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TASIMELTEON: A NOVEL DRUG IN NON-24 HOURS SLEEP WAKE DISORDER

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ABSTRACT

Free-running type or non 24 hour sleep wake disorder is a rare but chronic circadian rhythm sleep disorder (CRSD) that disrupts the sleep-wake cycle and affects the majority of totally blind individuals leading to insomnia. Tasimelteon, a melatonin receptor agonist has proved its potential as a circadian regulator that resets the biological clock in the suprachiasmatic nucleus (SCN) of the hypothalamus, thus synchronizing the body's melatonin and cortisol circadian rhythm with the day-night cycle in patients with non 24 hour sleep wake disorder. Its potential for use in jet-lag, mood disorders and depression due to circadian rhythm disorder is under evaluation. Tasimelteon (Hetlioz) by Vanda Pharmaceuticals Inc. was approved by U.S. Food and Drug Administration (FDA) on 31st January, 2014 for treatment of non 24 sleep wake disorder.

KEY WORDS: Tasimelteon, circadian rhythm sleep disorder, melatonin, free-running.

INTRODUCTION

Melatonin, the major hormone secreted by the pineal gland, was first identified by Aaron Lerner in 1958. Melatonin (5-methoxy-N-acetyltryptamine) is formed by sequential N-acetylation and O-methylation of indolamines. Its synthesis is controlled by external factors such as environmental light and corresponds to typical sleep-wake cycle. It is considered as

the chemical signal indicating the length of darkness, as its secretion is greatest during the dark hours of the night. As it is secreted in its highest levels during the night time in diurnally active vertebrates, it has been suggested that it has a crucial role in sleep promotion. Owing to its involvement in the regulation of circadian rhythms, any disruption in melatonin secretion may play an important part in the etiology of circadian rhythm sleep disorders (CRSD). This has advocated the use for exogenous melatonin in the treatment of CRSD. It is also being widely used as a natural supplement or, in its analogue variants, as a drug for various sleep disorders. Apart from regulation of circadian rhythms, this hormone has a number of important physiological functions including initiation and maintenance of sleep, anti-oxidative defense, immune regulation and aging, control of reproductive activity and tumor growth supression.[1-4]

In 1994, three melatonin receptors MT_1, MT_2 and MT_3 were characterized and cloned in humans. MT_1 and MT_2 are involved in sleep physiology. Both the MT_1 and MT_2 type of receptors belong to the family of G_i/G_0 protein-coupled receptors linked to the inhibition of adenylyl-cyclase and subsequent decrease of cyclic AMP.[5] Both the MT_1 and MT_2 type of receptors are demonstrated in almost all structures of CNS; although the hypothalamic suprachiasmatic nucleus (SCN) and the pars tuberalis of the pituitary have the highest density of these two receptors. MT_1 mediated inhibition of neurons in the suprachiasmatic nucleus helps to promote sleep by decreasing the wake promoting action of suprachiasmatic nucleus. MT_2 mediated signals in suprachiasmatic nucleus helps in phase shifting effects by activations of protein kinase C. This explains the action of melatonin as a chronobiotic.[1,2,6]

The sleep-wake cycle

The sleep-wake cycle is the most evident of the many 24-hour rhythms in humans. It is now recognized that many peripheral tissues in mammals have circadian clocks that regulate diverse physiologic processes. These independent tissue-specific oscillations are coordinated by a central neural pacemaker located in the suprachiasmatic nuclei (SCN) of the hypothalamus. The genetically determined period of this central neural pacemaker, averages ~24.2 hours in humans, is normally synchronized or entrained to the 24-hours period of the environmental light-dark cycle. Entrainment or *phase shifts* involves regular adjustments of the circadian pacemaker, which depends on exposure to environmental time cues, particularly the daily light–dark cycle. It is mediated via the retinohypothalamic tract, a monosynaptic pathway that links specialized, photoreceptive retinal ganglion cells directly to the SCN.

