The effect of repeated doses of temazepam and nitrazepam on human psychomotor performance

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1 The effects of six nightly doses of temazepam (20 mg), nitrazepam (10 mg) and placebo on saccadic eye movements, critical flicker fusion, choice reaction time and on subjective feelings were studied in a double blind cross-over study in eight volunteers.

2 Testing was performed on nights 1 and 6 of treatment.

3 Nitrazepam, a benzodiazepine with a long elimination half-life produced a residual performance impairment on night 1 that had disappeared by night 6, despite higher serum concentrations of the drug on the sixth night of treatment. Temazepam, with a shorter elimination half-life produced no significant performance impairment on night 1, but by night 6 a significant impairment of saccadic eye movements ($P < 0.05$), was seen 1 h after drug intake.

4 We conclude that tolerance developed to the sedative action of nitrazepam over the 6 night period of the study. No evidence of tolerance was seen with temazepam.

Keywords nitrazepam temazepam psychomotor performance

Introduction

The chronic use of benzodiazepines at both normal and high doses has been shown to lead to the development of physical dependence in some patients (Marks, 1978; Owen & Tyrer, 1983). Associated with this phenomenon is the development of tolerance, where prolonged treatment with the same dose of a benzodiazepine leads to a gradual diminution of effect. Despite this change in response having been reported (Giles *et al.*, 1977; Lader *et al.*, 1980) few studies have been carried out to measure the sedation produced by chronically administered benzodiazepines (Johnson & Chernik, 1982). The present study investigated the effects of 6 nights' treatment with nitrazepam (10 mg) and temazepam (20 mg) on human performance. Temazepam, a benzodiazepine with an elimination half-life of 8–15 h (Bittencourt *et al.*, 1979; Jochemsen & Breimer, 1982), has been demonstrated to be effective as an hypnotic (Nicholson & Stone, 1976; Hindmarch, 1976) and to be free of morning-after residual effects in doses up to 30 mg

(Harry & Latham, 1980). Nitrazepam, a benzodiazepine with a long elimination half-life (18–31 h; Reider & Wendt, 1973), has been shown to produce residual effects the morning after an evening dose of 5–10 mg (Ogara *et al.*, 1980), but has been reported to be effective as an hypnotic for a period of up to 24 weeks (Oswald *et al.*, 1982). The aim of this study was to investigate changes in performance impairment produced by two benzodiazepines with different elimination half-lives.

Three standard tests of sedation have been used in the study: critical flicker fusion threshold, choice reaction time and visual analogue rating scales. In addition, the peak velocity of saccadic eye movements was measured. Control of saccadic eye movements is exerted by several central structures: parts of thalamus, large areas of cortex, the basal ganglia, the cerebellum and the superior colliculus. However, there are small groups of neurones in the brain stem, close to the oculomotor nuclei, that have discharge patterns

which appear to be solely related to saccadic eye movements. It is thought that these neurones interact to form the immediate premotor machinery for saccade generation (Luschei & Fuchs, 1972; Fuchs & Kaneko, 1981). Peak saccade velocity has proved to be a rapid and sensitive marker of the drug induced sedation and stimulation in man (Griffiths *et al.*, 1985).

Methods

Experimental protocol

Eight drug-free healthy male volunteers took part in the study which was organised in a double-blind random cross-over manner. Three oral treatments were received by each volunteer: placebo, temazepam (20 mg, as a soft gelatine capsule) and nitrazepam (10 mg, as 1 tablet). Treatments were taken at approximately 22.00 h for 6 consecutive nights. Each treatment regime was separated by at least 3 weeks. Treatments were given in a double dummy manner so that the appearance of treatments did not differ. On the first and sixth night of each treatment regime, subjects slept in the department; on these nights their performance was measured at the following times: 22.00 h (medication taken at this time), 23.00 h, 07.00 h and 10.00 h. Blood samples were taken prior to each session. Caffeinated drinks were prohibited for 6 h preceding performance measurement on test nights. The last permitted food intake on test nights was at 19.00 h when subjects were asked to have a light, non-fatty meal. They were asked to abstain from alcohol for 24 h preceding commencement of each treatment regime and throughout each treatment. A standard, light, caffeine-free breakfast was provided at approximately 08.00 h. The study was approved by the hospital ethics committee and written informed consent was obtained from all volunteers.

Performance was assessed by saccadic eye movement analysis, critical flicker fusion threshold, and choice reaction time. Visual analogue scales were used to assess mood. All the tasks were performed in a sound attenuated room and were performed under the same lighting conditions.

Prior to the commencement of the study, subjects were trained to perform the tasks until their performance was steady.

Eye movement tests

Complete details of the eye movement recording system are reported elsewhere (Bittencourt *et*

al., 1981; Smith *et al.*, 1981). In brief, stick-on silver-silver chloride electrodes were placed lateral to both outer canthi, with a similar reference electrode on the forehead. Subjects sat with the head restrained by a head rest, and were asked to follow a spot of light (2 mm in diameter) moving horizontally at eye level, across a 650 mm wide oscilloscope, placed 650 mm from the nasion. Each recording session lasted about 4 min and consisted of two 2 min periods. The light spot moved horizontally through a sequence of step-like jumps of random amplitude (15–40°) spaced at random intervals (2.0–4.0 s). Computer analysis of the eye movement records were carried out blind by following procedures reported in detail elsewhere (Bittencourt *et al.*, 1981; Smith *et al.*, 1981).

