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Evaluation of Zolpidem, Triazolam, and Placebo as Hypnotic Drugs the Night Before Surgery

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Study Objective: *To compare the hypnotic effects of a bedtime dose of zolpidem, triazolam, and placebo.*
Design: *Double-blind, randomized, placebo- and active-controlled, parallel-group trial.*
Setting: *Six Canadian hospitals.*
Patients: *357 patients (aged 19 to 71 years) hospitalized the night before a surgical procedure.*
Interventions: *At bedtime, each patient received either zolpidem 10 mg, triazolam 0.25 mg, or placebo, and was allowed to sleep for a maximum of 8 hours.*
Measurements: *Outcome measures were subjective in nature and included a morning questionnaire, visual analog scales, and observation forms by study personnel. All continuous variables were analyzed by analysis of variance. All categorical data were compared using the Cochran-Mantel-Haenszel (CMH) test, and the percentage of patients asleep was compared using a CMH chi-square analysis. When significant overall treatment effects were observed, pairwise comparisons were undertaken. Compared with the placebo group, the following parameters were significantly ($p < 0.001$) different in the zolpidem and triazolam groups: sleep latency was shorter, total sleep time was longer, patients fell asleep more easily, and the number of patients awake 2 hours after drug administration was lower. There were no differences between any groups in next-morning somnolence or ability to concentrate. Both drugs were well tolerated, with adverse event incidence rates nearly identical to placebo.*
Conclusions: *In patients suffering from transient insomnia, a single dose of zolpidem 10 mg was as effective as triazolam 0.25 mg, and both were more effective than placebo and were well tolerated.* ©1997 by Elsevier Science Inc.

Keywords: Insomnia, transient; sleep patterns, preoperative; triazolam; zolpidem.

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Introduction

Zolpidem (N,N,6-trimethyl-2-(4-methylphenyl) imidazo[1,2-a]-pyridine-3-acetamide hemitartrate) is a non-benzodiazepine hypnotic with a rapid onset

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and short duration of action. It has a short elimination half-life of approximately 2.5 hours and no pharmacologically active metabolites.[1,2] The mechanism of action of zolpidem presumably involves its interaction at specific benzodiazepine binding sites of a certain population of central gamma aminobutyric acid-A (GABA-A) receptors.[3–5] Zolpidem has been shown to alleviate transient insomnia associated with sleeping in a strange environment[6] and with phase-advance of bedtime.[7] It has been shown to be efficacious in the treatment of short-term[8] and chronic insomnia.[9] Zolpidem studies in various insomniac populations have demonstrated maintenance of normal sleep architecture[10] and a low incidence of next-day disturbances of psychomotor performance.[11]

Transient insomnia is a condition that typically affects people with normal sleep patterns who may have a short period of insomnia due to environmental conditions or stress.[12] When the environmental situation is resolved, the insomnia will usually disappear. Patients hospitalized for diagnostic procedures or minor surgeries frequently experience this form of sleep disturbance. Short-acting hypnotics are of particular value as adjunctive medications for patients to induce sedation,[12] especially when given the night before surgery.[5] In models of transient insomnia, zolpidem 10 mg promotes sleep without impairing motor performance the subsequent day.[6,7] Triazolam[13] and other short-acting hypnotics[14,15] also have been used in the management of insomnia prior to surgical procedures. In controlled clinical trials, the short-term use of triazolam has been associated with disturbing side effects, including memory and motor impairment.[16–19] In some comparative trials, the effects of triazolam were more extensive and/or longer-lasting than those of zolpidem,[20,21] but in a recent study of dose-effect relationships of zolpidem, triazolam, and temazepam assessing a multitude of daytime performance tests, no difference was detected between zolpidem and triazolam at the doses employed in the present trial.[22]

The objective of this study was to compare the subjective efficacy and tolerability of a single nighttime dose of zolpidem 10 mg, triazolam 0.25 mg, or placebo to induce sleep in hospitalized patients when administered the night prior to a surgical procedure.

