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Ramelteon: A melatonin receptor agonist for the treatment of insomnia

Devi V, Shankar PK

ABSTRACT

Ramelteon is a novel MT1 and MT2 melatonin receptor selective agonist recently approved for the treatment of insomnia characterized by difficulty in sleep onset. It is a nonscheduled drug since it lacks the potential for abuse and does not interact with neurotransmitter receptors most associated with these phenomena. Although the effects of ramelteon use > 5 weeks are unknown, the available data confirms its safety and efficacy for short-term use. Clinical use and future research should uncover more information about ramelteon’s properties.

KEY WORDS: Humans, melatonin, ramelteon, receptors

Role of Melatonin in Sleep

Melatonin, a hormone secreted by the pineal gland is involved in regulatory sleep-wake cycles in humans and other mammals. Sleep initiation begins with the recognition of environmental light/dark signals by the receptors in the retina. These signals are transferred to the main circadian pacemaker which is located in suprachiasmatic nuclei (SCN) of the anterior hypothalamus. The SCN sends neuronal impulses to the pineal gland stimulating melatonin release into the bloodstream. Melatonin regulates not only the sleep-wake cycle, but also has effects on the cardiovascular system, reproduction and cell growth.

Melatonin-induced hypnotic and chronobiotic effects are mediated through the activation of melatonin receptors (MT1, MT2, MT3) in the SCN. MT1 is thought to regulate sleepiness, while MT2 is more likely to be involved in the readjustment of the circadian rhythm. The MT3 receptor, however, does not appear to be involved in the hypnotic and chronobiotic effects of melatonin.

Because of melatonin’s involvement in nocturnal sleep, exogenous melatonin has been used in the treatment of jetlag and shift work sleep disorders. Although, exogenous melatonin has direct sleep-promoting action, it has not shown any consistent effect on total sleep time or sleep efficiency due to very short biological half life (20-30 min). Moreover, lack of selectivity of melatonin at its target sites requires the design, synthesis and pharmacological studies of new selective melatonergic agonists with a longer duration of action. In July 2005, the US Food and Drug Administration approved the use of ramelteon (RozeremTM-Takeda pharmaceuticals, North America, Inc, Lincolnshire) a novel melatonin receptor agonist for the treatment of patients with insomnia characterized by difficulty with sleep onset.

Chemistry in Insomnia

Ramelteon, (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide is an indane analogue of melatonin. It is a selective melatonin receptor agonist with a high affinity for MT1 and MT2 receptors and a low affinity for MT3 receptors. Its binding affinity to the human MT2 receptor
M-II metabolite of ramelteon exerts selective action on MT1 and MT2 receptors, as does the parent compound, but it is only 10% lower than the MT2 subtype and fourfold higher than the MT3 subtype expressed in Chinese hamster ovary cells was threefold lower than the MT2 subtype and fourfold higher than the MT3 subtype affinity of melatonin. The affinity of ramelteon for hamster brain MT2, binding was 1/110 of melatonin.

Ramelteon has shown no measurable affinity for the GABA receptor complex, opiate receptors, serotonin receptors, ion channels, transporters and enzymes.

Pharmacokinetics

Ramelteon is rapidly absorbed following oral administration. A high-fat meal delays its absorption. Although 84% of orally administered drug is absorbed, the oral bioavailability is 1.8% due to extensive first pass metabolism. It is metabolized to hydroxyl and carboxyl derivatives in the liver via CYP1A2 (major), CYP2C (minor) and CYP3A4 (minor). There are four main metabolites M-I, M-II, M-III and M-IV, with M-II being the major moiety. The elimination half-life of ramelteon is 1-2.6 h which is considerably longer than melatonin. Following administration of single dose of ramelteon, 84% is eliminated renally and 4% is eliminated fecally. The total elimination of ramelteon is completed in 96 h. The M-II metabolite of ramelteon exerts selective action on M T1 and M T2 receptors, as does the parent compound, but it is only 10% as potent as ramelteon. The overall mean systemic exposure of M-II is approximately 20-100-fold higher than that of the parent compound, so it is likely to contribute to ramelteon’s biological effects. Repeated once daily dosing of ramelteon does not result in significant accumulation, owing to the short elimination half-life of ramelteon. It is reported that gender does not significantly influence clearance or half-life of ramelteon. However, ramelteon’s clearance is significantly decreased and half-life increased in the elderly when compared to young individuals. But the reduced clearance and higher plasma concentration of ramelteon is not associated with enhanced pharmacodynamic effects, which shows that the recommended clinical dose of ramelteon does not require modification based on age.

Dosage and Administration

Rozerem (ramelteon) is supplied as a round pale orange-yellow film coated tablet. The recommended dose is 8 mg orally 30 min prior to bedtime. The drug should not be taken with or immediately after a fatty meal. It should not be used in subjects with severe hepatic impairment. The drug should not be used along with CYP1A2 inhibitors like fluvoxamine, ciprofloxacin, norfloxacin or tacrine. It should be used with caution in moderate hepatic impairment and those taking other medications which inhibit CYP1A2. The drug has been found to be safe in patients with mild to moderate obstructive sleep apnea.

Clinical Trials Supporting Efficacy

The efficacy of ramelteon has been assessed in several placebo-controlled clinical trials involving patients with chronic insomnia and in a model of transient insomnia.

