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Review

Neuropharmacology of Levetiracetam as Anti-epileptic Medication

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ABSTRACT

United state food and drug administration approved Levetiracetam on 30th November 1999 for the use as adjuanctive therapy in the treatment of partial onset seizures in adults with epilepsy. Therapeutic indications of Levetiracetam includes monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy. Levetiracetam is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month of age with epilepsy, in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy, in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy. This article describes the pharmacological aspects of Levetiracetam that will helful to health professionals.

INTRODUCTION

Epilepsy is the fourth-leading neurological disease in the world affecting around 50 million in the world. The annual incidence of epilepsy is about 80 cases per 100,000 individuals.[1,2] The International League Against Epilepsy has classified epilepsy as focal, generalized, combined, and unknown. Focal epilepsy, the most common type occurs within the area limited to a single hemisphere.[3] The main target of antiseizure medications treatment is to achieve complete seizure freedom without inducing adverse events, to decrease mortality and morbidity, and to improve the patient's quality of life.[4]

Pharmacology

Levetiracetam is the commonly used antiseizure medication for focal epilepsy.[5] Levetiracetam is an (*S*)-enantiomer of the ethyl analog of piracetam, in the class of nootropic drugs which are considered to be pharmacologically safe. It is structurally unrelated to any other antiepileptic class and has a novel mechanism of action. Although the precise mechanism is unknown, in animal models it has been shown to bind to synaptic vesicle protein SV2A.

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This protein has been related to the modulation of synaptic vesicle exocytosis and neurotransmitter release. Animal models show that the affinity for SV2A is associated with protection against seizures making it an important target for new antiepileptic drugs. *In vitro* studies demonstrated oppositional activity to negative modulators of gamma-aminobutyric acid (GABA)-gated currents despite lack of binding affinity to GABA receptors.[6-13]

The pharmacological activity of levetiracetam was evaluated in mice, rats, hamsters, guinea pigs and dogs. These studies revealed that levetiracetam displayed protection in various animal models of chronic epilepsy reflecting both partial and primary generalized seizures. There was no anticonvulsant activity in two screening tests for antiepileptic drugs (AEDs), the maximal electroshock (MES) test and the maximal pentylenetetrazol (PTZ) test. Levetiracetam lacked anticonvulsant action against seizures induced by maximal stimulation with different chemoconvulsants and showed minor anticonvulsant action with submaximal stimulation and also in threshold tests, one exception being the protection observed against seizures induced by pilocarpine and kainic acid. There was no rebound effect upon withdrawal of treatment with levetiracetam. Levetiracetam has anxiolytic properties and does not negatively impact cognitive function in mice and rats.[14]

In vitro experiments, including ligand binding assays, have shown that the mode of action of levetiracetam is not due to any interaction with mechanisms of inhibitory and excitatory neurotransmission. Up to 1700ug/mL, levetiracetam did not result in significant ligand displacement at known receptor binding sites. Glutamate receptor-mediated neurotransmission, second messenger systems, muscimol-induced chloride flux, ion channel proteins, gamma butyric acid-transaminase, and glutamate decarboxylase activities were unaffected by levetiracetam. A stereoselective binding site for the drug has been demonstrated in synaptic membranes from the CNS and not in peripheral tissue. Benzodiazepine receptor antagonists had no effect on levetiracetam protection against seizures.[14]

Dosage

Levetiracetam is approved for partial seizures. The parenteral form is approved as an alternative for the treatment of partial seizures if oral form is not feasible. Dosage and directions: PO/IV-Adjunctive therapy for partial seizures, the initial dose is 500 mg twice daily with gradual upward titration to a maximum of 3 g/day. The dose is the same for monotherapy and for partial seizures with and without secondary generation. Minimum: 500 mg twice daily, Maximum: 3 g daily.[6,14]

