

DIAZEPAM AND 3-HYDROXYDIAZEPAM (TEMAZEPAM) AND SLEEP OF MIDDLE AGE

A.N. NICHOLSON & BARBARA M. STONE

Royal Air Force Institute of Aviation Medicine, Farnborough, Hampshire

- 1 Effect of diazepam (5 and 10 mg) and temazepam (10, 20 and 30 mg) on the sleep of six healthy middle aged (45–55 years) males was studied using electroencephalography for sleep measures, and analogue scales for subjective assessments of well being and sleep quality.
- 2 In placebo studies the sleep of the group was compared with that of young adults (20–29 years). In the older group there was a marked reduction in total sleep time ($P < 0.01$), an increase in latency to stage 3 sleep ($P < 0.01$), and an increase in percentage of stage 1 (drowsy) and stage 2 sleep ($P < 0.05$ and 0.001 respectively). There were no changes in percentage or latency of rapid eye movement sleep.
- 3 With the middle aged group there was no increase in total sleep time with diazepam and temazepam. Sleep onset latencies were shortened by 5 and 10 mg diazepam ($P < 0.05$), but there was no change with temazepam. Number of awakenings was reduced by 30 mg temazepam ($P < 0.01$), and the duration of awakenings was reduced by 5 and 10 mg diazepam ($P < 0.05$) and by 20 and 30 mg temazepam ($P < 0.01$). Awake activity was reduced by 5 and 10 mg diazepam ($P < 0.001$) and by 10 mg ($P < 0.05$) and 20 and 30 mg ($P < 0.001$) temazepam. The subjects assessed their sleep as improved with diazepam and with temazepam without residual effects on well-being.
- 4 Though the effect of diazepam (5–10 mg) and temazepam (10–20 mg) may not be so pronounced as that of other hypnotics, they are likely to be useful over an age range which includes, at least, young adulthood and late middle age. A particular advantage of these drugs is that within these dose ranges they are without residual effects on performance.

Introduction

Sleep changes with age, and in healthy males sleep from the early twenties to the late fifties becomes increasingly disturbed and less restful. There are more awakenings, and more of the sleep period involves awake activity and drowsy sleep, while there is less slow wave sleep, and total sleep time is decreased (Williams, Karacan & Hirsch, 1974). These changes occur within an important age range, and the possibility arises that over this span of life hypnotics may have different effects on sleep. It is in this context that we have studied two hypnotics, diazepam and 3-hydroxydiazepam (temazepam), each of which is likely to be without residual effects on performance within specified dose ranges (Clarke & Nicholson, 1978).

Methods

The subjects were six healthy male physicians aged between 45 and 55 years. Assessment of each

treatment (placebo or dose of a drug) involved three days. They slept at home for two nights, and on the third night they slept in the sleep laboratory. Each night the subjects retired at a set time between 23.00 and 23.30 h, and on the third night they reported at the sleep laboratory 1.5 h before their set time to retire. At 0.5 h before 'lights out' they completed assessments of their well-being related to a 100 mm analogue scale. Assessment (A) was: How did you feel during the day? *Tired* (00)—*Fresh* (100) and Assessment (B) was: How do you feel now? *Tired* (00)—*Wide Awake* (100). The drug or placebo was taken at 'lights out'. They remained in bed for at least 7.5 h, and 0.5 h after awakening completed four further assessments. The assessments and the extremes of the 100 mm analogue scales were C: I slept, *very poorly*—*very well*, D: Now I feel, *very sleepy*—*wide awake*, E: I fell asleep, *never*—*immediately* and F: After I fell asleep, I slept *very badly*—*very well*. In each case a favourable response tended toward the 100 extreme of the scale.

