepam but on using Tukey's test this just failed to reach significance ($t = 2.02$, d.f. = 28). Withdrawal was associated with anxiety greater than during baseline and this was significant when the three withdrawal weeks were compared with the baseline week ($t = 5.28$, d.f. = 27; $P < 0.01$) or the drug period ($t = 8.86$, d.f. = 40; $P < 0.01$). Additional examination of smoothed curves suggested peak withdrawal symptoms were on the third and fourth days. Analysis of variance demonstrated significant differences in self-rated powers of concentration among the conditions ($F = 6.38$, d.f. = 2,46; $P < 0.01$). There was a non-significant impairment during fosazepam, with definite impairment during the withdrawal period ($t = 3.1$, d.f. = 27; $P < 0.01$).

The morning ratings of sleep quality were significantly altered and showed improvement during the three drug weeks compared with the baseline week ($t = 3.55$, d.f. = 28; $P < 0.01$) and a brief impairment early in withdrawal compared with baseline (NS for the full withdrawal period). Analysis of variance showed significant differences in morning vitality ($F = 18.46$, d.f. = 2,46; $P < 0.01$). This was impaired during the drug period ($t = 5.62$, d.f. = 28; $P < 0.01$) and during the withdrawal period ($t = 2.79$, d.f. = 27; $P < 0.01$) compared with baseline.

Sleep

The findings of principal interest shown in Table 1 have been obtained by taking the mean of each subject's three nights under each of the four conditions of baseline, early drug, late drug and withdrawal and then obtaining the means and s.d. for the six subjects.

Total sleep duration increased during the drug period and during the late drug period this was significant compared with baseline ($F = 5.16$, d.f. = 1,34; $P < 0.05$). The lowest mean value for any of the individual twelve nights was on the first

Table 1 Sleep and fosazepam (60 mg). Mean results ± s.d. (n = 6) of each subject's three nights under each of the four conditions of baseline, early drug, late drug and withdrawal.

	Baseline	*Early drug*	*Late drug*	*Withdrawal*
Total sleep time (min)	400.1 ± 65.93	436.5 ± 49.9	455.3 ± 36.1	421.3 ± 47.6
Sleep latency (min)	48.9 ± 43.2	40.0 ± 34.7	33.2 ± 32.7	48.4 ± 41.7
REM latency (min)	69.9 ± 14.5	55.9 ± 8.6	87.5 ± 28.6	85.2 ± 26.8
Number of shifts to awake, first 6 h sleep	3.1 ± 2.7	1.0 ± 1.0	0.8 ± 0.5	2.6 ± 1.4
Intervening wakefulness (min) first 6 h sleep	18.0 ± 17.3	3.4 ± 3.3	9.8 ± 10.5	28.2 ± 21.9
Stage 1, first 6 h sleep (min)	22.8 ± 9.6	18.2 ± 4.5	30.1 ± 26.0	38.7 ± 18.1
Stage 3 + 4, first 6 h sleep (min)	82.3 ± 38.0	74.9 ± 33.3	61.7 ± 17.2	49.0 ± 23.3
% REM, first 6 h sleep	18.6 ± 5.8	14.6 ± 4.0	12.0 ± 2.1	15.5 ± 3.8
% REM in total sleep	21.7 ± 3.9	21.0 ± 3.8	19.3 ± 2.9	20.1 ± 1.2

withdrawal night, mean sleep duration being only 380.4 minutes. Subjects on average fell asleep more quickly during drug administration, though this did not quite reach significance on analysis of variance. Delay between sleep onset (first stage 2) and the first REM (paradoxical) sleep was not significantly affected.

