RAMELTEON: A MELATONIN RECEPTOR AGONIST

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Keywords: (Ramelteon), melatonin, pineal, MT1 receptors, MT2 receptors, sleep, GABA receptors, aging, desensitization

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A. Summary: Ramelteon, the first melatonin receptor agonist to win FDA approval, is presently marketed in the United States; its use is authorized to be marketed in the United States for “...the treatment of insomnia associated with sleep onset”. In laboratory tests ramelteon has not exhibited potential for being abused or causing dependency, nor has it been shown to interact with the neurotransmitter receptors that tend to be most associated with these phenomena. Hence unlike other hypnotic agents ramelteon is a non-scheduled drug. Few data have been published in peer-reviewed journals describing ramelteon’s efficacy or side-effects in patients who actually suffer from insomnia, and no comparison study has been performed to determine whether, when used at its recommended 8 mg dose, ramelteon has any advantage over physiologic doses of melatonin (0.2 – 0.5 mg), particularly for long-term use in older patients.
B. Introduction

Ramelteon is the first FDA-approved agent believed to act by mimicking the effects of the hormone melatonin. It does so, as described below, by combining with and activating melatonin’s MT1 and MT2 receptors in the brain, which may mediate melatonin’s sleep-promoting effects following its secretion from the pineal gland. When melatonin is administered to young adults during the daytime or early evening (for example, to those initiating eastbound travel, or undertaking shift work) it promotes sleep onset; when given at bedtime to older adults who suffer from prolonged nocturnal awakenings, it improves sleep efficiency and increases sleep time. The fully-effective oral dose of melatonin (0.2-0.5 mg, usually 0.3 mg) is the same for both uses, and is equal to the amount needed to elevate plasma melatonin levels to what they would normally be, during the night, in young adults (about 100-200 pg/ml, up from 2-10 pg/ml around noon). Among older people whose substantially-calcified pineals secrete less of the hormone, nocturnal plasma melatonin levels may only rise to 25-50 pg/ml; this deficiency apparently underlies their impairment in sleep efficiency and their hypnotic response to physiologic doses of melatonin.

Melatonin for human consumption is unavailable in most of the world because, to date, few companies have obtained the necessary data and solicited regulatory approval to market it as a drug. The hormone is sold in the United States as an unregulated dietary supplement of indeterminate purity, usually in doses substantially higher than the submilligram amounts needed to promote sleep. These supraphysiologic doses elevate plasma melatonin levels well beyond their normal range (e.g., to 960-2440 pg/ml after a
3 mg dose\textsuperscript{6,13}, and can cause hypothermia and hyperprolactinemia, among other side effects. Moreover by desensitizing the MT\textsubscript{1}\textsuperscript{15} and MT\textsubscript{2}\textsuperscript{16} receptors they lose their ability to promote sleep.

Hence, the actual contribution of exogenous melatonin to the treatment of sleep disorders has remained a disappointment. But since it is widely accepted that melatonin does, in fact, promote sleep, this situation has generated a commercial opportunity for synthetic analogs of melatonin – like ramelteon – which, because they would be regulated as a drug, would be of affirmed purity and would be used at a specific recommended dose\textsuperscript{17}. And since ramelteon, like melatonin itself, neither interacts with receptors for GABA or other neurotransmitters, nor predisposes to substance abuse or dependence\textsuperscript{17-20}, it has the great advantage, compared with most other sleep-promoting drugs, of not being a scheduled compound \textsuperscript{21-22}. Thus, if future clinical experience affirms ramelteon's efficacy and benign side-effect profile use of this drug may expand rapidly.

