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Testing the Effects of the Imidazopyridine Zolpidem on Memory: An Ecologically Valid Approach

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The present study explores whether memory impairments are found on the morning following intake of the hypnotic zolpidem which is a member of a new pharmaceutical class, the imidazopyridines. The procedure used is novel: it involves testing subjects in their own homes via the telephone. A previous study using this technique found significant deficits in performance on the morning following intake of the benzodiazepines, flunitrazepam and midazolam, on tasks which load heavily on both the speed and capacity aspects of the human information processing system. Using the same tests, results from the present study fail to find any significant effects on the morning following zolpidem intake.

KEY WORDS—Human information processing, memory, benzodiazepines, imidazopyridines, telephone testing.

INTRODUCTION

Zolpidem is an hypnotic agent of a new pharmacological class, the imidazopyridines (IZPs). The elimination of half-life of zolpidem is between 1·5 and 2·4 hours (Langtry and Benfield, 1990). As with the benzodiazepines (BZDs), the fundamental mechanism of action of this new group is mediated by the binding to the $GABA_A$–chloride channel–omega complex. Unlike the former group, however, zolpidem has been shown to have a far greater selectivity for the central omega or BZ_1 receptor. Its affinity for the central Bz_2 receptor is low and is also small for the peripherally and centrally located Bz_3 receptor. As a result of this selectivity, at the therapeutic dose, zolpidem shows little anticonvulsant, anxiolytic or myorelaxant effects (Arbilla *et al.*, 1985, 1986; Langer and Arbilla, 1987; Langer *et al.*, 1988; Langtry and Benfield, 1990). On the other hand, it does show obvious hypnotic properties. Zolpidem has been found to reduce the time to onset and to increase the duration of sleep in healthy volunteers when administered in doses as low as 5–7·5 mg at bedtime. In other words, it shows an effectivity which is comparable to BZD hypnotics administered at their appropriate dosages (Langtry and Benfield, 1990) and thus offers an interesting alternative to BZDs in the treatment of insomnia.

Why should the search for such an alternative be necessary? The popularity of the BZDs obviously relates to their effectiveness as safe sleep remedies. Unfortunately, however, this positive and intended night-time action is frequently followed by a number of undesired 'hangover' effects, including various forms of memory impairment. Compared to the BZDs as a pharmacological class, as yet relatively little research has been carried out with the IZPs, particularly in relation to the assessment of memory functioning in human subjects after zolpidem intake. Notwithstanding, results from the laboratory studies which have been carried out are, in large measure, encouraging: for example Langtry and Benfield (1990) reviewed a small number of studies on the effects of zolpidem on memory on patients with insomnia and found no effects of zolpidem 10 mg on memory functioning when tested the morning after drug administration. The present study seeks to extend the data available on the IZPs by comparing the effects of zolpidem with placebo on various information processing tasks. The particular methodology to be used in this study is novel. The volunteers taking part are not tested in the laboratory but, instead, in the comfort and security of their own homes via the medium of the telephone. The rationale underlying this choice of methodology is described elsewhere (Jackson *et al.*, in press). The basic procedure involves testing both accuracy and speed

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performance via a specially designed communication interface and the medium of the telephone. Using this novel technique it has proved possible to replicate performance deficits as a result of taking the well-known BZDs, midazolam and flunitrazepam (Jackson *et al.*, in press). The results of this study showed both the short-acting midazolam and the longer active flunitrazepam to have negative slowing or 'hangover' effects of on the human information processing system in healthy middle-aged volunteers. In particular, the test battery which includes tasks that load heavily on both the speed and capacity aspects of the information processing system, revealed significant deficits in performance in the two BZD conditions as compared to placebo.

The aim of the present experiment is to extend the BZD study by exploring whether or not the IZP zolpidem shows similar negative 'hangover' effects on the morning following intake. The telephone testing technique will again be used along with the same battery of tests in a two-way crossover design comparing zolpidem with placebo. Since the study was begun within a month of completion of the BZD study, and the same middle-aged healthy volunteers took part, no concurrent positive control was initially included in the present study. If, as we predict, no differences in performance are found between the control placebo condition from this study and the placebo condition from the previous BZD study, performance following midazolam and flunitrazepam intake will be accepted as the necessary and sufficient positive controls for validation of the new methodology.

