Education forum

New ray of hope for psychosis in parkinson's: Pimavanserin

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ABSTRACT

Parkinson's disease is often associated with hallucinations and psychosis. Till now typical and atypical antipsychotics (Clozapine & Quetiapine) are being used to manage these symptoms. Recently US FDA has approved a new drug Pimavanserin for the treatment of hallucination and delusion associated with parkinson's disease psychosis in a dose of 34 mg.

Keywords: *Hallucinations, delusions, psychosis, parkinsonism, pimavanserin*

Introduction

Parkinson's disease is often associated with hallucinations and psychosis. Typical and atypical antipsychotics are used to address hallucinations. Typical antipsychotics are classical dopamine blocking drugs which leads to dramatic worsening of parkinsonian motor symptoms so atypical antipsychotics are better choice for treatment of psychosis in parkinsonian disease. Clozapine is the most effective drug but it is associated with agranulocytosis hence regular blood monitoring becomes essential. [1] For this reason quetiapine is the preferred drug however its efficacy has not been established in placebo control trials. Recently US FDA has approved a new drug Pimavanserin for the treatment of hallucination and delusion associated with parkinson's disease psychosis.

Pharmacodynamics

Pimavanserin is a non dopaminergic atypical antipsychotic whose effect is mediated through combination of inverse agonist and antagonist activity at 5HT2A receptors and to lesser extent at 5HT2C receptors. It shows low binding to sigma 1 receptors and negligible affinity to 5HT2B, D2, muscarinic, histaminergic or adrenergic receptors, or to calcium channels.

Pharmacokinetics[2]

The pharmacokinetics of pimavanserin is similar in both the study population and healthy subjects. The mean plasma half life of pimavanserin is 57 hours and its active metabolite N-desmethylated metabolite AC-279 shows mean plasma half life of 200 hrs. The median Tmax of pimavanserin is 6 hrs (range 4-24) and generally unaffected by dose. It is highly protein bound (95%) in human plasma. PPB is dose independent and does not change significantly over dosing time from day 1 to day 14. The mean apparent volume of distribution is 2173 litre following administration of single dose of

34mg. It is predominantly metabolised by CYP3A4 to active metabolite AC-279. CYP3A5 and to lesser extent CYP2J2, CYP2D6, and FMO enzymes are also responsible for its metabolism. Approximately 0.55% is eliminated as unchanged drug in urine and 1.53% in feces after 10 days. Age, sex, ethnicity and weight do not have clinically relevant effect on the pharmacokinetics of pimavanserin. It has not been studied in patients with severe renal impairment or mild to severe hepatic impairment. Recommended dose of Pimavanserin is 34 mg, taken orally as two 17 mg tablets once daily with or without food.

Adverse reactions [3]

Nausea, constipation, Peripheral edema and confusional states are the most common adverse effects observed. Occurrence of hallucination, urinary tract infection and fatigue may lead to discontinuation of treatment.

Drug drug interactions

Pimavanserin does not require dosage adjustment along with carbidopa and levodopa. It prolong the QT interval so should not be given with drugs which prolong QT interval. Class 1A antiarrhythmics like quinidine, procainamide, disopyramide; class 3 antiarrhythmics like amiodarone, sotalol; antipsychotics like ziprasidone, chlorpromazine, thioridazine and antibiotics like gatifloxacin, moxifloxacin results in prologation of QT interval and increases the risk of cardiac arrhythmia. Strong CYP3A4 enzyme inducers and inhibitors may alter the levels of pimavanserin.

No teratogenic affect has been observed when given during period of organogenesis in rats but during pregnancy & lactation it causes maternal toxicity, weight reduction, dehydration, hunched posture, rales & reduced pup survival, pup weight, food consumption. No effect on sexual maturation, reproduction, learning & memory has been seen. Abortions were noted in pregnant rabbits.

No data available regarding presence of drug in human milk. Risk benefit ratio should be kept in mind while using the drug. Paediatric safety has not been documented. It can be used in elderly without dose alteration. It is contraindicated in patients of hepatic disease & severe renal impairment.

Clinical Studies [3]

The efficacy of Pimavanserin 34 mg was demonstrated in a 6 week, randomised, placebo controlled, parallel group study. In this study, total 199 patients were randomised in a 1:1 ratio Pimavanserin 34 mg or placebo once daily. Study patients (male or female and aged 40 years or older) had a diagnosis of Parkinson's disease (PD) established at least 1 year prior to study entry and had psychotic symptoms (hallucinations and/or delusions) that started after the diagnosis and that were severe and frequent enough to warrant treatment with an antipsychotic. At entry, patients were required to have a Mini-Mental State Examination (MMSE) score ≥21 and ability to self report the symptoms. The majority of patients were on Parkinson's disease medications at entry. These medications were required to be stable for at least 30 days prior to study and throughout the study period. The PD adapted scale for assessment of Positive Symptoms (SAPS-PD) was used to evaluate the efficacy of Pimavanserin 34 mg. Primary efficacy was evaluated based on change from baseline to week 6 in SAPS-PD total score. Pimavanserin (n=95) was statistically superior to placebo in decreasing the frequency and/or severity of

hallucinations and delusions in patients with PD psychosis as measured by central, independant and blinded raters using SPS-PD scale. Effect was seen on both hallucinations and delusions components of SAPS-PD. Pimavanserin did not show effect on motor function compared to placebo as assessed using Unified Parkinson's Disease Rating scale.

Conclusion

Pimavanserin in a dose of 34 mg is the first USFDA approved drug for treatment of hallucinations and delusions associated with Parkinson's disease psychosis. It is not approved for the treatment of patients with dementia related psychosis unrelated to hallucinations and delusions associated with Parkinson's disease. Most common adverse effects reported are peripheral edema and confusional state. When given along with CYP3A4 inducers or inhibitors its dose need to be modified. Since Pimavanserin is a recently launched drug, its pharmacovigilance becomes more important to know about any undocumented adverse effects.

Reference

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