

Levosulpiride Induced Parkinsonism and Other Movement Disorders



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Abstract

Drug induced Parkinsonism; the second leading cause of Parkinsonism remains often under recognised. Main culprits like neuroleptics get scrutinized while drugs like levosulpiride go unsupervised many a time. Levosulpiride is a enantiomer of the sulpiride with antidopaminergic activity at D2 receptor and agonistic activity at 5HT4 receptors. Due to inhibition of D2 receptors in the gastrointestinal system, there is increased gastric and gall bladder mobility as well as increased tone of lower esophageal sphincters. Central action at area postrema also renders helping hand as a potent antiemetic. It's used in dyspepsia, gastroparesis, burning mouth syndrome, cataplexy, acute labyrinthine dysfunction, glycemic control and premature ejaculation. Psychiatric illness such as depressive disorders, somatoform disorder and positive as well as negative symptoms in schizophrenia recommends levosulpiride use. Drug remains unmetabolised and excreted in urine unchanged which reduces the drug interactions. No teratogenic, mutagenic or oncogenic potential are found in animal experiments but no studies have been confident about its use in pregnancy. As the drug is excreted in breast milk it's highly advised to be restricted in lactating mothers.

Non- motor side effects include Sedation or drowsiness, hyperprolactinemia, postural hypotension, weight gain, QT prolongation and elevated liver transaminases have been reported. Motor side effect includes Parkinsonism, tardive dyskinesia, isolated tremors, orolingual dyskinesia, hemichorea and acute muscular dystonias with most common being Parkinsonism with ever rising incidence. Levosulpiride induced parkinsonism is mostly reversible condition upon cessation of the drug while sometimes the symptom complex persist indicating underlying dopaminergic dysfunction unmasked at an earlier occasion. Any patient presenting with parkinsonian features all and any drug the patient is on can be a potential culprit. Possible offenders can be halted for a while and reassessment will help in differentiating clinically. Investigation like MRI, SPECT will help in differentiating the levosulpiride induced Parkinsonism from idiopathic parkinson's disease. Hence it is imperative for primary care physicians to be involved in pharmacovigilance of Levosulpiride and any drugs, so as to ensure do more good than harm.

Keywords: Levosulpiride; Drug induced parkinsonism

Introduction

Drug induced Parkinsonism (DIP) is now the second leading cause of Parkinsonism behind idiopathic Parkinson's disease. DIP can be defined as reversible development of parkinsonian syndrome in patients treated with drugs which impair dopamine function [1]. However some drugs uncover a dormant dopaminergic pathway abnormality leading to full blown Parkinsonism. Many commonly prescribed safe drugs for common diseases are being reported to interfere with dopaminergic and cholinergic pathways causing classical parkinsonian manifestations. Movement disorders like tardive dyskinesia, tardive dystonia, akathisia, myoclonus, tremors are the commonly observed disorders with an offending drug as the etiological factor. Failure in identifying the drugs causing Parkinsonism, results in refractory symptoms with frequent outpatient/ inpatient visits forcing an economic burden and

untold morbidity on the patient's part. A community-based survey and a population-based study found DIP prevalence rates of 2.7% and 1.7%, respectively, whereas those of PD were 3.3% and 4.5%, respectively. However, 6.8% of the patients diagnosed with PD were later reclassified as having DIP [2]. This survey, thus reiterates the challenge of identifying the drugs impairing the dopaminergic pathway. The common culprits include neuroleptics such as chlorpromazine and clozapine, anti emetics such as metoclopramide and calcium channel blockers which are properly scrutinized after prescription. However, the repercussions of using Levosulpiride as a prokinetic drug are being brought to light recently. Levosulpiride, a selective dopamine D2-receptor antagonist, though appears as a seemingly harmless adjunct prescribed to a minor complaint, may end up being detrimental to the patient.

Levorotatory enantiomer of sulpiride, Levosulpiride is a benzamide derivative that selectively inhibits the dopamine D2 receptor in the central nervous system (CNS) and in the gastrointestinal (GI) tract. It's biologically more potent and better tolerated when compared to its counterpart isomer and racemic sulpiride [3]. Developed in Ravizza Farmaceutici S.p.A Italy; it has captured attention of many practitioners in few years out in market and also insinuated into many successful combinations. Classified into classes such as prokinetic agent, antidepressant and antipsychotic made its way into numerous prescriptions.