Our prediction, based on previously published findings which consistently report on inability to find 'hangover' effects, is that no residual effects will be found on the morning following zolpidem intake.

METHOD

Subjects

The nineteen volunteers (10 males, nine females) who took part in an earlier validation study (in print) continued to participate. They had an average age of 41·2 years (range 30–54) and had been recruited via an advertisement in the local press. A first selection had taken place by telephone according to previously agreed criteria. Subjects were screened by the project's medical supervisor who established their medical histories, emotional and health status. The volunteers had no known sleep disorders and reported themselves to have been drug free for at least 4 weeks prior to the study. They were instructed to refrain from alcohol consumption for at least 48 h before testing, and not to drink coffee or tea on the test morning until after testing. The project was approved by the Medical Ethics Committee of the University of Groningen and each subject gave informed consent to the project.

Medication and design

Zolpidem (10 mg) and a placebo were selected as treatment conditions. The two medications were identical in appearance. In the crossover design there were two treatment periods of 4 days separated by an interval period of 9 days. Testing took place on the morning following the fourth treatment night. The treatments were administered double-blind and the order was randomized. However, since the randomization was carried out prior to the start of the validation phase (reported in Jackson *et al.*, in press) and two subjects withdrew from this phase (both for reasons unconnected to the study), the order was not completely balanced, having eight subjects in one group and 11 in the other. Subject commencement was phased: there were five groups with three subjects per group and two groups with two subjects. Each group started on a different day. The main reason for consecutive starting days instead of a 'full-parallel' design is the fact that to control for time-of-day effects (for example Folkard and Monk, 1978; Idzikowski, 1984) a maximum of three subjects per day could be called on their home telephone, i.e. at 08·30, 09·00, and 9·30 a.m. The subjects were asked to take their tablets 30 min before they went to bed at a regular time (23–24 h). Drug compliance was checked by questioning each subject, tablet counting and by determining the drug and first metabolite level in the urine samples which were routinely collected each test morning. Samples were tested using high-performance liquid chromatography (HPLC) and gas liquid chromatography (GLC). Subjects were also required to complete subjective evaluation questionnaires relating to both sleep duration and quality. A general sleep quality questionnaire (GSKS) was taken before the start of the study. The GSKS comprises 15 questions which require subjects to judge the quality of their sleep in the period immediately prior to the start of the study. The score on this test is taken as the subject's baseline score. In order to check the efficacy of

the hypnotic drug treatment, on every morning following either drug or placebo treatment subjects were required to judge the duration of their sleep and to complete a sleep quality questionnaire (SQS: Mulder-Hajonides van der Meulen, 1980). A subject's mean score on the SQS following each treatment was subtracted from his/her baseline GSKS score. This difference score was used in further analysis.

Procedure

Training procedure. Since each of the subjects had already taken part in a previous study using the same tests and telephone technique, they were simply given a very short training session prior to the start of the session. This simply fulfilled the function of refreshing their memory for the test battery.

Telephone procedure. All testing was carried out in the subject's own home by means of the telephone. On test days, subjects were called at the same time each morning (either 08·30, 09·00 or 09·30 a.m.) and were required to perform the test battery. Two of the tests required a simple verbal response which could be spoken into the telephone just as with any normal conversation. The responses were collected via a specially designed communication interface connected to a tape-recorder. The remaining two tests required reaction time responses. Each subject had a small specially designed modem incorporating two buttons corresponding to a 'yes' and a 'no' response. Subjects were instructed that they should press one of the two buttons as quickly as possible. In other words, the procedure mimics a normal laboratory response procedure. The resulting data were again collected automatically by the communication interface.

Test battery

Parallel versions of all tests were designed. The tests were presented to all subjects in the same order on each testing occasion. The order is as follows:

(1) Verbal fluency task
(2) Free recall of shopping lists
(3) Syntactic reasoning task
(4) Semantic verification task.

Verbal fluency test. Subjects were given 2 min to produce as many examples as possible from categories (e.g. fruits) selected from the Dutch norms of Maring and Deelman (1989). The fluency score was the total number of correct items (not repetitions) produced. In cases of uncertainty about category membership, the subject's responses were judged by independent persons.

