IMMEDIATE AND RESIDUAL EFFECTS IN MAN OF THE METABOLITES OF DIAZEPAM

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1 Immediate and residual effects of diazepam and its metabolites on visuomotor co-ordination have been studied in man. Performance was observed from 10.0–16.0 h after overnight ingestion of diazepam (5 and 10 mg), temazepam (10, 20 and 30 mg), oxazepam (15, 30 and 45 mg) and nordiazepam (5 and 10 mg), and from 0.5–6.5 h after morning ingestion of diazepam (10 mg), temazepam (20 mg), oxazepam (30 mg), and nordiazepam (5 and 10 mg). Immediate and residual effects of diazepam and temazepam were also studied on a choice response time test.

2 Visuo-motor co-ordination was not impaired after the overnight ingestion of 5 and 10 mg diazepam, 10, 20 and 30 mg temazepam, 15 and 30 mg oxazepam and 5 and 10 mg nordiazepam, though there was a trend of impaired performance over the dose range used with temazepam 10.0 h after ingestion. With 45 mg oxazepam performance at 10.0 h was impaired compared with performance at 14.0 ($P < 0.01$) and 16.0 h ($P < 0.001$). Performance on the choice response time test was not impaired after the overnight ingestion of 5 and 10 mg diazepam and 10, 20 and 30 mg temazepam.

3 With morning ingestion visuo-motor co-ordination was impaired at 0.5 ($P < 0.01$) and 2.5 h ($P < 0.05$) after 10 mg diazepam, at 0.5 ($P < 0.001$) after 20 mg temazepam, and at 2.5 ($P < 0.01$) and 4.5 h ($P < 0.05$) after 30 mg oxazepam. Performance 6.5 h after 10 mg nordiazepam was impaired compared with performance 0.5 and 2.5 h ($P < 0.01$) after ingestion. Performance on the choice response time test was impaired 1.0 h after ingestion of 10 mg diazepam ($P < 0.01$) and 20 mg temazepam ($P < 0.05$).

4 It is considered that diazepam (5–10 mg), temazepam (10–20 mg) and oxazepam (15–30 mg) would be useful hypnotics within the dose ranges indicated, at least for occasional use, when impaired performance the next day would be unacceptable. The studies with nordiazepam suggest that, though this drug may have limited effects on performance, it may have persistent effects on behaviour consistent with its clinical use as an anxiolytic.

Introduction

Diazepam and its metabolites, 3-hydroxydiazepam (temazepam), 3-hydroxy-N-desmethyldiazepam (oxazepam) and N-desmethyldiazepam (nordiazepam), all possess hypnotic activity in man, though their effects on sleep differ. In particular, the activity of diazepam and its hydroxylated metabolites, temazepam and oxazepam, is limited to the night of ingestion (Nicholson & Stone, 1976; Nicholson & Stone, 1978; Nicholson, Stone & Clarke, 1976), whereas the effect of its demethylated metabolite, nordiazepam, like many other benzodiazepines, is prolonged, and even modifies the sleep of the recovery night (Nicholson, Stone, Clarke & Ferres, 1976). It is the limited activity of diazepam and its hydroxylated metabolites which suggest that these drugs may be particularly useful in the management of disturbed sleep if impaired performance the next day would be

unacceptable, and it is in this context that we have studied both the immediate and residual effects of these drugs on human performance.

Methods

Visuo-motor co-ordination and choice response time tasks were used to measure performance. Experiments were carried out in a sound attenuated and air conditioned room (temperature $18^{\circ} \pm 1^{\circ}\text{C}$; humidity $55 \pm 2\%$). Six healthy males were used with ages from 23–43 (mean 27) years, and their weights ranged from 67–83 (mean 72) kg. They were required to avoid alcohol within 24 h of the experiment, and were not

Figure 1 Choice response time test: The subject selects the hand which holds the disc matching the reference bar. In each of the above examples the matching disc is held in the right hand.

involved in any other form of drug therapy. There were no restrictions on the consumption of non-alcoholic beverages, and they ate a light breakfast on the morning of the performance studies.

