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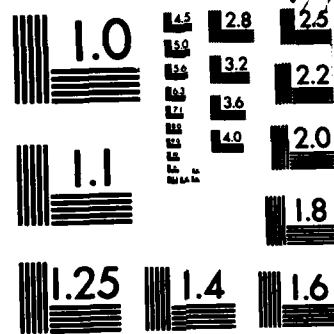
BENZODIAZEPINE EFFECTS ON AROUSAL THRESHOLD DURING
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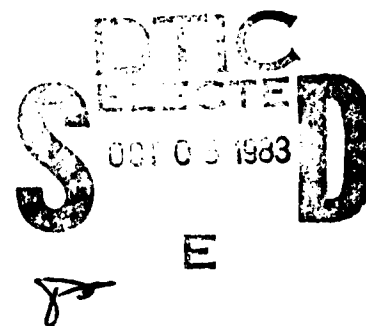
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REPORT NO. 83-17



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Laverne C. Johnson and Cheryl L. Spinweber



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SUMMARY

Noise is often the reason given for poor sleep, and sedative hypnotics are frequently used to insure "deeper" sleep and fewer awakenings. In a series of studies, the effects of benzodiazepines on arousal threshold during sleep have been investigated. Two studies, one using flurazepam, 30 mg, over 10 nights and one using triazolam, .5 mg, over 6 nights were conducted in the authors' laboratory. A third study at the University of Florida measured the effects of flurazepam, 30 mg, and pentobarbital, 100 mg, each administered on two nights. All drug threshold levels were compared to placebo values.

All three studies found that the sedative hypnotics increased arousal threshold to an intermittent pure tone. The placebo groups' highest mean arousal threshold was 70-75dB , compared to 100-110dB threshold values for the hypnotic group. The increase in arousal threshold occurred during the first hours of sleep, reaching a peak around 120-150 minutes post-ingestion. Return to sleep was also more rapid in medicated subjects, and the reduction in sleep latency followed the same time course as did the change in arousal threshold. Arousal threshold and sleep latency did not differ between drug and placebo groups after 3 hours post-administration.

The short acting benzodiazepine, triazolam, and flurazepam with its long acting metabolite did not differ in the magnitude of the elevation of arousal threshold, time course of effects across the night, or type of change over nights of consecutive use.



INTRODUCTION

Though objective EEG arousal data have indicated no significant difference between good and poor sleepers in auditory arousal threshold from sleep (Johnson, Church, Seales and Rossiter, 1979), poor sleepers invariable report that they are "light sleepers" and are easily awakened by noises. These poor sleepers also report difficulty in returning to sleep once awakened. Benzodiazepine sedative-hypnotics, when given to insomniacs, decrease sleep latency, awake time after sleep onset, number of body movements, and the number of nocturnal awakenings, as well as producing subjective reports of having slept more "deeply" and "restfully". These subjective reports of "deeper" sleep occur even though EEG recordings indicate a benzodiazepine-related decrease in deep sleep, stage 4.

Are there objective data to support this subjective report of "deeper" sleep? If there is an increase in arousal threshold, is it related to time post drug ingestion or to stage of sleep? Is there a difference in effects on arousal threshold over the night between a hypnotic with a long acting metabolite, half-life of 24-100 hours, and a short acting benzodiazepine having a half-life of 2-3 hours? This paper will review work from our laboratory relevant to these questions.

METHOD

STUDY 1. FLURAZEPAM:

In our initial study we investigated the effects of flurazepam, 30 mg, on the auditory arousal threshold of 12 male poor sleepers (sleep onset insomniacs, mean age 21.3 ± 1.0 years) selected on the basis of subjective complaints of poor sleep and EEG criteria of sleep latencies greater than 30 minutes on two consecutive screening nights (Johnson et al. 1979). After the 2 screening nights, all 12 poor sleepers received placebo for 7 baseline nights (study nights 1-7). Then 6 subjects received flurazepam 30 mg for 10 additional nights (study nights 8-17), and 6 continued to receive a placebo for the 10 nights. Except for the first 2 treatment nights, subjects slept in the laboratory on each study night. Lights out was at 2200 h and wake up was at 0530 h. Medication was

administered 15 minutes before lights out. EEG sleep activity was recorded according to standard criteria (Rechtschaffen and Kales, 1968). Only the arousal data are discussed in this paper.