Sleep was less broken on fosazepam, with fewer transitions into wakefulness in the course of accumulating 6 h of sleep, and in fact the means for all six drug nights were lower than for all six placebo nights. The mean duration of intervening wakefulness was reduced and rose sharply on withdrawal; the lowest three means of the twelve individual nights were the three early drug night means and these were significantly lower than baseline (F= 4.94, d.f. = 1,34; $P < 0.05$). The proportion of sleep spent in stage 1 (drowsiness) was little affected but became maximal on withdrawal (NS). Slow wave sleep stages 3 and 4 fell progressively during the experiment so that by the withdrawal week they were significantly lower than baseline (F = 5.97, d.f. = 1,34; $P < 0.05$). REM sleep as a percentage fell in the first 6 h of sleep during drug intake. The fall by the late drug period was significant in the first 6 h compared with baseline (F = 8.88; d.f. = 1.34; $P < 0.01$). No REM sleep rebound was seen within the period of the study.

No notable distribution effects of the drug were found in hour-by-hour analysis. Data of the individual nights suggested persistence of drug effects into the withdrawal period – thus the number of transitions into wakefulness, duration of intervening wakefulness and total duration of stage 1 were all found to rise to their maxima for the entire study on the fifth night after withdrawal and only on this night was the steady downward trend of stage 3 + 4 duration reversed.

Discussion

The effects of fosazepam on sleep resemble those reported for other benzodiazepines. The onset of sleep occurred sooner, it lasted longer and was less broken. There was a progressive and persisting decline of slow wave sleep, as has been reported in the case of chronic intake of flurazepam (Kales, Kales, Bixler & Slye, 1971), diazepam (Fisher, Kahn, Edwards & Davis, 1973; Kales & Scharf, 1973), flunidazepam, also known as flunitrazepam or Ro 5-4200 (Oswald, Lewis, Tagney, Firth & Haider, 1973; Monti, Trenchi, Morales & Monti, 1974), chlordiazepoxide (Hartmann & Cravens, 1973) and observed in recent unpublished studies of nitrazepam in this laboratory. REM sleep is not dramatically affected by most benzodiazepines but, at least with heavier doses, some reduction is brought about (Oswald & Priest, 1965; Kales, Kales, Scharf & Tan, 1970a; Hartmann & Cravens, 1973) and evidence of this can be found in the first 6 h of sleep of our subjects.

Subjective estimates of sleep have often been reported to show improvement when hypnotic drugs are given, for example, flurazepam (Kales & Scharf, 1973; Dement, Zarcone, Hoddes, Smythe & Carskadon, 1973) but little attempt has been

made to consider subjective variables following withdrawal. In the present study we have again found subjective sleep improvement during drug intake but concomitant loss of zest and freshness in the morning. There was a trend towards daytime anxiety reduction while on the drug but there was a prolonged and striking increase of anxiety following withdrawal. To this anxiety may presumably be attributed the poor daytime concentration and sense of subjective impairment on rising in the morning that were present following withdrawal.

Benzodiazepines and their active metabolites tend to be slowly eliminated so that, for example, maximal withdrawal effects on sleep are delayed after nitrazepam (Oswald & Priest, 1965). Kales, Allen, Scharf & Kales (1970b) noted persistence of the effects of flurazepam after withdrawal for two nights.

The anxiety ratings and a number of sleep variables in the present study suggested persistence of active drug for at least 3 days and it is of interest that when the investigation began we knew only that fosazepam had a short half-life but have lately learned that subsequent estimates of 8% conversion to desmethyldiazepam may be too low by a factor of three or more. We therefore must believe fosazepam to be metabolized in significant proportions to N-desmethyldiazepam, a cumulative substance with a half-life of about 3 days (communication from Hoechst Pharmaceuticals Ltd). This slowly-eliminated compound is an important metabolite of diazepam (Schwartz, 1973) and one must suppose that the prolonged anxiety and other effects we have seen following withdrawal of fosazepam would be no less likely after intake of benzodiazepines such as diazepam. If this is true it would point to a self-perpetuating feature in the clinical consumption of benzodiazepines in that they are taken to relieve anxiety but are responsible for enhanced anxiety as soon as an attempt is made to stop them.

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