The visuo-motor co-ordination task (Borland & Nicholson, 1974) required the subjects to position a spot inside a randomly moving circle displayed on an oscilloscope. The movement of the spot was controlled by a hand held stick. An error signal proportional to the distance between the spot and the centre of the circle controlled the difficulty of the task by modulating the mean amplitude of the movement of the circle. The position of the circle and spot, and so the radial error signal, were recorded. Subjects were trained on the task until they had reached steady performance. Each experimental run lasted 10 min, and during the run subjects reached their plateau performance within 100 s. The mean amplitude of the task over the last 500 s was computed, and this was the performance measure.

The choice response time task (Byford, 1977, personal communication) required the subject to inspect a series of pictures presented sequentially as photographic slides. Each slide showed a man holding a red disc in one hand and a blue disc in the other. The man was in one of four positions (upright facing the subject, upright with back to subject, upside down facing the subject, and upside down with back to subject) and the red or blue disc appeared in either hand. Beneath the figure was a horizontal bar with a red or blue band (Figure 1). There were 16 different slides. The subjects were required to decide which hand held the disc of the same colour as the band, and to indicate by pressing a right or left hand response button as appropriate. The subject was given 2.6 s in which to respond, and was required to respond as quickly and as accurately as possible. Slides were presented at 3 s intervals, and for each session there were four series of 80 slides.

Performance was measured at fixed times for each subject near to 09.00, 11.00, 13.00 and 15.00 h. In experiments in which residual effects were being studied the drug or placebo was ingested near to

23.00 h the night before, and in experiments in which immediate effects were being studied the drug or placebo was ingested near to 08.30 h the same morning. In experiments in which residual effects were being studied matching placebos were ingested the following morning, and in experiments in which immediate effects were being studied matching placebos were ingested the night before. In this way the design did not reveal whether residual or immediate effects were under investigation. The doses used for each drug are given in Tables 1–6. The experiments were carried out in the same subjects over a period of 8 months in four separate parts. Each part was concerned with a separate drug, and included a separate assessment of performance after placebo.

With visuo-motor co-ordination performance was measured 10.0, 12.0, 14.0 and 16.0 h after overnight ingestion, and 0.5, 2.5, 4.5 and 6.5 h after morning ingestion. With choice response time performance was measured 10.5, 12.5, 14.5 and 16.5 h after overnight ingestion, and 1.0, 3.0, 5.0 and 7.0 h after morning ingestion. After each task the subject was presented with a line 100 mm in length and was asked the question 'How well did you perform?'. The assessment was made by crossing the line between the extremes of 'Useless' and 'Perfect' and was quantified by measuring in mm the displacement of the mark from the 'Useless' extremity. Each experiment was double blind and the treatments were presented in random order. Change in performance, and in assessments of performance was analyzed by analysis of variance. Performance and assessments of performance after drugs were compared with performance and assessments of performance after placebo.

Each morning the subjects were required to assess their sleep and well-being between 0.5 and 1.0 h after awakening. The assessments and the extremes of the 100 mm analogue scales were A: I slept *very poorly*—*very well*, B: Now I feel *wide awake*—*very sleepy*, C: I fell asleep *never*—*immediately*, and D: After I fell asleep I slept *very well*—*very badly*. In each case a favourable response tended toward the 100 extreme of the scale.

Results

Effects of drugs on visuo-motor co-ordination are given in Tables 1–4 and illustrated in Figure 2. It was not possible to establish residual effects on performance with diazepam and temazepam, but there was a trend of impaired performance over the dose range ($P < 0.05$) 10.0 h after ingestion of temazepam. With oxazepam overnight there was also a trend of impaired performance over the dose range 10.0 h after

ingestion, and performance during the day 10.0 h after overnight ingestion of 45 mg was impaired compared with performance at 14.0 h ($P < 0.01$) and 16.0 h ($P < 0.001$). There were no residual effects of 5 and 10 mg nordiazepam.

