Br. J. clin. Pharmac. (1986), **21**, 647–653

Zopiclone produces effects on human performance similar to flurazepam, lormetazepam and triazolam

A. N. GRIFFITHS[1], D. M. JONES[2] & A. RICHENS[1]
[1]Department of Pharmacology and Therapeutics, University of Wales College of Medicine, Cardiff and
[2]Department of Applied Psychology, University of Wales Institute of Science and Technology, Cardiff

1 The cognitive function and psychomotor performance of 10 healthy male volunteers were measured following single oral doses of: zopiclone (7.5 mg), flurazepam (15 mg), lormetazepam (1 mg), triazolam (0.25 mg) and placebo.
2 The performance tests selected (stroop task, five choice serial reaction time, memory span, logical reasoning, mood and saccadic eye movement analysis) were thought to reflect aspects of normal daily activity.
3 The tests demonstrated a clear reduction of performance for all active treatments. No drug emerged as the most potent sedative overall, as each of the tests was affected to a different degree by each drug.
4 Drug effects were not qualitatively different between active treatments so that zopiclone was indistinguishable from the three benzodiazepines with which it was compared.

Keywords zopiclone benzodiazepines human performance saccadic eye movements

Introduction

Zopiclone is a cyclopyrrolone derivative which, although structurally unrelated to the benzodiazepines, shares their pharmacological profile. Binding studies have shown that zopiclone binds to brain benzodiazepine receptors but is not recognised by peripheral (renal) benzodiazepine receptors. Blanchard *et al.* (1983) investigating the modulating action of GABA and barbiturates on zopiclone binding have shown differences between zopiclone and benzodiazepines. They suggest that zopiclone may bind, in rat brain, to sites that do not correspond exactly to the benzodiazepine sites. This was confirmed by Trifilletti & Snyder (1984) who reported that zopiclone bound to a novel site linked allosterically to benzodiazepine receptors.

In man zopiclone is well tolerated and is rapidly and efficiently absorbed (> 75%). The plasma kinetics of zopiclone are generally well described by a two compartment open model with a half life of 5–6 h (Houghton *et al.*, 1984); a large total body clearance of 300 ml min^{-1} and a low renal clearance of 10 ml min^{-1} (Gaillot *et al.*, 1983). The dose of zopiclone selected for this study (7.5 mg) has been shown to be effective as an hypnotic (Wickstrom & Giercksky, 1980), and furthermore, Lader & Denney (1983) reported this dose to be the preferred hypnotic dose.

The marketed benzodiazepines selected for use in this study provided a cross section of elimination half-lives varying from the very short 2 h half-life of triazolam through lormetazepam with a 9–15 h half-life to flurazepam whose active metabolite, *N*-desalkylflurazepam, has a half-life of 65 h. Doses were selected with reference to those recommended by the manufacturers.

The present study used the effects of the drugs on saccadic eye movements as a measurement of the time course of sedative drug action. This approach has been previously reported (Bittencourt *et al.*, 1981, Tedeschi *et al.*, 1983). Into this framework, specific tasks of cognitive and psychomotor performance have been fitted to provide a more detailed insight into the nature of the induced sedation.

The aim of the study was to compare the effect of zopiclone with three marketed

benzodiazepines using a battery of tasks to assess psychomotor and cognitive performance.

Methods

Protocol

Ten male volunteers aged 20–22 years of age were recruited. All were declared healthy after a full medical examination and had normal haematological and blood biochemical screening tests both before and after the study. The treatments, zopiclone (7.5 mg), flurazepam (15 mg), lormetazepam (1 mg), triazolam (0.25 mg) and placebo, were matched for size, shape and colour by encapsulation. They were administered in a random order (using a conjugate latin square) and in a double-blind manner. Treatments were separated by at least 7 days. Volunteers were instructed to abstain from ethanol and caffeinated beverages for 24 h and 12 h respectively before treatment and throughout treatment days. On test days volunteers reported to the department at 08.00 h, drug intake was at approximately 09.30 h. A standard diet was provided for volunteers on test days. Volunteers were asked to perform the task battery before drug administration and 1, 4 and 10 h after. Saccadic eye movements were measured before and 0.5, 1, 2, 3, 4, 6, 8 and 10 h after drug intake.