An ascending series of stimulus tones was employed to obtain arousal thresholds. The stimuli were 1,000 Hz, 2 sec. tones delivered at 30 sec. intervals, through a speaker placed 46 cm above the subject's head. Before the subject was instructed to "go to sleep", awake auditory thresholds were determined on each arousal night. The awake auditory threshold varied between 35-38 dB (SPL re 0.0002 dynes/cm²) for all subjects. The background noise level varied from 32-34dB. During sleep, tones began at 35dB and were increased in approximately 5dB steps until the subject pressed a signal button three times and said, "I'm awake". Arousal thresholds were obtained during: (1) first stage 2, (2) first stage 4, (3) second REM period, (4) stage 2 following the second REM period and (5) at 0530 h, the time of the morning arousal. Each sleep stage had to be firmly established for a period of at least 3-5 minutes for a stimulus to be given. At least 30 minutes of uninterrupted sleep preceded each arousal except for arousal 1 where tones started 3-5 minutes following sleep onset (stage 2). Arousal tones were not given within 5 minutes of a body movement even when the movement did not change the sleep stage. The above schedule was followed on study nights 1 and 5 (baseline) and on nights 11 and 15 (treatment). Arousal threshold data were also collected on the first of the 3 follow-up nights, study night 18. After being aroused from sleep, the subject was told (via an intercom) to go back to sleep. The sleep latency was the time interval between this verbal command and the first sleep spindle, K-complex (stage 2), or REM epoch.

RESULTS

The flurazepam and placebo groups did not differ significantly in arousal threshold on any of the comparisons during placebo nights. The average arousal threshold for the subjects who later received flurazepam was 76 ± 16 dB, and for those who continued to receive placebo capsules, 75 ± 14 dB. Since there were no between-night effects for baseline study nights 1 and 5 and for treatment study nights 11 and 15, the data were combined (i.e., mean of 1 + 5 and 11 + 15) to examine placebo-flurazepam group differences. The average arousal threshold over

the night for the flurazepam group ($81 \pm 22\text{dB}$) was higher than for the placebo group ($71 \pm 17\text{dB}$) but not significantly, $t(10) = 1.14$.

Examination of our data from sleep stage arousals within the night indicated a time course effect. There was a gradual rise in arousal threshold during the first 2 hours post-administration and then a decrease for the remainder of the night (Fig. 1). To examine this time course, a stage-by-stage comparison was done. Although the arousal threshold was higher for the stage 4, REM, and second stage 2 arousals, the t-test indicated that only the mean stage 4 arousal threshold ($\bar{x} = 99 \pm 25\text{dB}$) for the flurazepam group was significantly higher than for the placebo group's mean arousal threshold ($\bar{x} = 73 \pm 13\text{dB}$), $t(10) = 2.30$, $p < 0.025$ (one tailed). The mean time since pill administration to the stage 4 arousal was 101 ± 45 minutes. The increase in arousal threshold for the flurazepam subjects was present on study night 11 and did not further increase (or decrease) on subsequent drug nights.