Materials and Methods

Patients

Hospitalized patients scheduled for elective surgery (such as hysterectomy, hernia repair, plastic surgery, or orthopedic procedures) with ASA physical status I and II were screened for this study. Patients gave a medical and sleep history, and underwent a physical examination prior to study entry. Patients were excluded from the study for the following reasons: pregnancy (females of child-bearing potential had to have a negative pregnancy test); lactation; recent history of chronic insomnia; significant medical or psychiatric illness; use of short-acting central nervous system (CNS) medications within two days of admission; use of alcohol on the day of admission; use of triazolam within the previous four nights; use of other short- or intermediate-acting hypnotics such as temazepam within seven nights; use of long-acting hypnotics or any type of medication that would interfere with the assessment of a hypnotic within 14 nights of admission to the hospital; use of cimetidine within two weeks prior to admission; a history of exaggerated response to benzodiazepines or other CNS depressants; a history (within one year) of addiction, drug abuse, or alcoholism; history of sleep apnea or nocturnal myoclonus; or an abnormal sleep schedule predicated by shift work. After approval by the Human Subjects Review Committees at the respective hospitals, all patients gave written informed consent prior to study entry. Seven patients refused therapy after enrollment and before randomization.

Test instruments

Scales used to evaluate efficacy included: (1) a morning questionnaire assessing sleep latency, total sleep time, number of awakenings, and wake time during sleep as continuous variables; sleep quality (1 = excellent, 2 = good, 3 = fair, 4 = poor), condition on awakening (1 = better than usual, 2 = as usual, 3 = a little worse than usual, 4 = much worse than usual), and ability to concentrate (1 = excellent, 2 = good, 3 = fair, 4 = poor) as categorical data; and (2) visual analog scales (VAS) evaluating feelings of somnolence (0 = very sleepy, 100 = not sleepy at all) and ease of falling asleep (0 = very easy, 100 = not easy at all). Both of these kinds of instruments are widely used and have been validated as tools for the subjective evaluation of sleep parameters and next-day effects of hypnotics.[6,9,23,24] In addition, a sleep observation form for study personnel was used to record whether the patient was awake or asleep at half-hour intervals for the first two hours and at one-hour intervals for the rest of the night.

Study Design

The study was a double-blind, randomized, balanced, placebo- and active drug-controlled, parallel-group trial conducted at six sites in Canada. Randomization was carried out by sealed envelope assignment at Lorex Pharmaceuticals, Skokie, IL.

Patients were admitted into standard hospital settings with one or more patients per room. Each patient received a single dose of study drug (10 mg zolpidem, 0.25 mg triazolam, or placebo) at bedtime between the hours of 9 and 11 PM. Prior to the study night, patients had been informed that if they were awake two or more hours after study drug administration, they could request additional sedative medication (rescue medication). The type of rescue medication was not standardized across study sites and was left to the discretion of the investigator.

Patients were awakened following a maximum of eight hours of allotted potential sleep time. Vital signs were recorded at awakening and prior to surgery, and patients completed a morning questionnaire on which the primary efficacy parameters were sleep latency and total sleep time.

Information regarding adverse events was obtained

during the night and the early morning before surgery, as well as following surgery, from spontaneous patient reports, the morning questionnaire, and physical examinations. After surgery, adverse event information was also collected by the coordinator from the patient's chart.

Statistical Analyses

In this single-dose study, all patients who took study drug and completed the morning questionnaire were included in the analysis.

Demographic variables were compared between treatment groups using either the Cochran-Mantel-Haenszel (CMH) test for categorical data or by analysis of variance (ANOVA) for continuous and ordered demography and sleep history measures. In the analysis of subjective sleep latency, data from all patients were used, including those who used rescue medication. The values of the subjective latency included in the proportional hazards statistical analysis were those reported by the patients. For patients who requested a rescue medication, the subjective sleep latency was taken to be greater than the elapsed time until the rescue medication was requested. The proportional hazards model was used to analyze these data. The effects of treatment, center, and treatment-by-center interaction were assessed using the Wald chi-square statistic. ANOVA was performed for other continuous variables. When significant overall treatment differences were observed, pairwise comparisons of the treatments were undertaken using the Student-Neuman-Keuls multiple comparison procedure. Categorical data (quality of sleep, ability to concentrate, morning sleepiness, condition on awakening) were summarized by mean scores and assessed by ANOVA. The percentage of patients asleep was compared among treatment groups using a CMH chi-square analysis. Observation time points beyond two hours were not analyzed because rescue medication became available to patients at this time. Data were analyzed using the BMDP and SAS (SAS, Inc., Cary, NC) statistical packages.

Results

Patients

The study group consisted of 357 hospitalized patients (120 patients given zolpidem, 119 given triazolam, and 118 given placebo) scheduled for elective surgery. The patients ranged in age from 19 to 71 years, with a mean weight of 69.2 kg (range 43 to 114 kg); 114 patients were men and 243 were women. Most of the patients were Caucasian (n = 323), the remaining participants were Black (n = 15), Asian (n = 12), Hispanic (n = 3), or other (n = 4). The three treatment groups were comparable with respect to demographic characteristics and sleep history of randomized patients.

