A Randomized, Crossover, Pharmacokinetics Evaluation of a Novel Continuous Release and Absorption Melatonin Formulation

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ABSTRACT

Objective: To evaluate the pharmacokinetic and safety profile of a novel continuous release and absorption melatonin (CRA-melatonin) compared with an immediate-release melatonin (IR-melatonin) product.

Methods: The REM Absorption Kinetics Trial (REMAKT), an open-label, single-center, randomized, single-dose, 2-way crossover trial, compared the pharmacokinetic and safety profile of CRA-melatonin (5 mg) with IR-melatonin (5 mg) in healthy adult volunteers. The study was conducted from March 18, 2016, to April 20, 2016.

Results: Ten subjects completed REMAKT. Plasma melatonin levels exceeded the targeted maintenance threshold level of 1,000 pg/mL for a median of 6.7 hours for CRA-melatonin compared with 3.7 hours for IR-melatonin. The median C_{max} was 4,690 pg/mL for CRA-melatonin and 23,352 pg/mL for IR-melatonin. In REMAKT, there were no treatment-emergent adverse events reported in the CRA-melatonin arm. Five treatment-emergent adverse events occurred with IR-melatonin.

Conclusions: The novel, well-tolerated CRA-melatonin was shown to achieve quick release and then continuous release and absorption of melatonin for up to 7 hours, making it a significant advancement in the pharmacokinetic release profile of exogenous melatonin delivery and, therefore, an important potential consideration as a baseline therapy for sleep.

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Chronic disorders of sleep and wakefulness affect an estimated 50 to 70 million adults in the United States.[1,2] The cumulative long-term effects of sleep loss have been associated with a wide range of damaging health consequences.[1] Sleep loss is also associated with increased age-specific mortality, and achieving 7 hours of sleep is associated with improved longevity.[1,3] Uninterrupted sleep allows patients to achieve a more normal sleep architecture, including both non–rapid eye movement (REM) and REM sleep.[1]

An ideal sleep agent would have a rapid onset of action to decrease sleep latency, a duration of action that prevents middle of the night and early morning awakenings, and, finally, a rapid decline in blood concentration level to enable morning alertness.[4] Additionally, it would allow sleep to occur with normal sleep architecture rather than a pharmacologically altered sleep pattern.[5] Various product categories have been developed over the years for non–sleep-related medical indications that have been subsequently utilized for sleep given their sedative side effects. Benzodiazepines, antidepressants, and over-the-counter, early generation antihistamines, for example, were originally developed to treat anxiety, depression, and allergies, respectively. These treatment options for sleep disorders have come with various limitations in efficacy,[6] safety, and tolerability.[5–9]

Melatonin (*N*-acetyl-5-methoxytryptamine), a natural indolamine hormone, is produced by the pineal gland. Unlike certain prescription hypnotics, melatonin-promoted sleep has normal sleep architecture.[5,10–12] Melatonin is associated with both a chronobiotic and hypnotic effect, depending on the dose and timing of administration.[5,11,13–16] The γ-aminobutyric acid-A effects of melatonin at the suprachiasmatic nucleus may explain some of its sleep-promoting effects.[5,17]

Humans produce peak adult melatonin levels in the teenage years, with a subsequent age-related decline.[18] This decline in endogenous melatonin levels may contribute to the common complaint of poor sleep quality among the elderly.[5] Melatonin replacement therapy provides a valid therapeutic approach for sleep disturbances in older patients as well as patients with decreased melatonin production due to disease or the use of certain drugs.[5]

Humans have their own internal clock that modulates the natural cycle of sleep and wakefulness. Normally, melatonin levels begin to rise in the mid to late evening, remain high for most of the night, and then drop in the early morning hours. The plasma concentration time curve of endogenous melatonin in the plasma of humans has been reported previously.[19] The natural plasma melatonin profile can be described as in the shape of a mesa plateau (mesa wave), with the endogenous level rising quickly over a period of 1 hour, staying relatively flat for the next 6 hours, and declining rapidly after 7 hours.

