Effects of zolpidem on saccadic eye movements and psychomotor performance: a double-blind, placebo controlled study in healthy volunteers

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- 1 Peak saccade velocity provides a valuable means of assessing the sedative effect of drugs in humans. The present study investigated the effects of zolpidem, an imidazopyridine hypnotic, on saccade velocity in healthy volunteers after single and repeated administration.
- 2 Zolpidem 5 mg, 10 mg and 20 mg significantly and dose dependently depressed peak saccade velocity during the 1.5 h after a single administration. On the morning after zolpidem administration, peak saccade velocity had returned towards pretreatment levels. Nitrazepam 10 mg also significantly depressed peak saccade velocity but the effect was maintained the following morning. The saccade response to zolpidem (5 and 10 mg) was undiminished after the seven nightly doses.
- 3 Nightly administration of zolpidem improved subjective sleep quality and there was no evidence of rebound insomnia following cessation of drug treatment.

Keywords zolpidem saccade velocity psychomotor performance hypnotic

Introduction

Zolpidem is an hypnotic belonging to a new chemical class, the imidazopyridines, which are structurally unrelated to the benzodiazepines. Zolpidem is a selective omega-one receptor ligand with a high intrinsic activity, and has a potent hypnotic effect [1] and weak anti-convulsant and muscle relaxant properties [2]. Zolpidem is an effective hypnotic in both volunteers and insomniac patients [3,4] and has a short half-life of 2.4 h.

Benzodiazepines form the mainstay of current drug therapy for insomnia. However, their use is associated with daytime residual effects [5,6,7] and the development of tolerance and dependence [8].

Saccadic eye movements are used continuously during normal visual activity and impairment is likely to have important consequences on visual acuity [9]. Peak saccade velocity is a sensitive indicator of sedation and is particularly sensitive to the sedative effects of benzodiazepines, opiates, barbiturates, carbamazepine, and ethanol [10]. Diazepam, for example, reduces both the duration and velocity of saccadic eye movements, and increases saccade latency [11].

The aim of the present study was to determine the effects of different doses of zolpidem on saccadic eye movement and psychomotor performance in 12 male

adult volunteers. In particular, it was of interest to establish: firstly, whether a night-time administration of zolpidem resulted in sedative effects the following morning and, secondly, whether tolerance developed to zolpidem during a 7 day course of treatment. Peak saccade velocity following a single administration of nitrazepam was recorded as a positive control.

Subjective sleep quality was also measured both during and after 7 days treatment with zolpidem. Critical flicker fusion threshold and reaction testing were also performed after zolpidem administration.

Subjects

The subjects were 12 male adult volunteers aged 20–30 years, confirmed as healthy at full medical examination and with normal haematology and blood biochemistry.

Subjects were tested following a single administration of nitrazepam 10 mg as a positive control to verify the experimental conditions before the main study.

According to a double-blind, crossover, randomised design, each subject received four 7 night treatments of zolpidem 5 mg, 10 mg, 20 mg and placebo, with a minimum interval of 2 weeks between each treatment.

The volunteers reported to the unit on nights 1 and 7 of each active treatment phase, but spent the other nights at home. Drug intake was at 22.00 h on nights 1, 6 and 7 and between 22.00 and 24.00 h on nights 2 to 5 inclusive.

The following performance measurements were made on nights 1 and 7: saccadic eye movement analysis, five choice serial reaction test, critical flicker fusion test, mood assessment, and Leeds Sleep Questionnaire. The Leeds Sleep Questionnaire was also performed following nights 3 and 7 of treatment and nights 8, 9 and 10, when treatment had been withdrawn.

Volunteers abstained from alcohol for 24 h and from caffeinated drinks for 12 h before the measurements were taken on nights 1 and 7. Alcohol intake was restricted at other times to no more than the equivalent of three glasses of wine per night. A low fat meal was taken before 19.00 h on measurement nights and a light caffeine-free breakfast was provided immediately following the performance assessment on the next morning, 9 h after drug intake.