Unfortunately, very little published information is presently available to help physicians decide whether to recommend ramelteon to patients with insomnia - only three peer-reviewed publications. In one of these\textsuperscript{23} healthy, non-insomniac subjects received single doses of the drug; in another\textsuperscript{24} insomniacs received the ramelteon for just two consecutive days; and in a third\textsuperscript{25} only subjective effects of the drug were described. Unreviewed abstracts have also been published describing 35-day studies in insomniacs or shorter studies in healthy subjects required to sleep in a laboratory\textsuperscript{26-27}, and an FDA report\textsuperscript{17}, briefly summarized two unpublished 35-day polysomnographic studies performed on insomniacs and described the drug as significantly reducing latency to persistent sleep. Apparently no study has examined the effects on sleep of administering
ramelteon to insomniac patients for more than 35 days, even though nothing in the drug’s package insert precludes its likely off-label use by aged insomniacs for prolonged periods. And no study has compared ramelteon’s efficacy and safety with that of melatonin, the hormone that the drug was designed to replace\textsuperscript{20}. Such comparative data would almost certainly have been required before a novel analog of any other hormone would have been granted regulatory approval.

Given the paucity of information currently available concerning ramelteon, plus the fact that it and melatonin apparently interact with the same MT1 and MT2 receptors, our ability to anticipate ramelteon’s clinical effects may be enhanced if we also consider those of melatonin itself. Melatonin does differ from ramelteon in that it also binds to a third protein, sometimes termed the “MT3 receptor” but actually a detoxifying enzyme. However this binding has not been shown to produce functional or behavioral consequences. Hence it seems unlikely that ramelteon’s failure to bind to MT3 differentiates its clinical effects from those of melatonin.

C. Effects of Ramelteon

a. Pharmacokinetics and Metabolism

When ramelteon [(S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno-[5,4-b]furan-8-yl)ethyl] propionamide; MW 259.34] is administered at its recommended 8 mg oral dosage it is rapidly absorbed, serum concentrations peaking after 0.5 – 1.5 hrs. at 5,700 pg/ml\textsuperscript{17-19} or about 20-40 times nocturnal plasma melatonin levels\textsuperscript{3,4}. Although at least 84% of the drug is actually absorbed its oral bioavailability is substantially lower (only 1.8%), because of extensive first-pass metabolism\textsuperscript{17}. About 82% of the drug in human serum is protein-bound, 70% of this to albumin\textsuperscript{17}. Intravenous ramelteon exhibits a high
mean volume of distribution in humans (74 liters), suggesting that it readily enters most
tissues.

Ramelteon is metabolized by oxidation to hydroxyl and carbonyl derivatives, and
rapidly eliminated, principally as urinary metabolites, within 96 hours of oral
administration. Its elimination half-life is short, i.e. 1.0 - 2.6 hrs, suggesting that the
drug does not accumulate in the brain after repeated daily dosings, however no data are
available on its actual brain levels in animals dosed repeatedly. If the brain does
accumulate ramelteon this would increase the likelihood that it – like pharmacologic
concentrations of melatonin itself – can desensitize the receptors on which it acts. One ramelteon metabolite designated M-II, does exhibit biological activity,
binding both to melatonin MT1 and MT2 receptors and to serotonin-2B receptors. Its
affinities for human MT1 and MT2 receptors are approximately one-tenth and one-fifth
those of unmetabolized ramelteon. Although this metabolite is 17-25-fold less potent
than ramelteon in vitro functional assays, it also circulates at much higher
concentrations, producing 20-100-fold greater mean systemic exposures. Thus it may
contribute to ramelteon’s biological effects. The consequences, if any, of M-II’s binding
to serotonin receptors await characterization, but could also be important given
serotonin’s known involvement in sleep.

Elderly subjects metabolize ramelteon significantly more slowly than younger
subjects, hence their total exposure to any dose (AUC) is almost twice as great. Total
exposure is also increased 4-10-fold among patients with mild or moderate hepatic
impairment but not in those with renal disease. The metabolic fate of ramelteon is
markedly affected by other drugs which happen to interact with CPY-1A2 enzymes, - for
example, the antidepressant fluvoxamine can cause a 190-fold increase in ramelteon’s
AUC. Many other drugs (and even a food: grapefruit juice) inhibit or induce CYP1A2,
and might thus be expected to affect blood levels of ramelteon28.