The study was granted ethical approval by the Joint Ethics Committee, University of Wales College of Medicine. Written informed consent, witnessed by an independent person, was obtained from each volunteer.

Saccadic eye movements

Saccadic eye movements are rapid conjugate shifts of gaze, the dynamics of which are controlled by groups of neurones situated in the brain stem. Peak saccade velocity has been shown to be a good marker of drug induced CNS depression. Drug effects in normal volunteers have been observed with barbiturates, opiates, benzodiazepines, carbamazepine, amphetamine and ethanol (Griffiths *et al.*, 1984).

Volunteers were instructed to follow the movements of a target presented to them on a television screen. Their eye movements were recorded by electro-oculography. The target moved horizontally through a sequence of jumps of 30–40° amplitude, with respect to the volunteer's nasion. Subsequently computer analysis of the recorded eye movements was carried out by a method described elsewhere (Griffiths *et al.*, 1984). Each measurement session lasted 3 min.

The Stroop test

This test measured the time taken to read a colour word when printed in an incongruous ink. For example, the word 'green' might be printed in red ink. The task of the subject was to give the response 'red' even though the natural and compelling tendency was to give the colour word 'green'. The time taken to make the response to a number of such items arranged on a card is usually considerably longer than to a similar number of colour words which do not involve such conflict. The task is thought to measure the degree to which the individual is able to suppress the conflict between the two types of response. The effect of a drug on these response times might be due to the effects on the speed of reading rather than on the interference *per se*. To control for this possibility, two other types of material were also presented along with the interfering material (the CW card). Their purpose was to give some indication of any effects on reading speed. In one (the W card), colour words were presented in black ink on a white background. In the other (the C card), patches of colour (of the same size as the material on the CW card) were presented. This gave a measure of the speed of colour naming.

The version of this test used consisted of three cards (C, W and CW); each arranged in a 10×10 matrix of colours or colour words as appropriate. The colour names (four colours) used were red, green, yellow and blue, these being the least ambiguous in their naming. For the CW card each of the four colour words was represented on a roughly equal number of occasions in each colour. Subjects were asked to name colours aloud as quickly as possible and to read each card in a systematic fashion from left to right. For each card the total time to read the hundred items and the number of errors were noted.

Logical reasoning

This task measured performance at a relatively high level of abstraction (Baddeley, 1968). On each trial subjects were presented with, first, a statement of a relation between two objects (for example, 'A follows B'), which was followed by an exemplar ('AB'). The subject was asked to decide whether each statement was true or false (the case just given is, of course, false). Other more complex instances included 'A does not precede B' and 'B is preceded by A'. A total of twenty five trials were given on each occasion and performance was measured in terms of total time to perform all trials and number of errors.

All the materials were presented and the responses timed and scored on a microcomputer.

Serial reaction

Subjects were required to make a speeded response to an unpredictable sequence of signals. The task consisted of a display board with five lights (light emitting diodes) mounted in the shape of a pentagon. The display board was inclined at approximately 40° to the horizontal and immediately behind the response board. Keys on the response board were arranged in a pentagonal pattern identical to the layout of the lights on the display board. The subject was required to press the key on the response board corresponding to the position of the illuminated light on the display board. Only one light was illuminated at a time. After a fixed interval (100 ms) another light was illuminated and again the subject had to respond with the appropriate key. This cycle of events continued for the whole length of the test (20 min). The sequence of lights was dictated by a software random number generator.

The task was self-paced in that the rate of work (and hence the rate at which lights appeared) was dictated by the speed of response of the individual. The short interval between making the response and the onset of the next light was not sufficient to allow a respite from the demands of the task and simply served to facilitate the detection of successive stimuli which appeared at the same location. This means that the task was extremely sensitive to factors which affected the rate of work and the production of errors.

The form of the task in this study was both generated and scored using a microcomputer. This allowed for a more sophisticated analysis than the type usually conducted on this type of task. In addition to providing an indication of the numbers of correct and incorrect responses in each 10 min segment of the task, the time taken for each response was displayed in a frequency distribution with 100 ms cells (to a maximum of 2 s). This was done separately for correct and incorrect responses for each 10 min segment of the task. In addition to these measures an index of the frequency of especially long responses (called 'blocks'), whose incidence is thought to reflect the onset of fatigue, was also derived. Blocks were defined as responses whose latency (i.e. the time taken to respond) was greater than twice the standard deviation of the distribution in which they appeared. The timing of responses was correct to the nearest 16 ms.