Humans are exquisitely sensitive to the resetting effects of light, particularly the shorter wavelengths (~460–500 nm) of the visible spectrum. Paradoxically the endogenous circadian rhythms of sleep tendency, sleepiness, and REM sleep propensity all peak near the habitual wake time, whereas the circadian wake propensity rhythm peaks 1–3 hours before the habitual bedtime. These rhythms are thus timed to oppose the homeostatic decline of sleep tendency during the habitual sleep episode and the rise of sleep tendency throughout the usual waking day, respectively. The timing and internal architecture of sleep are directly coupled to the output of the endogenous circadian pacemaker. Misalignment of the output of the endogenous circadian pacemaker with the desired sleep-wake cycle can, therefore, induce insomnia, decreased alertness, and impaired performance, evident in night-shift workers and airline travellers. As light cues are unavailable in totally blind people, disturbances of circadian rhythms are common.[7]

Non 24 hours sleep wake disorder

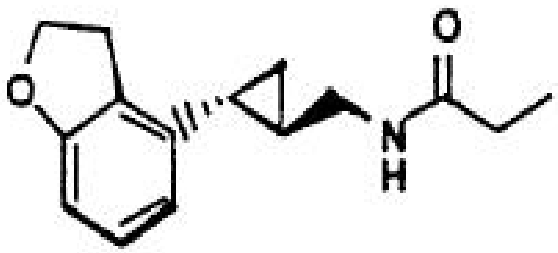
Among the various types of sleep disorders, Circadian rhythm sleep disorders (CRSDs) constitute a major part. According to the International Classification of sleep disorders, the essential feature of CRSDs is a persistent or recurrent pattern of sleep disturbance due primarily to alterations in the circadian timekeeping system or a misalignment between the endogenous circadian rhythm and exogenous factors that affect the timing or duration of sleep. There are six distinct CRSDs currently recognized in the International Classification of Sleep Disorders (ICSD-2), namely: 1) *delayed sleep phase type* 2) *advanced sleep phase type* 3) *irregular sleep-wake phase type* 4) *free-running type* 5) *jet lag type* and 6) *shift work type*.[8,9] Free-running type, also known as 'non 24 hours sleep wake disorder' or non-entrained type or hypernychthemeral sleep wake syndrome, is a rare, orphan, serious, chronic debilitating circadian rhythm sleep disorder (CRSD) that disrupts the sleep-wake cycle, for which there is no available treatment.[10,11] Though it is commonly seen in a blind person, it can occur in sighted patients due to genetic predispositions or significant decrease circadian photoreception due to pupillary miosis and reduced power of the crystalline lens.[7] In sighted people, usually the onset of free-running disorder occurs in their teens or twenties.[10] In the totally blind, the onset is probably coincident with the loss of sight. It affects the majority of totally blind individuals and it is approximately 80,000 Americans have this disorder.[12] In totally blind individuals, without input from the eyes, information about environmental light levels fails to reach the suprachiasmatic nuclei in the hypothalamus to synchronize the internal clock, thus reflecting a failure of entrainment. Therefore, this type of sleep disorder

occurs as a result of the misalignment of the endogenous master body clock to the 24-hour day, disrupting the sleep-wake cycle, resulting in insomnia with excessive daytime sleepiness.[4,7,8,13] Although the chief complaint is usually related to the sleep-wake pattern, but is has been observed that it is also responsible for the desynchrony of circadian rhythms, which include those of cortisol, core temperature, blood pressure, glucose control, have profound impacts in the cardiovascular and metabolic homeostasis of the body. Since the first description of this disorder in 1948, no definite drug therapy is available till today and the disorder is often under diagnosed or misdiagnosed.[12] In most cases, patients have been left either untreated or treated inappropriately. Therapeutic interventions for non 24 hours sleep wake disorder' is targeted at entraining the patient's circadian pacemaker at an appropriate phase relative to the environmental light/dark cycle. Use of low dose melatonin have been reported to improve sleep in such cases, and is also used to synchronized the circadian pacemaker with the 24 hours geophysical day.[10,14,15,16] In view of these findings, Tasimelteon (Hetlioz), a melatonin receptor agonist was approved by FDA on 31st January, 2014 for treatment of non 24 hours sleep wake disorder.[12] We present here a brief overview on the pharmacology of Tasimelteon based on the published data by Vanda Pharmaceuticals Inc.