Two 3-day assessments with ingestion of placebo on the third night in the sleep laboratory were used for adaptation of the subjects. The study was carried out in two parts. In the first part the subjects ingested on separate occasions 10, 20 and 30 mg temazepam, and in the second part 5 and 10 mg diazepam. Temazepam was available as soft gelatine capsules (Scherer formulation), and diazepam as hard capsules. On each occasion the subject ingested two identical capsules. Two additional placebos were included to provide control values related to each drug. The experiments were double blind, and the order of drugs and placebo was random within each study. Sleep with placebo of six healthy male volunteers aged between 20 and 29 years was recorded to provide comparative values, though the subjects of the two groups were not matched for nicotine and alcohol consumption.

All subjects were familiar with the laboratory, the techniques used in recording sleep activity, and consented to the experimental protocol. They were required to refrain from napping and undue exercise, and to abstain from caffeine and alcohol after mid-day on the day which involved recordings overnight. The sleep laboratory was sound attenuated, and the temperature ($18 \pm 1^\circ\text{C}$) and humidity ($55 \pm 2\%$) were controlled. At least 7 days separated each study. Details of recording techniques, scoring of electroencephalographic records into sleep stages, and statistical analysis of sleep measures and analogue scales are given in a previous paper (Nicholson, Stone, Clarke & Ferres, 1976).

Results

Sleep measures with placebo for the young adults and the middle aged are given in Table 1. The mean sleep onset latency for the young adults was somewhat high compared with other studies, though there was no significant difference between the two groups.

With the middle age group it was not possible to establish differences between sleep measures related to the separate diazepam and temazepam placebos, and so the values were combined. The effect of diazepam and temazepam on various sleep measures, on awakenings, on percentage of total sleep time occupied by each sleep stage, and on duration of sleep stages are given in Tables 2, 3, 4, 5 and 6, and illustrated in Figure 1. Subjective assessments of sleep and well-being are given in Table 7. The subjects assessed their sleep as improved with 5 and 10 mg diazepam and with 10, 20 and 30 mg temazepam, and these improvements were without assessments of residual effects on well-being.

Discussion

The present comparison of sleep in young adulthood and in middle age is in close agreement with the

findings of Williams *et al.* (1974). With the older group there was a marked reduction in total sleep time, and an increase in the latency to stage 3 and percentage stage 1 (drowsy) and stage 2 sleep, without change in percentage or latency of REM sleep. It may, therefore, have been expected that the effects of diazepam and temazepam on the sleep of the middle aged would have differed from that seen in young adults, but it is of particular interest that there was no increase in total sleep time with either diazepam or temazepam, even though these drugs increase the much longer sleep time of young adults (Nicholson & Stone, 1976).

Sleep onset latencies were similar between the two groups. They were reduced by diazepam in the older group, but it was not possible to establish such an effect with temazepam which, nevertheless, markedly shortens sleep onset latency in early adulthood. Awakenings and duration of awake activity were reduced by each drug, and 30 mg temazepam was particularly effective in the older subjects. However, whereas drowsy sleep was reduced by temazepam in early adulthood, there was less effect in middle age, and in young adults the onset of the first REM period was delayed by temazepam whereas in the older group it was not possible to establish such a change even when the dose range included 30 mg.

These and the previous observations on the effects of temazepam and diazepam on sleep in healthy man

Table 1 Values for various sleep measures between young adults and the middle age group (means for six subjects)

| Measure | Young adults | Middle age Group |
|--------------------------------|--------------|------------------|
| Total sleep time (min) | 414.5 | 378.9 *** |
| Sleep onset latency (min) | 27.1 | 22.3 |
| Latency (min) to Stage 3 sleep | 17.2 | 45.0 ** |
| Latency (min) to REM sleep | 104.1 | 79.0 |
| Duration (min) Stage 1 sleep | 30.6 | 35.1 |
| Duration (min) Stage 2 sleep | 218.0 | 247.4 *** |
| Duration (min) REM sleep | 104.9 | 97.2 |
| Percentage Stage 1 sleep | 7.1 | 8.7 * |
| Percentage Stage 2 sleep | 50.1 | 61.6 *** |
| Percentage REM sleep | 23.7 | 23.9 |