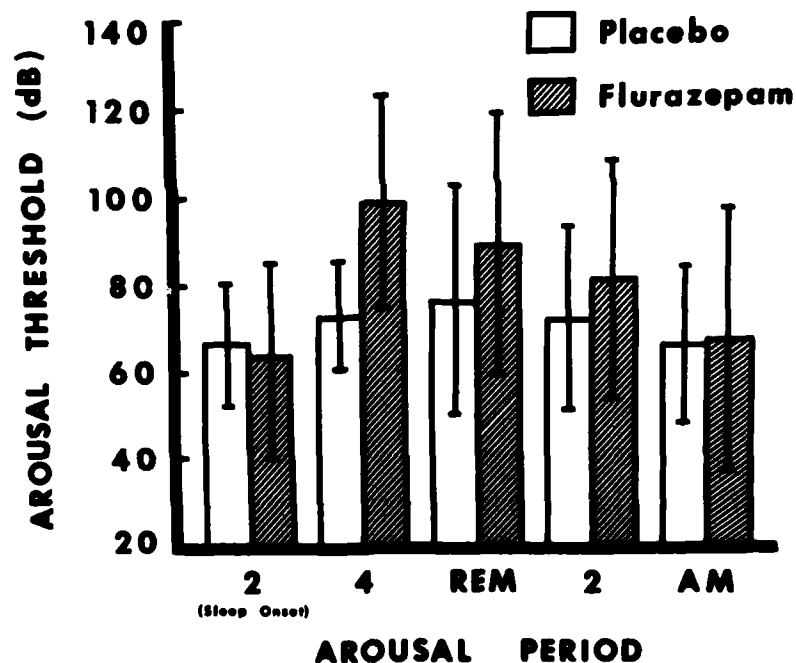


Fig. 1 - Flurazepam and placebo group mean ($\pm$ SD) auditory arousal thresholds by arousal periods (placed in chronological order).

No significant differences between the flurazepam and placebo groups were observed during the follow-up nights. On follow-up, the flurazepam group's arousal thresholds and sleep latencies returned to approximate baseline levels.

Study 2. TRIAZOLAM:

Triazolam is a short acting benzodiazepine hypnotic with a reported 2-3 hour half-life. In this study 20 male poor sleepers (mean age 21 ± 2.37 years), were recorded during one screening night, and three consecutive placebo-baseline nights. Following the placebo-baseline, 10 subjects continued to receive the placebo for 6 nights and 10 received triazolam, 0.5 mg, for 6 nights in a double blind paradigm. After the 6 treatment nights, all subjects received a placebo for 2 withdrawal nights. The selection criteria for poor sleepers and nighttime recording procedures were the same as in Study 1 (see Spinweber and Johnson, 1982).

While the arousal procedure was similar to that in Study 1, there were some differences. The threshold for arousal from sleep was obtained on 3 recording nights: night 3 (placebo-baseline), night 6 (second treatment night), and night 8 (fourth treatment night). Tones were 2 sec. long and occurred at 16 sec. intervals. Arousals were scheduled to reveal the time course of action of triazolam and were performed six times: (1) during the first stage 2 sleep, 5 minutes after sleep onset; (2) during the first SWS (stage 3 or stage 4) at least 20 minutes after the return to sleep following the first arousal; (3) in the stage 2, 150-210 minutes after lights out (0030-0130 h); (4) in stage 2, 270-330 minutes after lights out (0230-0330 h); (5) in stage 2, 370-430 minutes after lights out (0410-0510 h); (6) the morning arousal, at 0530 h.

The criteria which had to be met to initiate arousal procedures were similar to those of Study 1. The dB level for the highest tone presented and the latency (in minutes) from the time of awakening to the return to sleep were recorded.

RESULTS

Arousal threshold was significantly higher during treatment for triazolam subjects at the time of the first [$t(18) = 2.44, p < 0.025$], second [$t(16) = 5.65, p < 0.0005$], and third [$t(17) = 2.93, p < 0.005$] arousals (Fig. 2). (Not all subjects met the criteria for all arousals, thus altering the degrees of freedom reported above).

