Zolpidem modified-release in insomnia

Cynthia Kirkwood[1]
Jason Neill[2]
Ericka Breden[3]

[1]Department of Pharmacy; [2]School of Pharmacy, Virginia Commonwealth University; [3]Virginia Commonwealth University Medical Center, Richmond, VA, USA

Abstract: Zolpidem modified-release (MR) is the first hypnotic agent to be marketed in an extended-release formulation. Zolpidem MR is a two-layered, biphasic release tablet indicated for the management of induction of sleep and sleep maintenance. The pharmacokinetics of the drug are similar to those of immediate-release zolpidem. Two double-blind, placebo-controlled, parallel-group trials demonstrated efficacy in adults and elderly patients treated with zolpidem MR for 3 weeks without significant impairment in next-day psychomotor functioning. The most common adverse effects with zolpidem MR were dizziness, somnolence, and headache. A starting dose of zolpidem MR 12.5 mg is recommended for adults and 6.25 mg for elderly patients.

Keywords: zolpidem modified-release, hypnotics, insomnia

Introduction

Zolpidem, a non-benzodiazepine sedative/hypnotic, was marketed as the immediate-release product in the US in 1993 and in Europe in 1988 for the short-term treatment of insomnia (Roth et al 2006). Zolpidem is effective in reducing the time to sleep onset and increasing total sleep time, however its effect on sleep maintenance has not been consistently demonstrated (Scharf et al 1994; Roth et al 1995). The hypnotic effects of zolpidem have been reported primarily in the first 3 hours post-dose which can lead to subtherapeutic effects on sleep maintenance in the later portion of the night for some patients (Besset et al 1995).

In an effort to expand the coverage of sleep complaints and overcome the lack of efficacy in sleep maintenance, the manufacturer (Sanofi-Aventis) developed a modified-release (MR) formulation of zolpidem tartrate that was approved for use in the US in 2005. The coated, two-layer, zolpidem MR tablet is a biphasic release dosage form (Ambien CR Prescribing Information 2007). The first layer immediately releases drug while the second layer is controlled-release. The tablet was designed to mimic initial dosing while the extended-release of drug maintains a plasma concentration for a longer duration of time than the immediate-release product (Weinling et al 2006).

Pharmacology

Zolpidem tartrate is an imidazopyridine, nonbenzodiazepine hypnotic that differs in chemical structure from benzodiazepines and other hypnotics. The proposed hypnotic mechanism of action is via modulation of the gamma amino butyric acid (GABA) chloride ion channel macromolecular complex (Ambien CR Prescribing Information 2007). Zolpidem demonstrates preferential binding at the benzodiazepine type 1 receptor (BZ_1) on the α subunit of the $GABA_A$ receptor (Ambien CR prescribing information 2007). Unlike benzodiazepines that bind non-selectively to activate all benzodiazepine receptor subtypes, zolpidem's selectivity for the BZ_1 receptor confers sedative activity without producing appreciable anticonvulsant, anxiolytic, and myorelaxant effects (Drover 2004; Ambien CR Prescribing Information 2007).

Correspondence: Cynthia Kirkwood
Department of Pharmacy, School of Pharmacy, Virginia Commonwealth University, Box 980533, 410 North 12th Street, Smith Room 454, Richmond, VA 23298-0533, USA
Tel +1 804 828 8318
Fax +1 804 828 8359
Email ckkirkwo@vcu.edu

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Pharmacokinetics

Two pharmacokinetic studies of zolpidem MR have been published. The pharmacokinetic profiles of zolpidem MR 12.5 mg and the immediate-release zolpidem 10 mg were compared in a study of 24 men (Weinling et al 2006). The time to peak concentration (t_{max}) and elimination half-life for the modified- and immediate-release formulations were similar; however zolpidem MR maintained peak plasma concentrations for a longer duration of time (3–6 hours post-dose) in comparison with the immediate-release formulation (Weinling et al 2006). Greenblatt et al (2007) compared the pharmacokinetics and pharmacodynamics of single doses of immediate-release zolpidem 10 mg, zolpidem MR 10 mg, and placebo in 81 healthy volunteers in a 3-way crossover trial. The t_{max} of zolpidem MR (2.0 hours) was significantly longer than immediate-release zolpidem (2.4 hours) ($p < 0.004$). After dose normalization, the maximum concentration (C_{max}) for zolpidem MR was significantly lower than the C_{max} of immediate-release zolpidem (Greenblatt et al 2007).

