Daytime wakefulness following a bedtime oral dose of zolpidem 20 mg, flunitrazepam 2 mg and placebo

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1 The effects of zolpidem 20 mg, flunitrazepam 2 mg and placebo, administered at bed time, were studied in 12 healthy young male volunteers.

2 The assessments included, at awakening, subjective ratings of overnight sleep, cognitive function, psychomotor performance (digit symbol substitution, choice reaction time, flicker fusion threshold), subjective ratings of alertness, and plasma assay of residual drug concentration. Daytime sleep propensity during the day after dosing was evaluated with the multiple sleep latency test.

3 Compared with placebo, both active drugs improved subjective assessment of the ease of getting to sleep. At awakening, under flunitrazepam treatment, the reduction of performance, on memory and psychomotor tests, paralleled an increased subjective rating of sleepiness, but zolpidem treatment left subjects unimpaired compared with placebo. Similarly, daytime sleep propensity was enhanced throughout the following day under flunitrazepam treatment, but not under zolpidem treatment. Plasma assay for residual drug concentration at awakening found significant amounts of flunitrazepam and marginal amounts of zolpidem.

4 Results indicate that zolpidem 20 mg is devoid of residual effects in a range of tasks that were sensitive enough to demonstrate a prolonged wakefulness impairment following flunitrazepam 2 mg in healthy volunteers.

Keywords hypnotics zolpidem flunitrazepam healthy volunteers residual effect psychomotor performance multiple sleep latency test

Introduction

Decrease in daytime alertness may occur in up to two thirds of the insomniac patients treated with hypnotics (Dement *et al.*, 1984). Assessment of daytime sleepiness is therefore a major concern in evaluating hypnotic treatment.

The benzodiazepines, which are most widely used as hypnotics, have a range of elimination half-lives, from short (few hours) to medium length (10 to 20 h). Short-acting benzodiazepines, in appropriate dosage, have indeed been shown

to be less prone to impairing wakefulness than long-acting ones (Bliwise *et al.*, 1983; Mattmann *et al.*, 1982; Nicholson & Stone, 1980). However, both short and long-acting benzodiazepines have, in addition to their hypnotic activity, other pharmacological effects such as anterograde amnesia, myorelaxing or anxiolytic/disinhibiting effects that may give rise to side-effects.

It has been proposed that the wide pharmacological effects of benzodiazepines are sustained

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at a biological level by low benzodiazepine receptor-subtype selectivity, with the underlying assumption that to each receptor-subtype would correspond a different behavioural effect (Dubnick *et al.*, 1983; Lippa *et al.*, 1979).

Following this hypothesis, designing new drugs with enhanced binding selectivity to benzodiazepine receptor-subtypes, has led to the development of new chemical classes such as cyclopyrrolone or imidazopyridine derivatives.

Zolpidem is a new imidazo(1-2a)pyridine derivative with potent hypnotic activity in animals and humans (Depoortere *et al.*, 1988; Nicholson *et al.*, 1986). Although chemically unrelated to benzodiazepine compounds, zolpidem was shown to bind with affinity to the omega 1 site of the macromolecular complex which includes the chloride channel and the GABA A receptor (subtype 1 benzodiazepine) (Langer *et al.*, 1988).

Phase I studies have shown that 10 to 30 mg are well tolerated and that zolpidem is mainly eliminated through metabolic pathways, has no active metabolite, and has an elimination half-life of about 2 h (range 0.7–3.5 h) (Scharf *et al.*, 1988; Thenot *et al.*, 1988).

The present trial was a placebo controlled phase I study, designed to evaluate the state of alertness in 12 healthy male volunteers, the day following a night time dose of 20 mg zolpidem. Since negative results could well arise from insensitive measures, flunitrazepam 2 mg was introduced in the study as a positive control to validate the test procedures.

Flunitrazepam is a potent benzodiazepine hypnotic (Bixler *et al.*, 1977), and 'hang over effect' has already been demonstrated with this dosage the day following a night time administration (Bond & Lader, 1975). The pharmacokinetics of flunitrazepam are complex; it is mainly eliminated by metabolism and the elimination half-life has been found to be about 21.5 ± 1.7 h (Singlas, 1979; Wickstrom *et al.*, 1980).