Shopping lists. This test consisted of the consecutive presentation of 15 shopping items such as white tulips or raspberry jam. The items were presented one every 2 s. Subjects were required to recall the items verbally: the sequential order of recall was not important. For an item to be scored correct, both noun and adjective, i.e. both white and tulips, must be recalled.

Syntactic reasoning test. This task is a modified version of Baddeley's Syntactic Reasoning Task (1968). Subjects were presented with a series of 16 sentences each purporting to described the order of two letters (e.g. B follows A). Each sentence was followed by the two letters. Half of the time the letters were presented in the order described by the sentence ('yes' response: AB); in the other half, in the reverse order ('no' response: BA). Sentence difficulty within the series, ranging from simple active sentences through more complex sentences involving passive, negatives, or both, was manipulated. The task was self-paced. The sentence was presented for approximately 3000 ms and, after an interval of 1000 ms, was followed by the test pair (A–B or B–A). Subjects were instructed to respond by pressing the 'yes' or 'no' button on their modem as quickly and as accurately as possible. There were two dependent variables, namely the number of correct responses and the reaction times of the correct responses.

Semantic verification task. This task is a variation of one which has been found to be highly reliable and sensitive to a range of stressors (for example alcohol: Baddeley, 1981). It measures how quickly and accurately subjects can retrieve information from semantic long-term memory. Subjects were presented with 30 short sentences which related to everyday knowledge. Half of the sentences were true (for example tomatoes grow in greenhouses), and half false (for example psychologists are made in factories). Subjects were required to verify each sentence as being true or false by pressing the appropriate button of their modem. This was an experimenter-paced test with sentences being presented over a period of approx. 2500 ms. The pres-

entation period was followed by a 1000 ms response period. Failure to respond within these time limits resulted in a missing trial. Dependent variables included both speed and accuracy.

Statistical method. Statistical analyses, unless otherwise stated, were carried out using paired *t*-tests on SPSS/PC + (version 4·0).

RESULTS

No subjects withdrew from this phase of the study. Tablet counting and questioning met our prescribed criteria and results of the urine test were in complete accordance with the randomization schedule. No subjects had therefore to be excluded from the analyses. Throughout the remainder of this section, placebo and zolpidem will be referred to as P and Z conditions respectively.

Mean sleep duration

The subjective estimate of total sleep duration (averaged over the judgements on the four treatment nights) was virtually identical: 500 min for P, and 497 min for Z.

Sleep quality scale

The scale on both GSKS and SQS questionnaires ranges from a score of 0 (perfect sleep) to 15 (enormous sleep problems). The group mean score on the GSKS questionnaire was 1·8, indicating that, as a group, they normally did sleep well. The range of scores, however, varied from 0 to 10 and the standard deviation (SD) of the scores was large, 2·7. This was caused in large measure by three subjects, though one in particular stood out: he scored 10 in the general GSKS questionnaire; 8 on the SQS with placebo and 0 on the SQS with zolpidem.

The average score on the SQS with placebo was 3·5, and 2·1 with zolpidem. While the difference between the conditions is indeed significant at a 2 per cent level when a non-parametric sign test is used, the variation within each treatment condition is once again very large with SDs of 3·1 and 3·0 for P and Z conditions respectively. The analysis performed on difference scores (GSKS—mean SQS) per condition was not significant.

Test version effects

Since two parallel versions of each task were used, it was important to check for version effects. The *t*-tests carried out on all four tests to check for version effects failed to reach any level of significance.

Shopping lists

The mean numbers of items recalled for the P and Z conditions were 9·5 and 9·1 respectively. This difference was not significant ($t(18) = 0{\cdot}98$, $p < 0{\cdot}33$).

Verbal fluency

The mean scores for P and Z respectively were 13·4 and 13·2. This difference was not significant.

Syntactic reasoning

In this task there were two independent variables, namely the number of correct responses and the reaction times of the correct responses. The mean number of correct responses for the P and Z conditions were 11·5 and 11·6. This difference was not significant ($t(18) = -0{\cdot}19$, $p < 0{\cdot}85$). Similarly, the mean reaction times scores of 2·02 and 2·04 s for P and Z conditions were not different from each other ($t(18) = -0{\cdot}09$, $p < 0{\cdot}93$).