Sleep Induction

The two primary outcome measures from the morning questionnaire were self-reported sleep latency (minutes before the onset of sleep) and ease of falling asleep (*Table 1*). Subjective sleep latency was significantly shorter in the zolpidem and triazolam groups than in the placebo group, with no significant differences between the two active treatment groups. A 100 mm VAS was used to obtain a subjective next-day measure of ease of falling asleep (*Table 1*). Patients in both the zolpidem and triazolam groups rated themselves as falling asleep significantly more easily than did patients in the placebo group.

Table 1. Next-Morning Ratings of Treatment with Placebo, Zolpidem 10 mg, or Triazolam 0.25 mg

Parameter*	Placebo (n = 118)	Zolpidem (n = 120)	Triazolam (n = 119)	p-value
Continuous Variables (mean ± SE)				
Sleep latency† (min)	60.0^{A}	25.0^{B}	30.0^{B}	<0.001
Total Sleep Time	352.5 ± 9.2^{A}	378.4 ± 8.2^{B}	400.6 ± 8.1^{B}	<0.001
No. of Awakenings	2.8 ± 0.3^{A}	2.1 ± 0.2^{B}	1.4 ± 0.2^{C}	0.001
Wake Time during Sleep (min)	35.9 ± 6.3	36.4 ± 6.3	22.5 ± 4.2	0.014
Categorical Variables				
Sleep Quality‡	2.7 ± 0.1^{A}	2.0 ± 0.1^{B}	2.0 ± 0.1^{B}	<0.001
Condition upon Awakening§	2.3 ± 0.1	2.1 + 0.1	2.1 + 0.1	0.089
Ability to Concentrate‡	2.1 ± 0.1	2.0 ± 0.1	2.1 ± 0.1	0.210
Visual Analog Scales				
Ease of falling asleep‖	52.9 ± 3.0^{A}	27.9 ± 2.5^{B}	29.2 ± 2.6^{B}	<0.001
Morning Sleepiness**	59.0 ± 2.9	58.4 ± 2.7	62.8 ± 2.5	0.443

*Treatments that share the same letter (^{A,B,C}) are not significantly different ($p \geq 0.05$).

†Median, comparisons based on Wald chi-square.

‡1 = excellent, 2 = good, 3 = fair, 4 = poor.

§1 = better than usual, 2 = as usual, 3 = a little worse, 4 = much worse.

‖100 mm VAS (0 = very easy, 100 = not easy).

**100 mm VAS (0 = very sleepy, 100 = not at all sleepy).

Subjective Total Sleep Time

Since time in bed was limited to a maximum of eight hours, total sleep time represented a measure of sleep efficiency. Mean subjective total sleep time was significantly longer in the zolpidem and triazolam groups than in the placebo group (*Table 1*), and the two active groups did not differ significantly from each other.

Sleep Maintenance and Sleep Quality

Patients receiving zolpidem or triazolam reported significantly fewer waking episodes than did patients in the placebo group. In addition, patients receiving triazolam reported significantly fewer awakenings than did patients in the zolpidem group (*Table 1*). A significant treatment-by-center interaction was observed for number of awakenings; significantly fewer awakenings were observed after both zolpidem and triazolam than placebo at one center ($p = 0.003$). There was no statistically significant difference between groups in mean subjective wake time during the night (*Table 1*). Lastly, patients in the zolpidem and triazolam groups reported significantly better sleep quality than did patients in the placebo group (*Table 1*).

Rescue Medication

Of the 357 patients who received drug, 42 requested a "rescue medication" and were listed on the case report forms as having discontinued due to lack of efficacy. In agreement with the results on sleep induction, the proportion of such patients was higher in the placebo group (n = 27; 22.9%) than in the zolpidem (n = 8; 6.7%) and triazolam (n = 7; 5.9%) groups (overall CMH, $p < 0.001$). Of the 42 patients who requested a rescue medication, 14 patients received triazolam, 14 received lorazepam, 12 received flurazepam, and 2 received oxazepam.

Performance Ratings

As shown in *Table 1*, no significant differences were observed between the treatment groups in the ratings of ability to concentrate, morning somnolence, and condition on awakening.

Proportion of Patients Awake

The percentage of patients awake 0.5, 1.0, 1.5, and 2 hours after dosing were compared between the treatment groups. A significantly lower percentage of patients in the zolpidem and triazolam groups than in the placebo group were awake at each of the time points (*Table 2*).