Methods

Twelve healthy male volunteers entered the study having completed a screening procedure which included clinical examination, clinical laboratory evaluation, psychological, sleep and EEG assessments.

All subjects, informed of the aim of the trial, gave their written consent; the study was granted ethical approval by the Ethics Committee, Pitié-Salpêtrière Hospital, Paris.

All subjects were free from any somatic or psychiatric disease and clinical laboratory para-

meters were within the normal range. Subjects were free from any EEG abnormality, and none, in a sleep latency test procedure, had a sleep latency below 10 min prior to entrance.

Mean age of subject sample was 23.6 years (range 18–28) and body weight 68 kg (60–83); five subjects were tobacco smokers and seven non smokers; mean usual coffee consumption was 1.5 cups a day (range 0–5). Mean sleep time, and sleep quality were calculated from a 15 days sleep-log completed prior to entrance. Subjects' mean sleep time was 8.72 h (range 6.93–9.97) and sleep quality on a 10 point-scale was 8.2 (range 6.86–8.93).

Evaluation criteria

Sleep questionnaire Sleep parameters under trial conditions were assessed at awakening by means of a nine-item sleep questionnaire assessing:

- Q1. whether treatment helped sleep (not at all, a little, very much)
- Q2. sleep latency time (0–15, 15–30, 30–45, 45–60, more than 60 min)
- Q3. sleep latency compared with usual (slower, as usual, faster)
- Q4. number of awakenings
- Q5. sleep duration (less than 5 h, 5–6, 6–7, 7–8, more than 8 h)
- Q6. sleep duration compared with usual (less, as usual, more)
- Q7. sleep quality (light, medium, sound)
- Q8. feeling restored at awakening (less, as usual, more)
- Q9. dreams (unpleasant, no dream, pleasant).

Psychophysiological evaluations The test battery used in the study is among the most widely used in psychopharmacology (Hindmarch, 1980). Task procedures have been previously described and proved to be sensitive to sedative compounds (Warot *et al.*, 1988). The test battery included:

- digit symbol substitution test (DSST, number of correct substitutions done within 180 s);
- choice reaction time, visual and motor (VRT, MRT) and critical flicker fusion threshold (c.f.f.) using the Leeds psychomotor tester;
- visual analogue rating scales (anxious, sad, depressed, happy, relaxed, tired, drowsy, dizzy, clumsy, energetic, alert);
- short-term verbal memory (recall of 10 paired words immediately after presentation);

— long term visual memory (30 min delayed free and recognition recall of 12 simple pictures).

Clinical tolerability Clinical tolerability was evaluated by spontaneous symptoms report and symptoms check-list completion after each test-session.

Plasma drug determination Blood samples were collected at the end of each test session for subsequent assay of residual drug concentration. A sample of 8 ml blood was collected in a heparinized tube and centrifuged. Plasma was then frozen (-20°C) until assay. A high performance liquid chromatography method was used for zolpidem (analytical detection limit = 1 ng ml^{-1}) (Guinebault *et al.*, 1986); a gas-phase chromatography method, adapted for capillary column separation, was used for flunitrazepam determination (analytical detection limit = 0.5 ng ml^{-1}) (Da Silva & Bekersky, 1976).

Multiple sleep latency test Objective day-time sleep propensity was evaluated by multiple sleep latency test (MSLT). The test was performed in a sound-insulated dark room at 2 h intervals from 10.00 h to 18.00 h. Instruction given to subjects was: do not fight sleep. Electroencephalograms were recorded on a polygraph and continuously monitored. Recording was stopped after 1 min of definite stage I or after 20 min of recording if sleep did not occur. Sleep latency was counted from 'lights off' to the appearance of first stage I; sleep latency was counted at 20 min if sleep did not occur (Carskadon *et al.*, 1986).

Study design

After the completion of the screening procedures, and 1 week prior to the first dosing, subjects underwent a full day active training on performance tests so as to achieve a performance level which the experimenter considered to be asymptotic.