Levosulpiride selectively inhibits D2 receptors with moderate agonistic action on 5-HT4 receptor. Action at D2 receptors occurs in both central and periphery. Neuronal and muscular D2 receptor blockade in the gastrointestinal system asserts the prokinetic action while central inhibition of D2 receptors especially in the area postrema exerts antiemetic property. Central inhibitions also bring about unnecessary adverse reaction like hyperprolactinemia and dystonias. Action on 5HT4 receptors in cholinergic neurons releases acetylcholine which further promotes its prokinetic activity [4]. Several studies proved the efficacy of Levosulpiride in reducing the gastric emptying time to be more than placebo [5] (B5) and almost equivalent to that to cisapride [6] and domperidone [7] using various modalities like ultrasonography, radiology, scintigraphy, electrical impedance, intracavitary manometric monitoring and ¹³C-octanoic breath test. Normalizing the gastric electrical activity [8] and enhancement of gastric motility in both fed and fasting states [9] brought about relief to patients with functional dyspepsia. Levosulpiride also enhances gallbladder transit time, reduces gallbladder volume [10] and increases tone of lower esophageal sphincter [11]. Levosulpiride exhibits linear pharmacokinetics with bioavailability being more after intramuscular administration than tablets and oral solution (drops) [12]. The plasma t_{1/2} of the drug is about 6-8 hours. Drug remains unmetabolised and excreted in urine unchanged. Interaction with other drugs remains highly unlikely due to lack of hepatic metabolism. In animal studies conducted, levosulpiride showed low reproduction toxicity, mutagenic potential and oncogenic/carcinogenic potential in doses higher than normally used. It also doesn't demonstrate any toxicity from accumulation, tolerance, dependence or withdrawal syndrome [13].

Indications

Levosulpiride, as an atypical neuroleptic is beneficial in schizophrenia. At low doses, it binds to presynaptic receptors causing reduction in dopamine levels, while acting as an antagonist at postsynaptic receptors at higher doses. This property is useful in controlling both the positive and negative symptoms. It also has the therapeutic advantage of being an antidepressant at lower doses. Levosulpiride is used in the treatment of patients with refractory dyspepsia, i.e. in which

proton pump inhibitors yielded no relief, upper GI endoscopy was normal and no evidence of *H. pylori* infection [14].

Withdrawal of cisapride from market in 2000 because of its cardiovascular adverse effect [15], aroused interest for the search of alternatives treatment for the management of functional dyspepsia [16]. Levosulpiride being a suitable alternative, controls gastro intestinal motility through its action on dopaminergic and serotonergic pathways. The symptoms related to gastric emptying pattern like epigastric discomfort, postprandial fullness and bloating, while nausea, vomiting and early satiety are more improved with levosulpiride treatment [17] Levosulpiride has been demonstrated to improve glycemic control by improving gastric motility in type 1 diabetes mellitus without any change in insulin dosage [18]. This could be explained by a better synchronization between the onset of exogenous insulin and release of nutrients from the stomach into the intestine and their absorption in the general circulation [18]. The study finding supported the role of gastric emptying in maintaining glycemic control in IDDM patients [18]. Since DA seems to have a role in facilitating sexual arousal and in lowering the ejaculatory threshold, DA antagonists like levosulpiride are likely to have an inhibitory function and has been proved to be effective in premature ejaculation [19].

A double blind study of levosulpiride in patients with somatoform disorders showed benefit after 6 weeks [20]. Levosulpiride has also been used successfully in patients with burning mouth syndrome. A study conducted on 44 subjects suffering from idiopathic burning mouth syndrome revealed that levosulpiride was more effective in patients who have recently developed burning/ stinging oral sensation [21]. Levosulpiride has demonstrated promising prospects in the treatment of cataplexy in animal models with an added privilege of non reduction of the REM sleep [22]. Levosulpiride has been used with varying success in unilateral labyrinthine dysfunction as it has been shown to reduce the recurrence of attacks [23].

