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THE ROLE OF ROZEREM®, THE FIRST MELATONIN RECEPTOR AGONIST, IN THE TREATMENT OF INSOMNIA

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Over 100 million Americans of all ages fail to get a good night sleep. Approximately 70 million suffer from insomnia but only 6% are diagnosed. Furthermore, only half of those diagnosed receive treatment for their condition. Women are twice as likely as men to have difficulties falling asleep or staying asleep. The gender difference may be due to menstrual cycles, pregnancy, menopause, or postmenopausal factors.[1,2] When left untreated insomnia can lead to depression, impaired productivity, absenteeism from work, increased risk of accidents, and decreased quality of life. Insomnia has been linked to a variety of health problems including obesity, diabetes, hypertension, heart disease, and depression. According to the National Sleep Foundation, $14 billion is spent annually on healthcare related to insomnia and $28 billion is lost in productivity, medical expenses, sick leave, and property and environmental damage. Additionally, the prevalence of insomnia increases in the elderly – a rapidly expanding sector. In the elderly, untreated insomnia can complicate other common medical conditions such as arthritis, diabetes, heart disease, and depression.[2]

Insomnia is characterized by difficulty falling asleep, staying asleep, or poor quality of sleep leading to impairment of next-day functioning. Insomnia can be divided into acute and chronic. Acute insomnia is often caused by emotional or physical discomfort, including significant life stress, acute illness, jet lag, and environmental disturbances such as noise, light, and temperature. Chronic insomnia can be caused by various factors acting singly or in combination, and usually occurs in conjunction with other health problems. Factors such as chronic stress, hyperarousal, poor sleep hygiene and behavioral conditions can all cause chronic insomnia. Psychiatric disorders, medications, substance abuse, or specific sleep disorders such as restless leg syndrome (RLS), periodic limb movement disorder (PLMD), sleep apnea, and circadian rhythm sleep disorders are often seen in patients with chronic insomnia.[3]

There are various options available for the treatment of insomnia. Hypnotic medications are primarily for short-term management of insomnia, either as the sole treatment modality or as adjunctive therapy until the underlying problem is controlled. Barbiturates were formerly the gold standard but have fallen out of favor due to significant drug-drug interactions, respiratory depression, tolerance, psychological and physical dependence, and severe withdrawal complications. The most commonly prescribed hypnotic agents are benzodiazepines. They can induce, maintain, and improve sleep.[3] However, prolonged use or use of long-acting agents can lead to daytime sleepiness, cognitive impairment, coordination difficulties,

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and worsening depression. Roth et al. showed a significant decrease in memory recall after subjects were given flurazepam, lorazepam, and triazolam for two consecutive nights per week for 4 weeks.[4] Additionally, this class of medications can exhibit residual effects on attention.[5] Furthermore, their hypnotic effects were found to diminish after repeated administration.[6] They can alter sleep architecture by reducing the percentage of slow-wave sleep (SWS) and rapid eye movement (REM) sleep, increasing time spent in stage 2 and decreasing the number of stage shifts.[7] Newer non-benzodiazepines agents (i.e. zolpidem, zaleplon, and eszopiclone) exert their actions via modulation of the GABA-receptor complex. Even though they alter sleep architecture, residual effects on psychomotor performance and cognition are less pronounced compared to benzodiazepines. Like benzodiazepines, they exhibit the potential for drug dependence, amnesia, and dose-dependent rebound insomnia.[8] All of these medications are schedule IV controlled substances except barbiturates whose schedule varies based on the specific agent. Antidepressants are also commonly prescribed for insomnia even though they are not FDA-approved for this indication. They may be of greatest benefit in patients with concurrent psychiatric disorders. Tricyclic antidepressants have multiple side effects including anticholinergic effects, cardiac toxicity, orthostatic hypotension, and sexual dysfunction.[3,9] Antihistamines, such as diphenhydramine and doxylamine, are frequently found in over-the-counter sleep aids. These agents can cause daytime drowsiness, cognitive impairments, and anticholinergic effects. Tolerance and withdrawal effects have also been observed.[3,8]

Melatonin is a hormone released by the pineal gland that is thought to regulate sleep-wake cycles in human and other mammals. The production of melatonin varies according to the circadian rhythm, which is controlled by neuronal output from the suprachiasmatic nucleus (SCN) of the hypothalamus. In humans, melatonin production correlates with nocturnal sleep. An increase in melatonin levels in the evening is associated with the onset of sleepiness and an increase in sleep propensity. Exogenous melatonin has direct sleep-promoting actions. Endogenous secretion declines with age, which may explain the prevalence of sleep disturbances in the elderly.[10]

Ramelteon (Rozerem®), a novel melatonin receptor agonist manufactured by Takeda Inc., was approved by the FDA for the treatment of insomnia in July 2005. Ramelteon does not alter sleep architecture or cause tolerance, psychological or physical dependence, or rebound insomnia.[10] The intent of this article is to review the pharmacology, pharmacokinetics, adverse drug reactions, drug interactions and cost of ramelteon.