Saccadic eye movement analysis

Recordings were made immediately before, and 0.5, 1, 1.5, 9 and 11 h after drug intake. Volunteers followed the movements of a target presented on a television screen whilst eye movements were recorded electro-oculographically. Subsequent computer analysis of the recorded eye movements was performed by the method of Marshall and colleagues [12]. Peak saccade velocity was calculated in degrees per second.

Five choice serial reaction test

The test was performed before, and 9 and 11 h after drug intake. The subject was presented with a board mounted with five lights, arranged in the shape of a pentagon. Immediately in front of the display was a response board with keys arranged in a similar pattern. Lights were illuminated randomly, one at a time, and the subject was required to select the key corresponding to the illuminated light. There was a short delay (100 ms) between the illumination of two lights. The test lasted 20 min. The results were analysed by microcomputer.

Critical flicker fusion frequency test

The test was performed before, and 9 and 11 h after drug intake. Subjects were required to detect flicker in a set of four light-emitting diodes in foveal fixation at 1 m using the Leeds Psychomotor test kit, according to the psychophysiological method of limits for ascending and descending thresholds [13].

Mood

Mood was assessed before and 1 h after drug intake using a mood adjective check-list (MACL) with 48 items to which the subject responds on a four point scale (from 'definitely' to 'definitely not'). Two dimensions are represented: dimension A: vigour/fatigue and dimension B: tension/relaxation [14]. In addition, separate scores

were prepared for general arousal and hedonic tone (i.e. pleasure/displeasure).

Leeds sleep questionnaire

The sleep questionnaire of Parrot & Hindmarch [15] was administered in the form of a visual analogue scale. The questionnaire measured four factors; getting to sleep (GTS), quality of sleep (QOS), awakening from sleep (AFS) and behaviour following waking (BFW).

Total blood zolpidem concentrations

Blood zolpidem levels were determined by high performance liquid chromatography [16] on samples obtained on nights 1 and 7 of each treatment period.

Statistical analysis

Before the crossover of zolpidem doses and placebo, there was an initial night (night 0) when nitrazepam was administered in order to verify the experimental conditions. This was verified by the second analysis for night 0, including nitrazepam. The main analyses were based on comparisons between zolpidem doses and placebo.

Peak saccade velocity data were analysed in two ways. Firstly, the zolpidem and placebo results for both night 1 and night 7 were entered into a factorial ANOVA (peak saccade velocity by volunteer, treatment, time and day) which excluded data recorded during nitrazepam ingestion: a second factorial ANOVA was performed on data from night 1 and the night of nitrazepam treatment (peak saccade velocity by subject, treatment and time). The *F* values were derived using residual mean square from each analysis, including all variance attributable to possible three and four way interactions.

Following ANOVA Student-Newman-Keuls multiple range test was performed on the data, comparing each treatment with placebo at each time period: the test was performed twice with the data derived for night 1, once excluding and once including nitrazepam.

In the analysis of the critical flicker fusion frequency test data, treatment and placebo groups were compared using the Student-Newman-Keuls multiple range test.

Results of the five choice serial reaction test were analysed by Ulrich-Pitz repeated measures ANOVA.

It has been shown that the two waking factors of the Leeds Sleep Questionnaire (AFS and BFW) are highly significantly correlated, as are the two sleeping factors (GTS and QOS) [15]. In the present analysis the two broader terms were derived from the untransformed data and the treatments compared by Student-Newman-Keuls test.