b. Neurochemical Effects

The ability of ramelteon to bind to brain receptors for melatonin or to
numerous other brain proteins (e.g., neurotransmitter receptors; ion channels;
neurotransmitter transporters) was examined using, for melatonin receptors, cultured
Chinese ovary (CHO) cells cloned to contain MT1 or MT2 receptors or brain
homogenates containing “MT3 receptors”18. Ramelteon binding to other proteins was
assessed using commercial assay protocols. Since the binding of authentic melatonin to
MT1 or MT2 receptors was known to suppress cyclic AMP production, this effect was
also assessed in the CHO cells. (The putative “MT3 receptor” is actually a detoxifying
enzyme – quinine reductase 2 – 34 which can bind melatonin but which otherwise has no
known involvement in melatonin’s physiological effects nor in the side-effects (e.g.,
hypothermia) produced by pharmacologic doses. Ramelteon failed to bind significantly
to this “MT3 receptor”, however the significance of this lack of activity – like that of the
“MT3 receptor” itself – is uncertain.)

A binding protein was considered responsive to ramelteon if, at a 10 micromolar
concentration, the drug failed to inhibit by 50% or more the protein’s binding to its true
ligand. Using this criterion, ramelteon effectively inhibited the binding of radiolabeled
melatonin to brain MT1 or MT2 receptors. Also, like melatonin itself, ramelteon
inhibited the production of cyclic AMP in cloned CHO cells containing the melatonin
receptors. Ramelteon failed to suppress by more than 50% the receptor binding of the
other ligands tested, except for the binding of serotonin to its 5HT-1A receptors, for which the Ki value was 5.6 micromolar. Brain receptors failing to respond to ramelteon included the GABA receptors which mediate the therapeutic actions and side-effects of most other hypnotic agents, and also the receptors for opioids, benzodiazepines, dopamine, and other monoamines (excluding the 5HT-1A receptor). This neurochemical specificity probably explains the drug’s low abuse potential and its relatively good side-effect profile, described below.

The affinities for ramelteon of the MT1 and MT2 receptors are probably greater than those for melatonin itself. For the MT1 receptor the Ki’s for ramelteon and melatonin are, respectively $14 \times 10^{-12}$ and $80 \times 10^{-12}$, and for the MT2 receptor they are $112 \times 10^{-12}$ and $383 \times 10^{-12}$.<ref>18,19</ref> Peak plasma ramelteon levels after a therapeutic (8 mg) dose (i.e., 57,000 pg/ml<ref>19</ref>) are, however, hundreds of times greater than those generated by nocturnal melatonin secretion in younger people, or by administering a therapeutic (0.3 mg) dose of the hormone to anyone (i.e., 250 pg/ml or less<ref>13</ref>). Since supraphysiologic concentrations of melatonin markedly desensitize the MT1 receptor “...thereby affecting physiological responses ....following activation of MT1 melatonin receptors“<ref>15</ref>, and cause a similar long-lasting down-regulation of MT2 receptors in suprachiasmatic nucleus (SCN) neurons<ref>16</ref> it seems likely that significant receptor desensitization will develop among patients taking ramelteon for more than a few days — perhaps even exacerbating their insomnia. Hence the drug probably should not be used for prolonged periods, particularly by older people having difficulty staying asleep, until the risk of desensitization has been evaluated.

c. Clinical Effects
A single publication\(^2^4\) has presented objective data on the effects of ramelteon on patients with insomnia (N = 107; mean age 37.7 years); another\(^2^5\) has presented subjective data, based on sleep diaries (n=829; all subjects were 65 years of age or older). In the first, subjects received the drug (4, 8, 16, or 32 mg, separated by 5- or 12-day washout periods) on 2 consecutive evenings, thirty minutes prior to their habitual bedtime, and were monitored polysomnographically for 8 hours. All doses significantly reduced sleep latency by about 13 minutes; increased total sleep time by about 12 minutes (i.e., from 400 to 412 minutes); and increased sleep efficiency (from 83.5% to 86% for the 8 mg dose). No residual pharmacological effects were noted the following day. In the other publication\(^2^5\), also reanalyzed and described in reference 35, subjects received 4 or 8 mg of ramelteon or placebo nightly for 5 weeks. Significant reductions in subjective sleep latency (by 8 minutes, from 78.5 to 70.2 minutes) after either dose and increases in total sleep time assessed subjectively (by 8-10 minutes), were found after one week of treatment. The reductions in subjective sleep latency persisted for the 5 weeks of treatment. An unreviewed abstract also described studies on insomniacs in which ramelteon (8 mg and 16 mg) was given for 5 weeks to 405 patients (mean age 39.3 years)\(^2^7\). The ramelteon significantly decreased sleep latency, as assessed polysomographically, after 2, 16, or 30 days. Moreover, total sleep time and sleep efficiency were increased after 2 days of treatment, and no rebound insomnia or withdrawal effects were noted after cessation of treatment. Data also have been presented describing sleep-promoting effects of ramelteon among non-insomniac subjects in which transient insomnia had been induced by having them sleep in a sleep laboratory\(^2^3,^2^7\).
A laboratory study on ramelteon's abuse potential, performed on 14 subjects with a history of sedative/hypnotic or anxiolytic drug use, uncovered no differences in subjective test responses between those receiving ramelteon and those on placebo; the positive control drug used in the study, triazolam, did consistently demonstrate differences from placebo.