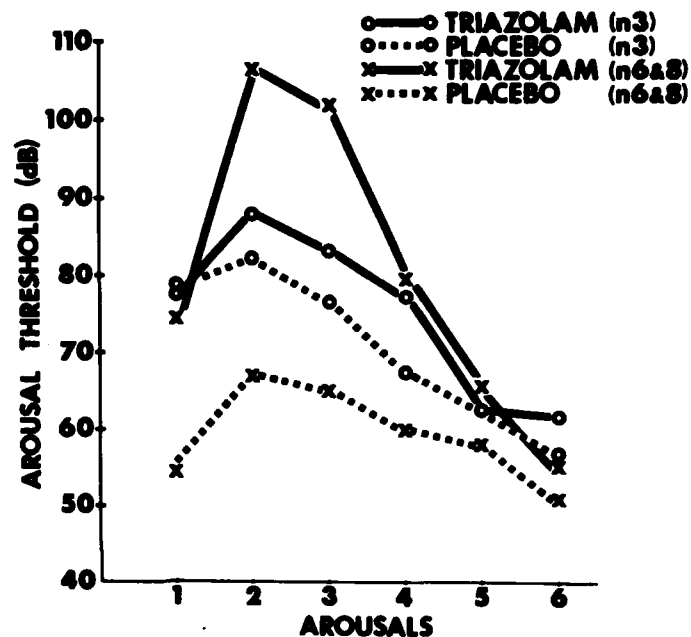


Fig. 2 - Mean arousal thresholds for the placebo-baseline night (n3) and for the mean of 2 treatment nights (n6 and 8).

Within-group analyses revealed that triazolam significantly raised arousal threshold for the SWS arousal [$t(9) = 3.40, p < 0.005$]; it was also found that placebo group subjects became more sensitive to the tone with repeated experience and had significantly reduced arousal threshold levels during the treatment for the first, second, and third arousals.

In Fig. 3 are the arousal threshold curves for both flurazepam and triazolam. The curve for the combined placebo groups is also drawn for comparative purposes.

The differences between the two hypnotic curves were not statistically significant for any arousal. The similarity of the two curves is most striking.

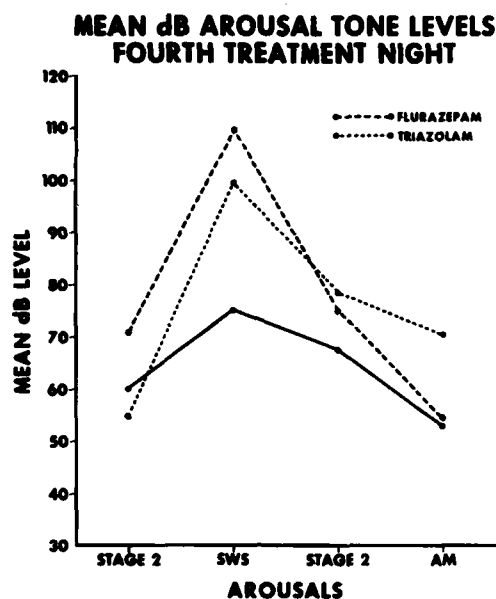


Fig. 3 - Comparison of arousal threshold for flurazepam and triazolam. Solid line is threshold for combined placebo groups.

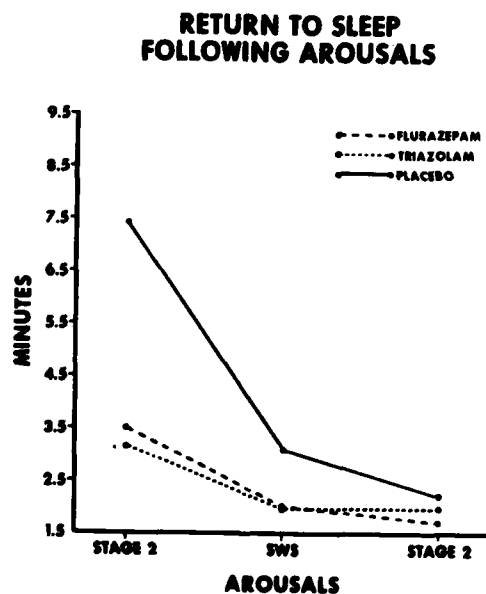


Fig. 4 - Latency of return to sleep (stage 2) following arousals.