Subjects were then randomly allocated to sequence treatment according to a 3 by 3 Latin Square Design. Each subject was given a single oral dose of zolpidem 20 mg, flunitrazepam 2 mg, or placebo, of identical appearance, at 1 week intervals.

On dosing days, subjects were required to abstain from alcohol and coffee consumption and to avoid napping; subjects attended the laboratory at 21.00 h, took their treatment under supervision at 21.30 h, and lights were switched off at 22.00 h. At awakening time the following day, which was systematically 9 h after lights-off,

subjects had to complete the nine-item sleep questionnaire. A standard breakfast was given excluding caffeine containing beverages. One hour after awakening, subjects undertook the 30 min performance test session. At the end of the test session a symptom check-list was completed and a blood sample was collected for subsequent assay of residual drug concentration.

The remainder of the day, subjects underwent the MSLT every 2 h from 10.00 h to 18.00 h.

Statistical analysis

Non parametric tests for dependent variables were done for ordinal data (sleep questionnaire) by means of Friedman test and Wilcoxon sign rank test for paired comparisons.

When variables were continuous, data analysis (psychophysiological test) was undertaken by ANOVA for mixed Latin Square Design including subject, period and treatment effect; between treatment comparisons were handled by Tukey Test.

Analysis of sleep latency (MSLT) was handled by variance analysis for Latin Square Design with repeated measures including subject, period and treatment factor and the time of sleep latency test as the repeated measure (Split Plot variance analysis).

Results

No dropouts from the study occurred due to adverse effects, and all subjects completed the study in full measure.

General tolerability

The treatments were well tolerated on the whole. At awakening, mild adverse effects were reported by six of 12 subjects.

Reported adverse effects were:

— ataxia, inebriate feeling, vertigo, or dysphoria, in six subjects, from mild to moderate intensity, reported only after flunitrazepam treatment.

— amnesia of the events occurring in the morning (test and questionnaire) was reported the next day by one subject following flunitrazepam treatment.

Sleep questionnaire

The sleep questionnaire results showed significant differences between the three treatments only for the first three questions, namely:

Q1. 'did the treatment help you to sleep' (Friedman test, $\chi^2 = 6.125$, $P = 0.046$);

- Q2. 'Time to fall asleep' (Friedman test, $\chi^2 = 7.292$, $P = 0.026$);
 Q3. 'Time to fall asleep compared with usual' (Friedman test, $\chi^2 = 7.625$, $P = 0.022$).

Flunitrazepam significantly helped subjects to sleep, sleep induction was reported shorter and faster than usual compared with placebo (Q1: $Z = 2.21$, $P = 0.026$; Q2: $Z = 2.21$, $P = 0.026$; Q3: $Z = 2.67$, $P = 0.007$).

Zolpidem also significantly shortened sleep latency compared with placebo (Q2: $Z = 2.00$, $P = 0.045$); no difference between flunitrazepam and zolpidem reached significance level.

Visual analogue rating scales

Results of mood and alertness visual analogue scales are presented in Table 1.

Significant treatment factor was found for most alertness describing items:

- 'Drowsy' ($F(2,20) = 22.36$, $P < 0.001$);
- 'Energetic' ($F(2,20) = 14.29$, $P < 0.0001$);
- 'Tired' ($F(2,20) = 3.46$, $P < 0.05$);
- 'Clumsy' ($F(2,20) = 11.45$, $P < 0.0001$);
- 'Dizzy' ($F(2,20) = 36.17$, $P < 0.0001$);
- 'Alert' ($F(2,20) = 21.85$, $P < 0.0001$).

For all these items, flunitrazepam was found to significantly impair wakefulness compared with placebo and zolpidem, while there was no statistically significant difference between zolpidem and placebo.

No treatment factor effect was found for any of the mood describing items ('Anxious', 'Sad', 'Depressed', 'Happy', or 'Relaxed').

Psychophysiological tests

Results of the tests are presented in Table 2.