Some evidence of small, next-day residual effects was observed among insomniac subjects receiving ramelteon for 35 days: At week one those receiving ramelteon (8 mg) had higher VAS scores—a measure of fatigue—than those on placebo, and at week three those on ramelteon exhibited lower immediate word recall. No evidence has been presented suggesting rebound insomnia or withdrawal effects among subjects receiving ramelteon for 35 days. The most common side-effects (compared with placebo) noted in Phase 1-3 studies on ramelteon have been somnolence, fatigue, dizziness, and an exacerbation of insomnia.

D. Effects of Melatonin

Two physiologic effects have been consistently noted following melatonin administration: promotion of sleep onset and maintenance, and the phase-shifting of circadian rhythms, including the melatonin rhythm. Both effects are produced by physiologic doses, i.e., 0.1 - 0.3 mg for sleep, and 0.3 - 0.5 mg for phase-shifting. Melatonin's actions on sleep reflect both of these effects, - a direct action which decreases sleep latency, increases sleep efficiency, and increases total sleep time; and an indirect action on the phasing of sleep onset and offset, mediated by changes in the timing of the sleep rhythm.

a. Sleep

A 1997 article on melatonin and sleep listed 24 papers, almost all of
which described sedation, fatigue, decreased alertness, increased reaction time, shortened
sleep latency (i.e., number of minutes needed to fall asleep), increased sleep efficiency
(i.e., percent of the total sleep period actually spent sleeping), and/or increased total sleep
time. A 2005 meta-analysis of 17 studies involving 284 subjects who satisfied inclusion
criteria, demonstrated a statistically significant decrease in sleep latency (by 4 minutes;
95% Confidence Interval 2.5-5.4) and significant increases in sleep efficiency (2.2%;
Confidence Interval 0.2-4.2) and total sleep duration (12.8 minutes; Confidence Interval
2.9-22.8) (Table 1). The inclusion criteria required that a study include at least 6
subjects, all adults; be randomized and double-blinded; involve placebo-controlled
clinical trials; and use objective measures of sleep evaluation. Studies could utilize
crossover or parallel group designs, however case reports were excluded. It was perhaps
noteworthy that statistical significance was attained in spite of major variations among
the studies in melatonin doses and routes of administration used; the general health of the
subjects; and the measures used to evaluate sleep.

The effects of exogenous melatonin on sleep have been examined under three
types of experimental conditions.

1) After administration of the hormone during the daily light period. This causes
blood melatonin levels to be transiently elevated, but then to return to baseline before the
initiation of nocturnal melatonin secretion. Such experiments have been used to
demonstrate that melatonin can decrease sleep latency at any time in the afternoon or
evening, and that this effect is independent of any action the hormone might have on
sleep rhythms (since no treatment can immediately shift the phase of a circadian rhythm
by 8-10 hrs.)³.
2) After administration of the hormone late enough in the daily light period, such that blood melatonin levels are still elevated when nocturnal melatonin secretion starts. The period during which plasma melatonin levels are continuously elevated is thus prolonged. Such experiments have simulated the use of melatonin to decrease sleep latency and maintain continuous sleep in, for example, a shift-worker or an eastbound world traveler required to start sleeping earlier in the evening.