TASIMELTEON

Chemistry

The IUPAC name is (1R, 2R)-N-[2-(2,3-Dihydrobenzofuran-4-yl) cyclopropylmethyl] propanamide. It has a molecular weight of 245.14 and the molecular formula is $C_{15}H_{19}NO_2$. The structural formula is:[17]



Mechanism of Action:[12]

The therapeutic goal of non 24 hours sleep wake disorder is to keep in phase the endogenous circadian rhythms with the local environment. Thus, the melatonin receptors which are present in high density at the suprachiasmatic nucleus (SCN) are targeted to exert melatonergic actions to phase shift circadian rhythm and promote sleep. Tasimelteon is a

MT_1 and MT_2 receptor agonist, with greater affinity to MT_2 receptor than MT_1, hence it is also known as Dual Melatonin Receptor Agonist (DMRA). Its major metabolites also bind, though at least with 10 times lower affinity to MT_1 and MT_2 receptors. Tasimelteon or its metabolite do not have affinity to other pharmacologically relevant receptors including receptors of neurotransmitter systems associated with abuse potential such as dopamine, norepinephrine, serotonin, gamma-aminobutyric acid (GABA), acetylcholine, opioid, N-methyl-D-aspartate (NMDA) and cannabinoid. Two recent randomized controlled trials (phase II and III) demonstrated that tasimelteon by improving sleep latency and maintenance of sleep with a shift in circadian rhythms, has the potential to treat patients with transient insomnia associated with circadian rhythm sleep disorders.[18,19] It acts as a circadian regulator that resets the biological clock in the suprachiasmatic nucleus (SCN) of the hypothalamus, thus synchronizing the body's melatonin and cortisol circadian rhythm with the day-night cycle in patients with non 24 hour sleep wake disorder. It phase advances circadian rhythm and minimizes disruption in sleep efficiency, wake after sleep onset and sleep latency. Preclinical studies showed that it has similar phase-shifting properties to melatonin, but with less vasoconstrictive effects.[20]

Pharmacokinetics[12]

The following Pharmacokinetic information is available.

Absorption

Tasimelteon is rapidly absorbed orally under fasting condition with a T_{max} of approximately 0.5 hours. Co-administration with fatty or high calorie meals delayed its absorption. However, in accordance with phase III efficacy studies (SET and RESET), tasimelteon can be administered without regard to meals.

Distribution

The apparent oral volume of distribution at steady state is 59-126 L and it is 89-90% plasma protein bound at therapeutic concentration.

Metabolism

Orally administered Tasimelteon undergoes rapid metabolism by CYP1A2 and CYP3A4. Phase I metabolism consists mainly of oxidation and oxidative dealkylation resulting in opening of the dihydrofuran ring followed by further oxidation to give a carboxylic acid. CYP1A1, CYP2D6, CYP2C19 and CYP2C9 also minimally metabolize tasimelteon. Phase II

metabolism is through phenolic glucuronidation. It is metabolized in humans to five metabolites: M9, M11, M12, M13, M14. The mean elimination half-life t1/2 of Tasimelteon is 1.32 ± 0.4 hours. The mean terminal elimination half-life ± standard deviation of the main metabolites ranges from 1.3 ± 0.5 to 3.7 ± 2.2 hours.

Excretion

The pharmacokinetics of tasimelteon is linear over doses ranging from 1 to 300 mg. More than 80% is excreted through urine and about 4% through the faeces and less than 1% is excreted unchanged in the urine. Repeated once daily dosing with tasimelteon does not result in PK parameter changes or significant accumulation owing to the short half-life of Tasimelteon.

Contraindications[21]

Patients should avoid engaging in activities requiring coordination and concentration, including driving or operating machinery after taking tasimelteon. It is contraindicated in pregnant and lactating mothers.

Dose regime

It is available as capsules for oral consumption. The recommended dose is 20 mg per day taken at bed time, to be taken at the same time every night. Because of individual difference in circadian rhythm, it may take weeks to months for its effect. Although exposure to tasimelteon was increased approximately 2-fold in subjects with hepatic impairment after a single 20 mg/day dose, dose adjustment is not necessary in patients with mild or moderate hepatic impairment. However it has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). No dose reduction is required in renal impairment as well as based on age, gender, or body mass index (BMI).[12]

Clinical use

FDA approved use of Tasimelteon for ‘non 24 hour sleep wake disorder’ in totally blind patients. Its potential for use in jet-lag, mood disorders and depression due to circadian rhythm disorder is under evaluation.[2,22,23]

Potential Drug interactions of Tasimelteon:[12]

1. Fluvoxamine, a strong inhibitor of CYP1A2 increased C_{max} of tasimelteon by 2 fold on co-administration. So, Tasimelteon should be used with caution in combination with Fluvoxamine and other CYP1A2 inhibitors.