In practice, the sleep maintenance effects of conventional melatonin supplementation (including those labeled as modified release) have been limited by absorption challenges in the distal gastrointestinal (GI) tract, coupled with the melatonin molecule's short half-life.[20]

Clinical Points

- Continuous release and absorption melatonin (CRA-melatonin) is designed to overcome the difficulty of release and absorption of melatonin beyond the highly acidic environment of the stomach.
- In a crossover trial with a stringent protocol to control for light, there was a substantial difference in favor of CRA-melatonin in the maximal plasma concentration, shape of the curve, and time above the targeted blood levels, which may help alleviate barriers to successful melatonin efficacy in sleep.
- Physicians desiring to avoid potentially harmful drugs with increasingly stringent label warnings may wish to consider CRA-melatonin as baseline therapy for sleep difficulties.

There has been a need for enhanced melatonin delivery systems that more closely achieve a pharmacokinetic (PK) profile replicating normal endogenous melatonin plasma patterns.

Continuous release and absorption melatonin (CRA-melatonin), containing an ultrapure form of melatonin, was designed to address the limitations of previously developed conventional melatonin formulations. Melatonin can only be dissolved, ionized, and absorbed in an acidic environment with a pH of less than 5.0 because of its pKa.[21] The unique design of this tablet allows for an initial rapid release of melatonin from the surface layer of the tablet, followed by the establishment of the hydrogel release-controlling matrix in the aqueous acidic environment (pH of 1 to 3.5) of the stomach. As the tablet moves into the higher pH (5.0) environment of the small intestine, which is above the pKa of melatonin, the acidic/buffer moiety in the tablet maintains the pH within the tablet below 4.0 for ≥ 7 hours. The hydrogel matrix, after proper hydration, allows continuous release of the active melatonin and acidic/buffer moiety into the lumen of the intestines. This novel approach facilitates delivery of the active melatonin to the brush border of the epithelial layers of the small and large intestines for uptake into the bloodstream. By maintaining an acidic environment within the CRA-melatonin tablet with a mild organic acid (citric acid), melatonin is intended to be steadily ionized, released, and then absorbed along a substantial portion of the GI tract.

This study was undertaken to prove the hypothesis that a specially formulated melatonin with a built-in acid pump would provide a PK profile that more closely aligns with the nocturnal, endogenous release profile as compared to the most commonly used conventional melatonin product.

METHODS

The REM Absorption Kinetics Trial (REMAKT) was an open-label, single-center, randomized, single-dose, 2-way crossover trial with 2 treatments and 2 treatment periods conducted from March 18, 2016, to April 20, 2016. The PK and safety profiles of 5-mg CRA-melatonin (brand name: REMfresh) and 5-mg immediate-release (IR)-melatonin (brand name: Natrol), administered orally in healthy volunteers, were compared and evaluated. The 5-mg IR-melatonin was chosen for comparison with 5-mg CRA-melatonin because it is the most common melatonin product taken by US consumers and, unlike the 2-mg form, was readily available in the marketplace for comparator access purposes. All subjects received each treatment at least 7 days apart. Subjects were confined to the clinic during each treatment period from approximately 2 hours prior to dosing through 12 hours after dosing. Subjects were dosed in the early morning following an overnight fast. This study design, which included daytime dosing, blood draws, and standardized ambient light exposure, prevented significant endogenous melatonin production.[22]

The REMAKT protocol was reviewed and approved by the Chesapeake Institutional Review Board. This study was conducted and monitored in accordance with the ethical principles of the World Medical Association Declaration of Helsinki (2008) and the International Conference on Harmonization Good Clinical Practice: Consolidated Guideline (1996). All study subjects provided informed consent prior to the initiation of any study-related procedures. This study does not fall into the categories that require registration with ClinicalTrials.gov.

