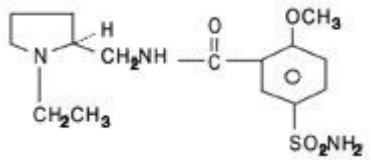
Drug Review

Levosulpiride : A Review

Sparsh Gupta, Gobind Rai Garg, Sumita Halder, Krishna Kishore Sharma
Department of Pharmacology,
University College of Medical Sciences & G.T.B. Hospital, Dilshad Garden, Delhi-110095

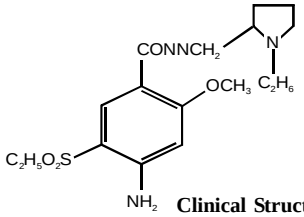
Dopamine is a neurotransmitter known to be involved in the regulation of mood and behavior. Psychotic illness is thought to be caused due to disturbance of neurotransmitters (chiefly dopamine) in the brain. Schizophrenia is a psychotic illness characterized by dopamine over activity in the brain and so anti dopaminergic drugs are a useful component of the therapy for the management of this disease.

Levosulpiride is the levo enantiomer of sulpiride. It is a substituted benzamide which is meant to be used for several indications: depression, psychosis, somatoform disorders, emesis and dyspepsia. It is physically present as a white crystalline powder with the chemical structure as follows:



The levo enantiomer shows better/similar pharmacological actions and lower incidence of toxic effects than both dextro as well as the racemic forms of the drug.

Amisulpride is a substituted benzamide which is also used for various psychiatric indications. It has a half life of 12 hours and its bioavailability is 48%. It is weakly metabolized by liver and is primarily eliminated through the renal route. Its chemical structure is as follows :



Clinical Structure of Amisulpride

Mechanism of action

Levosulpride is an atypical antipsychotic agent that blocks the presynaptic dopaminergic D_2 receptors.[1] Like its parent compound, levosulpiride[2] shows antagonism at D_3 and D_2 receptors present presynaptically as well as postsynaptically in the rat striatum or nucleus accumbens[2]. The preferential binding of the presynaptic dopamine receptors decreases the synthesis and release of dopamine at low doses whereas it causes postsynaptic D_2 receptor antagonism at higher dose. This receptor profile of the drug along with its limbic selectivity explains its effectiveness in the management of both positive and negative symptoms of schizophrenia.[3]

Pharmacokinetics

The parent drug is given in a dose of 400-1800 mg orally daily although a much lower dose is effective for producing antidepressant effect (about 50-300 mg).The plasma $t_{1/2}$ of the drug is about 6-8 hours. The drug is chiefly excreted through the renal route.

Indications

1. ***Psychiatric illness:*** the primary indication of this drug is in the management of both positive and negative symptoms of schizophrenia. It is also used in patients of depression.
2. ***Burning mouth syndrome:*** Burning mouth syndrome (BMS) is a condition of unknown etiology where there is a complaint of a burning sensation in the mouth in the absence of any underlying medical or dental cause. The pain is predominantly localized to tongue or lips with minimal oral signs. Levosulpiride at a dose of 100 mg/day demonstrated beneficial effect (decreased burning or stinging oral sensation) in BMS.[4]

3. ***Acute unilateral labyrinthine dysfunction:*** levosulpiride has been shown to induce recovery in unilateral labyrinthine dysfunction. When the drug was administered at a dose of 25 mg three times a day for a period of 10 days, it produced lesser residual labyrinthine dysfunction and reduction in the recurrence of attacks.[5]
4. ***Cataplexy:*** Animal studies have demonstrated the beneficial effects of levosulpiride in the management of cataplexy without much adverse effects. Another advantage with the use this drug is non reduction of the REM sleep.[6] Earlier canine studies have already suggested the role of D_2/D_3 receptors in the regulation of cataplexy.[7]
5. ***Gastroparesis and glycemic control in diabetics:*** the selective antagonistic action of levosulpiride on the D_2 receptors also makes it useful as a prokinetic drug. Its use in a dose of 25 mg tds orally for a period of 6 months has been shown to increase glycemic control in IDDM subjects by effectively managing gastroparesis in them.[8] Administration of levosulpride in a dose of 25 mg four times a day produces beneficial effect in patients with diabetic cholecystoparesis as evidenced by reduction of basal mean gall bladder volume.[9]
6. ***Premature ejaculation:*** Premature ejaculation is defined as a failure of the normal voluntary control over ejaculation. It is usually managed with the use of antidepressants and other adjuvant drugs. In a double blind study, administration of levosulpiride 25 mg once daily for 60 days provided significant improvement in control over ejaculation (76.47% drug treated patients as compared to 26.66% patients receiving placebo). Dopamine has been shown to be facilitate sexual arousal and in decreasing ejaculatory threshold. So, levosulpiride being a dopamine antagonist may be responsible for the beneficial effect by this mechanism.[10]

Side effects

The following side effects can occur with the use of this drug;