Adverse Effects

Levosulpiride is used widely in several Asian and European countries to treat nausea, vomiting, and functional dyspepsia. Levosulpiride, being a neuroleptic agent is known to cause drowsiness as a result of reducing afferent signals to the reticular activating system. Though to a lesser extent than other antipsychotics, it has, nevertheless, been known to cause neuroleptic malignant syndrome constituted by hyperpyrexia and muscle rigidity, leading to muscular damage. Effects on the pituitary gland situated outside the blood brain barrier lead to weight gain; raised plasma prolactin levels causing breast enlargement, mastalgia and lactation, which are attributed to the virtue of dopaminergic antagonism, these side effects can be avoided with lower dosages. Tolerance develops to autonomic consequence such as postural hypotension. Generally, domperidone is considered to be safe for the management of GI discomfort, even in patients with PD, because it does not cross

the blood-brain barrier [24]. Thus, prescribing levosulpiride to the geriatric and pediatric patients is harmful and is best avoided in the two age groups

A case of QT prolongation has been reported when levosulpiride was administered to a patient on citalopram for reactive depression [25]. Levosulpiride may act as a moderate antagonist at 5-HT₃ receptors as well as a moderate agonist at serotonin 5-HT₄ receptors. In addition, it has, at least in part, similar effects as the benzamide derivative cisapride, which also possesses class III antiarrhythmic activity [26]. Citalopram is a selective serotonin reuptake inhibitor that is used for the treatment of major depression, with a better cardiac safety profile than tricyclic antidepressants [27]. Conclusion was drawn that levosulpiride may express partial 5-HT₄ receptor agonist activity also at the ventricular level, thus favoring the development of electrical storm if an underlying proarrhythmic mechanism is present, as occurred with citalopram-induced QT prolongation in the patient [25].

Veralipride, another benzamide derivative is frequently being used as an alternative to hormonal therapy due to its generally well tolerated effect on menopause-related symptoms [28,29]. The central nervous system effects of veralipride, especially on the hypothalamus, are described as secondary to hyperprolactinaemia, either as a feedback in tuberoinfundibular dopamine neurons or secondary to an opioid agonistic effect [30]. The parkinsonian syndrome was described as a case report by Milandre et al. [31] and Franghignoni and Tesio in 1995. Masmoudi et al. [32], also reported on a parkinsonian syndrome, adding four other veralipride-induced dyskinesia [32]. An instance of worsening of parkinsonian symptoms on consumption of veralipride has been reported. The patient who was diagnosed to have Idiopathic Parkinson's Disease (IPD), previously responsive to levodopa, presented with worsening of rigidity, bradykinesia, which, after the withdrawal of veralipride, returned to the baseline [33].

Even though the occurrence of Levosulpiride Induced Movement disorder (LIM) is rare in patients with normal kidney function, Levosulpiride induced Movement disorders occurs much more commonly in chronic kidney disease patients contrary to the belief. Hence the dose of levosulpiride should be modified in patients with chronic kidney disease [34]. Other contraindications include known epilepsy, porphyrias, tumours like prolactinoma, pheochromocytoma and carcinoma breast, alcoholic intoxication. The drug is known to be secreted in breast milk, so, its use should be restricted in breastfeeding women [35].

Levosulpiride induced parkinsonism and other movement disorders

Case vignette: A 72yr old male with a history of coronary artery disease, type 2 diabetes mellitus, essential hypertension, dyslipidemia for which he was on regular medications,

presented with complaints of tremors in his right hand. The resting tremors gradually and progressively involved all the four limbs, prominently observed in the lower limbs with associated rigidity, impairing his ability to carry out his routine activities. Physical examination revealed the presence of orolingual tremors, hypophonia, impassive face, stooped posture, positive glabellar tap and shuffling gait suggestive of parkinsonism. The patient had been prescribed a combination of pantoprazole with Levosulpiride for gastritis for the past 1year. On discontinuation of Levosulpiride for 2weeks, there was considerable reversal of symptoms, as evidenced by the improvement in his UPDRS score from 48 to 13.

Until recently, the drug-induced movement disorders related to levosulpiride were under-recognized, but it has now been shown that levosulpiride frequently causes Parkinsonism [36]. Extrapyramidal effects by levosulpiride is based on the affinity constants for the D₂ receptors. Dopaminergic antagonism at the pre synaptically and post synaptically present D₂ and D₃ results in upregulation of receptors, rendering them supersensitive to minute amounts of dopamine. The consequent reduction in cholinergic activity with successive reduction in GABA activity results in increased involuntary movement which is manifested as tardive dyskinesia. Tardive dyskinesia is observed late in therapy as rhythmical facial and oral movements. Levosulpiride has also been reported to cause acute muscular dystonia of hands, leg, tongue muscles and akathisia [35]. Other motor manifestations include rhythmic sinusoidal oscillation of the anterior upper neck.