Critical flicker fusion threshold (CFFT)

Subjects were required to detect flicker in a set of four light-emitting diodes in foveal fixation of 1 m according to the psychophysiological method of limits for ascending and descending thresholds (Woodworth & Schlosberg, 1958). The CFFT was obtained from the average of flicker and fusion readings taken over a series of 10 presentations. The apparatus used was the Leeds psychomotor tester (Hindmarch, 1979).

Choice reaction time (CRT)

Subjects were required to scan an array of small lights which are illuminated on a random basis. As soon as they detected the light, they were asked to touch the appropriate response button to extinguish the light (Hindmarch, 1979). The CRT was obtained from the average of 20 individual tests. The apparatus used was the Leeds psychomotor tester.

Visual analogue scales

Subjects rated their subjective feelings with the following five line scales; depressed–euphoric, active–inactive, tired–alert, relaxed–tense and anxious–calm. Each scale was 100 mm long. The final scores were determined by measuring in mm from the end of the line to the subject's mark.

Serum drug concentration measurement

Temazepam was measured by a gas chromatographic method derived from that of Belvedere *et al.* (1972) and nitrazepam by a gas chromatographic method derived from that of de Silva *et al.* (1978). Analytical precision was obtained by

the inclusion of one quality control sample in every batch of 10 specimens.

Statistics

Performance data was analysed by four way analysis of variance (dependent variable by subject, treatment, time and night). The F ratios were calculated with respect to the residual sum of squares for each analysis, this included any variance attributable to a four way interaction. Student-Newman-Keuls multiple range test was used to test for any differences between the mean dependent variable for all subjects at each measurement time on each day for each treatment. The visual analogue scales were analysed by a randomized block analysis of variance by ranks and then by Dunett's test.

Results

Saccadic eye movements

Peak saccade velocity following each of the three treatments is illustrated in Figure 1. Analysis of variance of the peak saccade velocity showed the main effects of subject, treatment, time and night to be significant at $P < 0.05$ or better. Of the two way interactions drug/night ($F_{2,42} =$

6.29, $P < 0.01$) and time/subject ($F_{21,42} = 2.89$ $P < 0.005$) were significant. No three way interactions were significant. Student-Newman-Keuls test performed on the mean data showed nitrazepam to decrease velocity significantly when compared to placebo on night 1 at 23.00 h ($P < 0.001$) and at 07.00 h ($P < 0.05$). Temazepam decreased velocity significantly when compared to placebo only on night 6 at 23.00 h ($P < 0.05$).

Critical flicker fusion threshold (CFFT)

The mean data from this task is plotted in Figure 2. The analysis of variance of CFFT data showed the following main effects to be significant: drug, time, subject all at $P < 0.001$ or better. Only the two way interaction day/time was not significant ($P > 0.05$). The drug/day/subject and drug/time/subject three way interactions were significant at $P < 0.02$ and $P < 0.002$ respectively. No significant differences could be found between any treatment at any time using Student-Newman-Keuls multiple range test.

Choice reaction time

Both temazepam and nitrazepam produced marked increases in reaction time with respect to their pretreatment values; most strikingly on night 1 but also on night 6. The mean data is

Figure 1 Mean peak saccade velocity on nights 1 and 6 of each 6 night treatment regime in which eight volunteers received placebo (■), temazepam 20 mg (▲), nitrazepam 10 mg (●). Statistical significance is represented # $P < 0.05$, ## $P < 0.01$.

Figure 2 Mean critical flicker fusion threshold on nights 1 and 6 of each 6 night treatment regime in which eight volunteers received placebo (■), temazepam 20 mg (▲), nitrazepam 10 mg (●).

plotted in Figure 3. Analysis of variance (choice reaction time by subject, treatment, time, night) showed all the main effects to be significant at $P < 0.02$ or better. The following two way interactions were significant drug/time ($P < 0.001$), drug/subject ($P < 0.001$), day/subject ($P < 0.01$), time/subject ($P < 0.005$). No three way interactions were significant at $P < 0.05$. No significant differences could be found between treatments with Student-Newman-Keuls multiple range test.

Mood ratings

The only change in mood detected by the visual analogue scales was produced by nitrazepam at 23.00 h on night 1 where subjects rated themselves as being more relaxed than tense ($P < 0.05$).

Serum drug concentrations

The serum concentrations of nitrazepam and temazepam are plotted in Figure 4. Serum nitrazepam concentrations were significantly higher on night 6 than on night 1 as shown by paired t -tests at each measurement time ($P < 0.002$ or better). Serum temazepam concentrations only were significantly higher on night 6 from those on night 1 at 23.00 h ($t = 2.916$; $P < 0.05$).