Conditions within this task were also compared using *t*-tests. These showed reaction times on positive sentences to be significantly faster than on negative sentences: 1·6 vs 2·3 ($t(18) = -2{\cdot}74$, $p < 0{\cdot}02$).

Semantic verification

Again, both speed and accuracy of verification were used as dependent variables in this task. Accuracy of verification for both conditions was identical and approached the maximum possible score, 95·7 per cent.

Reaction time. There was no difference between the P and Z groups. The times were 1·15 (SD 0·20) and 1·15 s (SD 0·24) respectively.

Practice effects

Given that the subjects in the present study had already taken part in a previous study using parallel versions of the same test battery, it seemed important to check for practice effects. This was done by comparing the results with placebo in the original experiment with those from placebo in the pres-

Table 1. Comparison of results in placebo condition in a previous study using the same subjects (Jackson *et al*, in press) with those of placebo condition in the present study.

	Placebo original study		Placebo present study			
Test	Mean	SD	Mean	SD	*t*-value	*p*-value
VF Test	13·1	3·8	13·4	5·2	0·28	0·78
SL Test	9·3	2·9	9·7	2·8	1·03	0·31
SR correct	11·5	2·9	11·9	2·9	0·32	0·75
SR RT	1·7	0·8	2·0	1·1	2·22	0·05*
SV correct	28·4	2·3	28·8	0·9	0·95	0·36
SV RT	1·3	0·3	1·2	0·2	−1·72	0·10

RT = reaction time in seconds; VF = verbal fluency test; SL = shopping list recall; SR = syntactic reasoning test; SV = sentence verification test.

ent study. The results of all conditions are shown in Table 1. An inspection of the table shows only one result to reach significance: this was in the reaction time data in the syntactic reasoning task ($t = -2{\cdot}22$, $p < 0{\cdot}05$). However, this difference is not in the direction that would have indicated a practice effect. Instead the reaction times were slower on the second placebo! A closer look at the data showed one score to be way out of range for one subject in the present study; a further analysis excluding the data of this subject revealed a more marginally significant result ($t = -1{\cdot}87$, $p < 0{\cdot}08$).

DISCUSSION

In the present study, which employed volunteers with no known sleep difficulties, subjective judgements of both quantity and quality of sleep were obtained. The quantitative judgements showed no difference between the control and drug conditions, with the judged amount of sleep for both conditions—8 h—being what one would expect from healthy adults who are following their normal daily routine.

The subjective sleep quality scale used (the SQS) produced data which certainly suggested that the subjects rated their sleep as qualitatively better following zolpidem than placebo (significant at 2 per cent level with non-parametric tests). Given the large within-treatment variability found in the data, however, caution in drawing conclusions may be warranted. Adopting such a conservative conclusion, the present study shows that normally good sleepers judge that they sleep just as well following zolpidem as placebo, and report no deleterious after-effects. These subjective judgements support our findings of no deleterious 'hangover' effects on objectively measured performance following zolpidem intake.

Although, as yet, only a small number of studies have been carried out with zolpidem, those that are reported in the literature do offer encouraging results since they fail to find 'hangover' effects on the morning following ingestion (Langtry and Benfield, 1990). The results of the present study extend these positive and encouraging findings: unlike the BZD midazolam (Jackson *et al.* in press) which has a similar half-life to the IZP zolpidem, the latter hypnotic showed no deficits on either the capacity or speed aspects of the human information processing system when compared with performance following a placebo treatment. The validity of the method used gains support from the finding that the placebo conditions in both the earlier BZD study and the present study do not differ from each other. Of interest also is the fact that this absence of morning-after effects with zolpidem was found within the context of a real-life study. Since an important goal of behavioural psychopharmacology must surely be to explore how normal persons, who take an hypnotic on medical prescription, behave under the influence of doses which do not prevent them carrying out their normal daily activities, such ecological studies are obviously extremely relevant. The new telephone technique developed in our laboratory allows us to carry out real-life studies and has proved successful in showing that, unlike the BZDs midazolam and flunitrazepam (Jackson *et al.*, in press), zolpidem does not seem to produce deleterious effects on the morning after ingestion—at least in a group of healthy volunteers. As yet, the new telephone testing technique has not been examined in a population which manifests insomnia complaints. Its success to date, however,

suggests that this non-invasive and non-intrusive method offers an interesting new tool for psychopharmacological studies.

