LEVOMILNACIPRAN: A NEW FDA APPROVED ANTIDEPRESSANT

Praveen Tripathi1, Sujit Kumar Kar2, PriyankaGoyal3

ABSTRACT

Levomilnacipran is a newer antidepressant belonging to the group of selective serotonin and norepinephrine reuptake inhibitors (SNRIs). It has got approval by US FDA for use in depression, recently. It is a congener molecule of milnacipran and side effect profile is similar to that of milnacipran.

Keywords - Levomilnacipran, SNRI, depression

Levomilnacipran ER received its first global approval on 25 July 2013 for the treatment of MDD in the USA (1). It is a newer selective serotonin and norepinephrine reuptake inhibitor (SNRI). The chemical name of levomilnacipran is (1S, 2R)-2-(amino-methyl)-N,N-diethyl-1-phenylcyclopropane carboxamide hydrochloride. Levomilnacipran is the IS, 2R-enantiomer of milnacipran.

[Figure - 1: the chemical structure of Levomilnacipran]

Pharmacokinetics

Three randomized Phase I studies assessed the pharmacokinetics of levomilnacipran (6). At steady state, levomilnacipran concentration is dose proportional (at dosages of 25–300 mg once daily) (4). In a population based pharmacokinetic analysis, delayed first-order absorption and first-order elimination best described the pharmacokinetics of levomilnacipran (7).

The bioavailability of oral Levomilnacipran ER capsules is as high as 92 % and the absorption is not significantly affected by simultaneous intake of food (4). The mean time to reach maximum plasma concentration after oral administration is 6-8 h and mean half-life is 12.4-12.9 h (6). Around 22 % of drug was plasma protein bound over a concentration range of 10-1,000 ng/ml. Interconversion between levomilnacipran and its stereoisomer does not occur in humans (4).

Levomilnacipran is metabolized by desethylation and hydroxylation (principally by cytochrome P450 2D6).

comparison to serotonin uptake with norepinephrine/serotonin potency ratio of (0.6) (3).

Levomilnacipran is selective in its receptor profile and does not show any significant binding to off target receptors such as serotonergic, a- and (5-adrenergic, muscarinic and histaminergic receptors, and Ca2+, Na+, K+ or Cl channels. It does not inhibit monoamine oxidase (2, 4). However, it has some affinity for the NMDA-type glutamate receptor (Kj 1.7 umol/L)(5).

Levomilnacipran is found to be more potent than contemporary SNRIs like Venlafaxine and Duloxetine as found in studies (3).

Pharmacodynamics

Levomilnacipran is a potent and selective SNRI with greater potency for inhibition of norepinephrine relative to serotonin reuptake (2). Compared with the SNRIs duloxetine or venlafaxine, levomilnacipran has over 10-fold higher selectivity for norepinephrine relative to serotonin reuptake inhibition (2).

Studies have shown that, in vitro, levomilnacipran is a potent and selective inhibitor of both norepinephrine and serotonin transporters with inhibition constant (Ks) of 92.2 nM and 11.2 nM respectively (3). It has slightly higher inhibitory effect on norepinephrine uptake in comparison to serotonin uptake with norepinephrine/serotonin potency ratio of (0.6) (3).
[CYPJ3A4, with minor contribution by CYP2C8, CYP2C19, CYP2D6 and CYP2J2]. The major metabolites are desethyl levomilnacipranp-hydroxy-Levomilnacipran. Both metabolites are then conjugated with glucuronides (4). The elimination of levomilnacipran and its metabolites is primarily by kidney. Around 58% of drug is excreted unchanged. The elimination t½ is around 12 hours (4).

Studies have found that no dose adjustment is needed for patients with mild renal impairment; however in patients with moderate and severe renal impairment should not exceed 80 and 40 mg once daily, respectively (8). No dosage adjustment is required for patients with mild, moderate or severe hepatic impairment (4).

As co-administration with strong CYP3A4 inhibitors can result in increased levomilnacipran levels, it is recommended to adjust its dose when being administered with such drugs. No dosage adjustment is recommended while co-administering levomilnacipran ER and a CYP3A4 inducer or substrate. In vitro, alcohol was found to accelerate drug release, hence co-administration with alcohol is not recommended (4).

No dose adjustment has been recommended for elderly patient (> 65 years).