Zolpidem MR is rapidly absorbed after oral administration and reaches a peak median concentration in 1.5 hours (range, 0.5–3.5 hours). The C_{max} of zolpidem MR was 82% of the immediate-release product and the absolute bioavailability was 68% (Weinling et al 2006). Administration of zolpidem MR with food decreased the peak concentration by 30% and area under the plasma concentration curve (AUC) by 23%. The median t_{max} was prolonged from 2 to 4 hours with food and the product labeling indicates that ingestion with food may delay the hypnotic effects of zolpidem MR (Ambien CR prescribing information 2007).

Plasma protein binding of zolpidem is about 92.5%. It is primarily metabolized via cytochrome P450 3A4 isoenzymes to inactive metabolites. The major routes of metabolism include hydroxylation and oxidation (Salva and Costa 1995). Zolpidem MR has an average elimination half-life of 2.8 hours (range, 1.62–4.05 hours) (Ambien CR Prescribing Information 2007). Accumulation was not observed in adult and elderly patients who received once a day dosing for a period of 2 weeks (Ambien CR Prescribing Information 2007).

Special populations

The t_{max} and elimination half-life of 6.25 mg of zolpidem MR in the elderly was 2 and 2.9 hours, respectively. The safety and efficacy of zolpidem MR has not been established in children less than 18 years of age (Ambien CR Prescribing Information 2007).

An evaluation of the pharmacokinetics of zolpidem MR in patients with hepatic or renal impairment has not been reported. The half-life of the immediate-release formulation of zolpidem was increased from 2.2 to 9.9 hours in patients with cirrhosis (Ambien CR Prescribing Information 2007). A reduction in the initial dosage of zolpidem MR is recommended for patients with hepatic insufficiency. The pharmacokinetics of immediate-release zolpidem in patients with renal impairment were not altered and dosage adjustments are not necessary in this patient population (Ambien CR Prescribing Information 2007).

Efficacy trials

Roth et al (2006) conducted a worldwide, multicenter, double-blind, placebo-controlled, parallel-group study in 212 adult outpatients, aged 18–64 years, with primary insomnia (diagnosed using Diagnostic and Statistical Manual of Mental Disorders, 4th Edition). The purpose of this study was to evaluate the efficacy and safety of zolpidem MR 12.5 mg. The duration of treatment was 21 days with 2 nights at the outset of the study and 2 nights at the end of the study consisting of single-blind placebo. The placebo substitution at the end of the trial was to determine the effect of discontinuing drug. The patients received zolpidem MR 12.5 mg or placebo at bedtime for a total duration of 3 weeks. The efficacy parameters were determined by polysomnography (PSG) in a sleep laboratory, specifically the latency to persistent sleep (LPS), sleep efficiency (SE), wake time after sleep onset (WASO), and number of awakenings (NA). Daytime subjective sleep estimates were derived from sleep questionnaires that were completed each morning and evening by study subjects. Evaluation with PSG for 8 hours occurred for 3 evaluation periods – on nights 1/2, 15/16, and 22/23. Within 30 minutes of awakening, subjects completed a battery of tests to assess daytime symptoms and psychomotor impairment (ie, morning sleep questionnaire, Digit Symbol Substitution Test [DSST], and Rey Auditory Verbal Learning Test [RAVLT]) (Roth et al 2006).

One hundred and ninety-two subjects completed the Roth et al study. Zolpidem MR significantly reduced the LPS on nights 1/2 ($p < 0.0001$) and nights 15/16 ($p < 0.0338$) and increased SE on nights 1/ 2 ($p < 0.0001$) and nights 15/16 ($p < 0.0172$) (Roth et al 2006). There was a significant improvement in sleep maintenance through reduction in WASO during the initial 6 hours of sleep and in number of awakenings with zolpidem MR compared with placebo on nights 1/2 and 15/16 ($p < 0.0001$). After adjustment for baseline differences in the treatment groups patients in the zolpidem MR group were awake for an average of about 34 minutes less over the first 6 hours of sleep on nights 1/2

and about 30 minutes less on nights 15/16 compared with placebo. There was no difference in next-morning psychomotor performance on the DSST and RAVLT between the zolpidem MR and placebo groups. Subjective reports of sleep improvement did not consistently support zolpidem-MR over placebo. Upon discontinuation of zolpidem MR there was a significant worsening of LPS, WASO and SE ($p < 0.05$) compared with baseline only on the first night. Somnolence, nausea and dizziness were reported more frequently in zolpidem MR-treated patients (Roth et al 2006).

