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Ramelteon: a Novel Hypnotic for the Treatment of Insomnia

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Introduction

Insomnia is the inability to fall asleep or remain asleep, or the experience of nonrestorative sleep, resulting in clinically significant distress or adverse consequences on daytime functioning. It has been associated with difficulty concentrating, a higher risk of accidents due to fatigue, an increased prevalence of comorbid psychiatric conditions such as generalized anxiety disorders and major depression, and higher than expected rates of hypertension, chronic pain, diabetes mellitus, and obesity. (Walsh 2004; National Sleep Foundation)

According to the 2002 Canadian Community Health Survey, an estimated 13.4% of Canadians aged 15 or older (3.3 million) had insomnia. (Tjepkema 2005) Close to a third of these (29%) reported that they had taken sleep medication at least once in the previous 12 months. Twenty-three percent had used prescription medication and 6.5% had used medication that was not prescribed.

Currently, the most commonly prescribed agents used to treat insomnia have been benzodiazepines, such as lorazepam and temazepam, or the non-benzodiazepines, zopiclone and zaleplon. Other agents that are used include OTC products (e.g., melatonin, valerian and the antihistamines) and the off-label use of antidepressants, particularly trazodone. There are three non-benzodiazepine hypnotic agents available in the United States (not

Canada), namely eszopiclone, zolpidem and ramelteon.

This newsletter reviews ramelteon, a melatonin receptor agonist, the newest hypnotic to be released in the US.

Melatonin

Melatonin is a hormone that promotes sleep induction and maintenance and contributes to the regulation of the body's circadian rhythms (Pandi-Perumal 2006). It is released from the pineal gland (as well as from other organs) into the circulation and distributed throughout the body. Melatonin is also released into the cerebrospinal fluid where concentrations are higher than in the serum (Tricore 2003). It exerts its sedative effects by activating the melatonin receptors, MT1 and MT2. The receptor, MT2, also contributes to the readjustment of the circadian rhythms (Dubocovich 2003; von Gall 2002). The MT1 and MT2 receptors are located in the major circadian pacemaker, the suprachiasmatic nucleus, a small area in the hypothalamus.

Melatonin has been used successfully in the treatment of insomnia in the elderly (Zhdanova 2001), in delayed sleep phase syndrome (Kayumov 2001) and in children with various sleep disorders (Weiss 2006, Jan 2000). However, the effects of melatonin on decreasing sleep latency and on total sleep time have not always been found to have consistent results.

The Agency of Health Care Research and Quality completed a meta-analysis of melatonin for the treatment of sleep disorders which reported that

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melatonin decreases sleep onset latency in normal sleep and in people with primary sleep disorders (Buscemi 2004). The authors, however, concluded that the results had no clinical significance. Another meta-analysis concluded that melatonin is not effective in treating most primary sleep disorders in short-term use (four weeks or less) although it decreases sleep onset latency and is safe for up to three months (Buscemi 2005, Buscemi 2006).

Inconsistent results in these studies may have been due to variable doses and to different populations in the trials. Another reason for its lack of effect, in some cases, may be due to melatonin's very short elimination half-life (20 to 50 minutes).

A melatonin agonist with a longer half-life may result in a higher response rate than previously found with the short-acting endogenous hormone itself.

Ramelteon

Pharmacology

Ramelteon is a synthetic melatonin agonist with very high affinity for the MT1 receptor and slightly less for the MT2 receptor. It has no activity at the benzodiazepine, opioid or dopamine receptors (Kato 2005) which suggests that it is unlikely to be abused. It has very low affinity for the serotonin-1A (5-HT1A) receptor site, but does not reach concentrations high enough to affect the serotonin system at clinically useful doses. (Kato 2005)

Pharmacokinetics

Ramelteon is rapidly and well absorbed after oral administration and reaches peak serum concentrations within 0.5-1.5 hours. It has very low absolute bioavailability (2% of a 16 mg dose) because of extensive first pass metabolism. (Karim 2006) It is highly protein bound to plasma albumin with a half-life in the range of 1.0-2.6 hours which is longer than melatonin at 20 to 50 minutes. Ramelteon is extensively metabolized to four different metabolites, one of which, metabolite M-II, is active at the MT1 and MT2 receptor sites. Although it is only about 10% as potent as the parent compound, it circulates at much higher concentrations systemically than the parent compound, so it is likely to add to ramelteon's biological effects. (Karin 2006) The metabolite M-II has a half-life that is 2-5 hours longer than ramelteon.

Drug Interactions

The major hepatic isoenzyme responsible for metabolism of ramelteon is CYP1A2 and consequently its levels can be substantially increased by inhibitors of CYP1A2 such as fluvoxamine,

ciprofloxacin, mexiletine, norfloxacin, tacrine or zileuton. (Wurtman 2006) It is metabolized to a lesser extent by CYP2C and CYP3A4. Increases in ramelteon levels have also been reported when it was given with the CYP2C9 inhibitor, fluconazole, and the CYP3A4 inhibitor, ketoconazole. Rifampin, a strong inducer of the CYP enzyme system significantly reduced ramelteon and M-II levels. Loss of efficacy may occur if given with strong CYP enzyme inducers. (Wurtman 2006)

Efficacy

Three clinical studies of ramelteon in the treatment of insomnia have been published. (Erman 2006, Roth 2005, Roth 2006) A randomized, double-blind, placebo-controlled five period crossover study with 107 patients examined four different doses of ramelteon (4, 8, 16 and 32 mg) and placebo for two nights each. (Erman 2006) Eligible patients had insomnia for more than three months before the study with a mean latency to persistent sleep (LPS) longer than 20 minutes and a mean wake time of longer than 60 minutes in a sleep laboratory. There was a washout period of five to 12 days between treatments.