2. Dose adjustment may be needed in people who smoke as smoking is a moderate CYP1A2 inducer.
3. Rifampin, a strong CYP3A4 and moderate CYP1A2 inducer reduced exposure to Tasimelteon, thus needing dose adjustments.
4. Ketoconazole, a strong CYP3A4 inhibitor increases tasimelteon's exposure by approximately 54%, compared to administration of tasimelteon alone. However, no dose adjustment is recommended as the clinical significance of this change is unclear.
5. Tasimelteon at 20 mg/kg dose does not have any additive effect or psychomotor performance or memory task when combine with other CNS depressant like midazolam or alcohol.

Adverse effects and Safety Profile[12]

Tasimelteon is well-tolerated in the indicated population of totally blind individuals with Non-24-Hour Disorder and the safety profile is favorable. Pre clinical studies showed no significant reproductive toxicity, embyotoxicity, genotoxic and carcinogenic findings at clinically relevant exposures for humans. Clinical study 1103, a thorough QT study, a four-period, randomized, double-blind, multiple-dose, crossover study, demonstrated that it has no potential to interefere with cardiac repolarization. In both the SET pivotal efficacy study and the RESET randomized withdrawal study, events reported among tasimelteon-treated patients were comparable to events occurring in placebo-treated patients. Among all tasimelteon-treated patients in placebo-controlled Phase 2 and 3 efficacy studies, no serious adverse events (SAE) or laboratory abnormalities were reported. Throughout the clinical development program, the most common adverse reactions occurring at a level clinically different from placebo are headache and vivid or unusual dreams. Others like raised alanine aminotransferase, upper respiratory tract infection, urinary tract infection, somnolence, conduction disorder, sleep disorder and nasopharyngitis were also reported.

CONCLUSION

The benefits of tasimelteon in the treatment of totally blind patients with this serious and orphan Non-24-Hour Disorder have been established in two pivotal clinical studies. Specifically, tasimelteon was shown to entrain (synchronize) the Master clock to a 24-hour period, as measured by both the melatonin and cortisol circadian rhythm measurements. More than fifty percent of patients that received tasimelteon treatment for an adequate duration (approximately one circadian cycle length or 40 to 80 days) and at the same time every night

were successfully entrained. In addition tasimelteon was shown to restore the 24-hour synchrony of the sleep-wake cycle. As a result, tasimelteon significantly and meaningfully improved the timing and amount of sleep episodes, allowing sleep to be consolidated during the night and minimized sleep during the day. Physician derived global functioning impression showed consistent improvements in the overall function and well-being of tasimelteon-treated study participants. Tasimelteon was also shown to be well tolerated with a mild side effect profile compatible with chronic use, thus making it suitable for the treatment of Non-24 sleep disorder in the totally blind.

REFERENCES

1. Seithikurippu R, Perumal P, Srinivasan V, Spence DW, Moscovitch A, et.al. Ramelteon: a Review of its Therapeutic Potential in Sleep Disorders. Adv Ther 2009; 26(6): 613-626.
2. Dawoodi Z, Shah N, De Sousa A. Melatonin agonists: a brief clinical review. Delhi Psychiatry Journal 2012;15:(2): 268-73.
3. Bush ES, Mayer SE. 5-Hydroxytryptamine (Serotonin): Receptor Agonists and Antagonists In: Brunton LL, Lazo JS, Parker KL, editors. Goodman & Gilman's Pharmacology: The Pharmacological Basis of Therapeutics. 11th ed. New Delhi: The McGraw Hill Companies Inc.; 2006: p. 297-315.
4. Dennehy C, Tsourounis C. Herbs and Nutritional Supplements. In: Koda-Kimble MA, Young LY, Alldredge WA, Corelli RL, Guglielmo BJ, Kradjan WA, Williams BR, editors. Applied Therapeutics- The clinical use of Drugs. 9th ed. New York: Lippincott Williams & Wilkins; 2009: p. 3-1-3-42.
5. Katzung BG. Histamine, serotonin & ergot alkaloids. In: Katzung BG, Masters SB, Trevor AJ, editors. Basic and clinical pharmacology. 11th ed. New Delhi: Tata McGraw Hill Companies Inc.; 2009: p. 271-292.
6. Other transmitter and modulators. In: Rang HP, Dale MM, Ritter JM, Flower RJ, Henderson G. Rang and Dale's Pharmacology. 7th ed. New York: Elsevier Churchill Livingstone; 2012: p. 461-475.
7. Hardeland R. Neurobiology, Pathophysiology, and Treatment of Melatonin Deficiency and Dysfunction. The Scientific World Journal 2012:1-18
8. Sack RL, Auckley D, Auger RR, Carskadon MA, Wright Jr KP, et.al. Circadian Rhythm Sleep Disorders: Part I, Basic Principles, Shift Work and Jet Lag Disorders. SLEEP 2007; 30(11): 1460-83.