Pharmacokinetics

The pharmacokinetics of levetiracetam have been studied in healthy adult subjects, adults and pediatric patients with epilepsy, elderly subjects, and subjects with renal and hepatic impairment. Levetiracetam is rapidly and almost completely absorbed after oral administration. The pharmacokinetics are linear and time-invariant, with low intra- and inter-subject variability. The extent of bioavailability of levetiracetam is not affected by food. Levetiracetam is not protein-bound (<10% bound) and its volume of distribution is close to the volume of intracellular and extracellular water. Sixty-six percent (66%) of the dose is renally excreted unchanged. The major metabolic pathway of levetiracetam (24% of dose) is an enzymatic hydrolysis of the acetamide group. It is not liver cytochrome P450 dependent. The metabolites have no known pharmacological activity and are renally excreted. The plasma half-life of levetiracetam across studies is approximately 6-8 hours. It is increased in the elderly (primarily due to impaired renal clearance) and subjects with renal impairment.[14-16]

Special Populations

Elderly

Pharmacokinetics of levetiracetam were evaluated in 16 elderly subjects (age 61-88 years) with creatinine clearance ranging from 30 to 74 ml/min. Following oral administration of twice-daily dosing for 10 days, total body clearance decreased by 38% and the half-life was 2.5 hours longer in the elderly compared to healthy adults. This is most likely due to the decrease in renal function in these subjects.[14,17]

Pediatric Patients

The pharmacokine of levetiracetam was evaluated in 24 pediatric patients (age 6-12 years) after a single dose (20 mg/kg). The apparent clearance of levetiracetam was approximately 40% higher than in adults.[14,17]

Gender

Levetiracetam Cmax and AUC were 20% higher in women (N=11) compared to men (N=12). However, clearances adjusted for body weight were comparable.[14,17]

Race

Formal pharmacokinetic studies of the effects of race have not been conducted. Cross-study comparisons involving Caucasians (N=12) and Asians (N=12), however, show that pharmacokinetics of levetiracetam were comparable between the two races. Because levetiracetam is primarily really excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.[14,17]

Renal Impairment

The disposition of levetiracetam was studied in subjects with varying degrees of renal function. Total body clearance of levetiracetam is reduced in patients with impaired renal function by 40% in the mild group (CLcr = 50-80 mL/min), 50% in the moderate group (CLcr = 30-50 mL/min), and 60% in the severe renal impairment group CLcr <30 mL/min). Clearance of levetiracetam is correlated with creatinine clearance. In auric (end-stage renal disease patients, the total body clearance decreased by 70% compared to normal subjects CLcr >80mL/min). Approximately 50% of the pool of levetiracetam in the body is removed during a standard 4-hour hemodialysis procedure. Dosage should be reduced in patients with impaired renal function receiving levetiracetam, and supplemental doses should be given to patients after dialysis.[14,17]

Hepatic Impairment

In subjects with mild to moderate hepatic impairment, the pharmacokinetics of levetiracetam were unchanged. In patients with severe hepatic impairment, total body clearance was 50% that of normal subjects but decreased renal clearance accounted for most of the decrease. No dose adjustment is needed for patients with hepatic impairment.[14,17]

Contraindications

This product should not be administered to patients who have previously exhibited hypersensitivity to levetiracetam.[14]

Warnings

Neuropsychiatric Adverse Events

Levetiracetam use is associated with the occurrence of central nervous system adverse events that can be classified into the following categories: 1) somnolence and fatigue, 2) coordination difficulties, and 3) behavioral abnormalities. Somnolence, asthenia and coordination difficulties occurred most frequently within the first four weeks of treatment.[14]

Precautions

Hematologic Abnormalities

Minor, but statistically significant, decreases compared to placebo in total mean RBC count (0.03 x $10^6/mm^2$), mean hemoglobin (0.09 g/dL), and mean hematocrit (0.38%), were seen in levetiracetam-treated patients in controlled trials. A total of 3.2% of treated and 1.8% of placebo patients had at least one possibly significant (≤ 2.8 x 10^9/L) decreased WBC, and 2.4% of treated and 1.4% of placebo patients had at least one possibly significant (≤ 1.0 × 10^9/L) decreased neutrophil count. Of the treated patients with a low neutrophil count, all but one rose towards or to baseline with continued treatment. No patient was discontinued secondary to low neutrophil counts.[14]

Hepatic Abnormalities

There were no meaningful changes in mean liver function tests (LFT) in controlled trials; lesser LFT abnormalities were similar in drug and placebo-treated patients in controlled trials (1.4%). No patients were discontinued from controlled trials for LFT abnormalities except for 1 (0.07%) epilepsy patient receiving open treatment.[14]

Drug Interactions

Drug-Drug Interactions between Levetiracetam and Existing Antiepileptic Drugs (AEDs)