A significant treatment factor was found for:
 — C.f.f. threshold ($F(2,20) = 12.52$, $P < 0.0001$);
 — Visual reaction time (VRT: $F(2,20) = 13.19$, $P < 0.0001$);
 — Motor reaction time (MRT: $F(2,20) = 12.52$, $P < 0.0001$);
 — DSST ($F(2,20) = 33.05$, $P < 0.0001$);
 — Immediate recall (paired words: $F(2,20) = 5.22$, $P < 0.014$);
 — Delayed free recall of pictures ($F(2,20) = 28.23$, $P < 0.0001$).
 No significant treatment effect was found for delayed recognition recall.

Drug comparisons showed significant decrease in performance with flunitrazepam as compared with placebo and zolpidem for all the tests noted above. None of the comparisons revealed a significant difference between placebo and zolpidem.

MSLT

Sleep latency as a function of time of day and treatment is presented in Figure 1.

Split-plot ANOVA analysis showed significant treatment effect ($F(2,20) = 6.37$, $P < 0.007$) and no time or treatment by time interaction effect.

Therefore only overall sleep-latency mean values in the day were compared for differences between all possible pairs of means.

Table 1 Visual analogue scales (VAS): subjective assessments of mood and alertness at awakening 10 h after zolpidem 20 mg, flunitrazepam 2 mg or placebo medications administered at bedtime. Results are mean ($\pm$ s.e. mean) of 12 subjects for each adjective measured on 100 mm scale. Multiple comparisons were handled by Tukey test; Studentized range with corresponding α (two tailed) probabilities are presented

Item (100 mm)	Placebo	Flunitrazepam (2 mg)	Zolpidem (20 mg)	ZOL vs FLU Tukey test	FLU vs PLA Tukey test
Drowsy	50.50 (2.89)	74.08 (2.89)	50.25 (2.89)	$q = 8.25$ $P = 0.001$	$q = 8.159$ $P = 0.001$
Alert	52.00 (2.46)	31.00 (2.46)	49.58 (2.46)	$q = 7.55$ $P = 0.001$	$q = 8.537$ $P = 0.01$
Dizzy	50.58 (2.36)	74.33 (2.36)	49.00 (2.36)	$q = 10.73$ $P = 0.001$	$q = 10.06$ $P = 0.001$
Energetic	49.00 (2.72)	27.33 (2.72)	46.92 (2.72)	$q = 7.20$ $P = 0.001$	$q = 7.967$ $P = 0.001$
Tired	48.08 (3.68)	59.42 (3.68)	47.08 (3.68)	$q = 3.35$ $P = 0.10$	$q = 3.081$ $P = 0.10$
Clumsy	49.33 (1.68)	62.17 (1.68)	49.33 (1.68)	$q = 7.64$ $P = 0.001$	$q = 7.643$ $P = 0.001$

Table 2 Psychophysiological evaluations at awakening 10 h after zolpidem 20 mg, flunitrazepam 2 mg or placebo medications administered at bedtime. Results are mean ($\pm$ s.e. mean) of 12 subjects for each task

Tests	Placebo	Flunitrazepam (2 mg)	Zolpidem (20 mg)	ZOL vs FLU Tukey test	FLU vs PLA Tukey test
C.f.f. (Hz)	26.00 (0.21)	24.96 (0.21)	26.42 (0.21)	q = 6.95 P = 0.001	q = 4.95 P = 0.01
VRT (ms)	301.17 (4.41)	325.33 (4.41)	295.00 (4.41)	q = 6.88 P = 0.001	q = 5.48 P = 0.005
MRT (ms)	112.25 (2.75)	127.17 (2.75)	108.83 (2.75)	q = 6.67 P = 0.001	q = 5.42 P = 0.005
DSST (score in 180 s)	125.50 (1.81)	106.00 (1.81)	122.08 (1.81)	q = 8.88 P = 0.001	q = 10.77 P = 0.001
Paired word (max = 7)	6.72 (0.19)	5.83 (0.19)	6.29 (0.19)	q = 2.42 P = NS	q = 4.68 P = 0.01
Delayed free recall (max = 12)	10.00 (0.36)	6.50 (0.36)	9.67 (0.36)	q = 8.81 P = 0.001	q = 9.72 P = 0.001

C.f.f. = Critical flicker fusion threshold; VRT = Visual component of choice reaction time; MRT = Motor component of choice reaction time; DSST = digit symbol substitution test. Multiple comparisons were handled by Tukey test; Studentized range with corresponding α (two tailed) probabilities are presented

Tukey test ranked the three treatments as follows: Zol>Pla>Flu with zolpidem being significantly different from flunitrazepam ($q(3,20) = 5.30$, $P < 0.01$).