Both hypnotics reduced the latency to return to sleep after arousal when compared to placebo (Fig. 4). The flurazepam group had a significantly shorter mean sleep latency following the first arousal period during treatment nights. During subsequent arousals, the sleep latencies for both flurazepam and placebo groups were short and did not differ significantly from each other. For triazolam subjects, latency of return to sleep following arousal during treatment was significantly reduced for the first, second, and third arousals.

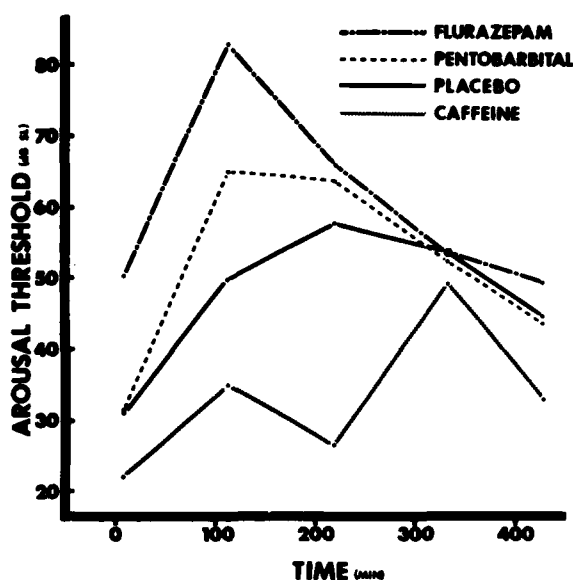
CONCLUSIONS

These data show that these two benzodiazepines do increase arousal threshold. Bonnet, Webb and Barnard (1979) have reported a similar increase in arousal threshold after ingestion of flurazepam, 30 mg. Of particular interest is the similar time of night effect we found for flurazepam with its long acting metabolite N-desalkylflurazepam and for the short acting triazolam. A similar time of night effect was found for flurazepam and also for pentobarbital by Bonnet et al. (1979). In our two studies as well as that of Bonnet et al. (1979), arousal threshold increased during the first two hours after administration, then decreased for the remainder of the night. The 0530 h arousal was very similar to that found 3-5 minutes after initial sleep onset and at these times the thresholds for placebo and drug groups were similar.

This time of night effect appears to be related to time post-administration and not due to stage of sleep. While our highest arousal levels were found during SWS, Bonnet et al. (1979) awakened their subjects only from stage 2 sleep, and they also found the highest arousal threshold near the second hour of sleep (see Fig. 5).

It is well established that with consecutive nights of use, there is a build up in plasma levels of N-desalkylflurazepam, but no build up of triazolam in plasma is seen. This contrasting pattern of accumulation in plasma was recently demonstrated over 37 nights of administration of triazolam and flurazepam

FIG. 5 - Time course of flurazepam, pentobarbital, placebo and caffeine as measured from auditory arousal threshold from stage 2 sleep. Adapted from Bonnet et al. 1979.



(Johnson, Spinweber, Seidel and Dement, 1983; Mittler, Seidel, Van den Hoed, Greenblatt and Dement, in press). It is generally assumed that with a build up of N-desalkylflurazepam levels there are more sedative effects. However, recent studies have indicated the absence of a clear relationship between N-desalkylflurazepam plasma levels and daytime performance (Johnson and Chernik, 1982; Mendelson, Weingartner, Greenblatt, Garnett and Gillin, 1982). Johnson et al. (1983) also found that triazolam and flurazepam produced similar patterns of EEG changes during 37 treatment nights and 5 withdrawal nights. Both hypnotics showed an increase in sleep spindles and a decrease in delta activity.

What are the implications for those who complain of poor sleep because of noise? Most benzodiazepines will increase arousal threshold especially during the first hours of sleep and during this time period benzodiazepines are effective in assisting the return to sleep after being awakened. Our data suggest that these hypnotics would be less useful in maintaining sleep in noisy environments during the early morning hours. But once the sleep process is well established, it becomes more resistant to internal and external disruption of its night patterns. However, the results of the review by Johnson and Chernik (1982) indicate that it is unlikely that the hypnotically induced "deeper" sleep will lead to improved daytime performance.

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