A separate study reported in the product labeling describes results of a trial in 205 elderly outpatients with primary insomnia. This was a randomized, double-blind, placebo-controlled, parallel-group study evaluating zolpidem MR 6.25 mg for 3 weeks. A total of 198 subjects completed the study. Efficacy was determined using PSG on nights 1/2 and 15/16. Study participants completed sleep questionnaires daily. There was a significant reduction in WASO in the zolpidem MR group compared with placebo as measured over the first 6 hours of nights 1/2 and the first 4 hours of nights 15/16. Zolpidem MR decreased LPS during both evaluation periods compared with placebo. Patient-rated global improvement in sleep indicated that zolpidem MR "was superior" to placebo during the first two nights and on nights 15/16 (Ambien CR Prescribing Information 2007).

The package labeling indicates that wakefulness measured by PSG was increased in the zolpidem MR group "at the end of the night" compared with placebo in both of these efficacy trials (Ambien CR Prescribing Information 2007).

Adverse effects

About 3.5% of patients discontinued zolpidem MR therapy secondary to an adverse event during clinical trials (n = 201). The most common reasons for discontinuation were somnolence (1%) and dizziness (1%). Similarly, trials in the US with zolpidem immediate-release (n = 1701) reported 4% of patients discontinued treatment secondary to an adverse drug reaction (eg, daytime drowsiness, dizziness, headache and nausea/vomiting; all < 1%) (Ambien Prescribing Information 2005; Ambien CR Prescribing Information 2007).

The most frequently reported adverse effects in adults taking zolpidem MR were headache (19%), somnolence (15%), dizziness (12%), and nausea (7%). Comparable adverse effects were observed in elderly patients – headache (14%), somnolence (8%), and dizziness (6%); however nausea was infrequently reported. About 6% of elderly patients experienced nasopharangitis. Although headache was the most frequently reported adverse event in both adult and elderly populations the difference in incidence of this adverse effect in patients receiving zolpidem MR vs placebo was minimal (19% vs 16%, and 14% vs 11%, respectively) (Ambien CR Prescribing Information 2007).

Disorientation, visual disturbances, hallucinations, and balance disorders were reported more frequently in the package labeling with zolpidem MR than the immediate-release formulation (Ambien Prescribing Information 2005; Ambien CR Prescribing Information 2007). A summary of 20 case reports identified visual, auditory, tactile and hypnogogic hallucinations related to the use of zolpidem immediate-release (Toner et al 2000). It appears that hallucinations may be dose dependent and occur more frequently in women (80%) (Toner et al 2000). Elko et al (1998) reported that hallucinations may be related to concurrent antidepressant use (58.8%) and begin 15–60 minutes after taking zolpidem immediate-release. The duration of hallucinations ranged from short (about 30 minutes) or prolonged and last for up to 7 hours (Elko et al 1998). Nocturnal sleep-related eating disorder was reported in a case series of 5 patients with zolpidem immediate-release doses of 5–30 mg nightly that resolved when the drug was discontinued (Morgenthaler and Silber 2002). The United States Food and Drug Administration (FDA) requested labeling changes on all sedative hypnotics to warn of complex sleep-related behaviors (eg, sleep driving, sleep-eating) and severe allergic reactions in March of 2007 (FDA 2007).

Residual effects

Medications used to treat insomnia can cause next-day residual effects and rebound insomnia. Five clinical studies (ie, 3 adult, 2 elderly) determined zolpidem MR did not have a significant effect on vigilance, memory, or motor function eight hours post nighttime dose. However, a total of 15% of adult and 6% of elderly patients taking zolpidem MR reported next-day somnolence compared with 2% and 5%, respectively, of those taking placebo. In two clinical studies, rebound insomnia was observed on the first night after abrupt discontinuation of zolpidem MR in patients with primary insomnia. On the second night symptoms were not worse than those reported at baseline (Ambien CR Prescribing Information 2007).

