SELECTIVE DUAL OREXIN RECEPTOR ANTAGONISTS (DORAS): THE NEW PARADIGM IN TREATING INSOMNIA

Dr Chandrasekhar Krishnamurti
M.D., Associate Professor (Anesthesiology), NRI Institute of Medical Sciences, Sangivalasa, Visakhapatnam 531162, A.P., India

INTRODUCTION

Sleep is a physiological state that has been shown to be necessary to maintain homeostasis, proper body functioning and mental health in humans. The control of sleep and wakefulness is a complex process involving the coordinated activity of numerous neuronal circuits within small group of hypothalamic neurons that synthesize and release orexins (also known as hypocretins). Orexin receptor antagonists (ORA) differ from benzodiazepines and non benzodiazepines in that they have no effect on GABA and, instead of promoting sleep, these drugs inactivate wakefulness. Thus the adverse effects commonly observed with benzodiazepines and non benzodiazepines are virtually eliminated and these drugs can be used daily on a long-term basis with no risk of rebound insomnia or physical dependence. ORA are associated with improved sleep induction and maintenance parameters without producing impairments in cognitive function as measured by digit symbol substitution test (DSST) and the revised short form of the Mini-Mental State Examination (MMSE).

OREXINS

Orexins were isolated in 1998 when it was observed that the orexin or hypocretin system were excitatory neuropeptides playing an important role in the sleep–wake cycle and critical to maintaining wakefulness.(1,2)

Fig 1. Projections of the hypocretin (orexin) system (A), to cholinergic neurons, reticular formation and spinal cord; (B), to thalamus and basal ganglia; (C), to basal forebrain; (D), to amygdala and dopaminergic neurons including substantia nigra; (E), to locus coeruleus

Fig 2. Dual Orexin receptors and their antagonist

Almorexant

Almorexant exhibits a dose-dependent increase in both rapid eye movement (REM) and non-REM (NREM) sleep and reduced wakefulness without residual or rebound sleep effects. It does not elicit cataplexy or other tolerability signals of concern in animal experiments. Almorexant increases sleep efficiency, reduces sleep latency, and increases total sleep time (TST) at doses greater than 200 mg in healthy volunteers. In Phase II proof-of-concept studies reduced latency to persistent sleep (LPS) and reduced wake after sleep onset (WASO) was observed at a 400-mg dose. During the course of Phase III RESTORAL1 study (2007-2009), human tolerability issues resulted in the termination of clinical development of the drug. (4,5)

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ABSTRACT

The control of sleep and wakefulness is a complex process involving the coordinated activity of numerous neuronal circuits within small group of hypothalamic neurons that synthesize and release orexins (also known as hypocretins). Orexin receptor antagonists (ORA) differ from benzodiazepines and non benzodiazepines in that they have no effect on GABA and, instead of promoting sleep, these drugs inactivate wakefulness. This results in improved sleep induction and maintenance parameters without producing impairments in cognitive function and other adverse effects permitting daily use on a long-term basis with no risk of rebound insomnia or physical dependence.

KEYWORDS

Selective dual orexin receptor antagonists, insomnia

REFERENCES

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Suvorexant

Suvorexant was the next dual orexin receptor antagonist (DORa) to be introduced and it has a unique clinical profile.

With a molecular formula C_{39}H_{44}ClNO_{3}F (Fig 1) and molecular weight of approximately 450,932 g/mol, suvorexant acts by binding inhibition of orexin A and B (OXIR and OXZR), neuropeptides. The drug has a favorable tolerability, limited side-effect profile low, potential for addiction or dependence, and safe in patients with moderate hepatic or renal dysfunction, a desirable finding in the elderly population. There is no evidence of rebound insomnia after a minimum of three months and a maximum of 12 months of its use. The recommended initial daily dose is 10 mg when onset of sleep occurs between 56 and 68 minutes after oral administration. Dose can be titrated to a maximum of 40 mg and escalation is advised only in those patients who can tolerate lower doses with no adverse effects. Median peak plasma concentrations occur approximately two hours after administration and is unaffected by food intake. Plasma concentrations are higher in obese women than in men with a normal body mass index (BMI). Suvorexant has a volume of distribution of 105.9 L, is highly protein bound (99.5%) and primarily metabolized by the cytochrome P450 (CYP3A4) enzyme system (with some contribution from CYP2C19) into M9, an inactive metabolite that is eliminated by the gut. There is no renal elimination. Half-life is 12 hours, and an increase in plasma concentrations up to 8–19 hours and steady-state plasma concentration occurs in about three days with daily administration. Potent CYP3A inhibitors such as fluconazole may increase plasma concentrations significantly while moderate inhibitors such as diltiazem can be used safely, especially in the elderly when lower doses (10 mg). CYP3A inducers, such as rifampin can result in significantly reduced suvorexant plasma concentrations.