With morning ingestion of 10 mg diazepam performance was impaired at 0.5 ($P < 0.01$) and 2.5 h ($P < 0.05$), with morning ingestion of 20 mg temazepam performance was impaired at 0.5 h ($P < 0.001$) and with morning ingestion of 30 mg

Table 1 Analysis of variance and significance levels for change in performance (compared with placebo) on visuo-motor co-ordination (arbitrary units) after diazepam (mean for six subjects)

Source	Degrees of freedom	Mean squares	F	Significance levels
Subjects (S)	5	1.367116	10.15	***
Drug (D)	3	0.685570	5.09	*
Time (T)	3	0.119004		
S × D	15	0.134665		
S × T	15	0.228075	2.76	**
D × T	9	0.218751	2.65	*
S × D × T	45	0.082685		
Total	95			
<i>Approximate time of performance measure (h)</i>				
<i>Diazepam</i>	<i>09.00</i>	<i>11.00</i>	<i>13.00</i>	<i>15.00</i>
5 mg night	−0.05	0.13	−0.13	−0.16
10 mg night	−0.15	0.09	−0.04	−0.19
10 mg morning	−0.77	−0.50	−0.03	−0.19

Least significant differences from placebo for means of 6: 5% = 0.44; 1% = 0.59; 0.1% = 0.78 between doses; 5% = 0.33; 1% = 0.47; 0.1% = 0.58 within doses (* = 5%; ** = 1%; *** = 0.1%).

Table 2 Analysis of variance and significance levels for change in performance (compared with placebo) on visuo-motor co-ordination (arbitrary units) after temazepam (mean for six subjects)

Source	Degrees of freedom	Mean squares	F	Significance levels
Subjects (S)	5	0.803839	2.19	
Drug (D)	5	1.039778	2.83 (S × D)	*
Time (T)	3	1.704884	8.93 (S × T)	**
S × D	25	0.366905		
S × T	15	0.190993	2.07	*
D × T	15	0.406136	4.41	***
S × D × T	75	0.092050		
Total	143			
<i>Approximate time of performance measure (h)</i>				
<i>Temazepam</i>	<i>09.00</i>	<i>11.00</i>	<i>13.00</i>	<i>15.00</i>
10 mg night	−0.01	−0.06	−0.12	−0.16
20 mg night	−0.20	−0.15	−0.13	−0.24
30 mg	−0.31	0.00	−0.22	−0.12
10 mg morning	−0.22	−0.11	−0.09	−0.24
20 mg morning	−1.54	−0.39	−0.25	−0.22

Least significant differences from placebo for means of 6: 5% = 0.53; 1% = 0.71; 0.1% = 0.93 between doses; 5% = 0.35; 1% = 0.46; 0.1% = 0.60 within doses (* = 5%; ** = 1%; *** = 0.1%).

Figure 2 Immediate effects of drugs on visuo-motor co-ordination (a) and choice response time (b). ● diazepam 10 mg, ▲ temazepam 20 mg, ■ oxazepam 30 mg, ○ nordiazepam 10 mg.

Table 3 Analysis of variance and significance levels for change in performance (compared with placebo) on visuo-motor co-ordination (arbitrary units) after oxazepam (mean for six subjects)

Source	Degrees of freedom	Mean squares	F	Significance levels
Subjects (S)	5	2.233709	20.56	***
Drug (D)	4	1.035212		
Time (T)	3	0.365286		
S × D	20	0.628597		
S × T	15	0.618546	5.69	***
D × T	12	0.398920	3.67	***
S × D × T	60	0.108630		
Total	119			

Approximate time of performance measure (h)				
Oxazepam	09.00	11.00	13.00	15.00
15 mg night	0.08	-0.16	0.21	0.07
30 mg night	-0.24	-0.28	-0.14	0.06
45 mg night	-0.52	-0.30	0.09	0.38
30 mg morning	-0.13	-0.96	-0.76	0.00

Least significant differences from placebo for means of 6: 5%=0.64; 1%=0.86; 0.1%=1.15 between doses; 5%=0.38; 1%=0.51; 0.1%=0.66 within doses (* = 5%; ** = 1%; *** = 0.1%).

oxazepam performance was impaired at 2.5 ($P < 0.01$) and 4.5 h ($P < 0.05$). The immediate effect of 10 mg nordiazepam was different with respect to time compared with placebo. Performance during the day after morning ingestion of 10 mg nordiazepam diverged from that of placebo ($P < 0.05$), and was impaired 6.5 h after ingestion ($P < 0.001$) compared with performance at 0.5 and 2.5 h.