Plasma assay

Significant amounts of flunitrazepam were found in all 12 subjects 11 h after drug administration with a mean concentration of 2.86 ± 0.28 ng ml⁻¹.

Significant amounts of zolpidem were also detected in five subjects 11 h after drug administration while in seven subjects concentrations were below the analytical detection limit and mean drug concentration was 5.75 ± 2.48 ng ml⁻¹.

Neither compound was found in the plasma after placebo administration.

Discussion

In the study population of young healthy subjects with optimal sleep parameters, it was still possible to demonstrate some efficacy of both hypnotics on sleep induction. Though this is not the first objective of the study to demonstrate the hypnotic activity of zolpidem 20 mg, which had already been done in previous clinical studies, these results suggest an equivalent activity of zolpidem 20 mg and flunitrazepam 2 mg, on sleep induction at least.

At awakening however, flunitrazepam induced a marked decrease in subjective and objective indicators of wakefulness, whereas zolpidem was not found different from placebo condition in any of these evaluations.

Accordingly, the lack of residual effect observed after zolpidem is unlikely to be the result of insensitive measures, but is compatible with the reported plasma kinetics of this drug. Zolpidem has a tenfold shorter elimination half-life (2 h vs 20 h) than flunitrazepam. The concentration findings in our study are consistent with

Figure 1 Multiple Sleep Latency Test (MSLT) results (mean $\pm$ s.e. mean). Comparison of zolpidem 20 mg (ZOL, $\circ$) flunitrazepam 2 mg (FLU, Δ) and placebo (PLA, $\bullet$) in 12 healthy volunteers the day following a bedtime medication. Sleep latency is measured by the time in minutes from lights off until the first 60 s period of definite stage I; Sleep latency is counted at 20 min if sleep did not occur. Statistical analysis: Drug effect (ANOVA Latin Square for Repeated Measure) $F(2,20) = 6.37$, $P < 0.007$; no significant Time or Time $\times$ Drug interaction effect.

previous report of zolpidem and flunitrazepam kinetic parameters. At the time of test and sampling, zolpidem concentrations were about 2% of reported maximal plasma concentration ($260 \pm 15 \text{ ng ml}^{-1}$) while flunitrazepam concentrations were still about 20 to 30% of reported maximal plasma concentrations ($10\text{--}15 \text{ ng ml}^{-1}$).

Memory impairment is of special interest in the profile of residual effects of flunitrazepam. Anterograde amnesia following flunitrazepam treatment is well documented, but this effect is usually reported shortly after administration in the range of time of the maximum plasma concentration (George & Dundee, 1977; Wickstrom & Godtliebsen, 1988). In the present study both short and long term memory impairment were present at least 10 h after flunitrazepam dosing. In one subject the amnesic effect was strong enough to induce a complete amnesia from the morning study session.

In contrast no memory deficit could be demonstrated after zolpidem administration. Since zolpidem concentrations at evaluation time were most probably far below the efficacy threshold, the lack of memory impairment after zolpidem cannot be related to enhanced hypnotic selectivity. More specific studies with evaluation times at peak effect are required to test for this hypothesis.

In the present study the residual effect of flunitrazepam upon wakefulness could be followed all through the following day, as demonstrated by the MSLT results. MSLT has been shown to be a useful and sensitive indicator of impaired wakefulness in clinical practice and for efficacy and residual effect evaluations of

hypnotic drugs (Borbely *et al.*, 1985; Duka *et al.*, 1988).