Potential drug interactions between levetiracetam a and existing AEDs (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin, and primidone) were assessed by evaluating the serum concentrations of levetiracetam and these AEDs during placebo-controlled clinical studies. These data indicate that levetiracetam does not influence the plasma concentration of existing ADs and that these ADs do not influence the pharmacokinetics of levetiracetam.[14]

Oral Contraceptives

Levetiracetam (500 mg twice daily) did not influence the pharmacokinetics of an oral contraceptive containing 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel, or of the luteinizing hormone and progesterone levels, indicating that impairment of contraceptive efficacy is unlikely. Coadministration of this oral contraceptive did not influence the pharmacokinetics of levetiracetam.[14,18]

Digoxin

Levetiracetam (1000 mg twice daily) did not influence the pharmacodynamics (ECG) of digoxin given as a 0.25 mg pharmacokinetics and dose every day. Coadministration of digoxin did not influence the pharmacokinetics of levetiracetam.[14]

Warfarin

Levetiracetam (1000 mg twice daily) did not influence the pharmacokinetics of R and S warfarin.

Prothrombin time was not affected by levetiracetam. Coadministration of warfarin did not affect the pharmacokinetics of levetiracetam.[14]

Probenecid

Probenecid, a renal tubular secretion blocking agent, administered at a dose of 500 mg four times a day, did not change the pharmacokinetics of levetiracetam 1000 mg twice daily. C^{SS} max of the metabolite, ucb L057, was approximately doubled in the presence of probenecid while the fraction of drug excreted unchanged in the urine remained the same. Renal clearance of ucb L057 in the presence of probenecid decreased 60%, probably related to competitive inhibition of tubular secretion of ucb L057. The effect of levetiracetam on probenecid was not studied.[14]

Pregnancy & Lacatation

Tomson and colleagues studied the pharmacokinetics of levetiracetam during pregnancy, delivery, lactation, and the neonatal period. There observations suggest considerable transplacental transport of levetiracetam and fairly slow elimination in the neonate. Plasma concentrations of levetiracetam in nursed infants are low despite an extensive transfer of levetiracetam into breast milk. Pregnancy appears to enhance the elimination of levetiracetam resulting in marked decline in plasma concentration, which suggests that therapeutic monitoring may be of value.[19] Johannessen and collegues studied the levetiracetam concentrations in serum and in breast milk at birth and during lactation. There data indicate an extensive transfer of levetiracetam from mother to fetus and into breast milk. However, breast-fed infants had very low levetiracetam serum concentrations, suggesting a rapid elimination of levetiracetam.[20]

CONCLUSION

Levetiracetam is an antiepileptic drug marketed since 2000. Its novel mechanism of action is modulation of synaptic neurotransmitter release through binding to the synaptic vesicle protein SV2A in the brain. Its pharmacokinetic advantages include rapid and almost complete absorption, minimal insignificant binding to plasma protein, absence of enzyme induction, absence of interactions with other drugs, and partial metabolism outside the liver.

It is approved as adjunctive therapy for partial-onset seizures both in adults and children 1 month and older. The metabolism of levetiracetam has no effect on the cytochrome P450 enzyme system so it is favorable in terms of no drug-drug interactions. No dose adjustment is needed in hepatic impairment but dose needs to be adjusted in patients with renal impaired. The drug seems to be well-tolerated in pregnancy and teratogenic potential is less than first generation anti-epileptics. The anticonvulsant levels seem to decline toward the latter part of pregnancy requiring close monitoring of the drug levels. The intravenous formulation is approved for patients 16 years or older if oral administration of the drug is not feasible.

It has been demonstrated effective as adjunctive therapy for refractory partial-onset seizures, primary generalized tonic-clonic seizures, and myoclonic seizures of juvenile myoclonic epilepsy. Its main adverse effects in randomized adjunctive trials in adults have been somnolence, asthenia, infection, and dizziness. In children, the behavioral adverse effects of hostility and nervousness were also noted. Levetiracetam is an important addition to the treatment of epilepsy. We believe that there is a need for larger, prospective, multicenter, randomized double comparative blind trials in order to further clarify the role of this anticonvulsant in acute seizure management.

Conflict of Interest

The authors declare that there are no conflicts of interest relevant to this article.

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