The effects of diazepam and temazepam on the total response time of the choice response time task

are given in Tables 5 and 6. There was impaired performance 1.0 h after ingestion of 10 mg diazepam ($P < 0.01$) and 20 mg temazepam ($P < 0.05$). It was not possible to establish effects on accuracy of matching.

With visuo-motor co-ordination the subjects reported impaired performance 0.5 h ($P < 0.05$) after morning ingestion of 10 mg diazepam, 0.5 h ($P < 0.01$) after the morning ingestion of 20 mg temazepam, and 2.5 and 4.5 h ($P < 0.05$) after the morning ingestion of

Table 4 Analysis of variance and significance levels for change in performance (compared with placebo) on visuo-motor co-ordination (arbitrary units) after nordiazepam (mean for six subjects)

Source	Degrees of freedom	Mean squares	F	Significance levels
Subjects (S)	5	3.1370	8.20	***
Drug (D)	4	0.1449		
Time (T)	3	0.5849		
S × D	20	0.3828		
S × T	15	0.5781	6.61	***
D × T	12	0.1332		
S × D × T	60	0.0875		
Total	119			

Approximate time of performance measure (h)

<i>Nordiazepam</i>	<i>09.00</i>	<i>11.00</i>	<i>13.00</i>	<i>15.00</i>
5 mg night	0.00	0.38	0.11	0.04
10 mg night	-0.01	0.17	0.06	-0.06
5 mg morning	-0.18	0.04	0.19	-0.01
10 mg morning	0.18	0.06	-0.19	-0.39

Least significant differences from placebo for means of 6: 5% = 0.53; 1% = 0.72; 0.1% = 0.95 between doses; 5% = 0.34; 1% = 0.45; 0.1% = 0.59 within doses (* = 5%; ** = 1%; *** = 0.1%).

Table 5 Analysis of variance and significance levels for change in performance (compared with placebo) on choice response time (ms) after diazepam (mean for six subjects)

Source	Degrees of freedom	Mean squares	F	Significance levels
Subjects (S)	5	340086	30.92	***
Drug (D)	4	36580	3.32 (S × D)	*
S × D Error (a)	20	10999		
Time (T)	3	8266	3.14	*
S × T	15	3453	1.31	
T × D	12	5630	2.14	*
S × T × D Error (b)	60	2631.65		
Total	119			

Approximate time of performance measure (h)

<i>Diazepam</i>	<i>09.30</i>	<i>11.30</i>	<i>13.30</i>	<i>15.30</i>
5 mg night	-6	-52	-120	-63
10 mg night	-23	11	-43	-4
10 mg morning	125	17	-30	19

Least significant differences from placebo for means of 6: 5% = 92.0; 1% = 123.0; 0.1% = 163.0 between doses; 5% = 59.2; 1% = 78.8; 0.1% = 102.5 within doses (* = 5%; ** = 1%; *** = 0.1%).

30 mg oxazepam, but assessments were not changed with nordiazepam. Assessments of performance in the choice response time task were not altered.

The subjects reported improved sleep over the dose ranges used with diazepam (assessment A, $P < 0.05$), temazepam (assessments A & C, $P < 0.05$), oxazepam (assessments A & D, $P < 0.001$) and nordiazepam (assessments A & C, $P < 0.05$). Residual effects on waking were reported with oxazepam (assessment B, $P < 0.05$) related to the 45 mg dose.