Two published trials examined the residual psychomotor and cognitive effects of zolpidem MR (Blin et al 2006; Hindmarch et al 2006). Blin et al compared the effects of a single-dose of zolpidem MR 12.5 mg and flurazepam 30 mg (as the control drug) with placebo in 18 healthy, Caucasian subjects in a double-blind, placebo-controlled, 3-way

crossover (Blin et al 2006). The subjects were between the ages of 18–40 years (mean 26.3 ± 4.6 years). The dosing was separated by at least a 21-day washout period and 5 neuropsychological tests were performed 8.5 hours after night-time dosing to assess psychomotor and cognitive effects. These tests included the critical flicker fusion frequency (CFF), Hicks choice reaction time (CRT), immediate and delayed recall of supraspan word lists (iWR and dWR, respectively), compensatory tracking task (CTT), and DSST. Two questionnaires were used to evaluate subjective assessment of sleep – the Leeds sleep evaluation questionnaire (LSEQ) and the Bond and Lader visual analog scale (VAS). On the psychomotor and cognitive tests there was no significant difference between zolpidem MR and placebo in changes on mean CFF, CRT, iWR, dWR, CTT deviation, or DSST. The mean response time on CRT was significantly longer with zolpidem MR compared with placebo ($p = 0.0105$). Flurazepam treatment resulted in significant changes in all measures except the DSST compared with placebo indicating residual effects of this benzodiazepine. Results on the subjective measures showed that both zolpidem MR and flurazepam were effective in ease of falling asleep and the perceived quality of sleep on the LSEQ compared with placebo. Only flurazepam scored significantly lower on LSEQ measures of ease of awakening and behavior after awakening. On the Bond and Lader VAS, flurazepam impaired alertness and both study drugs significantly increased calmness compared with placebo. The limitations of this study were the small sample size, and reduced generalizability of results to patients with insomnia, elderly patients, and non-Caucasians.

Hindmarch et al reported results of a randomized, double-blind, placebo-controlled, 4-way crossover trial in 24 healthy elderly subjects (mean age 70.7 ± 3.8 years). Each subject received zolpidem MR 6.25 mg, zolpidem MR 12.5 mg, placebo, and flurazepam 15 mg (as the control drug). The psychometric tests performed were identical to those used in the Blin et al 2006 trial. The LSEQ was the only subjective assessment performed. Twenty-three subjects completed the trial. There was no significant difference between both doses of zolpidem MR and placebo on psychomotor performance tests. There was a significant difference in performance between flurazepam and placebo on all tests, except DSST. On the subjective testing, both doses of zolpidem MR and flurazepam demonstrated significant improvements in ease of getting to sleep and the quality of sleep compared with placebo. Somnolence and dizziness were the most frequently reported adverse effects for all drug treatments. Elderly subjects administered 6.25 mg of zolpidem MR experienced adverse effects similar to adults (≤64 years of age) who received zolpidem MR 12.5 mg. The major limitation in this study was that it was conducted in healthy elderly subjects; the residual effects of zolpidem MR in patients with insomnia are not known (Hindmarch et al 2006).

A criticism of both the Blin et al and Hindmarch et al studies of residual effects of zolpidem MR is the selection of flurazepam as the control drug. Flurazepam is a long-acting benzodiazepine with known daytime effects post-dose where a difference would be likely to have occurred (Kupfer and Reynolds 1997).

Rebound insomnia

Within two placebo-controlled studies assessing patients with primary insomnia, after abrupt discontinuation of zolpidem MR, rebound insomnia was reported the first night. The second night, symptoms were no worse than those reported at baseline. (Roth et al 2006; Ambien CR Prescribing Information 2007)

Drug interactions

Data on the drug interactions of zolpidem MR are based on studies performed with the immediate-release formulation. Zolpidem has additive effects on psychomotor performance when administered with alcohol or chlorpromazine and reduction of alertness with imipramine (Ambien CR Prescribing Information 2007). Additive depressant effects of zolpidem are anticipated when it is combined with drugs known to depress the central nervous system. The benzodiazepine receptor antagonist flumazenil reversed the hypnotic effect of zolpidem (Ambien CR Prescribing Information 2007).

