



Ramelteon: A Melatonin Receptor Agonist for the Treatment of Insomnia

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Introduction

The management of insomnia involves use of non-pharmacological and appropriate pharmacological treatment (1). Benzodiazepine receptor agonists are most commonly prescribed agents for insomnia. But they are associated with a cognitive impairment, along with potential for abuse and dependence (2). The treatment with ramelteon, a novel MT_1 and MT_2 (melatonin receptor) selective agonist does not appear to impair cognition or motor performance. Data from clinical studies suggest that ramelteon is not likely to cause abuse, physical dependence or withdrawal effects (3).

Role of Melatonin in Sleep

Melatonin, a hormone secreted by the pineal gland is involved in regulatory sleep-awake cycles in humans and other mammals (4). 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 in to the blood stream (5). Melatonin regulates not only the sleep-wake cycle but also has effects on cardiovascular system, reproduction and cell growth (5). The melatonin induced hypnotic and chronobiotic effects are mediated through the activation of melatonin receptors (MT_1 , MT_2 , MT_3) in the SCN. MT_1 is thought to regulate sleepiness, while MT_2 is more likely to be involved in the readjustment of circadian rhythm (4). MT_3 receptor, however, is not appearing to be involved in the hypnotic and chronobiotic effects of melatonin (6).

Because of melatonin's involvement in nocturnal sleep, the exogenous melatonin has been used in the treatment of jet lag and shift work sleep disorders (7,8). Although, the exogenous melatonin has direct sleep promoting action, it has not showed any consistent effect on total sleep time or sleep efficiency due to very short biological half

life (20-30 min) (9,10). In July 2005, the US FDA approved the use of Ramelteon, a novel melatonin receptor agonist as 8 mg tablet for the treatment of insomnia (11).

Chemistry

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 (4,5).

Mechanism of Action

Ramelteon is a selective melatonin receptor agonist with a high affinity for MT_1 and MT_2 receptor and a low affinity for MT_3 receptors. Ramelteon has showed no measurable affinity for GABA receptor complex, opiate receptors, serotonin receptors, ion channels, transporters and enzymes (4).

Pharmacokinetics

Ramelteon is rapidly absorbed orally. High fat meal delays its absorption. Although 84% of orally administered drug is absorbed, the oral bioavailability is 1.8%. It is metabolized to hydroxyl and carboxyl derivatives in liver via CYP1A2 (major), CYP2C (minor), and CYP3A4 (minor). The elimination half life of ramelteon is 1-2.6 hours which is considerably longer than melatonin. Following administration of single dose of ramelteon, 84% eliminated renally and 4% eliminated fecally. The total elimination of ramelteon is completed in 96 hours. Repeated once daily dosing of ramelteon does not result in significant accumulation owing to the short elimination half life of ramelteon (12). Ramelteon's clearance is significantly decreased and half life increased in elderly when compared to young individuals. Gender does not significantly influence clearance or half life of ramelteon. But the reduced clearance and higher plasma concentration of ramelteon is not associated with enhanced pharmacodynamic effects, which shows that recommended clinical dose of ramelteon does not require modification based on age or gender (13).

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Dosage and Administration

The recommended dose is 8mg orally 30minutes prior to bed time. The drug should not be taken with or immediately after fatty meal. It should not be used in subjects with severe hepatic impairment (14). The drug should not be used along with CYP1A2 inhibitors like fluvoxamine, ciprofloxacin, norfloxacin or tacrine (15). The drug is found to be safe in patients with mild to moderate obstructive sleep apnea (16).

Clinical Trials Supporting Efficacy

The efficacy of ramelteon has been assessed in several placebo controlled clinical trails (14,17,18) involving patient with **chronic insomnia** and in a first night model of transient insomnia. In all the studies, ramelteon produced significant reduction in average latency to persistent sleep onset, compared to placebo measured by Polysomnography (PSG). A randomized, double blind, placebo-controlled clinical trail using a model of **transient insomnia** related to sleeping in a novel environment evaluated single dose efficiency of the drug in treating transient insomnia. using PSG analysis showed significant improvement in latency to persistent sleep as well as total sleep time with ramelteon (19).

Adverse Effects

Common adverse effects observed with ramelteon were head ache, somnolence, dizziness, fatigue, depression, nausea and retropharyngeal pain, decreased libido, galactorrhea (17,20). Residual effects and impairment of cognitive function were not seen (17). No rebound insomnia or withdrawal effects were reported (18). It did not show its potential for abuse or motor and cognitive impairment at up to 20 times the recommended therapeutic dose (3). Laboratory studies have demonstrated the carcinogenic potential but there is no information about the mutagenic potential (20).

Conclusion

Ramelteon provides a unique therapeutic mechanism for the treatment of insomnia. It is a nonscheduled drug. Its approval allows physicians to prescribe ramelteon for insomnia with difficulty in sleep onset. Extensive research is needed on carcinogenic and mutagenic potential of ramelteon and its metabolite to substantiate its long-term use.

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