9. Gulyani S, Salas RE, Gamaldo CE. Sleep Medicine Pharmacotherapeutics overview-Today, Tomorrow, and the Future (Part 1: Insomnia and Circadian Rhythm Disorders) CHEST 2012; 142 (6): 1659 – 68.
10. Uchiyama M, Lockley SW. Non 24 -Hour Sleep Wake Syndrome in Sighted and Blind Patients. Sleep Med Clin 2009; 4(2): 195–211.
11. Boivin DB, James FO. Insomnia due to circadian rhythm disturbances. In: Szuba MP, Kloss JD, Dinges DF, editors. Insomnia – Principles and Management. Cambridge: Cambridge University Press; 2003: p. 155-195.
12. Tasimelteon Advisory Committee Meeting Briefing Materials. Vanda Pharmaceuticals Inc. 14 Nov. 2013. Available at www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittees/UCM374388.pdf [Last accessed on 16-5-14]
13. Okawa M, Uchiyama M. Circadian rhythm sleep disorders: Characteristics and entrainment pathology in delayed sleep phase and non-24 sleep–wake syndrome. Sleep Medicine Reviews 2007; 11: 485–496.
14. Czeisler CA, Winkelman JW, Richardson GS. Sleep Disorders. In: Longo DL, Fauci AS, Kasper DL, Hause SL, Jameson JL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. 18th Ed. New Delhi: The McGraw Hill Companies Inc.; 2012: p. 213-223.
15. Mendelson W. Sleep disorder. In: Sadok BJ, Sadok VA. Kaplan and Sadock's Comprehensive Textbook of Psychiatry. 8th ed. New York: Lippincott Williams and Wilkins; 2005: p. 2022 – 2034.
16. Nutt DJ. Psychotropic drugs. In: Bennett PN, Brown MJ, editors. Clinical Pharmacology. 10th ed. London: Elesvier Churchill Livingstone; 2008: p.330-371.
17. Hardeland R. New approaches in the management of insomnia: weighing the advantages of prolonged-release melatonin and synthetic melatoninergic agonists. Neuropsychiatric Disease and Treatment 2009; 5: 341–54.
18. Rajaratnam SMW, Polymeropoulos MH, Fisher DM, Roth T, Scott C, et.al. Melatonin agonist tasimelteon (VEC-162) for transient insomnia after sleep-time shift: two randomised controlled multicentre trials. Lancet 2009; 373: 482–91.
19. Rajaratnam SMW, Cohen DA, Rogers NL. Melatonin and Melatonin Analogues. Sleep Med Clin 2009; 4(2): 179–193.
20. Arendt J, Rajaratnam SMW. Melatonin and its agonists: An update. BJP 2008; 193: 267-269.

21. Tasimelteon. Drug Information Provided by Gold Standard. Available at https://www.clinicalkey.com [Last accessed on 20.5.14]
22. Choy M, Salbu RL. Jet Lag Current And Potential Therapies. Pharmacy & Therapeutics 2011; 36 (4): 221-224,231.
23. Adams KS, Crouse EBL. Melatonin Agonists in the Management of Sleep Disorders: A focus on Ramelteon and Tasimelteon. Ment Health Clin. 2014; 4(2):48.