Assay within batch quality control coefficient of variation were found to be as follows: nitrazepam ($100 \mu\text{g l}^{-1}$) 7.6% temazepam ($125 \mu\text{g l}^{-1}$) 3.4%. Molar conversion units (mg l^{-1} to nmol l^{-1}) for nitrazepam: multiply by 3.55; for temazepam multiply by 3.3.

Discussion

The doses of nitrazepam and temazepam were selected for their approximate equipotence. In a previous study using saccadic eye movement analysis (Bittencourt *et al.*, 1981), 5 mg nitrazepam was shown to be much less potent than 20 mg temazepam. In the present study a higher dose of 10 mg nitrazepam was selected. Changes in the performance of the tasks were produced by both active treatments. The changes were broadly consistent across tasks. Nitrazepam on night 1 at 23.00 h produced the largest deterioration of performance seen during the study. Despite substantial recovery overnight, the subject's performance had not returned to pre-drug levels at 07.00 h the following morning. This was shown significantly by peak saccade velocity, while critical flicker fusion threshold showed the same trend without reaching statistical significance. By night 6 the response to nitrazepam had changed, such that performance of the tasks

Figure 3 Mean choice reaction time on nights 1 and 6 of each 6 night treatment regime in which eight volunteers received placebo (■), temazepam 20 mg (▲), nitrazepam 10 mg (●).

was better or barely worse than placebo. The serum concentrations of nitrazepam almost doubled between night 1 and night 6 due to the long elimination half-life of the compound. Despite this, performance was less impaired on night 6 than it had been on night 1. This indicates the development of tolerance to a sedative effect of nitrazepam over the 6 night period of the study.

Temazepam on night 1 produced a deterioration of performance of all tasks at 23.00 h and 07.00 h. The fall at 07.00 h was as profound as that at 23.00 h. On night six at 23.00 h temazepam reduced saccade velocity significantly ($P < 0.05$) when compared to placebo, this corresponded to the highest measured serum concentration of temazepam found during the study. Temazepam, therefore, had not produced the same degree of tolerance that was seen with nitrazepam over the 6 night period of the study.

The two compounds have differing half-lives, such that one accumulated over the 6 night period (nitrazepam) while the other did not (temazepam). The persistence of high concentrations of nitrazepam at benzodiazepine receptors in the brain might have had a greater desensitizing action than the smaller exposure to temazepam. This could explain why tolerance occurred to the effects of nitrazepam but less so to temazepam. Crawley *et al.* (1982) have suggested that the magnitude and duration of any observed receptor subsensitivity following chronic benzodiazepine exposure depends on the receptor binding affinity of the administered benzodiazepine. They showed a decrease in the

apparent number of benzodiazepine binding sites in the mouse forebrain, following chronic dosing with clonazepam but not following chronic dosing with chlordiazepoxide. The work of Braestrup & Squires (1978) indicated that clonazepam binds avidly ($K_i = 1.9$ nM) while chlordiazepoxide binds weakly ($K_i = 574$ nM). Nitrazepam and temazepam are not as widely separated in their binding affinities as are clonazepam and chlordiazepoxide. Nitrazepam has a K_i of 19 nM (Braestrup & Squires, 1978) while temazepam has a K_i of approximately 50 nM. (There is no K_i value quoted for temazepam in the literature; we have estimated this figure from the work of Mohler & Okada (1978) who showed there to be a highly significant correlation ($r = 0.78$; $P < 0.005$) between receptor affinity (K_i) and therapeutic potency (average recommended therapeutic dose in $\mu\text{mol day}^{-1}$). Hence nitrazepam is more likely to produce receptor subsensitivity than is temazepam.

The combination of the effects of differing elimination half-lives and binding affinities may account for the difference in tolerance acquisition between temazepam and nitrazepam seen in this study. It should be recognised that the evidence referring to change in receptor numbers following chronic exposure to benzodiazepines is confused. Different studies have produced conflicting results showing either no change, decreases or even increases in the receptor number following chronic benzodiazepine treatment.

The speed with which tolerance develops to the action of benzodiazepines will control the period for which these drugs are therapeutically

Figure 4 Mean serum concentrations ($\pm$ s.d.) of nitrazepam and temazepam following repeated oral treatment with nitrazepam (10 mg) and temazepam (20 mg).

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effective. There is controversy over the period for which benzodiazepines are useful as hypnotics. The Food and Drug Administration (FDA, 1979) have reported that the benzodiazepines lose their hypnotic action after a period of between 3 and 14 days continuous use, while other sources claim that nitrazepam is lastingly effective as an hypnotic for up to 18 (Adam *et al.*, 1980) or 24 weeks (Oswald *et al.*, 1982). Our study would support the views expressed by the FDA with respect to nitrazepam as its ability to impair performance was lost by night 6.

This study provided an opportunity to compare the sensitivity of the tasks to different levels of sedation. Wittenborn (1979) reviewed the literature concerning benzodiazepines and psychomotor performance, and concluded that critical flicker fusion frequency was one of the most sensitive of tests. Our study indicates that saccadic eye movement analysis may be an even more sensitive measure of psychomotor performance.

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