Pharmacology

Melatonin exerts its action through G-protein coupled receptors. The three subtypes of mammalian melatonin receptors that have been identified are MT_1, MT_2, and MT_3. The MT_1 and MT_2 receptors in the SCN are involved in the maintenance of circadian rhythm. Ramelteon is a melatonin receptor agonist with high affinity for both MT_1 and MT_2, and with low activity at MT_3. The MT_1 receptor regulates sleepiness while MT_2 helps the body shift easily between phases of day and night. Together they maintain the circadian rhythm, regulating the normal sleep-wake cycle. Ramelteon has no appreciable affinity for the GABA receptor complex or for receptors that bind neuropeptides, cytokines, serotonin, dopamine, noradrenaline, acetylcholine, and opiates. Its major metabolite, M-II, is active and has approximately one tenth to one fifth the binding affinity of the parent molecule for the MT_1 and MT_2 receptors. In in vitro functional assays, it is 17- to 25-fold less potent than the parent molecule. However, M-II circulates at higher concentration than the parent compound producing 20 – 100-fold greater mean systemic exposure. M-II has a weak affinity for $5\text{-}HT_{2B}$, but no appreciable affinity for other receptors.[11]

In animal models, ramelteon has a sleep-promoting action without causing learning, memory, or motor function impairment. It also has no potential for abuse. Preclinical studies conducted in rats by Miyamoto and colleagues demonstrated that performance was unaffected in both the Morris water maze and delayed matching position test by ramelteon doses ranging from 3 to 30 mg/kg.[12] On the contrary, performance in these learning tasks showed a dose-related impairment following the administration of diazepam and triazolam. Additionally, the effects of ramelteon and diazepam on motor coordination were assessed. Diazepam caused a dose-dependent impairment of motor coordination while ramelteon did not. Furthermore, unlike benzodiazepines and morphine, ramelteon did not exhibit rewarding properties in the conditioned place preference test. Therefore, it is postulated that ramelteon does not exhibit an abuse potential.[11]

Table 1. Summary of phase II clinical trials.

Study	Design	Inclusion	Endpoints	Treatment arms	Results
Roth et al.[17] (n=375)	DB, MC, RD, PBC	Usual sleep duration of 6.5 to 8.5 h Usual sleep latency of ≤ 30 minutes Bedtime between 8:30pm and midnight Within 20% of IBW Overall good health	Primary – LPS measured by PSG Others – TST, WASO, time in each stage, number of awakenings	Single oral dose of 16 mg, 64 mg, or placebo given 30 minutes prior to bedtime	LPS (mins) R16 – 14.1±15.1 (p<.001*) R64 – 15.5±15.4 (p<.001*) PBO – 24.6±21.9 TST (mins) R16 – 425.4±37.6 (p<.007) R64 – 422.4±34.8 (p<.033) PBO – 411.3±41.7
Erman et al.[18] (n=107)	DB, RD, PBC, CO	Insomnia complaints >3 months Mean LPS >20 minutes[†] Mean wake time >60min over 2 nights	LPS, TST, subjective sleep efficiency	Single oral dose of 4, 8, 16, or 32 mg or placebo given 30 minutes prior to bedtime for 2 nights	LPS (mins) R4 – 24.0 R8 – 24.3 R16 – 24.0 R32 – 22.9 PBO – 37.7 (p<0.001[‡)] TST (mins) R4 – 411.0 R8 – 412.9 R16 – 411.2 R32 – 418.2 PBO – 400.2 (p=NA[§)]

DB: double-blind. MC: multi-center. RD: randomized. PBC: placebo-control. PBO= placebo. CO= Cross-over. LPS: latency to persistent sleep. PSG: polysomnography. TST: total sleep time. WASO: wake time after sleep onset. R: ramelteon. *Pairwise comparison with placebo by the Dunnett t test (from analysis of variance). [†]Measured by polysomnography. [‡] P value for every dose of ramelteon. [§] P value was not reported.