Significant differences *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$

Table 2 Effect of diazepam and temazepam on various sleep measures (means for six subjects)

| Measures | Placebo | Diazepam (mg) | | Temazepam (mg) | | | C/V |
|------------------------------|---------|---------------|--------|----------------|--------|--------|-----|
| | | 5 | 10 | 10 | 20 | 30 | |
| Total sleep time (min) | 378.86 | 370.58 | 384.17 | 362.92 | 386.17 | 390.50 | 8 |
| Stage shifts in first 6 h | 66.28 | 71.50 | 55.17 | 63.17 | 59.50 | 58.67 | 21 |
| Sleep onset latency (min) | 22.33 | 10.00 | 15.08 | 17.75 | 17.50 | 15.92 | 35 |
| Latency (min) to Stage 3 | 45.03 | 42.00 | 32.08 | 40.33 | 40.42 | 32.83 | 100 |
| Latency (min) to Stage REM | 79.0 | 77.42 | 87.75 | 94.58 | 107.50 | 99.00 | 45 |
| REM/NREM ratio | 0.32 | 0.36 | 0.35 | 0.29 | 0.28 | 0.29 | 27 |
| Total sleep time/time in bed | 0.85 | 0.90 | 0.91 | 0.87 | 0.90 | 0.92 | 3 |

Coefficient of variability (C/V) = s.d. × 100/mean
 Significance levles: ** $P < 0.01$, * $P < 0.05$

Table 3 Effect of diazepam and temazepam on number and duration (min) of awakenings to 0 + 1 during the first 6h of sleep (means for six subjects)

| Measure | Placebo | Diazepam (mg) | | Temazepam (mg) | | | C/V |
|----------------|---------|---------------|-------|----------------|-------|------|-----|
| | | 5 | 10 | 10 | 20 | 30 | |
| Number | 8.56 | 6.67 | 6.50 | 8.50 | 7.33 | 4.67 | 26 |
| Duration (min) | 30.92 | 20.67 | 13.67 | 26.67 | 16.33 | 9.08 | 37 |

Coefficient of variability (C/V) = s.d. × 100/mean
 Significance levels: *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$

Table 4 Effect of diazepam and temazepam on percentage of total sleep time occupied by each sleep stage (means for six subjects)

| Sleep stage | Placebo | Diazepam (mg) | | Temazepam (mg) | | | C/V |
|-------------|---------|---------------|-------|----------------|-------|-------|-----|
| | | 5 | 10 | 10 | 20 | 30 | |
| Awake | 4.79 | 3.28 | 2.87 | 4.05 | 2.75 | 2.25 | 40 |
| 1 | 8.67 | 6.88 | 5.65 | 8.28 | 7.02 | 5.63 | 27 |
| 2 | 61.59 | 61.48 | 65.00 | 64.22 | 67.12 | 67.78 | 9 |
| 3 | 5.37 | 5.85 | 4.52 | 4.93 | 4.45 | 5.02 | 64 |
| 3 + 4 | 5.82 | 5.97 | 4.52 | 5.20 | 4.45 | 5.02 | 61 |
| REM | 23.92 | 25.67 | 24.87 | 22.33 | 21.42 | 21.57 | 19 |

Coefficient of variability (C/V) = s.d. × 100/mean
 Significance levels: ** $P < 0.01$, * $P < 0.05$

Table 5 Effect of diazepam and temazepam on duration (min) of sleep stages in first 6h of sleep (means for six subjects)

| Sleep stage | Placebo | Diazepam (mg) | | Temazepam (mg) | | | C/V |
|-------------|---------|---------------|-------------|----------------|-------------|-------------|-----|
| | | 5 | 10 | 10 | 20 | 30 | |
| Awake | 14.08 | 7.83 *** | 7.42 *** | 10.83 * | 7.92 *** | 4.42 *** | 29 |
| 1 | 25.78 | 22.25 | 17.33 | 25.33 | 20.75 | 15.42 | 32 |
| 2 | 219.47 | 225.00 | 235.17 | 233.50 | 243.17 | 249.25† | 9 |
| 3 | 21.39 | 21.67 | 15.00 | 17.50 | 17.83 | 19.58 | 60 |
| 3+4 | 23.06 | 22.08 | 15.00 | 18.50 | 17.83 | 19.58 | 58 |
| REM | 77.61 | 81.75 | 78.08 | 71.67 | 70.33 | 71.33 | 20 |