- Acute muscular dystonia characterized by abnormal movements (twitching, tremor etc.) of hands, leg, tongue and facial muscles.
- Sedation or drowsiness (because of decrease in sensory inputs to reticular activating system)
- Increase in plasma prolactin levels manifested by breast enlargement, production of milk and stopping of menstrual periods. This can be taken care of with the use of lower dose of this drug.[4]
- Neuroleptic malignant syndrome (characterized by hyperpyrexia, muscle rigidity, increased myoglobin and creatine kinase; the last two suggestive of muscle damage.
- Akathisia (uncontrollable desire to move about without any anxiety).
- Tardive dyskinesia, it occurs late in the therapy and its features include involuntary rhythmical movements of face, mouth and jaw. The reason for tardive dyskinesia is synthesis of newer DA receptors which are supersensitive to even a small amount of DA. This causes a decrease in cholinergic activity in the striatum followed by decrease in GABA release. This decreased in inhibitory GABA is responsible for increased involuntary motor activity.
- Postural hypotension (because of autonomic blockade), tolerance develops to this effect after some time.
- Weight gain.
- Elevated liver transaminases.

Drug interactions

1. ***Antacids and Sucralfate:*** They can decrease the absorption of the drug from the intestine. So, these medicines should not be taken along with levosulpiride. There should be a minimum 2 hour time lag between the two medicines.
2. ***Alcohol :*** there is increased chance of sedation.
3. ***Smoking:*** increased metabolism of the drug may require higher dose.
4. ***Antihypertensive medications:*** concomitant use may enhance the hypotensive effect seen with the drug.
5. ***Anticholinergics:*** increased incidence of anticholinergic side effects.
6. ***Levo dopa:*** It may oppose the antipsychotic action of the drug, conversely levosulpiride can

cause decrease the efficacy of levo-dopa in the management of Parkinsonism.

7. ***Arrhythmia*** especially prolonged QT interval with the concurrent use of
   - Atomoxetine
   - Antiarrhythmics
   - Terfenadine
   - Chloroquine, quinine
   - Cisapride
   - Drugs causing hypokalemia (corticosteroids, laxatives, diuretics like furosemide)

Contraindications

The following are the conditions where the drug should either be used cautiously or is contraindicated:

- Elderly people
- Children less than 14 years of age
- Parkinson disease
- Severe renal or hepatic insufficiency
- History of epilepsy
- Porphyrias
- Breast cancer
- Alcohol intoxication
- Certain tumors like phaeochromocytoma and pituitary prolactinoma
- Hypokalemia
- The drug should be used cautiously in pregnancy (only when it is expected to benefit the mother more than the possibility of risking the fetus).
- The drug is known to be secreted in breast milk, so, its use should be restricted in breastfeeding women.

References

1. Rossi F, Forgione A. Pharmacotoxocological aspects of levosulpiride. Pharmacol Res 1995; 31 : 81-94.
2. Schoemaker H, Claustre Y, Fage D, Rouquier L, Chergui K, et al. Neurochemical characteristics of amisulpiride, an atypical dopamine D_2/D_3 receptor antagonist with both presynaptic and limbic selectivity. J Pharmacol Exp Ther 1997 Jan; 280 : 83-97.
3. Danien JM, Rein W, Fleurot O. Improvement of schizophrenic patients with primary negative symptoms treated with amisulpiride. Am J Psychiatry 1999 Apr; 156 : 610-6.
4. Demarosi F, Tarrozi M, Lodi G, Canegallo L, Rimondini L, Sardella A. The effect of levosulpiride in burning mouth syndrome. Minerva Stomatol 2007; 56 : 21-6.
5. Zanetti D, Civiero N, Balzanelli C, Tonini M, Antonelli AR. Improvement of vestibular compensation by Levo-sulpiride in acute unilateral labyrinthine dysfunction. Acta Otorhinolaryngol Ital. 2004 Apr; 24 : 49-57.
6. Okura M, Reihl J, Mignot E, Nishino S. Sulpiride, a D_2/D_3 blocker reduces cataplexy but not REM sleep in canine narcolepsy. Neuropsychpharmacology 2000; 23 : 528-38.
7. Honda K, Reihl J, Mignot E, Nishino S. Dopamine D_3 agonists into the substantia nigra aggravate cataplexy but do not modify sleep Neuroreport. 1999; 10 : 31111-8.
8. Melga P, Mansi C, Ciuchi E, Giusti R, Sciaba L, Prando R. Chronic administration of levosulpiride and glycemic control in IDDM patients with gastroparesis Diabetes Care; 21: 55-8.
9. Mansi C, Savarino V, Vigneri S, Sciaba L, Perilli D, Mele MR, et al. Effect of D_2 dopamine receptor antagonist levosulpiride on diabetic cholecystoparesis Aliment Pharmacol and Ther 1995; 9 : 185-9.
10. Grecco E, Polonio Balbi P, Speranza JC. Levosulpiride – a new solution for premature ejaculation? Int J Impotence Res 2002; 14 : 308-9.