Results

Saccade velocity

On night 1 of each study period nitrazepam and all doses of zolpidem significantly reduced peak saccade velocity with respect to placebo 1.5 h after dosing (Figure 1). On

Figure 1a Peak saccade velocity following single administration of zolpidem (□ 20 mg, ◇ 10 mg, △ 5 mg) nitrazepam (○ 10 mg) or placebo (+). Twelve volunteers received zolpidem 5 mg, 10 mg or 20 mg, nitrazepam 10 mg or placebo at 22.00 h and saccadic eye movements were recorded at intervals thereafter.

b) Peak saccade velocity following 7 nights administration of zolpidem (□ 20 mg, ◇ 10 mg, △ 5 mg) or placebo (+). Twelve volunteers received zolpidem 5 mg, 10 mg or 20 mg, or placebo nightly for 7 days. Following drug administration at 22.00 h on the final night of treatment, saccadic eye movements were recorded.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.005$, **** $P < 0.001$.

night 7, however, the only significant reduction occurred with zolpidem 20 mg at 1 and 1.5 h post dosing. The absolute falls in saccade velocity produced by zolpidem on nights 1 and 7 were similar. The lack of a significant difference produced by zolpidem 5 and 10 mg on night 7 may be attributable to an unexpected fall in placebo saccade velocity on night 7. The reductions in saccade velocity induced by zolpidem were dose-related, although the differences between zolpidem treatments failed to achieve significance. Figure 2 represents the mean values of the effect calculated as a percentage of the placebo value obtained for each subject at each sampling time, as a function of mean blood concentrations on night 1 after the 10 mg dose. By morning (9 h after drug administration) there were no significant residual effects after

Figure 2 Mean value of effect calculated as a percentage of the placebo value for each subject at each sampling time, as a function of mean blood concentrations on night 1 after zolpidem 10 mg.

Table 1 The mean of 12 volunteers critical flicker fusion threshold following 5 mg, 10 mg and 20 mg zolpidem and placebo on nights 1 and 7 of 7 nights treatment

Treatment	Mean CFFT (Hz)					
	Night 1			Night 7		
	0	9	11	0	9	11
Placebo	31.77	30.33	30.58	31.68	30.52	30.66
Zolpidem						
5 mg	30.91	29.5	30.05	31.46	30.27	29.84
10 mg	31.53	29.96	30.52	31.89	30.15	30.26
20 mg	31.51	30.12	30.70	31.97	30.36	30.78

zolpidem intake at any dosage on either night 1 or night 7. Nitrazepam, however, demonstrated a profound residual effect 9 h after ingestion on night 1.

Critical flicker fusion threshold (CFFT)

No significant differences were observed between placebo and any zolpidem group with respect to CFFT 9 and 11 h after dosing. There appear to be no dose-related changes in CFFT (Table 1).

Five choice serial reaction time

Five choice serial reaction time was unaffected by drug treatment (Table 2) suggesting that there was no significant residual effects the morning after zolpidem intake.

Mood

The mood check-list results were factor analysed for general arousal, dimension 'A', dimension 'B' and hedonic tone. There were no consistent differences between the different zolpidem doses and placebo.

Leeds sleep questionnaire

Two analyses were performed: the first on nights 1, 3 and 7 to analyse drug effects, the second on nights 8, 9 and 10 to analyse withdrawal effects. Zolpidem 20 mg enhanced the perception of sleep state (GTS and QOS) on nights 1, 3 and 7 (all $P < 0.001$ vs placebo) (Figure

Table 2 The mean number of errors on the five choice serial reaction time test 2 recorded in the first (I) and second (II) 10 min of the task

Treatment	Mean number of errors					
	0 (h post drug)		9 (h post drug)		11 (h post drug)	
	I	II	I	II	I	II
a Night 1						
Placebo	17.6	24.3	17.0	14.6	16.0	18.4
Zolpidem						
5 mg	12.8	16.6	15.6	13.5	19.1	15.3
10 mg	14.1	15.5	16.4	16.4	2.07	17.3
20 mg	15.6	11.5	8.8	11.6	11.9	15.2
b Night 2						
Placebo	20.7	27.2	21.0	22.0	27.1	21.1
Zolpidem						
5 mg	13.1	16.3	16.0	14.5	27.6	24.3
10 mg	14.7	18.41	10.9	15.8	19.6	17.0
20 mg	12.2	17.91	15.1	16.9	22.4	15.7

Figure 3 Effect of zolpidem on perception of sleep. Twelve volunteers received nightly administration of zolpidem 5 mg (▨), 10 mg (■) or 20 mg (■) or placebo (□) for 7 nights. Sleep was assessed using the Leeds sleep questionnaire (Sleeping state factor). * $P < 0.05$, ** $P < 0.01$.