Chronic insomnia

A multicenter, double-blind, placebo-controlled, crossover study enrolled 107 patients aged 18-64 years. Each patient was randomized to receive each of 4, 8, 16 or 32 mg of ramelteon and placebo with 5 to 12 days of washout period between treatments. The drug was administered 30 min prior to bedtime for two consecutive nights and sleep latency and total sleep time were measured by polysomnography (PSG). Statistically significant reduction in latency to persistent sleep and increase in total sleep time was seen with all tested doses of ramelteon [Table 1].

Another randomized, double-blind, parallel group trial enrolled 405 patients aged 18-64 with chronic insomnia, who received one of two doses of the drug (8 mg or 16 mg) or placebo, every night before bed for 35 days. Polysomnography was performed to record latency to persistence sleep, total sleep time, sleep efficiency, wake time after sleep onset and number of awakenings on the first two nights in each week of 1, 3 and 5 of treatment. Compared to placebo, each dose of ramelteon produced significant decrease in latency to persistent sleep and increase in total sleep time at week 1. Significant improvements in sleep latency were maintained at week 3 and week 5 [Table 1]. However, wake time after sleep onset and number of awakenings were not significantly different with ramelteon 8 mg or 16 mg compared to placebo.

A third randomized, double-blind, placebo-controlled clinical trial enrolled 829 patients aged 65 years and older with chronic insomnia. Subjects received one of two doses of the drug (4 mg or 8 mg) or placebo for five weeks. Patient-reported sleep data were collected using sleep diaries. Compared with placebo, there was a statistically significant reduction in sleep latency and increase in total sleep time at week 1 with both doses of ramelteon [Table 1]. The reduction in sleep latency was also seen at week 3 with 8 mg of ramelteon (60.3 vs. 69.3 min, P<0.003) and at week 5 with 4 mg (63.4 vs. 70.6 min, P=0.28) and 8 mg (57.7 vs. 70.6 min, P<0.001) of ramelteon.

Transient insomnia

A randomized, double-blind, placebo-controlled clinical trial using a model of transient insomnia related to sleeping in a...
null environment evaluated single-dose efficacy of the drug in treating transient insomnia. The trial enrolled 375 healthy adults aged 35-60 years, who received a single dose of the drug (16 mg or 64 mg) or placebo before spending one night in a sleep laboratory. The PSG analysis showed significant improvement in latency to persistent sleep, as well as total sleep time with ramelteon.[12]

**Adverse Effects**

The most common adverse effects observed in patients treated with 8 mg of ramelteon were headache (7%), somnolence (5%), dizziness (5%), fatigue (4%), exacerbated insomnia (3%), nausea (3%), upper respiratory tract infection (3%), depression, retropharyngeal pain, decreased libido and galactorrhea.[1,3,16,17,23] These adverse effects were not dose-related.[18] Next day residual effects and impairment of cognitive function were not seen with ramelteon.[3,4] Furthermore, no rebound insomnia or withdrawal effects were reported following five weeks of treatment.[4,5] In a double-blind crossover study, ramelteon did not show its potential for abuse or motor and cognitive impairment at up to 20 times the recommended therapeutic dose.[7] Laboratory studies have demonstrated the carcinogenic potential of ramelteon and its active metabolite M-II. The no effect level for hepatic tumor in male mice was 30 mg/kg/day, which is 103 times and three times the concentration of ramelteon and metabolite M-II respectively, measured after the therapeutic dose. However, the no effect level for hepatic tumors in female mice was 100 mg/kg/day. Though this drug failed to demonstrate mutagenicity in Ames and other in vitro tests, micronuclei formation was observed in Chinese hamster lung cells after metabolic activation.[16] But there is no information about the mutagenic potential of metabolites in other reported tests for mutagenesis.

**Conclusion**

How does ramelteon add to the current armamentarium of sedative-hypnotic agents? Currently, benzodiazepines and non-benzodiazepines are commonly prescribed for the management of insomnia. However, benzodiazepines are associated with adverse effects like daytime sedation, addiction and potential to cause withdrawal symptoms and rebound insomnia.[2] Although non-benzodiazepines are less likely to change sleep patterns than benzodiazepines, their major limitation are their cost and abuse potential.[24] The evidence supporting the utility of other treatment options such as antidepressants and antipsychotics is limited. Although melatonin promotes both sleep onset and sleep maintenance, its lack of specificity for melatonin receptor subtypes, a short half-life and a variation in preparation cause withdrawal symptoms and rebound insomnia.[2] Although melatonin promotes both sleep onset and sleep maintenance, its lack of specificity for melatonin receptor subtypes, a short half-life and a variation in preparation due to lack of regulation by FDA, limits its usefulness in the management of insomnia.[19]

Ramelteon provides a unique therapeutic mechanism for the treatment of insomnia. Its approval allows physicians to prescribe ramelteon for insomnia with difficulty in sleep onset. The main advantage with ramelteon is that thus far there is no evidence of cognitive impairment, rebound insomnia, withdrawal effects or abuse potential. However, clinical comparison with other hypnotic agents will be needed to better differentiate this product. Ramelteon has not been studied in patients with severe chronic obstructive pulmonary disease or pain conditions. Extensive research is needed on the carcinogenic and mutagenic potential of ramelteon and its metabolites to substantiate its long-term use.

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