Drug Review

Opipramol: A Novel Drug

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Introduction

Opipramol is an iminostilbene derivative and belongs to the dibenzazepine group developed by Schindler and Blattner in 1961. Due to the similarity of the basic tricyclic structure and certain similarities in the pharmacological profile, opipramol initially expected to be tricyclic antidepressants. Although it is structurally very similar to imipramine, it does not represent a tricyclic antidepressant drug as it does not inhibit the neuronal uptake of norepinephrine and/or serotonin. It was reported to be a rather potent sigma ligand with high affinity to sigma 1 and lower affinity to sigma 2 sites with pronounced D2-, 5-HT2-, and H1-blocking potential. So opipramol is an atypical anxiolytic and antidepressive drug. It is a psychotropica drug commonly used for therapy of somatoform disorders, general anxiety disorders, anxious-depressive states.

Mechanism of action

Opipramol acts as a high affinity sigma receptor agonist, primarily at the σ₁ subtype, but also at the σ₂ subtype with somewhat lower affinity. Sigma receptors are known to be a unique set of proteins located in the endoplasmic reticulum of many tissues. In the endoplasmic reticulum, δ receptors play a key role in potentiating intracellular calcium mobilization, acting as a sensor/modulator of calcium signaling. Occupancy of σ₁ receptors by agonists causes translocation of the receptor from endoplasmic reticulum to the peripheral areas (membranes) of the neurons, where σ₁ receptors may regulate ion channels, neurotransmitter receptors and neurotransmitter release, including that of dopamine, serotonin, norepinephrine, glutamate, acetylcholine. It is this property which is responsible for opipramol’s therapeutic benefits against anxiety and depression. The action of opipramol is said to be biphasic in that initially there is prompt improvement of tension, anxiety and insomnia noticeable early in treatment followed by a gradual elevation of mood. Opipramol is, therefore, a tranquillizer with a thymoleptic component. After subchronic treatment, opipramol significantly down-regulated σ₂ but not σ₁ sites. Opipramol also acts as a low to moderate affinity antagonist for the D₂, 5-HT₂, H₁, H₂, and muscarinic acetylcholine receptors. H₁ and H₂ receptor antagonism account for its antihistamine effects, and muscarinic acetylcholine receptor antagonism is responsible for its anticholinergic properties.

Pharmacokinetics

Opipramol is completely and quickly absorbed from the gastrointestinal tract. Its terminal plasma half-life is 6-1 1 hours. After single oral administration of 50 mg the maximum plasma concentration of opipramol is reached after 3.3 hours and amounts to 15.6 ng/ml. After single oral administration of 100 mg the maximum plasma concentration of opipramol is reached after 3 hours and amounts to 33.2 ng/ml. The bioavailability of opipramol amounts to 94%. The plasma protein binding amounts to approximately 91% and, the volume of distribution is approximately 10 L/kg.

Opipramol is partially metabolized in the liver to deshydroxy ethyl- opipramol. It is metabolized mainly through the CYP2D6 isoenzyme.

It is eliminated over 70% renally and 10% in unaltered form. The remaining portion is eliminated through faeces.
Clinical results

The well-tolerated anxiolytic opipramol is the first psychotropic drug with proven efficacy in somatoform disorders with effects on symptoms of somatization, anxiety, and depression. The compound is also effective and safe in GAD.

A multicentric, randomized, 6-week, placebo-controlled clinical trial was performed in a total of 200 patients suffering from somatoform disorders according to ICD-10. In the main outcome criterion, the somatic subscore of the Hamilton Anxiety Scale, and in nearly all other outcome criteria opipramol (200 mg/day) was statistically more effective than placebo. A similar number of adverse events were noted in both groups. The results of this first-placebo-controlled study in somatoform disorders suggest efficacy of opipramol in this.

Freyberger et al. examined opipramol in real world situation in an 8 week observational study carried out on 1324 patients who were diagnosed as suffering from somatoform disorder according to ICD-10. Opipramol was administered at least 50 mg/ day to maximum 300 mg/ day. Success of treatment was registered with 85% of the patients. This real world study in 1324 patients shows that opipramol is effective in treatment of somatoform disorder.