Safety Evaluations

No patient who received zolpidem or triazolam experienced a serious or unexpected adverse event. One patient who received placebo experienced severe nausea two hours after dosing, which continued for 14 hours; the patient was discontinued from the study. The incidence of other adverse events was small and similar in the three groups.

Discussion

Both zolpidem 10 mg and triazolam 0.25 mg effectively improved subjective sleep characteristics when administered as a single dose on the evening prior to elective surgery. This observation is in agreement with results reported recently on numerous other outcome measures.[22] The improvement of sleep was of a similar magnitude in the two groups, with no significant difference between them. Compared with patients in the placebo group, patients in both active treatment groups reported significantly shorter sleep latency, they fell asleep more easily, total sleep time was longer, and they reported a better quality of sleep and fewer awakenings. Among the 42 of a total of 357 patients who requested rescue medication, 27 were in the placebo treatment group. Overall, in people with normal sleep patterns, the present data confirm previously reported results with zolpidem and triazolam obtained in insomniac patients.[25]

Zolpidem has been reported to be an efficacious hypnotic in other models of transient insomnia,[6,7] and benzodiazepines have been used to induce sleep on the evening prior to surgery.[13] There are several considerations that could actually argue against such usage. Administration of a benzodiazepine during a hospital admission has been identified as a risk factor in becoming a chronic user of these drugs.[26] In addition, development of tolerance

Table 2. Number (%) of Patients Awake during First Two Hours after Dosing

Hours After Dosing	Placebo (n = 118)	Zolpidem (n = 120)	Triazolam (n = 119)	Overall p-value (CMH)
0.5	92 (78)^{A}	69 (58)^{B}	65 (55)^{B}	<0.001
1.0	60 (51)^{A}	26 (22)^{B}	29 (24)^{B}	<0.001
1.5	43 (36)^{A}	10 (8)^{B}	15 (13)^{B}	<0.001
2.0	33 (28)^{A}	13 (11)^{B}	12 (10)^{B}	<0.001

CMH = Cochran-Mantel-Haenszel statistical test.
^{A,B}Percentages with the same superscripted letter are not significantly different (CMH chi-square; $p \geq 0.05$).

has been reported with repeated use of benzodiazepines. Although tolerance might occur following a prolonged stay with benzodiazepine usage, it appears unlikely to result from a single dose of a benzodiazepine, and, for that matter, of any hypnotic.

A similar argument applies to the risk of rebound insomnia that, theoretically, could impact the already disturbed postoperative sleep.[27] Rebound insomnia has been reported after chronic use of the 0.5 mg dose,[28,29] but not after a single dose of 0.25 mg of triazolam. No objective rebound insomnia has been reported with zolpidem,[9] although subjective outcome measures have captured a certain degree of sleep disturbance after abrupt discontinuation of prolonged treatment. In the balance, the benefit of a full night's sleep following a single dose of hypnotic prior to elective surgery has to be weighed against the minimal risk of dependence and rebound insomnia.

Another aspect of the use of zolpidem and triazolam is the reported memory impairment with benzodiazepines,[16,17] an effect that was not shared by zolpidem in some parallel trials[20,21] but was similar for zolpidem and triazolam in a recent study.[30] In this trial, no adverse events indicating memory impairment were found to occur in either group.

The next morning, patients perceived no effect on ability to function, which is in concordance with previous objective observations for both triazolam and zolpidem and is most likely related to the short half-life of these two hypnotics.[2,12] Based on spontaneous reporting during the eight-hour sleep period and at waking, there was no difference in the adverse incidence rates between the zolpidem and triazolam groups or between the placebo and the two active treatment groups.

At the time of this study, patients were routinely admitted on the night before their surgical procedure. Practice has now changed, with significant reductions in preoperative admissions. Many patients are now being operated on as outpatients or a same-day admission basis. Nonetheless, sleep patterns may be disturbed due to the stress of the upcoming procedure, even in patients who are in their usual environment. Anesthesiologists often have the chance to interview these patients in a preadmission setting. Patients who have a high degree of anxiety about the surgical procedure, or who actually request sedation the night before surgery, could be prescribed a hypnotic that they could take at home. Zolpidem or triazolam also may be beneficial in patients who have been hospitalized before their surgical procedure and in whom preoperative nighttime sedation is indicated.

In conclusion, the present results indicate that the nonbenzodiazepine zolpidem and the benzodiazepine triazolam are effective and safe medications when administered for transient insomnia the night before surgery. Both agents improved sleep to a comparable degree, and both hypnotics were rated significantly better than placebo. Zolpidem and triazolam were well tolerated, and there was no indication of perceived impairment on awakening.

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