MSLT results of the present study do not demonstrate a circadian rhythm for sleepiness under placebo conditions, as previously described, and this could point to some lack of sensitivity of the study procedure. However MSLT was robust enough to allow a between-drug discrimination. Sleep latency was shortened after flunitrazepam compared with placebo and zolpidem. The subjective and psychomotor task performance findings are consistent with the lack of effect of zolpidem on sleep latency.

When considering the possible residual effect of an hypnotic, one must also consider, beside its pharmacokinetics, the range of doses used. Although the 10 mg dose of zolpidem is the commonly marketed dose in France, and clinical data have shown this dose to be the first active one (Monti, 1989; Nicholson & Pascoe, 1986; Oswald & Adam, 1988), the choice of zolpidem dosage in this study was directed by the facts that other data have shown the 20 mg dose to be more effective (Weintraub *et al.*, 1988), and, in general practice, that increasing the dose to 20 mg is recommended in case of inadequate response.

The lack of residual effect in healthy volunteers, following 20 mg zolpidem, in a range of evaluations that were sensitive enough to demonstrate impairment of wakefulness following a bed time dose of 2 mg flunitrazepam, suggests that hang-over effects in clinical practice will be less likely with zolpidem. This requires further study.

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References

- Bixler, E. O., Kales, A., Soldatos, C. R. & Kales, J. D. (1977). Flunitrazepam, an investigational hypnotic drug: sleep laboratory evaluations. *J. clin. Pharmac.*, **17**, 569–578.
- Bliwise, D., Seidel, W., Karakan, I., Mitler, M., Roth, T., Zorick, F. & Dement, W. C. (1983). Daytime sleepiness as a criterion in hypnotic medication trials: comparison of triazolam and flunitrazepam. *Sleep*, **6**, 156–163.
- Bond, A. J. & Lader, M. (1975). Residual effects of flunitrazepam. *Br. J. clin. Pharmac.*, **2**, 143–150.
- Borbely, A. A., Balderer, G., Traschel, L. & Tobler, I. (1985). Effect of midazolam and sleep-deprivation on daytime sleep propensity. *Arzneimittel Forschung*, **35**, 1696–1669.
- Carskadon, M. A., Dement, W. C., Mitler, M. M., Roth, T., Westbrook, P. R. & Keenan, S. (1986). Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. *Sleep*, **9**, 519–524.
- Da Silva, J. A. F. & Bekersky, J. (1976). Determination of 1-4 benzodiazepines and diazepam 2-ones in blood by electron-capture gas chromatography. *Anal. Chem.*, **48**, 10–19.
- Dement, W. C., Seidel, W. & Carskadon, M. A. (1984). Issues in the diagnosis and treatment of insomnia. *Psychopharmacology*, **1**, Supplement, 11–43.
- Depoortere, H., Decobert, M., Riou-Merle, F. & Granger, P. (1988). Pharmacoe-EEG profile of zolpidem: an imidazopyridine hypnotic agent. In *Imidazopyridines in sleep disorders*, eds Sauvanet, J. P., Langer, S. Z. & Morselli, P. L., pp. 81–96. New York: Raven Press.
- Dubnick, B., Lippa, A. S., Klepner, C. A., Coupet, J., Greenblatt, E. N. & Beer, B. (1983). The

