Clinical Evaluation of the Ion Powered Pump Melatonin Delivery System

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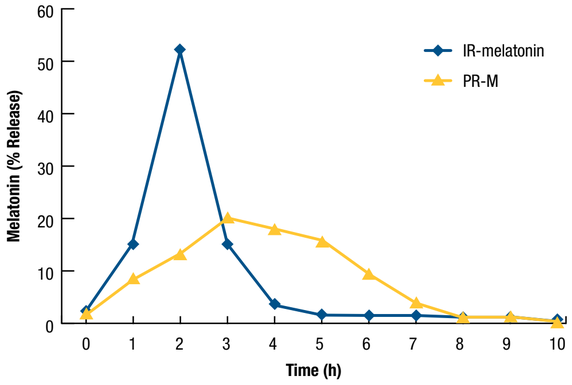
Introduction

Melatonin levels decline with age, an important factor in poor quality sleep among older people.[1] In addition to difficulty falling asleep, sleep in older populations is characterized by increased fragmentation of the sleep architecture and sleep maintenance problems. Melatonin supplementation has been shown to promote and maintain sleep in older populations.[1] Previously, prolonged-release melatonin (PR-M), which has been marketed internationally, was designed to provide a serum melatonin profile more closely related to the normal physiological release pattern compared with immediate-release melatonin (IR-melatonin).

Figure 1. Pharmacokinetic Profile of Prolonged-Release Melatonin (PR-M) Compared to Immediate-Release (IR-melatonin)[1]



A pharmacokinetic study looking at serum melatonin levels in healthy males after ingestion of the 2 mg dose of PR-M shows peak concentration of melatonin in the blood occurring at 2.6 hours and persisting over 3.5 hours after ingestion and declining towards the morning.[1] IR-melatonin peaks after 2 hours and rapidly declines over the next 2 hours.

In well-conducted sleep studies, PR-M demonstrated statistically significant improvements in sleep quality, morning alertness, sleep latency, and quality of life in patients aged 55 years and older compared with IR-melatonin and placebo.[1,2] In addition, as shown in Table 1, the responder rate for concomitant improvement in quality of sleep and morning alertness, and in each of them separately, was significantly higher for PR-M compared with placebo, in studies reported by the PR-M innovator.[2]

Table 1. % Responders to PR-M vs Placebo Showing Concomitant and Clinically Meaningful Improvement in Quality of Sleep and Morning Alertness[2]

	QOS & BFW Responders		QOS Responders		BFW Responders	
Treatment	PR-M	Placebo	PR-M	Placebo	PR-M	Placebo
N	265	272	265	272	265	272
Responders	32.4%	18.7%	48%	34.5%	40.3%	30%
Difference	13.7%		13.5%		10.3%	
Odds ratio	2.08		1.75		1.57	
P value	0.0003		0.0017		0.012	

Pooled Analysis (N. I, VII, IX). QOS, (quality of sleep); BFW, (behavior following wakefulness)

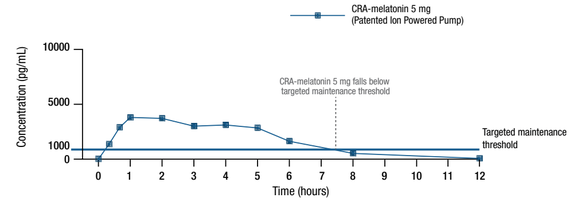
In spite of an improved formulation, a lower than anticipated plateau time for PR-M (4.4 h)[2] resulted from lower absorption in the intestines with this formulation.[3] Building upon the body of evidence from PR-M studies, the patented Ion Powered Pump (IPP) delivery system utilized in continuous-release and absorption melatonin (CRA-melatonin) was designed to overcome the challenges of absorption in the intestines[3] and, thereby, extend the plateau time (known as the Mesa Wave) to approximate the target of 7 hours and improve sleep maintenance.

Methods

- Randomized, crossover clinical PK evaluation comparing 5 mg CRA-melatonin (REMfresh) with the market-leading 5 mg IR-melatonin in 10 healthy non-smoking adults
- The active ingredient in CRA-melatonin (Ultramel) is an ultra pure (99%) proprietary synthetic melatonin
- Blood was taken pre-dose and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 8 and 12 hours following administration and was assayed for melatonin by a validated LC-MS/MS method
- PK parameters, including the time course, C_{max}, T_{max}, and plateau time for melatonin were determined by inspection
- Time to reach initial target (1000 pg/mL) and duration of time above the target threshold levels for melatonin were determined by interpolation

Results

Figure 2. Median Concentrations of Plasma Melatonin after 5 mg CRA-melatonin



The median time it took plasma melatonin levels to exceed the initial threshold level of 1000 pg/mL was 0.42 hours for CRA-melatonin. The median C_{max} was 4,690 pg/mL for CRA-melatonin, and the median time to reach this concentration (T_{max}) was 1.5 hours. Melatonin levels showed a median plateau time of 6.7 hours with CRA-melatonin. There were no treatment-emergent adverse events seen with CRA-melatonin.

Conclusions

- CRA-melatonin shows an enhancement over the already advanced profile of PR-M. There was a faster time to C_{max}, a median plateau time-extending to 6.7 hours and rapid fall-off in plasma levels
- The faster time to C_{max} is anticipated to result in improved sleep onset
- The extended plateau time and rapid fall-off at the end of the Mesa Wave is anticipated to improve sleep maintenance and morning alertness

References

1. Zisapel N. Melatonin and sleep. *The Open Neuroendocrinology J.* 2010;3:85-95. **2.** European Medicines Agency. Assessment Report for *CIRCADIN*. 2007. **3.** Zisapel N, inventor; Neurim Pharmaceuticals Ltd., assignee. United States Patent Application Publication: Methods for treating patients suffering from drug dependencies which lead to plasma melatonin deficiencies. Pub. No. US 2003/0040539. February 27, 2003.

DISCLOSURES

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