Zolpidem co-administered with haloperidol, digoxin, warfarin, cimetidine, or ranitidine did not result in altered pharmacokinetics of either drug (Salva and Costa 1995; Ambien CR Prescribing Information 2007). Sertraline 50 mg was shown to significantly increase the C_{max} and decrease the t_{max} of zolpidem by 43% and 53%, respectively (Allard et al 1999; Ambien CR Prescribing Information 2007).

Potential inhibitors and inducers of the CYP 3A4 pathway may affect zolpidem pharmacokinetics, although the clinical significance of such alterations appears minimal. Ketoconazole impaired the DSST scores and recall scores, increased the area under the plasma concentration curve (AUC), and prolonged the elimination half-life of zolpidem immediate-release (Greenblatt et al 1998). Coadministration of zolpidem with fluconazole or itraconazole did not produce significant changes in zolpidem pharmacokinetics or pharmacodynamics (Greenblatt et al 1998). Rifampin administered at 600 mg/day

for 5 consecutive days reduced the AUC, C_{max}, half-life, and pharmacodynamic effects of zolpidem (Villikka et al 1997; Ambien CR Prescribing Information 2007).

Dosing and administration

The generally recommended starting dose of zolpidem MR is 12.5 mg by mouth immediately before bedtime for the average adult patient. A lower dose of 6.25 mg is suggested for the elderly, and for patients with debilitations or hepatic insufficiency (Ambien CR Prescribing Information 2007). Zolpidem MR is an extended-release tablet, therefore it should be swallowed whole, and not cut-in-half, divided, crushed or chewed. This drug should also be stored at temperatures between 15 °C and 25 °C (59 °F–77 °F) (Ambien CR Prescribing Information 2007).

According to the manufacturer, persons taking zolpidem MR should be warned against engaging in activities that require complete mental alertness or motor coordination (eg, operating machinery or driving a car) after taking zolpidem MR. Additionally, zolpidem MR should not be ingested with alcohol, and may cause additive effects when used with other CNS depressants (Ambien CR Prescribing Information 2007).

Economics of insomnia

Insomnia has a significant negative economic impact that can be described in terms of direct and indirect costs. Direct costs, that include use of healthcare services and the cost of prescription and non-prescription sleep medications, have been estimated to be US$13.9 billion (Walsh and Englehardt 1999). Expenditure on sleep medications was included in this figure and was estimated to be US$809.92 million (Walsh and Englehardt 1999; Martin et al 2004). Indirect burdens of insomnia reflect a decrease in societal economic output and are attributable to absenteeism, loss of productivity, and accidents (Walsh 2004). The cost for these losses has been placed at nearly US$28 billion (National Sleep Foundation 2005). Insomnia was associated with medical complications and an increased risk for substance abuse (Stoller 1994; Leger et al 2002). The estimated cost of insomnia-related depression was US$1 billion per year and the cost of alcohol abuse resulting from insomnia ranged from US$8.5 to US$11.6 billion per year (Stoller 1994; Martin et al 2004). An economic evaluation of zolpidem MR in insomnia has not been reported to date.

Summary

The place of zolpidem MR in therapy is unknown at this time. The fact that it is the first extended-release hypnotic to be approved for sleep induction and maintenance makes it unique. There are no head-to-head clinical comparisons of the efficacy of zolpidem immediate-release or other hypnotics (ie, temazepam, eszopiclone, zaleplon) with zolpidem MR. It is only speculative that it has a longer duration of effect than the immediate-release product or that it is similar in efficacy to other hypnotics used in patients with sleep maintenance complaints. Pharmacokinetically, this formulation offers a longer duration of time in which the plasma concentration of zolpidem is elevated post-dose. Pharmacodynamically, zolpidem MR potentiates sleep maintenance for greater than 3 hours and up to 6 hours compared with placebo in patients with primary insomnia (Roth et al 2006). Overall, zolpidem MR provides an additional pharmacotherapeutic option in patients whose sleep is not maintained by immediate-release zolpidem to provide a longer duration of sleep.

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