Pharmacokinetics

Ramelteon is rapidly absorbed with median peak concentrations occurring at approximately 0.75 hours following oral administration in a fasting state. In a phase I study of six healthy male subjects, a single oral dose of ramelteon 16 mg was rapidly absorbed with time to maximum concentration (T_{max}) of 0.3 hours with a half-life (t ½) of 1.2 hours. Of the total dose, 84% was eliminated via the kidneys while only 4% was eliminated in the feces. Another phase I study in eighteen healthy male subjects compared a single oral dose of ramelteon 16 mg to ramelteon 2 mg intravenous (IV) infusion. Although 84% is absorbed, only approximately 1.8% is bioavailable. From the results of these studies, ramelteon appears to undergo extensive-first pass metabolism.[11,13,14]

When administered with a high-fat meal, the area under the curve (AUC) of ramelteon was increased, peak plasma concentration (C_{max}) was decreased, and T_{max} was delayed. The effect of food was studied in 24 healthy subjects randomized to receive a single dose of 16 mg ramelteon orally with or without food. The results over a 24-hour period showed that the presence of food increased AUC by 31%, C_{max} was lowered by 22%, and T_{max} was delayed by approximately 55 minutes (P<0.001). The similar effects of foods on AUC values are observed with M-II metabolite. Based on these findings, the manufacturer recommends against taking ramelteon with or immediately after a high-fat meal.[11,15]

In vitro studies showed that 82% of ramelteon is bound to plasma protein (70% to albumin). Furthermore, plasma protein binding is independent of concentration. The mean volume of distribution after intravenous administration is 73.6 L, suggesting substantial tissue distribution. The drug is metabolized primarily via oxidation to hydroxyl and carbonyl derivatives, with glucuronidation as a secondary metabolic pathway. CYP1A2 is the major isozyme involved in the hepatic metabolism of ra-

melteon; the CYP2C subfamily and CYP3A4 isozymes also metabolize ramelteon to a lesser degree.[11]

A phase I study by Greenblatt and colleagues evaluated the effects of age and gender on ramelteon's pharmacokinetics. Subjects were divided into four treatment groups: young (age 18-34), elderly (age 63-79), male and female. Following oral administration of 16 mg ramelteon, blood samples were obtained during the 24 hours after administration to analyze plasma concentrations of ramelteon and its major metabolite, M-II. Results indicated that AUC values for both the parent compound and M-II were significantly elevated in the elderly, regardless of gender. Subsequent studies showed that not only was AUC elevated in the elderly, C_{max} and t ½ values of both parent and M-II were significantly elevated.[16] The study suggests that gender does not have an impact on the pharmacokinetic of ramelteon whereas age has a prominent effect.

Clinical Trials

Table 1 summarizes two separate phase II clinical trials which found that ramelteon had significant effects on promoting sleep.

Roth et al conducted a randomized, double-blind, placebo-controlled study to evaluate the efficacy of ramelteon for the treatment of transient insomnia in healthy adults. A total of 375 subjects were randomized to three arms, 16 mg (n=126), 64 mg (n=126), and placebo (n=123). The primary efficacy measure was the mean latency to persistent sleep (LPS) as measured by polysomnography (PSG). Other efficacy measures were total sleep time (TST), wake time after sleep onset (WASO), percentage of sleep time in each sleep stage, and number of awakenings. There were no significant differences in the baseline demographics and characteristics between the three arms. Subjects were administered a single-dose of placebo or ramelteon 30 minutes prior to scheduled bedtime followed by PSG recordings performed continuously for 8 hours. Ramelteon dosages of 16 mg and 64 mg decreased the mean LPS compared to placebo (14.1 min, 15.5 min, 24.6 min, respectively, P<0.001). Similarly, 16 mg and 64 mg of ramelteon demonstrated an increased in TST compared to placebo (425.4 min P=00.7, 422.4 min P=0.033, 411.3 min, respectively). However, the differences between WASO, number of awakenings, and percentage of sleep time in each stage were not statistically significantly different. Subjects receiving 16 mg of ramelteon reported the shortest subjective sleep latency. Adverse effects were reported by at least 2% of subjects in each treatment group but no serious adverse effects were reported or observed. The dose-response curve appears to be flat. Despite a 4-fold increase in dose, there are only small differences in LPS and TST.[17] Thus, lower doses may offer the similar benefit with fewer side effects.