Memory span

The test was composed of strings of consonants presented individually on the screen of the microcomputer at a rate of one item per second. The length of each list was between 20 and 40 letters. Each list ended unpredictably. In this way, subjects were unable to recruit themselves to concentrate for a relatively short period as they might with a list of fixed length. In each experimental session twenty lists were presented. Two versions of the list were deployed over the period of the experiment to minimize learning of the lists.

The subjects were asked to write down as many as they could of the last few items in the list after the list was stopped. Emphasis was placed on reporting the items in the correct order on a response blank which was provided for each session.

Errors were scored with respect to their correct serial order (that is, an item was regarded as being correct if it appeared in the appropriate order in the sequence). Results were presented in terms of the proportion of items which were incorrectly reported in each serial position. As might be expected, errors rise to a maximum some five to seven items before the end of the list.

Mood

The mood of the subjects was assessed by self rating using the Thayer-Nowlie Mood Adjective Checklist (Thayer, 1978). Subjects were asked to rate the appropriateness of each of 45 adjectives to their current state using the following categories: 'definitely', 'slightly', 'cannot decide' and 'sure not'.

Results

Saccadic eye movements

The peak saccade velocity data (Figure 1) was analysed initially by three way analysis of variance (peak saccade velocity by subject, treatment and time) and then at each time interval by Student – Newman-Keuls multiple range test. The analysis of variance showed all the main effects and two way interactions to be significant at $P < 0.001$ or better except subject/time that was significant at $P < 0.002$. All the active treatments significantly depressed velocity with respect to placebo ($P < 0.05$) between 1 and 3 h. Lormetazepam was the only active treatment not to be significantly different from placebo

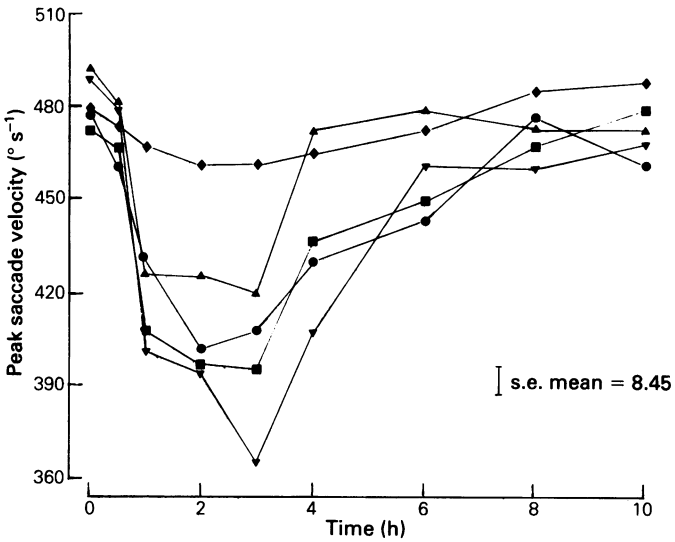

Figure 1 Mean peak saccade velocity (° s^{-1}) plotted against time after drug intake (h); ◆ placebo, ■ zopiclone 7.5 mg, ● flurazepam 15 mg, ▲ lormetazepam 1 mg, ▼ triazolam 0.25 mg.

at 4 h. At 6 h none of the treatments were significantly different from placebo. Triazolam produced the most profound fall of saccade velocity followed by zopiclone, flurazepam and lormetazepam respectively. The largest fall in velocity occured between 0.5 h and 1 h for triazolam, lormetazepam and zopiclone while flurazepam showed a more gradual onset of action.

Performance measures

The results were analysed by a repeated measures (within subject) analysis of variance; untransformed scores were used. The factors included were treatment and time. The analysis of some tasks had additional factors such as task halves and material type also included. Tukey's 'a' test was used to show significant differences between treatments.

Five-choice serial reaction task

The parameters derived from this task were: the number of correct responses, the number of errors and the number of 'blocks'.

Corrects: The number of correct responses in both 10 min portions of the task was sensitive to the effect of drug (main effect $P < 0.01$, time × drug interaction $P < 0.01$). The analysis of variance also showed a main effect for task halves ($P < 0.05$) with fewer correct responses being made in the second half of the task.