Sample Set and Inclusion/Exclusion Criteria

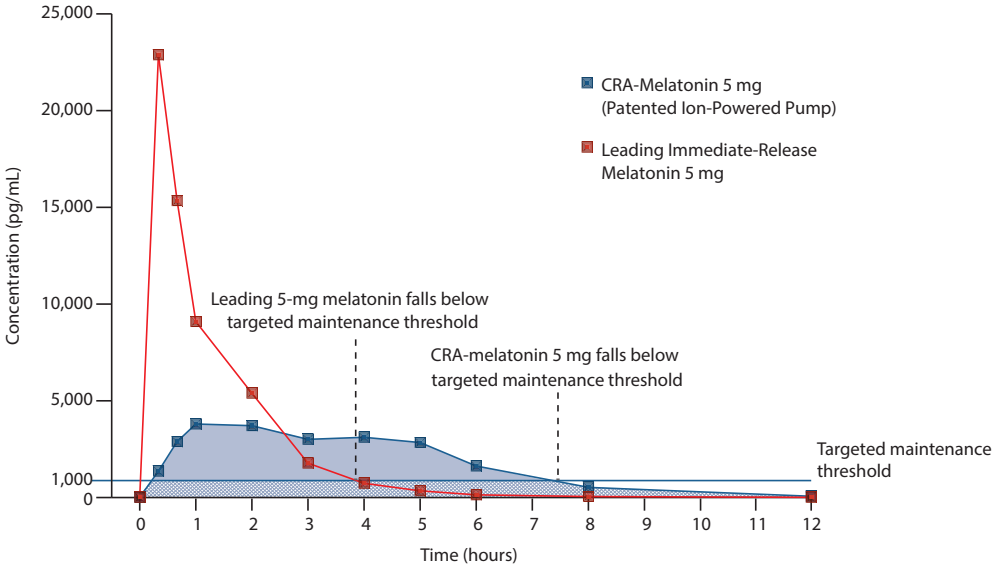
A study population of 10 was established after a review of the literature, including the review of a PK trial design for 2-mg prolonged-release melatonin (PR-melatonin) that supported its approval as a prescription drug in Europe.[22,23] Additionally, critical dimensions of melatonin bioavailability, including the short half-life, the absence of enterohepatic recirculation, and intersubject variability, were considered.

Randomization was performed by Clinical Pharmacology of Miami, Inc (Miami, Florida), using a validated system. Each subject received treatment at least 7 days apart according to the randomization schedule. The trial was open label; thus, no blinding was needed.

Ten subjects (4 men, 6 women) aged 18–40 years (mean = 25.5 years, SD = 7.75) completed the study. There were no protocol violations. The body mass index range was 22.8–29.9 kg/m^2 (mean = 27.5 kg/m^2, SD = 2.46), with weight at screening ranging from 67.0 to 94.6 kg (147.7–208.6 lb) (mean = 77.3 kg, SD = 8.17 [mean = 170.4 lb, SD=18.0]) and height ranging from 150 to 188 cm (mean = 167.8 cm, SD = 10.64). Seven subjects had Fitzpatrick skin type 3, and 3 had type 2. Skin types 1, 2, and 3 are considered white per the Fitzpatrick Skin Type Scale.[24] Two of the subjects used alcohol. Healthy young volunteers were enrolled to prevent interference due to possible comorbid conditions. Subjects had normal circadian sleep-wake cycles per subject history. Female subjects of child-bearing potential agreed to use an acceptable method of birth control during the study.

Subjects were excluded from the study if they were smokers, had a history of drug or alcohol abuse, had a

Figure 1. Median Concentrations of Plasma Melatonin After Dosing With 5-mg CRA-Melatonin or 5-mg IR-Melatonin[a]



[a]Plasma melatonin concentrations were measured 0–12 h after receiving 5 mg of CRA-melatonin or 5 mg of IR-melatonin.
Abbreviations: CRA-melatonin = continuous release and absorption melatonin, IR-melatonin = immediate-release melatonin.

history of cancer within 5 years prior, or had any of the following conditions: sleep apnea or other sleep disorder (including shift workers), heart disease, uncontrolled high blood pressure, renal or hepatic disease, type I or II diabetes, bipolar disorder or other psychiatric disorders, Parkinson disease, thyroid disease, or immune disorders.