One of the studies concerning Levosulpiride induced movement disorders, revealed that levosulpiride induced disabling parkinsonism or severe oro-lingual dyskinesia in many patients; 21(24.7%) of the 85 patients with LIP were rated as Hoehn and Yahr stage III-V and all 9 patients with oro-lingual dyskinesia had severe difficulties in speech and chewing [36]. In a study comprising 132 patients with drug-induced movement disorders, 91 were exposed to levosulpiride. The most common levosulpiride-induced movement disorder was Parkinsonism (93.4%), followed by tardive dyskinesia (9.9%), and isolated tremor (3.3%). The study also noted that 48.1% of the patients with LIP did not improve after withdrawing the drug [37]. There have been a few instances of hemichorea induced by Levosulpiride. The underlying mechanism is largely believed to be striatal dysfunction as evidenced by hypoperfusion of basal ganglia on Brain SPECT [38].

Management

The clinical diagnostic criteria for DIP are defined as 1) the presence of parkinsonism, 2) no history of parkinsonism before the use of the offending drug, and 3) onset of parkinsonian symptoms during use of the offending drug [36]. Thus, reversible LIM may be defined as the complete absence of abnormal involuntary movement after cessation of levosulpiride. Irreversible LIM may be defined as the persistence or recurrence

of the abnormal involuntary movements after discontinuation of levosulpiride, or other medication used to treat LIM [36]. A detailed neurological and psychological assessment plays a crucial role in classification of severity of the disability. UPDRS, Hoehn and Yahr stage and symmetry of Parkinsonism and psychological questionnaires are useful tools in diagnosing as well as gauging the recovery.

Studying normal MRI and F-FIP-PET scans of parkinsonian patients has revealed the fact that DIP caused by prokinetic drugs, is a result of anatomical changes such as increased right cerebellar cortical volume, areas of cortical thinning in subcortical structures which lead to cognitive dysfunction. Conversely, a higher prevalence of DIP in patients with cognitive dysfunction suggests that cognitive dysfunction itself may be a risk factor [39]. DATs are presynaptic proteins which regulate the dopaminergic transmission. The dopaminergic nigrostriatal pathway can be imaged by employing DAT ligands by Single Photon Emission Computerized Tomography (SPECT). SPECT radioligands include 123I-N-3-fluoropropyl-2 β -carbomethoxy-3 β -(4iodophenyl)nortropine (123I-FP-CIT or 123I- β -CIT-FP), 123Iloflupane, DaTSCAN, and 123I-2 β -carbomethoxy-3 β -(4iodophenyl)tropane (123I- β -CIT). PET scans may be superior to SPECT for imaging DATs, in that the lower energy of positrons provides higher resolution, resulting in better image quality with widespread clinical applications. DAT scans may show symmetric uptake of radiotracer in the bilateral striatum in patients with pure DIP, even if they have significant Parkinsonism [40]. Thus DAT scans are helpful in distinguishing PD uncovered by the drug from pure DIP. DAT imaging can also be employed to determine the clinical course of DIP patients.

In a study, among the 85 patients with LIP, 52 were clinically assessed at one year postdiagnosis: LIP in 27 patients (51.9%) was reversible, whereas it was irreversible in others; In the 27 patients with reversible LIP, the mean interval from cessation of levosulpiride to disappearance of Parkinsonism was 3.4 \pm 2.4 months [36]. Identification and discontinuation of the offending drug leads to reversal of symptoms within weeks to months. However Parkinsonism may persist or progress in 10-50% of the patients [40].

Conclusion

Levosulpiride induced parkinsonism is often under recognized possibly due to unawareness of the condition. It has been shown that almost half of the patients diagnosed with levosulpiride induced Parkinsonism progress to irreversible Parkinsonism. A drug used for relatively trivial condition leading on to a chronic disabling disorder warrants urgent attention. A clear cut warning on the drug envelope is warranted. The treating physician should look for early extra pyramidal side effects and stop the drug on slightest suspicion of such symptoms or signs increasing the awareness among doctors about the risk of using this drug injudiciously must be carried out on an urgent basis.

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