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REFERENCES

Arbilla, S., Depoortere, H., George P. and Langer, S. Z. (1985). Pharmacological profile of zolpidem at benzodiazepine receptors and electrocorigram in rats. *Naunyn-Schmeidebergs Archives of Pharmacology*, **330**, 248–251.

Arbilla, S., Allen, J., Wick, A. and Langer S. Z. (1986). High affinity (3H)-zolpidem binding in the rat brain: an imidazopyridine with agonist properties at central benzodiazepine receptors. *European Journal of Pharmacology*, **130**, 257–263.

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

Baddeley, A. D. (1981). The cognitive psychology of everyday life. *British Journal of Psychology*, **72**, 257–269.

Folkard, S. and Monk, T. H. (1978). Time of day effects in immediate and delayed memory. In: *Practical Aspects of Memory*, Gruneberg, M. M., Morris, P. E. and Sykes, R. N. (eds). Academic Press, New York, pp. 303–310.

Fossen, A., Godlibsen, D. B., Loyning, Y. and Dreyfus, J. F. (1982). Effects of hypnotics on memory. *International Pharmacopsychiatry*, **17**, 116–126.

Hindmarch, I. (1984). Psychological performance models as indicators of the effects of hypnotic drugs on sleep. *Psychopharmacology Supplement*, **1**, 58–68.

Idzikowski, C. (1984). Sleep and memory. *British Journal of Psychology*, **75**, 439–449.

Jackson, J. L., Louwerens, J. W., Cnossen, F. and de Jong, H. T. P. (In press). Testing the effects of hypnotics via the telephone: Fact or fiction? *Psychopharmacology*.

Langer, S. Z. and Arbilla, S. (1987). Complexities of central and peripheral benzodiazepines receptors: A proposal for a new pharmacological nomenclature. Sleep Research Proceedings, 5th International Congress of Sleep, Copenhagen.

Langer, S. Z., Arbilla, S., Scatton, B., Niddam, R. and Dubois, A. (1988). Receptors involved in the mechanism of action of zolpidem. In: *Imidazopyridines in Sleep Disorders*, Sauvenet, J. P., Langer, S. Z. and Morselli, P. L. (eds) (L.E.R.S. Monograph series, volume 6). Raven Press, New York, pp. 55–70.

Langtry, H. D. and Benfield, P. (1990). Zolpidem. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential. *Drugs*, **40**, 291–313.

Lister, R. G. (1985). The amnesic action of benzodiazepines in man. *Neuroscience and Biobehavioral Reviews*, **9**, 87–94.

Maring, W. and Deelman, B. G. (1989). Aspecten van het geheugen bij ouderen en dementie. In: *Grijze Cellen, Wijze Cellen*, W. B. Brouwer *et al.* (eds). Verkeerskundig Studie-centrum, Haren, pp. 111–114.

Mendelson, W. B. (1990). Insomnia: The patient and the pill. In: *Sleep and Cognition*, R. R. Bootzin, J. F. Kihlstrom and D. L. Schacter (eds). American Psychological Society, Washington, D. C., pp. 95–107.

Morselli, P. L., Larribaud, J. Guillet, Ph, Thiercelin, J. F., Barthelet, G., Grilliat, J. P. and Thébault, J. J. (1988). Daytime residual effects of Zolpidem: A review of available data. In: *Imidazopyridines in Sleep Disorders*, Sauvenet, J. P., Langer, S. Z. and Morselli, P. L. (eds) (L.E.R.S. Monograph series, volume 6). Raven Press, New York, pp. 183–191.

Mulder-Hajonides van der Meulen, W. R. E. H. (1980). Measurement of subjective sleep quality. Paper presented at the European Sleep Conference, Amsterdam.