Study Setting

Lighting was carefully standardized, as melatonin is not produced endogenously in the presence of ambient light. This standardization included using the same windowless room on the dosing day and was maintained over the entire blood sampling period. Lighting in the room was kept constant. All light readings were between 500 lux and 600 lux and never varied more than 52 lux on any given day. These levels were considered to be well above the minimum light level to suppress endogenous melatonin.[25] Three light meter readings were done on test days: in the morning between 7:00 AM and 8:00 AM, in the afternoon between 12:00 PM and 1:00 PM, and in the evening between 5:00 PM and 6:00 PM. Subjects were required to fast (no food or beverage other than water) for 8 hours prior to the test visits.

Data Collection

Sample collection and safety assessment time points were considered appropriate to achieve the objectives of this study. The PK sampling schedule was selected to help provide an adequate estimation of the maximum concentration and a reliable estimate of the times above a threshold level. The permissible time windows for collection of PK samples and procedures were as follows: for samples obtained up to 1 hour postdose, a window of ±3 minutes of the nominal time was permitted; for the remaining samples, a window of ±5 minutes from the nominal time was permitted. The sampling window needed to be as narrow as practicable in the first hour to identify the burst release and to mitigate excessive variability with the first 5 sampling time points. The safety assessments planned were considered appropriate to adequately identify any safety-related concerns that may have arisen during the study. Adverse events and vital signs were assessed throughout the study. Assessment of adverse events was adjudicated by the trial's medical monitor.

Laboratory Blood Collection and Analysis Method

Blood samples for determination of melatonin at predose and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 8, and 12 hours postdose were collected in K_2EDTA vacutainer tubes. Blood samples were obtained via direct venipuncture or by a venous catheter (heparin lock) following administration of each product. At each time point, a minimum of 5 mL of venous blood was collected in K_2EDTA vacutainer tubes. Immediately after each collection, the vacutainer tubes were centrifuged at 4°C at 3,000 rpm for 10 minutes. Plasma samples were analyzed for concentrations of melatonin and the internal standard (melatonin-d4) by a validated liquid chromatograpy with tandem mass spectrometric method.

Data Analysis

For each subject, plasma concentration time data for melatonin was used for the calculation of the following PK parameters: C_{max}, T_{max}, and $T_{threshold}$ (time above target threshold concentration). Time to reach initial threshold (100 pg/mL) concentration, targeted maintenance threshold (1,000 pg/mL) concentration, and duration of time above the target threshold levels for melatonin were determined by a proportional linear interpolation.

In REMAKT, a 1,000-pg/mL plasma melatonin concentration threshold was set to support sleep maintenance. This target was set at approximately 10 times the endogenous concentration for melatonin in healthy young subjects since animal studies[26] of drug transport across the blood-brain barrier have shown an approximately 10-fold lower concentration of exogenous melatonin in the brain versus plasma.

All subjects who received at least 1 dose of either formulation of melatonin were included in the safety and PK analysis. Plasma concentrations of melatonin were tabulated and plotted for each subject and summarized with descriptive statistics by treatment.

RESULTS

Within the first hour of dosing, a median C_{max} of 4,690 pg/mL was reached for CRA-melatonin compared to a median C_{max} of 23,352 pg/mL for IR-melatonin (Figure 1). For CRA-melatonin, levels exceeded the target sleep maintenance threshold level of 1,000 pg/mL for a median of 6.7 hours, resulting in a flat-topped mesa-like plateau, compared with a median of 3.7 hours for IR-melatonin (Figure 1). A relatively rapid decline of plasma melatonin levels to predosing endogenous levels occurred by the 8-hour time point for CRA-melatonin and by the 5-hour time point for IR-melatonin. There were no treatment-emergent adverse events (TEAEs) associated with CRA-melatonin. Five TEAEs occurred in 2 patients with IR-melatonin. Four of these TEAEs were GI side effects: emesis (2 patients), stomach cramps, and nausea; 1 TEAE was related to the central nervous system: irritability.