EVIDENCES FROM CLINICAL STUDIES

Treatment of Major Depressive Disorder

Three 8 week, randomized, double blind, placebo controlled studies conducted in patients of major depressive disorder (age 18-78 yrs) found Levomilnacipran to be an effective antidepressant. (9-11)

In a fixed dose study (9), patients received 40 mg (n = 178), 80 mg (n = 179), or 120 mg (n = 180) of levomilnacipran once daily, or placebo (n = 176). In another similar study (10), patients received either 40 mg (n = 188) or 80 mg (n = 188) of levomilnacipran once daily, or placebo (n = 186). In a third flexible dose study (11), patients received 40 to 120 mg (n = 217) of levomilnacipran once daily, or placebo (n = 217) with 21%, 34%, and 44% levomilnacipran patients on 40 mg, 80 mg, and 120 mg, respectively at the end of their treatment.

All three studies measure improvement on the Montgomery-Asberg Depression Rating Scale (MADRS) and demonstrated superiority of levomilnacipran over placebo. Also levomilnacipran was found to be superior over placebo as measured by improvement in the Sheehan Disability Scale (SDS) functional improvement total score. Post-hoc analyses did not reveal any relationship between treatment outcome and age, gender, and race.

Side effects

Levomilnacipran ER was generally well tolerated in clinical trials in patients with MDD (9-12). The most common adverse reactions (incidence > 5% and at least twice the rate of placebo) are: nausea, constipation, hyperhidrosis, ejaculatory dysfunction, urinary hesitancy, tachycardia, vomiting, and palpitations (9 -11). The only dose-related adverse events were urinary hesitancy (4, 5 and 6% of levomilnacipran ER 40, 80 and 120 mg/day vs. 0% of placebo recipients) and erectile dysfunction (6,8 and 10 vs. 2 %, respectively) (4).

Levomilnacipran ER has been associated with elevated blood pressure (4). In the short-term, placebo-controlled trials of levomilnacipran ER in patients with MDD, a total of 0.3% of levomilnacipran ER and 0.1% of placebo recipients experienced sustained hypertension.

Levomilnacipran does not prolong corrected QT interval to any clinically relevant extent, at doses 2.5 times the maximum recommended dose (4). Levomilnacipran may cause mild derangement in hepatic enzymes. Slight increase in aspartate aminotransferase (AST) and alanine aminotransferase was observed in recipients of levomilnacipran ER compared with recipients of placebo (9). Discontinuation of antidepressant treatment may lead 16 discontinuation adverse events, particularly when discontinuation is abrupt (4). Meta-analysis of trials of levomilnacipran revealed that the risk of weight gain is not clinically significant (13).

DOSAGE AND ADMINISTRATION

Levomilnacipran is available in the form of extended release capsules (14). The recommended oral dose of levomilnacipran is 40 mg to 120 mg once daily with or
without food. The initial dose is 20 mg once daily which is to be increased after two days to 40 mg once daily. Depending on efficacy and tolerability dosage can be further increased by 40 mg at intervals of two days or more to a maximum dose of 120 mg(4).

CONTRAINDICATIONS

Levomilnacipran is contraindicated if there is hypersensitivity reaction to levomilnacipran or milnacipran or uncontrolled narrow angle glaucoma [4]. Use of levomilnacipran to be avoided within 14 days of stoppage of monoamine oxidase inhibitors (MAOIs) and co-administration with linezolid or intravenous methylene blue (4).

WARNINGS AND PRECAUTIONS

In certain special circumstances levomilnacipran to be used cautiously and the risks associated with use of levomilnacipran are as below (4):

- Suicidal thoughts and behaviors in adolescents and young adults
- Serotonin syndrome: Especially when co-administered with other serotonergic agents
- Hypertension and tachycardia: Blood pressure and heart rate to be monitored before starting levomilnacipran and then periodically
- Abnormal bleeding: Especially when administered with aspirin, NSAIDs and anti-coagulants
- Narrow angle glaucoma: Possibility of mydriasis with use of levomilnacipran leading to worsening of symptoms of glaucoma
- Urinary hesitancy or retention
- Manic/hypomanic switch
- Seizures
- Discontinuation syndrome
- Hyponatremia

As per animal studies, it may produce harm to the fetus and there is no data on human studies (4).

References


13. Citrome L. Levomilnacipran for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antidepressant - what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? M J Clin Pract. 2013 Nov; 67(11):1089-104.


Acknowledgement: NIL
Conflict of interest: NIL

How to cite this article: Praveen Tripathi, Sujit Kumar Kar, Priyanka Goyal; Levomilnacipran: A New FDA Approved Antidepressant: Indian Journal of Behavioural Sciences, Vol. 24 (1) June 2014, 51-54