The precise form of the drug × time interaction is shown in Table 1. At 1 h, zopiclone (7.5 mg) and triazolam (0.25 mg) significantly ($P < 0.05$) reduced the number of correct responses with respect to placebo.

Errors: Errors (Table 2) were represented as a proportion of the total number of the correct responses. There was a marked increase in the incidence of errors in the second half of the task ($P < 0.001$). The effects of drugs and times were significant as main effects ($P < 0.05$; and $P < 0.001$) and as an interaction ($P < 0.001$).

The largest effect produced by the drugs was 1 hour after drug intake, where lormetazepam,

Table 1 Mean numbers of correct responses in the serial reaction task for the whole of the 20 min period of the task for each drug treatment and at four intervals after the ingestion of the drug

	Period			
Drugs	*0 h*	*1 h*	*4 h*	*10 h*
Placebo	987	970	963	976
Triazolam	991	788*	920	974
Lormetazepam	993	832	965	951
Zopiclone	951	705*	865	972
Flurazepam	946	829	894	951

* Significant differences from placebo ($P < 0.05$)

Table 2 Mean number of errors and mean percentage error in parenthesis of the serial reaction task for the whole of the 20 min period of testing for each of the drug treatments at five intervals following the ingestion of the drug

Drugs	*Period*			
	0 h	*1 h*	*4 h*	*10 h*
Placebo	19.4 (2.03)	22.3 (2.41)	22.4 (2.46)	21.3 (2.34)
Triazolam	27.5 (2.84)	54.1* (7.35)	33.5 (3.75)	25.5 (2.82)
Lormetazepam	20.2 (2.08)	44.1* (5.90)	21.9 (2.39)	24.3 (2.71)
Zopiclone	18.3 (2.02)	42.7* (7.00)	23.6 (3.19)	22.8 (2.47)
Flurazepam	22.1 (2.35)	22.6 (4.21)	32.9 (3.97)	23.8 (2.57)

* Significant differences from placebo ($P < 0.05$)

zopiclone and triazolam were all significantly different from placebo ($P < 0.05$).

Blocks: The analysis of variance showed no significant effect of drugs on these slow responses either as a main effect or as an interaction.

Logical reasoning

There were few errors on this task. An analysis of variance of the time to complete the task showed both drug and time to be significant main effects and also to have a significant interaction ($P < 0.05$). The data are shown in Figure 2. All the drugs had their most profound action at 1 h. Zopiclone, triazolam and flurazepam were all significantly different from placebo ($P < 0.05$) at 1 h, while at 4 h only zopiclone and triazolam maintained this statistical difference.

Stroop test

The scores of the three stroop cards (W, C and CW cards) were analysed by a two-way analysis of variance (drugs and times). Except for the interaction between drug and type of card all other terms in the analysis were significant ($P < 0.05$). Inspection of the data in Table 3 shows that the drugs tended to increase reading time on all three cards and that in some cases the trend on the interference card (CW) was greater than on the other cards.

In order to examine the data from this task in more detail an interference measurement was

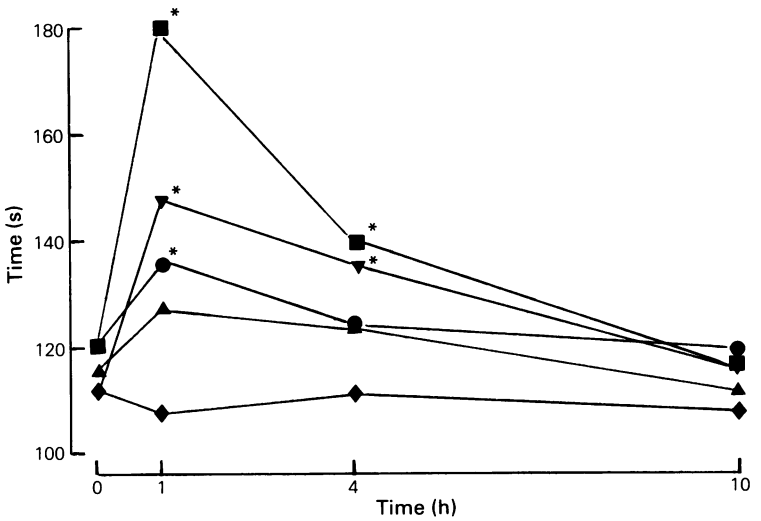

Figure 2 Mean times to complete the logical reasoning task (s) plotted against time after drug intake; ◆ placebo, ■ zopiclone 7.5 mg, ● flurazepam 15 mg, ▲ lormetazepam 1 mg, ▼ triazolam 0.25 mg
* $P < 0.05$ compared with placebo.