3) After administration of the hormone at the end of the light period, e.g., to older insomniacs with low nighttime plasma melatonin levels. The intent has been to prolong the portion of the night during which their plasma melatonin concentrations are elevated to the same range as those of non-insomniac young adults.

In all of these situations, exogenous melatonin has decreased sleep latency and, when tested, increased sleep duration and sleep efficiency. A 0.2-0.5 mg dose was usually found to be either as effective as, or more effective than, higher pharmacologic doses, which tend to lose efficacy when administered for several days. The physiologic dose has no effect on body temperature, affirming that, while pharmacologic doses do cause hypothermia, melatonin's ability to promote sleep is not mediated by such a change, as had been suggested. The hormone tends to have no consistent effect on sleep architecture (Table 1), neither increasing nor decreasing the portion of the sleep period during which subjects exhibit REM. Its effects, in general, have differed from those usually associated with hypnotic drugs, since after melatonin subjects can readily keep from falling asleep if they so choose, and their cognitive abilities the morning after receiving the hormone are unchanged or improved.
A relatively large (N = 30) study, was performed on people who were 50 years of age or older; did or did not suffer from clinically-significant insomnia (i.e. sleep efficiencies of 70-80% in the insomniacs vs. 92% in controls); and received each of four randomized doses of melatonin (0; 0.1; 0.3; or 3.0 mg;) orally for a week, separated by one-week washout periods. The hormone was found to produce statistically and clinically significant improvements in sleep efficiency among the insomniacs, with the 0.3 mg dose causing the greatest effect (P < 0.0001) (Table 1): total sleep time increased by 19 minutes, and sleep efficiency rose from 78% to 88%. The effect of the melatonin was greatest during the middle portion of the nocturnal sleep period, when sleep efficiency was increased from 70% to 92%. No effects were noted in subjects without insomnia, and among the insomniacs there were no changes in total sleep time; latency to sleep onset (which is not abnormal in this population) or to REM sleep; or percent time spent in any of the sleep stages. Dose-related increases in plasma melatonin levels were observed, the 0.3 mg dose causing peak levels in the range usually observed nocturnally among young adults. By ten hours after administration of the 0.1 or 0.3 mg doses plasma melatonin levels did not differ from those after placebo treatment; however after the 3.0 mg dose plasma melatonin levels remained significantly elevated for much of the following day. This high dose but not the other two also caused significant hypothermia. The study concluded that many older people with poor sleep efficiency might benefit if their low nocturnal melatonin levels were corrected.

A prolonged-release preparation containing 2 mg of melatonin has recently been shown to improve sleep quality and next-morning alertness in insomniac patients aged 55 years or older, using a sleep evaluation questionnaire, a diary and other subjective
measurements. This preparation elevates plasma melatonin levels to 390 pg/ml after 1.5-2.5 hours and sustains plateau levels for 3.1-4.4 hours, after which they decay to baseline within 9-10 hours (N. Zisapel, personal communication).

b. Circadian Rhythms: Phase-Shifting and Jet Lag

That exogenous melatonin can synchronize and shift the phases of various human circadian rhythms is generally accepted. As little as 0.5 mg of pure melatonin42, or 0.05 mg of melatonin in corn oil43 (which causes earlier peaks in, and the more rapid disappearance of, elevated plasma melatonin levels) advanced the onset of nocturnal melatonin secretion when administered at 5 PM, and larger doses caused greater phase advances. (The hormone shifted the core body temperature rhythm, however a statistically significant effect was found only after a dose that elevated plasma melatonin levels well beyond their normal range, i.e., to 1327 pg/ml42), affirming that physiologic elevations in plasma melatonin fail to affect body temperature. Melatonin can also control the timing of the sleep and sleepiness rhythms, - an effect readily demonstrated among blind people with free-running melatonin and sleep rhythms43 but also among sighted individuals. Moreover physiologic doses (0.3 mg) reportedly entrain a variety of otherwise free-running rhythms in blind people44.

