Suvorexant: A boon for Sleepless Nights

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ABSTRACT

Insomnia is characterized by difficulty in falling asleep, difficulty maintaining sleep, or experiencing nonrestorative sleep. Insomnia is the most common medical complaint in general practice. Low efficacy and various side effects limit the use of existing treatment option. Suvorexant is an orexin receptor antagonist (ORA), first in a new class of drugs in development for the treatment of insomnia. It inhibits the wakefulness-promoting orexin neurons of the arousal system thereby promoting the natural transition from wakefulness. It also improves sleep onset and sleep maintenance and has a favorable tolerability and limited side-effect profile.

Keywords: insomnia; orexin; suvorexant; sleep.

Introduction

Orexins are neuropeptides synthesized from hypothalamus. There are two types of orexins viz. orexin A and orexin B. Both are endogenous ligand for G-protein coupled receptors.[1]

Insomnia persistently affects the quality and quantity of sleep. Currently approved treatments for insomnia primarily target γ-aminobutyric acid-A (GABA-A) receptor signalling and include benzodiazepines and GABA-A receptor modulators.[2]These drugs are used to address this sleep disorder, but have the potential for side effects such as tolerance and dependence, making them less attractive as maintenance therapy. [1, 2]Forward and reverse genetic approaches in animals have implicated orexin signalling (also referred to as hypocretin signalling) in the control of vigilance and sleep/wake states. Screening for orexin receptor antagonists using in vitro and in vivo methods in animals has identified compounds that block one or other of the orexin receptors viz. single orexin receptor antagonists (SORAs) or dual orexin receptor antagonists (DORAs]) respectively. SORAs have primarily been used as probes to further elucidate the roles of the individual orexin receptors, while a number of DORAs have progressed to clinical development as pharmaceutical candidates for insomnia[2,3]. The DORA, almorexant demonstrated significant improvements in a number of clinically relevant sleep parameters in animal models and in patients with insomnia but its development was halted[4-6]. Orexin receptor antagonists potentially represent a targeted, effective and well-tolerated new class of medications for insomnia.

Suvorexant is an orexin receptor antagonist. The orexin or hypocretins neuropeptide signalling system is a central promoter of wakefulness[1,3]. Inhibition of orexin receptors is thought to suppress wake drive[4]. FDA announced the approval of suvorexant on August 13, 2014, for the treatment of insomnia[7].

Mechanism of action

Suvorexant is a potent dual orexin receptor antagonist that blocks both orexin receptor-1 and orexin receptor-2. It promotes sleep through inhibition of orexin A and B, neuropeptides that promote wakefulness[2,4,5].

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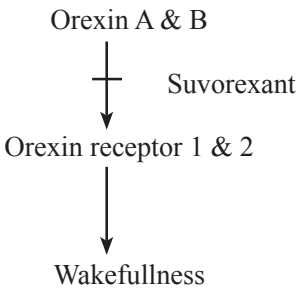

Figure 1: Mechanism of action of suvorexant

Pharmacokinetics

The onset of action is rapid (56-68 min) with median peak plasma concentrations occur approximately 2 hours after oral administration and are not affected by food. It has volume of distribution of 105.9 L and is highly protein bound (99.5 %). It is primarily metabolized by cytochrome P450 (CYP3A4) enzyme system. It is eliminated primarily via inactive metabolites in the feces. The half-life is approximately 12.2 hours. Steady state plasma concentrations occur in about three days with daily administration[7,8].

Clinical efficacy

The safety and efficacy of suvorexant were based on clinical trials involving more than 500 participants. In the studies, patients taking suvorexant fell asleep faster and spent less time awake during the remainder of the night compared to the patients taking placebo[4,9]. In a randomized, double-blind, placebo controlled trial of suvorexant ranging from 10 to 100 mg involving 22 healthy young males, there was significant changes in both latency to persistent sleep and waking after sleep onset as well as corresponding increase in sleep efficiency and choice reaction time[5].

In another randomized double blind placebo controlled multicentric trial, suvorexant was found to improved sleep efficacy over four weeks in non elderly adults with primary insomnia, efficacy was assessed primarily via polysomnography (PSG) measurements along with morning and evening questionnaires, administered via an electronic patient diary to record patient's self-assessments of sleep[2].

Precautions & Contraindication

There is no such contraindication to the use of suvorexant although not to be used in narcolepsy and compromised respiratory function[7,8]. Precautions should be taken in conditions like abnormal thinking and behavioral changes, depression, hallucinations and sleep paralysis[8]. There is risk of impaired alertness and motor coordination, including impaired driving[10-12].

Adverse effects

The most frequent adverse effects are somnolence (>5%), drowsiness and fatigue. Other occasional adverse effects are dizziness, headache, elevated aminotransferase levels, upper respiratory tract infection, etc[7,12,13].

Dosing

Recommended dose is 10 mg per oral once daily at bed time within 30 minutes of going to bed with at least 7 hours remaining before the planned time of awakening. Dose can be increased maximum upto 20 mg once daily[7,12].

Drug interactions

Potent CYP3A inhibitors such as fluconazole increase plasma concentrations of suvorexant. CYP3A inducers such as rifampin result in significantly reduced suvorexant plasma concentrations. Suvorexant is a mild inhibitor of CYP3A, but when administered with CYP3A substrates, including oral contraceptives and warfarin, it had minimal effects[8,12,14].

CONCLUSION

Suvorexant is an effective orexin receptor antagonist with a unique clinical profile and the first in a new class of drugs in development for the treatment of insomnia. Though benzodiazepines and non-benzodiazepines are effective for insomnia, their adverse-effect profiles and recommended limitations on long-term use called for other options. Patients who experience both sleep onset and sleep maintenance insomnia may be particularly challenging to treat. The recent approval of orexin antagonist has led to the new era in the treatment of insomnia.

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