In a 4 week, multicentric, randomized, double-blind, placebo-controlled study, Moller HJ et al., examined opipramol in patients with generalized anxiety disorder (ICD-10). The patients who fulfilled the inclusion criteria were randomly assigned to the placebo, the opipramol or the alprazolam group. There was significantly greater reduction in total anxiety score (HAM-A) in opipramol (p < 0.02) and alprazolam (p < 0.004) group as compared to placebo. So opipramol is superior to placebo in the treatment of GAD and equiefficacious to alprazolam in the treatment of GAD. Since opipramol exhibits no dependence or misuse-potential in contrast to alprazolam and other benzodiazepines, it is very well usable for a long term treatment, which is mostly necessary in the therapy of GAD.

In 6 week double-blind, randomized, comparative trial, Tetreault et al., studied the action of opipramol and imipramine with relation in to the placebo and compared the action of two drugs in treatment of neurotic depression. Results of this study showed that opipramol and imipramine are superior to placebo in treatment of neurotic depression. Opipramol has a more rapid onset of action than imipramine.

Indications

Opipramol is typically used in the treatment of somatoform disorders and generalized anxiety disorder (GAD).

Dosage and administration

The usual recommended dose of opipramol for adults is 50 mg in morning, 50 mg in the afternoon and 100 mg in the evening. The dose can be reduced to 50-100 mg daily (preferably in the evening) or increased up to 100 mg 3 times daily depending on its efficacy and tolerability. It can be administered before or after meals. In children and adolescents effectiveness of opipramol is not proven. So its use is not recommended in children and adolescents up to 17 years. No adequate data is available regarding use of opipramol during pregnancy. It should be prescribed during pregnancy, particularly in the first trimester, only if absolutely necessary. It should not be used during lactation period, since it is secreted in small quantities into mother’s milk. A reduction in the dose of opipramol is necessary for patients with impaired renal function as 70% of drug is excreted through kidney.

Adverse reactions

Opipramol is a well-tolerated drug. Opipramol produces less side effects as compared to SSRIs and SNRIs. Commonly reported side effects with opipramol at the beginning of treatment include fatigue, dry mouth, blocked nose, hypotension and orthostatic dysregulation. Occasionally reported side effects are dizziness, tachycardia, palpitation, tremor, weight gain, abnormal ejaculation, impotence, constipation, skin rash, urticaria. Very rare side effects (< 0.01%) include seizure, motor disorders (akathisia, dyskinesia) ataxia, polyneuropathy, hair fall, jaundice. Opipramol does not cause drug dependence. Opipramol exhibits no misuse-potential and dependence. It is very well usable for a long term treatment. Blood parameters, blood pressure and pulse rate did not show any significant change.

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Precautions

Opipramol should not be taken with alcohol, or in patients with benign prostatic hyperplasia, overt liver and kidney disorders, brain damage of different etiology, epilepsy, cerebrovascular insufficiency. Opipramol should be discontinued at the appearance of allergic skin reaction. It is recommended to check the liver enzymes during long term treatment. All patients, who have been treated with opipramol, regardless of indication, should be monitored closely with regard to clinical worsening, suicide risk and other psychological symptoms, especially during initial phase of therapy or after change of dose. With such patients, an alternation in therapy regimen including a possible discontinuation of medication should be considered.

Drug interaction

Concomitant treatment with SSRIS and opipramol can lead to additive effect on serotonergic system. With fluoxetine or fluvoxamine there may be an increase in the plasma concentration of opipramol. Sodose reduction of opipramol is required. Concomitant use of opipramol with \( \beta \)-blockers (propranolol), antiarrhythmics of class Ic, tricyclic antidepressants can lead to change in the drug plasma concentration of these drugs and of opipramol. Barbiturates and anti-convulsants can lower plasma concentration of opipramol. Neuroleptics (e.g. haloperidol, risperidone) can increase plasma concentration of opipramol. So dose adjustment is required.

Conclusion

Opipramol possess a number of attributes that are important in the treatment of somatoform disorder and generalized anxiety disorder: significant efficacy, better tolerability than SSRIs, SNRI, TCA and benzodiazepines, no dependence or misuse potential, shorter onset of action as compared to SSRIs / SNRIs.

References