Erman and colleagues evaluated the efficacy and dose-related safety of ramelteon for the treatment of primary chronic insomnia as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). This was a double-blind, placebo-controlled, crossover study comprised of 107 subjects who were randomized to 4, 8, 16, or 32 mg of ramelteon or placebo. Medication was administered 30 minutes prior to bedtime for two consecutive nights. PSG was performed continuously for 8 hours each night. The results were similar to those observed by Roth et al. All doses of ramelteon revealed a significant reduction in LPS with mean values of 24.0, 24.3, 24.0, 22.9, and 37.7 minutes (P<0.001) for 4, 8, 16, 32 mg, and placebo, respectively. There were no statistically significant differences between the five arms in WASO, subjective TST, orsleep quality.[18]

Dosage and Administration

Ramelteon is available in 8 mg tablets. The recommended dose of ramelteon is 8 mg taken 30 minutes prior to bedtime. From one phase II study, ramelteon appears to have a flat dose-response curve, thus the need for a higher dose should be investigated further. The package insert recommends that ramelteon not be taken with or immediately after a high fat meal. Pharmacokinetic characteristics of ramelteon studied in subjects with mild and moderate hepatic impairment yielded an increase of 4- fold and 10-fold in exposure of the drug, respectively. Exposure to M-II increased slightly. Ramelteon should be used with caution in patients with mild to moderate hepatic impairment. Pharmacokinetics have not been evaluated in patients with severe hepatic impairment, therefore this population should not receive ramelteon. Pharmacokinetic characteristics in populations with mild, moderate, severe renal impairment and those on chronic hemodialysis suggest renal adjustment is not needed.[11]

Table 2. Adverse events in phase II clinical trials.[17,18]

Adverse Effects	Placebo	Ramelteon 4-32 mg	Ramelteon 16-64 mg
Headache (%)	1.6	19.6	6.3-7.1
Somnolence (%)	2.4	7.5	2.4-4.8
Nausea (%)	0.0	--	1.6-2.4
Dizziness (%)	0.8	--	0.8-2.4
Fatigue (%)	0.0	--	2.4-4.0
Pharyngolaryngeal (%)	--	7.5	--

Adverse Effects

Results from two phase II studies have shown that ramelteon ranging from 4 mg to 32 mg does not cause serious adverse effects. However, subjects who have received 64 mg reported a statistically significant decrease in alertness and ability to concentrate. The most common adverse event was headache. Other side effects include fatigue, somnolence, nausea, and dizziness. Table 2 summarizes the side effects from two phase II studies.[17,18]

Three long-term studies comprised of a total of 2082 subjects, of whom 829 were elderly, showed no evidence of rebound insomnia. In a 35-night, double-blind, placebo-controlled, parallel-group study in adults with chronic insomnia, patients were divided into two groups receiving either 8 mg or placebo. There was no difference in next-morning residual effects between ramelteon-treated patients versus placebo-treated patients.[11]

Drug Interactions

Ramelteon is metabolized primarily in the liver, mainly via the CYP1A2 isozyme; the CYP2C subfamily and CYP3A4 have minor involvement. Therefore inhibitors, inducers, or substrates of CYP1A2 will alter the pharmacokinetics of ramelteon. Co-administration of fluvoxamine, a strong CYP1A2 inhibitor, resulted in a 190-fold and 70-fold increase of AUC and C_{max} of ramelteon, respectively. Therefore, ramelteon should not be taken with fluvoxamine. Even though the impact of other weaker CYP1A2 inhibitors in combination with ramelteon have not been adequately studied, ramelteon should be prescribed with caution to patients who are on these drugs. Ketoconazole and fluconazole increase exposure to ramelteon as well as M-II. Rifampin, a strong CYP enzyme inducer, decreased the total exposure of both ramelteon and M-II approximately 80% after a single dose of 32 mg of ramelteon.[11]

Cost

The average retail cost for a one-month supply of ramelteon is $96.09. (Survey of retail pharmacies in Gainesville, FL area.)

Summary

Ramelteon is a novel melatonin receptor agonist that works by stimulating MT_1 and MT_2 receptors, thereby reducing sleep latency and improving overall quality of sleep. The novel mechanism of action provides a new approach to managing insomnia. Results from clinical studies in animals and humans showed no potential for dependence or tolerance. Ramelteon is an alternative to benzodiazepines and non-benzodiazepine agents, especially in patients with a history of substance abuse. Ramelteon is not a controlled substance and the abuse potential is lower compared with sedative hypnotics. Furthermore, ramelteon has a favorable side effect profile. Ramelteon does not cause rebound insomnia, next-morning residual effects, nor alter the architecture of sleep. Ramelteon should effectively complement the current pharmacological arsenal for treating insomnia.

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