Table 3 Mean scores (reading times in seconds) on the stroop test. The table shows scores for the three component cards (W, C, and CW) for each drug and at each period of testing following the ingestion of the drug.

Drugs	Period 0 h	1 h	4 h	10 h
		Card W		
Placebo	35.6	36.6	36.2	35.3
Triazolam	35.9	42.5	38.6	36.5
Lormetazepam	37.1	41.1	38.3	36.7
Zopiclone	37.1	45.0	40.5	37.1
Flurazepam	35.8	38.0	37.1	36.8
		Card C		
Placebo	46.4	44.6	46.0	45.3
Triazolam	45.9	52.4	47.9	44.9
Lormetazepam	47.6	52.4	47.7	45.7
Zopiclone	47.3	62.3	53.0	48.2
Flurazepam	41.6	49.3	46.2	46.2
		Card CW		
Placebo	61.0	60.5	59.7	59.6
Triazolam	60.3	67.6	66.5	60.5
Lormetazepam	60.8	73.7	64.3	60.5
Zopiclone	62.2	83.1	69.8	58.9
Flurazepam	60.8	70.9	65.0	61.0

derived. The measure was calculated according to the following formula (CW-C)/W. This computation removed the effects of changes in reading speed and colour naming speed leaving what may be regarded as a pure measure of the resolution of the word/colour conflict. An ANOVA containing these derived scores showed a significant drugs × time interaction ($P < 0.05$). Despite this interaction being significant there were no significant differences between any of the treatments and placebo.

Memory span

The overall number of correct responses at each assessment time was analysed. The ANOVA showed only the time factor to be significant. There was no effect of drug either as a main effect or as an interaction.

Mood

The following three factors were derived from the mood adjective check-list: activation (component adjectives: active, energetic, vigorous), deactivation (component adjectives: drowsy, sluggish, tired) and concentration (component adjectives: concentrating, engaged in thought, earnest, serious). Analysis of the factors showed there to be no significant differences between mood ratings attributable to drug either as a main effect or as an interaction.

Discussion

All the psychological methods of assessment used in this study demonstrated a clear sedative trend after all the active treatments. However, memory span, five-choice serial reaction time blocks and mood ratings did not show changes attributable to drug intake. No one treatment emerged as the most potent sedative as the tasks were affected by the drugs to varying degrees. This analysis of drug effects on tasks has a major danger associated with it; the sensitivity of a task to a drug may be mistaken for 'faculty'. In other words, if a task is found to be sensitive to a drug (and others within a battery not sensitive) it is tempting to argue that a particular kind of mental function is impaired by the drug. This does not necessarily follow. It may well be that the sensitive task contains a feature (like its level of difficulty) which makes it susceptible to the effect of a drug rather than to some demand which it makes on a particular type of mental function. However, we have taken a general pragmatic approach in selecting tasks that are apparently representative of the range of intellectual function for every day work activities as the best estimate of human performance.

Saccadic eye movements were recorded frequently to provide a measure of the time course of drug action; peak effects were between 2–3 h for all drugs with the onset of action being between 0.5 and 1 h after drug intake for all drugs.

The similarity of time course of action of these compounds was surprising since there was a wide variation in the plasma-elimination half-lives of the compounds. A similar finding was reported by Bittencourt *et al.* (1981) using a saccadic eye movement method. A possible explanation is that the therapeutic doses of the compounds have been selected to produce the desired duration of action rather than magnitude of effect, so that in an acute situation any benzodiazepine, irrespective of its half-life, will be effective for a similar length of time. Clearly this will not be the case when dosing is chronic and long half-life compounds have a chance to accumulate.