DISCUSSION

In this randomized, open-label, crossover PK and safety trial (REMAKT), CRA-melatonin was shown to achieve quick release and then continuous release and absorption of melatonin for up to 7 hours, providing the targeted mesa wave profile compared to the high C_{max}/fast decline profile of the IR-melatonin product.

Prior to the development of CRA-melatonin, several modified-release formulations of melatonin have been developed with the goal of providing exogenous melatonin profiles that match normal endogenous levels. The initial attempts, deploying various excipients (eg, hydroxypropylmethylcellulose) or dosage forms (eg, bead technology) to provide sustained release and absorption, exhibited challenges in maintaining high plasma melatonin levels after the first 4 hours following administration of the dose.[27–31] Subsequently, a 2-mg prolonged-release melatonin (PR-melatonin) approved by the European Medicines Agency in 2007 as a prescription drug in Europe[23] and elsewhere[32] made additional progress toward achieving the mesa wave-like profile, with a median plateau time of 4.4 hours.[23] PR-melatonin, in several randomized, placebo-controlled trials, has demonstrated clinically meaningful improvements in quality of sleep, behavior following waking,[33,34] and wake time after sleep onset,[35] providing further support for the correlative effect of melatonin blood levels and sleep.

CRA-melatonin did not result in the ultrahigh C_{max} or the shorter half-life that was seen with IR-melatonin. The latter had a C_{max} of more than 23 times the targeted sleep maintenance threshold needed for maintaining sleep. Although it was not the primary endpoint in REMAKT, no tolerability issues in the form of reported adverse events were observed in the CRA-melatonin arm. Some tolerability issues were observed in the IR-melatonin arm. Given the limited number of subjects participating in the trial, however, caution should be exercised in projecting this observation to a larger patient population. Finally, it should be noted that adverse effects of exogenous melatonin supplementation are few, and it is generally regarded as safe in recommended dosages.[36] There is very little evidence in short-term usage to suggest toxicity or undesirable effects of melatonin in humans.[13]

This study was limited in the sense that it was not a conventional sleep outcomes trial. While this study had an N of 10, the assumptions that led to the selection of the sample size did seem to be appropriate given the clear differences that emerged in the PK profiles between IR-melatonin and CRA-melatonin. Additional studies and real-world evidence to determine the clinical relevance of these findings should be thoughtfully considered.

The results of this study demonstrate that the release profiles of these 2 products, CRA-melatonin and IR-melatonin, are vastly different. This study was not designed to assess whether the differences in melatonin levels would translate clinically, as subjects were necessarily not permitted to sleep. However, important inferences can be made on the expected sleep patterns. CRA-melatonin, with its continuous release and absorption of pH-independent melatonin through a substantial portion of the GI tract and then accompanied by a sharp fall off, is anticipated to improve sleep maintenance and morning alertness. CRA-melatonin shows an enhancement over the release profile of PR-melatonin by extending in vivo exposure to 7 hours, making it an important advancement in the use of melatonin as a chronobiotic, potentially with drug-free hypnotic effects, to initiate and maintain sleep. Finally, there is a paucity of published PK studies of the melatonin products currently on the market. This study is important and may be of clinical relevance, as melatonin use in US adults more than doubled between 2007 and 2012, with a reported 3.1 million users in 2012.[37]

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Additional information: The position of the US Food and Drug Administration (FDA) about what human studies must be registered with ClinicalTrials.gov is available at https://clinicaltrials.gov/ct2/manage-recs/fdaaa. Under the rule (42 CFR 11.22 implementation on January 18, 2017), applicable clinical trials (ACTs) are those that evaluate at least 1 drug, biological, or device product regulated by the FDA. This study does not qualify as an ACT. In addition, it was undertaken in the 2015–2016 time period and met relevant scientific standards that existed at that time for non–FDA-regulated supplements (including melatonin, a food product).

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