Objective sleep laboratory polysomnography (PSG) data, providing for measures of sleep maintenance (wake after sleep onset [WASO]), sleep duration (total sleep time [TST]) and sleep onset (latency to persistent sleep [LPS]). Patients evaluated in the human trials met DSM-IV criteria for primary insomnia, and relatively free from co-morbidities (e.g. depression, pain), and otherwise generally healthy.

The 10 mg dose was the least consistently effective dose. Suvorexant was effective on all measures versus placebo both acutely, from the earliest time point assessed (Night 1 for objective measures, and Week 1 for subjective measures), and chronically with efficacy generally sustained over 3 months. While suvorexant reduced WASO, it did not appear to alter the number of awakenings during the night as assessed by PSG. It decreased the total number of awakenings with increased “long” awakenings (> 2 min), while slightly increasing the total number time spent in “short” awakenings (< 2 min). The reduction in long awakenings increased the odds of patient-reported good/excellent sleep quality twofold, while the increase in short awakenings had no effect on sleep quality, supporting the expectation that long awakenings are more impactful for patients with insomnia than short awakenings. On average, a patient returned to sleep from their longest awakening more than twice as fast on suvorexant than on placebo. Suvorexant effects on sleep onset and sleep maintenance were maintained consistently over 12 months, without evidence of tolerance to long-term nightly treatment. Incidence of sleep-related hallucinations was 0.4% and sleep parasomnia 0.2%. Both sleep-related hallucinations and sleep paralysis occur spontaneously in the general population, and hallucinations have been reported with other sleep-promoting medications like zolpidem. There are no reports of complex sleep behaviours like sleep walking and sleep eating. Suicidal ideation is infrequent but dose-related: 0.2% on suvorexant 20/15 mg and 0.5% on suvorexant 40/30 mg. Neither suvorexant 20/15 mg or 40/30 mg impaired next morning driving performances. While rebound insomnia is not an issue for the majority after discontinuing the drug, mild elevations in sleep disturbance can occur in some individuals for the first few nights.

Pharmacovigilance assessment of safety data in over 600,000 patients indicates that suvorexant's safety profile remains consistent. Abrupt discontinuation of the drug after chronic use does not result in rebound insomnia or withdrawal effects. There are no contraindications to the use of suvorexant and it can be used daily on a long-term basis with no risk of physical dependence. Suvorexant does not alter the underlying normal neurophysiology of during NREM and REM sleep evaluated using quantitative electroencephalography (qEEG) spectral analyses of the power in various frequency bands (e.g. in delta of ascending frequency, delta, theta, alpha, sigma, beta, gamma). (8, 9)

As the sleep profile changes with aging, the elderly have been shown to have more significant problems with sleep maintenance (disrupted sleep), and to shift to a pattern of earlier retiring and early morning awakenings with increased napping during the day. Age has no significant impact on suvorexant pharmacokinetics but dosing recommendations for the elderly are identical to those for the non-elderly (the recommended starting dose is 10 mg, which may be increased to a maximum of 20 mg).

Suvorexant is contraindicated in patients with narcolepsy as this condition is associated with a progressive degeneration of orexin neurons. Antagonism of orexin receptors can mimic signs or symptoms of narcolepsy, particularly cataplexy with sudden intrusion of rapid eye movement [REM] elements into the waking state associated with sudden loss of muscle tone.

CONCLUSION

Orexins have play a crucial role in sleep physiology and seem the correct target for novel therapies for insomnia. DORAs lack myorelaxation, have non-addictive properties and their beneficial effect on sleep architecture provides the orexin pathway can improve sleep onset and duration without major changes in the patient's neurophysiology as assessed by EEG.

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The most notable effects of suvorexant on sleep architecture are minimal mean increases in REM percentage. ORA would maintain sleep over the course of a night more effectively than a GABAergic drug. It is superior in maintaining sleep over the course of a night than inducing sleep onset, whereas the opposite (greater sleep onset than sleep maintenance effects) appears to be true for zolpidem.

Putative application of DORAs in the treatment of depression and migraine, diseases often accompanying insomnia, are also of potential interest. Suvorexant is a safe alternative for sustained benefits in the treatment of insomnia (difficulty with sleep onset or sleep maintenance) in adults 18 years of age and older. DORAs suppresses food intake and advances the onset of a normal satiety sequence. Orexin can generate weight loss by releasing excess energy as heat instead of storing it. Orexin deficiencies can cause obesity in both humans and animals, while high levels of orexin can guarantee a lean body mass.

This feature may make it a choice in treating binge eating, appetite disorders, obesity and diabetes management in the future.

REFERENCES