Melatonin's ability to phase-shift circadian rhythms underlies its common use to prevent or treat "jet lag" - particularly that associated with eastbound travel (possibly because the melatonin can be taken while the traveler is still awake): A 1999 review45 cited 9 placebo-controlled field studies on this use, of which 7 were successful in that improvements were noted in subjective (and in one case objective) measures of sleep and alertness. Adequate data are not available on the relationship between the efficacies of a particular melatonin dose in treating jet lag and in raising plasma melatonin levels. Some
investigators recommend taking the melatonin at a specific time [e.g., at 2 AM in the traveler's new geographic environment]; others simply propose "...a ... pre-flight early evening treatment before an eastbound flight, followed by treatment at bedtime for four days after arrival.\textsuperscript{45} Westbound, the traveler is advised to take the melatonin late in the evening, in order to sustain nocturnal plasma melatonin levels for as long into the night as possible. A 2003 Cochrane Review on "Melatonin for the prevention and treatment of jet lag" concluded that "Melatonin is remarkably effective in preventing or reducing jet lag...\textsuperscript{46} A more recent (2006) meta-analysis concluded that melatonin has not been shown to be effective in treating sleep disorders such as jet lag and shift work disorder, nor insomnias secondary to e.g., neurologic disease\textsuperscript{47}. This review failed to include many publications in which melatonin had been found effective for jet lag, nor to consider the prior meta-analyses which concluded that the hormone is efficacious. Moreover almost all of the studies it did cite had utilized very high, probably desensitizing melatonin doses.

c. Other Reported Effects

It has been suggested\textsuperscript{48,49} that melatonin is a potent antioxidant, and that melatonin supplements may protect against such age-related diseases as atherosclerosis, cancer, and Alzheimer's disease. None of these proposed uses has been tested in a controlled clinical trial nor, of course, has any been approved by the FDA. And all remain questionable because of their lack of confirmations; the enormous melatonin concentrations or doses needed to produce the effect; the failure of the investigators to provide data on actual blood or tissue melatonin concentrations after treatment; and the lack of studies comparing melatonin's effects with those of known antioxidants like
Vitamins C or E. It has usually been possible to demonstrate antioxidant or free radical
c scavenger effects in vitro, however, such demonstrations generally have required
melatonin concentrations 1,000 - 100,000 times those ever occurring in vivo. Similarly,
while high doses of melatonin (10-450 mg/kg body weight parenterally) have sometimes
been shown to elicit antioxidant effects in experimental animals in vivo, neither their
long-term safety nor their effects on the animals’ blood melatonin levels have been
characterized. In humans such megadoses might ultimately be expected to impair sleep
or various circadian rhythms by desensitizing melatonin receptors.

In several small studies melatonin was found to reduce blood pressure when given
to normotensive men or women in daytime or early evening, or to patients with
essential hypertension. This possible effect should be explored further in subjects given
ramelteon, as should whether therapeutic doses of the drug cause hypothermia.

D. Conclusions

Ramelteon, a potent agonist for melatonin’s MT1 and MT2 receptors, shares with
melatonin the ability to reduce sleep latency, and is approved for this use by the FDA. It
is not an agonist for benzodiazepine or GABA receptors, nor for those of other
neurotransmitters thought to mediate the hypnotic effects or addictive potential of most
hypnotic drugs; moreover, ramelteon has not manifested abuse potential in laboratory
tests. Hence, probably unique among prescription hypnotics, ramelteon is a non-
scheduled drug. The longest, still-unpublished studies on ramelteon’s use in insomniacs
have lasted only 35 days, and in the longest such study described in a peer-reviewed
publication the drug was administered for only two days. Hence it is not yet possible to
conclude that, with chronic administration, ramelteon will retain its efficacy and
propensity for causing only benign side effects. That ramelteon might indeed lose
efficacy with repeated use is suggested by its relatively high peak blood levels (compared
with those of melatonin) after a standard therapeutic dose, and by the tendency of the
MT1 and MT2 receptors to become desensitized when exposed to supraphysiologic
levels of their agonist.
Acknowledgements

Studies performed in the author’s laboratory were supported by the U.S. National Institutes of Health. The Massachusetts Institute of Technology owns a U.S. patent on the use of melatonin to promote sleep.
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