Discussion

It is evident that diazepam and its hydroxylated metabolites may be appropriate for occasional use in the management of disturbed sleep when impaired performance the next day is to be avoided. However there are certain precautions which should be taken in the use of these drugs by persons involved in skilled activity. With diazepam, daily use could lead to an accumulation of its long acting metabolite nordiazepam, and, so, it is advised that, not only should the dose of diazepam be within 10 mg, as residual effects are observed above this range (Borland & Nicholson, 1977), but, that it should not be repeated at intervals of less than 48 h. Within this dose range, diazepam has useful hypnotic activity (Nicholson, Stone & Clarke, 1976). Oxazepam, 15–30 mg, is also without residual effects, but the relatively slow absorption of the drug (Wyeth—Internal Report) and the lack of effect on sleep onset latencies (Nicholson & Stone, 1978) may reduce its usefulness, though,

otherwise, it is an effective hypnotic. With temazepam there was only a trend toward impaired performance over a dose range which included 30 mg. However, within the dose range 10–20 mg, temazepam has a marked hypnotic effect (Nicholson & Stone, 1976), and, like oxazepam, has the advantage that its metabolism is not complicated by a long acting metabolite, and so repeated ingestion may not be contraindicated.

These observations are in broad agreement with other studies. In a previous study Borland & Nicholson (1975) observed recovery from impaired performance with 10 mg diazepam around 7.0 h after ingestion. Similar results have since been reported by Seppälä, Kortilla, Häkkinen & Linnoila (1976), who observed perceptual speed, reactive and co-ordination skills, and visual functions related to driving. Recovery from impaired performance within a few hours after ingestion of diazepam has also been shown by Hart, Hill, Bye, Wilkinson & Peck (1976) in a variety of tasks including auditory vigilance and reaction time, short term memory and digit symbol substitution. With temazepam our results are comparable with those of Hindmarch (1975), though we have been unable to demonstrate unequivocally a residual effect on performance with the 30 mg dose. Other workers have observed the slow onset of impaired performance with oxazepam. Molander & Duvhök (1976) recorded maximum depression of critical flicker fusion frequency 3.0 h after ingestion of 20 and 40 mg, and impaired co-ordination with 40 mg oxazepam.

The present studies also suggest, as have previous

Table 6 Analysis of variance and significance levels for change in performance (compared with placebo) on choice response time (ms) after temazepam (mean for six subjects)

Source	Degrees of freedom	Mean squares	F	Significance levels
Subjects (S)	5	286690	15.33	***
Drug (D)	7	11676	<1	
S × D Error (a)	35	18700		
Time (T)	3	12969	3.17	*
S × T	15	4095	3.12	***
T × D	21	3303	2.52	***
S × T × D Error (b)	105	1312.64		
Total	191			

Approximate time of performance measure (h)				
Temazepam	09.30	11.30	13.30	15.30
10 mg night	0	−13	−6	−33
20 mg night	−5	5	53	−13
30 mg night	−37	−26	−26	−30
10 mg day	28	37	−11	0
20 mg day	93	31	−15	−21

Least significant differences from placebo for means of 6: 5% = 92.5; 1% = 124.0 between doses; 5% = 41.8; 1% = 55.6; 0.1% = 72.4 within doses (* = 5%; ** = 1%; *** = 0.1%).

studies (Tansella, Zimmerman-Tansella & Lader, 1974, Palva & Linnoila, 1976) that nordiazepam in the dose range 5–10 mg has limited effects on performance. The delayed appearance of impaired performance after nordiazepam seen in the present studies may be due to the ability of subjects to overcome, at least in part, any effect of the drug, or the impaired ability of subjects to sustain high levels of performance for several hours. In previous studies we have shown persistent effects of nordiazepam on sleep (Nicholson, Stone, Clarke & Ferres, 1976), and residual, though limited, sequelae of a precursor of

nordiazepam on performance (Borland & Nicholson, 1977). The observations are consistent with the long half life of nordiazepam and with its use as an anxiolytic, and suggest that nordiazepam, or drugs with nordiazepam as an important metabolite, are appropriate to the management of insomnia secondary to psychopathology when a persistent day-time effect with minimal changes in performance is required.

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