Pitolisant for Narcolepsy

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INTRODUCTION

Narcolepsy is a rare, lifelong neurologic disorder for which currently no cure is available. It is a sleep disorder characterized by excessive daytime sleepiness (EDS) and abnormal REM Sleep manifestations. It affects approximately 0.026-0.05% of population in North America and Europe.[1] Adolescents and Young Adults are mainly affected. At present pharmacotherapy to treat the condition properly remains inadequate.

International classification of sleep disorders classifies narcolepsy into Type1 and Type2 (NT1 & NT2).[2] NT1 is characterized by presentation of cataplexy and CSF orexin deficiency. Autoimmune hypothesis suggests that histamine compensates for the orexin deficiency by increasing number of histaminergic neurons. Orexin is found to be a sleep-wake state stability supporting neuropeptide. NT2 patients don't have cataplexy and don't show CSF orexin deficiency.

Histamine 3 (H3) receptor is almost exclusively distributed in nervous system, located in brain primarily in cerebral cortex, hypothalamus, hippocampus and basal Ganglia. It functions as an auto- and hetero- receptor. Experimental and clinical demonstration of H3 receptor was first done by Arrang et al in 1983 and 1987 respectively.[3] H3 receptor was first cloned by Lovenberg in 1999. Histaminergic neurons are involved in a large number of functions including wakefulness, attention and memory.

Current therapy of narcolepsy produces only partial relief of symptoms. First line agents are sodium oxybate, modafinil and its R-enantiomer armodafinil. Second line agents include SNRIs, SSRIs, TCAs, MAO-B inhibitors etc.

PITOLISANT

Pitolisant was recently approved (FDA approval date, 14th August 2019) for treating Excessive Daytime Sleepliness (EDS) in narcolepsy as Tablet Wakix (4.5 mg and 18 mg). It has been granted orphan drug designation for treatment of narcolepsy by US-FDA and EMA.

Pitolisant is first in class drug, acting on H3 receptor, as a competitive antagonist

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/ inverse agonist[4], increasing synthesis and release of histamine over basal level. Mechanism of action of Pitolisant is not fully clear. Likely mechanism has been suggested by studies in narcoleptic orexin knockout mice. It seems to act mainly at presynaptic level through activation of histaminergic neurons in brain which also increases the levels of other neurotransmitters in brain mainly noradrenaline, dopamine and acetylcholine, ultimately resulting in increased wakefulness and increased REM sleep latency.

CHEMICAL NATURE

It is 1,3,3,4-chlorophenyl, propoxy propyl piperidine hydrochloride, a non- chiral molecule so doesn't exhibit stereoisomerism. It is a white crystalline powder, highly soluble in water, methylene chloride and ethanol but insoluble in chlorhexane.

PHARMACOLOGICAL PROFILE

It is absorbed rapidly from gastrointestinal tract. Peak plasma concentration is attained in approximately 3 hours. It is highly serum protein bound (91 - 96%), evenly distributed between plasma and RBC. It is eliminated mainly via urine (63%). Plasma t1/2 of pitolisant is10-12 hours. Steady state plasma concentration is attained in 5-6 days. It crosses blood-brain barrier, placenta and enters milk. It is metabolized by glycine conjugation into inactive metabolite which gets excreted in urine. Metabolism is mediated by CYP3A4 and CYP2D6.[5] Pharmacokinetic parameters in elderly do not differ significantly from that in young subjects. Pitolisant is an inducer of CYP3A4, CYP2B6, and CYP1A2 while inhibitor of CYP2D6 & OCT1 (as evidenced by in-vitro studies). Concomitant use with strong CYP3A4 inducers decreases pitolisant exposure by 50%. In moderate hepatic impairment, plasma t½ approximately doubles & AUC increases by a factor of 2.4. In renal impairment t½ remains unaltered while Cmax & AUC increases.

Most common adverse effects are neuropsychiatric manifestations. Common adverse effects are insomnia (6%), nausea (6%), and anxiety (5%). Others are mild headache, depression, irritability, dizziness, hallucination, vertigo, weight gain, decreased appetite, diarrhoea, leg pain, apathy, sweating and malaise. Body weight needs to be closely monitored. There are no withdrawal symptoms / syndromes. Abuse potential, although not found in animal studies, can't be excluded. The drug is not recommended in severe liver or renal impairment.

Pitolisant prolongs QTc and has arrhythmogenic potential, so it should not be used in patients prone to arrhythmia or with drugs known to prolong QTc. Pregnant patients or those planning to be pregnant receiving have to be registered for being monitored. A recent report by EMA advised cautious use in subjects with psychiatric disorders and suicidal ideation. Since H3 is involved in enhancement of memory, there is chance of diversion of its use as a substance to improve intellectual performance.

Safety and efficacy have not been evaluated in patients under 18 years of age and in pregnancy.

CLINICAL STUDIES

Pitolisant FDA approval was based on two, multicentered, double blind, randomized placebo controlled studies in patients ≥ 18 years of age, who met ICDS criteria for narcolepsy with Epworth Sleepiness Score (ESS) scale ≥ 14.6 Studies had eight weeks treatment period; 3 weeks dose titration period (dose started at 9mg/day, increased to 18 mg per day and then to 36 mg per day or decreased to 4.5 mg per day, followed by 5 week stable dose period). Harmony[1] trial had 95 patients with median age 37 years and Harmony 1bis had 166 patients with median age 40 years. Both studies were placebo and active controlled comparative studies.

CONCLUSION

Pitolisant is the first and only treatment approved for patients with narcolepsy that is not scheduled as a controlled substance by US-DEA. This promising molecule may prove beneficial in future in sleep apnoea related to EDS. Other possible future uses may be in parkinson's disease, alzheimer's disease, attention deficit hyperkinetic disorder, schizophrenia, epilepsy, depression etc.

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