PERSPECTIVES OF LOSIGAMONE IN EPILEPSY TREATMENT

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Patients with drug resistant epilepsy represent about 40% of the whole population of epileptic patients. These patients require more than one antiepileptic drug. In animal models of epilepsy, it is possible to determine which combinations produce supra-additive anticonvulsive effects with minimal or even no adverse reactions. The experimental data can be helpful for predicting effective drug combinations in patients with refractory epilepsy. Losigamone is a new antiepileptic drug with an unknown mechanism of action. The drug belongs to the group of β-methoxy-butenolides, and exists as a racemic mixture of two enantiomers (AO-242 and AO-294). The drug is eliminated by oxidation. Cytochrome CYP2A6 appears to be the main isoenzyme responsible for the metabolism of losigamone. In vitro, losigamone exerts anti-convulsant activity in the picrotoxin model in CA1 and CA3 hippocampal areas, the low Ca²⁺ model in CA1 area and the low Mg²⁺ model in the entorhinal cortex and hippocampus. In vivo, the drug exhibits significant efficacy against maximal electroshock-induced seizures in rodents and pentetrazole-induced clonic convulsions in mice. Potency of losigamone varies with the respective seizure test, animal species used in experiments and route of drug administration. Toxicity studies do not indicate any teratogenic risk of the drug, at least in animals. In clinical trial, losigamone proved to have satisfactory effectiveness and good tolerance in the treatment of partial and secondary generalized seizures. The enantiomer AO-242 seems to be more potent than AO-294 or racemate.

Key words: losigamone, antiepileptic drugs, refractory epilepsy, experimental models of epilepsy