The failure to find an effect on memory is not surprising in view of the findings of Johnson & Chernik (1982) who reviewed 52 studies carried out between 1959–81 on sedative-hypnotics and human performance. They reported that of the studies concerning benzodiazepines and memory impairment, only 35% of studies

reported decrements in performance. These changes being dependent on the particular benzodiazepines used, their doses, and the nature of the memory task employed. These factors are important since potent effects on memory following benzodiazepine ingestion have been clearly demonstrated in the literature.

A slowing of response speed was shown by the serial reaction task. This was associated with an increase in errors, an indication that the volunteers became generally more inefficient. Furthermore, the failure to find an effect with blocks indicates that this inefficiency did not take the form of momentary slow responses but was due to a general slowing and inaccuracy of performance. The logical reasoning task demonstrated slowness but not inaccuracy (no significant increase in errors). This result may be due to the instructions given to perform the task, which favoured accuracy rather than speed. Nevertheless, the effect of the drugs was to lengthen the interval between correct responses.

The doses of these drugs were not equipotent on these tasks, lormetazepam (1 mg) impaired performance less than the other treatments. However, all the compounds effected the tasks in a qualitatively similar manner. Hence the spectrum of activity of zopiclone, as assessed by this battery of tasks, was indistinguishable from those of the three marketed benzodiazepines with which it was compared.

The authors would like to thank Dr E. Allen, Dr A. Anderson and Mr R. W. Marshall for their co-operation and help in the execution of this study.

The study was supported by May & Baker Ltd.

References

Baddeley, A. D. (1968). A three minute reasoning test based on grammatical transformation. *Psychonomic Science,* **10**, 341–342.

Bittencourt, P. R. M., Smith, A. T., Wade, P. & Richens, A. (1981). The relationship between peak velocity of saccadic eye movements and serum benzodiazepines concentration. *Br. J. clin. Pharmac.,* **12**, 523–533.

Blanchard, J., Boireau, A. & Sulou, L. (1983). Brain receptors and zopiclone. *Pharmacology,* **27**, Suppl. 2, 59.

Gaillot, S., Heusse, D., Houghton, G. W., Marc Aurele, J. & Dreyfus, J. F. (1983). Pharmacokinetics and metabolism of zopiclone. *Pharmacology,* **27**, Suppl. 2, 76.

Griffiths, A., Marshall, R. W. & Richens, A. (1984). Saccadic eye movements analysis as a measure of drug effects on human psychomotor performance. *Br. J. clin. Pharmac.* **18**, 73S–82S.

Houghton, G. W., Dennis, M. J., Templeton, R. & Martin, B. K. (1985). The pharmacokinetics and metabolism of zopiclone. *Int. J. clin. Pharmac. Ther. Tox.,* **23**, 97–100.

Jensen, A. R. & Rohwer, W. D. (1966). The Stroop colour-word test. A review. *Acta Psychologica,* **24**, 36–93.

Johnson, L. C. & Chernik, D. A. (1982). Sedative hypnotics and human performance. *Psychopharmacology,* **76**, 101–113.

Lader, M. & Denney, S. (1983). The residual effects of zopiclone – a dose effect study. *Pharmacology,* **27**, Suppl. 2, 27.

Leonard, J. A. (1959). 5 choice serial reaction apparatus. *Medical Research Council Applied Psychology report* No. 326/57.

Stroop, J. (1935). Studies of interference in serial verbal reactions. *J. exp. Psychol.,* **18**, 642–662.

Tedeschi, G., Smith, A. T., Dhillon, S. & Richens, A. (1983). Rate of entrance of benzodiazepines into the brain determined by eye movement recording. *Br. J. clin. Pharmac.,* **15**, 103–107.

Thayer, R. E. (1978). Factor analytic and reliability studies on the activation-deactivation adjective check list. *Psychological Reports,* **42**, 747–796.

Trifilletti, R. R. & Snyder, S. H. (1984). Anxiolytic cyclopyrrolones zopiclone and suriclone bind to a novel site linked allosterically to benzodiazepine receptors. *Mol. Pharmac.,* **26**, 458–469.

Wickstrom, E. & Gierckskey, K. E. (1980). Comparative studies of zopiclone, a novel hypnotic and 3 benzodiazepines. *Eur. J. clin. Pharmac.,* **17**, 189–196.

(Received 6 August 1985, accepted 9 January 1986)