There was a significant reduction in all ramelteon groups compared with placebo ($p < 0.001$) with mean LPS values of 24.0, 24.3, 24.0, 22.9, and 37.7 minutes in the ramelteon 4, 8, 16 and 32 mg groups and the placebo group respectively. The mean total sleep time (TST) increased by 11 to 18 minutes in all groups treated with ramelteon compared with placebo. However, significant differences were not found in the subjective measures of sleep, except for the 16 mg dose, which was associated with reports of significantly shorter sleep latency ($p=0.015$).

In the second randomized, double-blind, placebo-controlled clinical trial, ramelteon was studied in 375 individuals with no sleep disorder. (Roth 2005) Two doses of ramelteon (16 and 64 mg) were tested in individuals 35 to 60 years of age. A significant decrease in LPS and increase in TST was recorded with both doses of ramelteon. However, patients subjectively only reported a significantly shorter sleep latency with 16 mg of ramelteon; no other subjective reports differed from placebo.

The third randomized, placebo-controlled trial involved 829 patients, 65 years of age or older, with chronic insomnia. (Roth 2006) There were three treatment options: placebo, ramelteon 4 mg or ramelteon 8 mg for five weeks. Outcome was measured subjectively with sleep diaries. A significant reduction in sleep latency was found for both doses at weeks 1 and 5 ($p=0.003$), but only for the 8 mg dose at week 3 ($p<0.001$). Sleep latency was reduced by

approximately 13 to 29 minutes. No significant change in TST was found with ramelteon 8 mg at any time point, but the 4 mg dose significantly increased TST after weeks 1 and 3 compared with placebo. Rebound insomnia and withdrawal were measured for a week after treatment was discontinued. The discontinuation of ramelteon was not associated with rebound insomnia or withdrawal.

Tolerability and safety

Adverse events:

In phase I-III studies with 3,594 patients, 5% of ramelteon patients discontinued because of adverse events (versus 2% on placebo). The five most common adverse events were headache (7%), somnolence (3%), fatigue (2%), dizziness (3%) and nausea (2%). None of these events occurred significantly more frequently than with placebo and, in fact, somnolence, fatigue, dizziness, and nausea occurred more frequently with placebo. (Rozerem)

Endocrine studies:

No clinically significant effects on thyroid, adrenal or reproductive function were found in a four-week study in 99 patients who received 16 mg/d. Further investigations with 122 patients taking 16 mg/d for six months found a 34% increase from baseline in plasma prolactin in women, compared to a 4% decrease in the placebo group ($p=0.003$).

However, mean prolactin levels remained within the normal reference range and patient reported menstrual patterns did not differ between the ramelteon and placebo groups. (Rozerem)

Ramelteon did not suppress endogenous melatonin levels when studied in animals for 14 days. (Miyamoto 2001)

Residual effects, rebound insomnia and abuse potential:

No withdrawal effects or rebound insomnia were found after cessation of 8 mg of ramelteon in any of the clinical trials even after five weeks of treatment. (Erman 2006, Roth 2005, Roth 2006)

No abuse potential or motor and cognitive impairments were noted in a study with 14 subjects with a history of sedative/hypnotic drug abuse in doses of up to 160 mg/d of ramelteon. (Johnson 2006)

Overdose:

Although no cases of deliberate overdoses were recorded during clinical trials, the highest dose of ramelteon administered in clinical trials was 160 mg/d. (Johnson 2006) At 20 times the recommended dose (8 mg/d) no untoward clinical effects were reported.

Dosage and Administration

The recommended ramelteon dosage is 8 mg taken orally within 30 minutes of bedtime. It should not be given with or immediately following a high fat meal. Patients with mild to moderate hepatic impairment may use ramelteon with caution but it is not recommended for those with severe impairment. No dosage adjustments are recommended for those with renal impairment including severe impairment or those who require hemodialysis. There are no dosage recommendations for pediatric patients or those with severe sleep apnea or severe chronic obstructive pulmonary disease as there is no published data available. (Rozerem)

Conclusion

Ramelteon has reduced sleep latency by 13 to 29 minutes but it has not been found to be consistently useful in increasing total sleep time. Therefore it appears to be most useful for patients who have trouble initiating sleep. It has minimal effects on sleep architecture and no tolerance to its hypnotic effects has been reported over five weeks. Ramelteon's lack of affinity for the GABA_A, opiate and dopamine accounts for the absence of next-day residual psychomotor and amnesic effects as well as the lack of abuse potential. It is well tolerated with an adverse event frequency of < 7% for treatment emergent events in the phase I-III trials.

Ramelteon seems safe for short-term treatment, however future investigations are required to determine its safety for extended use. It has not been found to suppress endogenous melatonin levels in animals over a period of 14 days. Ramelteon's effect on endogenous melatonin levels needs to be studied in humans over a longer period of time. Longer term studies are also required to determine if it causes desensitization of MT1 and MT2 receptors as these are present throughout the body and not only in the central nervous system. Finally, head-to-head studies are required to compare it to other hypnotics to expand on ramelteon's differential profile.

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