Coefficient of variability (C/V) = s.d. × 100/mean

Significance levels: *** $P < 0.001$, * $P < 0.05$

† Effect significant at 5% level over dose range 10–30 mg

Table 6 Effect of diazepam and temazepam on 2 hourly distribution (min) of sleep stage 2 from sleep onset latency (means for six subjects)

| Interval (h) | Placebo | Diazepam (mg) | | Temazepam (mg) | | | C/V |
|--------------|---------|---------------|-------|----------------|-------|---------|-----|
| | | 5 | 10 | 10 | 20 | 30 | |
| 0–2 | 77.4 | 86.83 | 93.33 | 90.58 | 89.92 | 94.00† | 14 |
| 2–4 | 72.56 | 72.92 | 78.58 | 74.33 | 78.83 | 87.50†† | 15 |
| 4–6 | 69.50 | 65.25 | 63.25 | 68.58 | 74.42 | 67.75 | 18 |

Coefficient of variability (C/V) = s.d. × 100/mean

† Effect of temazepam over dose range (10–30 mg) significant at 5% level

†† Linear effect of temazepam over dose range (10–30 mg)

Table 7 Effect of diazepam and temazepam on subjective assessments (means for six subjects)

| Assessment | Placebo | Diazepam (mg) | | Temazepam (mg) | | |
|------------|---------|---------------|------------|----------------|-----------|-------------|
| | | 5 | 10 | 10 | 20 | 30 |
| A | 67.4 | 75.3 | 60.3 | 61.8 | 67.2 | 54.8 |
| B | 40.6 | 59.5 | 40.5 | 41.0 | 50.2 | 32.2 |
| C | 47.2 | 74.0 * | 77.5 ** | 71.0 * | 72.2 * | 86.7 *** |
| D | 54.5 | 65.7 | 42.5 | 57.8 | 59.6 | 58.8 |
| E | 73.5 | 84.8 | 84.2 | 79.2 | 78.7 | 89.2 |
| F | 54.3 | 74.8 * | 70.1 | 75.5 * | 77.5 * | 84.3 ** |

Significance levels: ** $P < 0.001$, * $P < 0.01$, * $P < 0.05$

The assessments were A—How did you feel during the day? *Tired–Fresh*, B—how do you feel now? *Tired–Wide awake*, C—I slept, *Very poorly–Very well*, D—Now I feel, *Very sleepy–Wide awake*, E—I fell asleep, *Never–Immediately* and F—After I fell asleep, I slept *Very badly–Very well*.