- separation of 3H-benzodiazepine binding sites in brain and benzodiazepine pharmacological properties. *Pharmac. Biochem. Behav.*, **18**, 311–318.
- Duka, T., Goerke, D., Dorow, R., Holler, L. & Fichte, K. (1988). Human studies on the benzodiazepine receptor antagonist β -carboline ZK 93426: antagonism of lormetazepam's psychotropic effects. *Psychopharmacology*, **95**, 463–471.
- George, K. & Dundee, J. W. (1977). Relative amnesic actions of diazepam, flunitrazepam and lorazepam in man. *Br. J. clin. Pharmacol.*, **4**, 45–50.
- Guinebault, P., Dubruc, C., Hermann, P. & Thenot, J. P. (1986). High performance liquid chromatography determination of zolpidem, a new-sleep inducer, in biological fluids with fluorimetric detection. *J. Chromatogr.*, **383**, 206–211.
- Hindmarch, I. (1980). Psychomotor function and psychoactive drugs. *Br. J. clin. Pharmacol.*, **10**, 189–209.
- Langer, S. Z., Arbilla, S., Scatton, B., Niddam, R. & Dubois, A. (1988). Receptors involved in the mechanism of action of zolpidem. In *Imidazopyridines in sleep disorders*, eds Sauvanet, J. P., Langer, S. Z. & Morselli, P. L., pp. 55–70. New York: Raven Press.
- Lippa, A. S., Critchett, D., Sano, M. L., Klepner, C. A., Greenblatt, E. N., Coupet, J. & Beer, B. (1979). Benzodiazepine receptors: cellular and behavioral characteristics. *Pharmac. Biochem. Behav.*, **10**, 831–843.
- Mattmann, P., Loepfe, M., Scheitlin, T., Schmidlin, D., Gerne, M., Strauch, I., Lehmann, D. & Borbely, A. A. (1982). Daytime residual effects and motor activity after three benzodiazepine hypnotics. *Arzneimittel Forschung*, **32**, 461–465.
- Monti, J. M. (1989). Effect of zolpidem on sleep in insomniac patients. *Eur. J. clin. Pharmacol.*, **36**, 461–466.
- Nicholson, A. N. & Pascoe, P. A. (1986). Hypnotic activity of an imidazopyridine (zolpidem). *Br. J. clin. Pharmacol.*, **21**, 205–211.
- Nicholson, A. N. & Stone, B. M. (1980). Activity of the hypnotics, flunitrazepam and triazolam, in man. *Br. J. clin. Pharmacol.*, **9**, 187–194.
- Oswald, I. & Adam, K. (1988). A new look at short-acting hypnotics. In *Imidazopyridines in sleep disorders*, eds Sauvanet, J. P., Langer, S. Z. & Morselli, P. L., pp. 253–259. New York: Raven Press.
- Scharf, M. B., Kaffeman, M., Rodgers, L. & Segal, J. (1988). Single dose tolerance study of zolpidem. In *Imidazopyridines in sleep disorders*, eds Sauvanet, J. P., Langer, S. Z. & Morselli, P. L., pp. 175–181. New York: Raven Press.
- Singlas, E. (1979). Pharmacocinétique du flunitrazepam. *Presse Med.*, **31**, 2519–2523.
- Thenot, J. P., Hermann, P., Durand, A., Burke, J. T., Allen, J., Garrigou, D., Vajta, S., Albin, H., Thebault, J. J., Olive, G. & Warrington, S. J. (1988). Pharmacokinetics and metabolism of zolpidem in various animal species and in humans. In *Imidazopyridines in sleep disorders*, eds Sauvanet, J. P., Langer, S. Z. & Morselli, P. L., pp. 139–153. New York: Raven Press.
- Warot, D., Krebs, M. O., Bensimon, G., Payan, C., Danjou, P., Lacomblez, L. & Puech, A. J. (1988). Dose-effect study of levomepromazine on psychomotor and memory tasks in healthy volunteers. *Human Psychopharmacology*, **3**, 127–132.
- Weintraub, M., de Oliveira, G., Moscucci, M., Kelvie, W. & Surasky, S. (1988). A two-night preference technique for assessing the dose response and efficacy of hypnotics in insomniac patients. In *Imidazopyridines in sleep disorders*, eds Sauvanet, J. P., Langer, S. Z. & Morselli, P. L., pp. 241–251. New York: Raven Press.
- Wickstrom, E., Amrein, R., Haefelfinger, P. & Hartmann, D. (1980). Pharmacokinetic and clinical observations on prolonged administration of flunitrazepam. *Eur. J. clin. Pharmacol.*, **17**, 189–196.
- Wickstrom, E. & Godtlibsen, O. B. (1988). The effect of quazepam, triazolam, flunitrazepam and placebo, alone and in combination with ethanol, on daytime sleep, memory, mood and performance. *Human Psychopharmacology*, **3**, 101–110.

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