3). Zolpidem 10 mg showed a similar effect ($P < 0.01$ on night 1; $P < 0.001$ on nights 3 and 7). Zolpidem 5 mg showed no similar significant effect. There were no significant effects on waking state (AFS and BFW) with any treatment.

Total blood zolpidem concentrations

Total blood zolpidem concentrations generally peaked around 1.5 h after drug administration, and peaks were dose related. Mean levels were slightly lower on day 7 than on day 1 (Figures 4a and 4b). There was an important degree of inter-individual variation; the coefficient of variation being never less than 42%.

Discussion

Peak saccade velocity was significantly and dose-dependently depressed by zolpidem, and the depression was related to whole blood concentrations of the drug. There was a slight attenuation of the depression in saccade velocity between day 1 and 7, which could be a

reflection of the lower plasma zolpidem concentrations observed on day 7 or the development of a small degree of tolerance, but the lack of a significant difference in peak saccade velocity produced by zolpidem 5 and 10 mg on night 7 may have been attributable to an unexpected fall in placebo saccade velocity on night 7. The quantitatively similar depression induced by zolpidem (5 and 10 mg) on days 1 and 7 suggests a lack of

Figure 4a) Total blood zolpidem concentrations-day 1. Twelve volunteers received a single dose of zolpidem 5 mg (△), 10 mg (◇) or 20 mg (□). **b)** Total blood zolpidem concentrations-day 7. Twelve volunteers received nightly administration of zolpidem 5 mg (△), 10 mg (◇) or 20 mg (□) for 7 nights. Total blood zolpidem concentrations were determined by h.p.l.c.

tolerance. In a study by Griffiths *et al* [17] where nitrazepam 10 mg significantly depressed peak saccade velocity after a single administration, the effect was absent after six nights of treatment, which could have indicated a tolerance phenomenon.

Also in contrast to the effects of nitrazepam, the depression in peak saccade velocity induced by zolpidem was fully reversed by morning (at the 11 h determination of saccade velocity vs placebo) indicating that there is no carry-over effect.

There were no changes of significance in the five choice serial reaction time test or critical flicker fusion threshold, nor daytime residual effect with zolpidem, confirming the results observed in peak saccade velocity tests.

Critical flicker fusion threshold measures levels of central nervous system arousal. It can be used to investigate changes in the overall interactive activity of the central nervous system produced by psychoactive drugs. The results obtained in the present study confirmed the findings of a previous study in which the effects of zolpidem 20 mg, flunitrazepam 2 mg and placebo administered at bed time were observed in 12 healthy

young male volunteers [18]. Drug comparisons in this study showed a significant decrease in performance with nitrazepam as compared with placebo and zolpidem, whereas there was no significant difference between placebo and zolpidem in a range of psychophysiological tests including critical flicker fusion threshold.

Both 10 mg and 20 mg zolpidem significantly improved subjective sleep quality in these healthy volunteers but zolpidem 5 mg did not appear to modify sleep parameters. There was no significant evidence of rebound insomnia following cessation of zolpidem treatment as judged by the Leeds sleep questionnaire, and mood scores were unaffected.

In conclusion, zolpidem has a promising pharmacodynamic profile as an hypnotic agent. It significantly depressed peak saccade velocity and improved subjective sleep quality after single and repeated administration, without significant morning residual effects and with little evidence of tolerance. These results in healthy young volunteers suggest zolpidem may induce less carry-over impairment of vigilance or tolerance than nitrazepam when used as an hypnotic agent in a patient population.

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