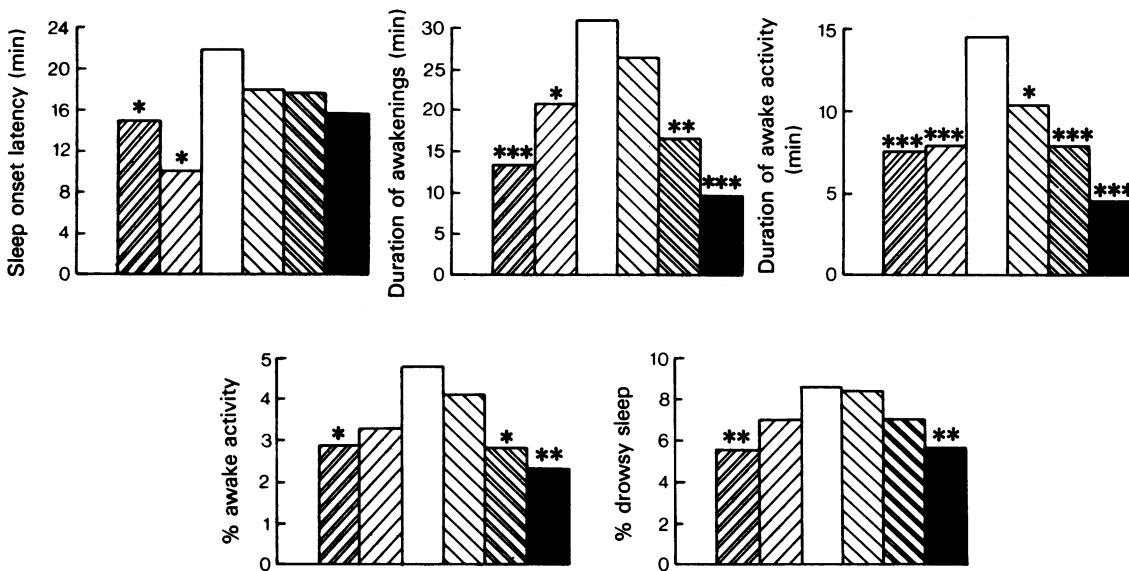


Figure 1 Main effects of diazepam (5 and 10 mg) and temazepam (10, 20 and 30 mg) on sleep measures in the middle aged group (means for six subjects). Significance levels *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$. ▨ diazepam 5 mg, ▩ diazepam 10 mg, ▤ temazepam 10 mg, ▥ temazepam 20 mg, ▦ temazepam 30 mg and □ placebo.

are supported by studies with insomniacs. Kales & Scharf (1974) observed that diazepam (5–15 mg) was effective for both sleep induction and maintenance, while Mitler, Phillips, Billiard, Spiegel & Zarcone (1975) and Bixler, Kales, Soldatos, Scharf & Kales (1978), both using 30 mg temazepam nightly, observed increased total sleep time and reduced awake activity in insomniacs aged between 46 and 61 years, and a reduction in the number of awakenings in insomniacs aged between 20 and 51 years respectively. There were methodological differences between the studies with temazepam related to the allowed duration of night-time sleep, and the lesser effects of temazepam reported by Bixler *et al.* (1978) may have been related to these differences.

It would appear that, though the effect of diazepam and temazepam on sleep is modified by age, both drugs are likely to be useful as hypnotics over an age range which includes young adulthood and late middle age. The hypnotic effect of diazepam and temazepam may not be so pronounced as other hypnotics, but they are particularly useful because, within certain dose ranges (diazepam 5–10 mg; temazepam 10–20 mg), they are without residual effects on performance (Borland & Nicholson, 1975; Hindmarch, 1976; Clarke & Nicholson, 1978). Temazepam has the added advantage that, unlike diazepam, its metabolism is not complicated by the accumulation of an active, long-acting metabolite, and so daily ingestion would not be contraindicated.

These studies have not provided evidence for an increase in the effect of hypnotics with age, though other studies have suggested that hypnotics may have an enhanced effect in old age. It has been suggested (Evans & Jarvis, 1972) that the effect of hypnotics in the elderly may be due to slower clearance, and a similar argument has been used to explain why drowsiness after diazepam is more common in patients over 70 years compared with those under 40 years. Klotz, Avant, Hoyumpa, Schenker & Wilkinson (1975) observed that, though the clearance of diazepam was the same in old and young subjects, the apparent volume of distribution increased linearly with age, and the half life was prolonged. On the other hand, Castleden, George, Marcer & Hallett (1977) found similar plasma concentrations in both young and elderly subjects with nitrazepam, and the half times in these two groups were similar. With nitrazepam, distribution was not affected by age in the manner shown for diazepam, and so increased effects on psychomotor performance were related to increased sensitivity of the brain. However, increased sensitivity to hypnotics in the elderly may not be part of a continuum involving the main span of life. The decrease in effect of hypnotics on sleep from young adulthood to middle age, and the increase in effect on performance in old age could involve separate processes. The brain may become less sensitive to hypnotics during life, but other factors, such as pharmacokinetics and impaired integrity of the blood

brain barrier, may be involved in the increased effects, such as impaired performance, observed in the elderly.

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