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Case Study

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A CASE REPORT OF LEVOSULPIRIDE INDUCED PARKINSONISM

Cijy John[1], Shinto Sen[1], Aparna Grigorious[1], Lakshmi R.[1]* and Kevin Reji[2]

[1]Department of Pharmacy Practice, St. Joseph's College of Pharmacy, Cherthala, Kerala, India.
[2]Department of Neurology, Lourdes Hospital, Post Graduate Institute of Medical Science and Research, Ernakulam, Kerala, India – 682012.

***Corresponding Author: Dr. Lakshmi R.**

Department of Pharmacy Practice, St. Joseph's College of Pharmacy, Cherthala, Kerala, India.

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ABSTRACT

Levosulpiride is a prokinetic drug frequently prescribed for gastric motility disorders. Although it is commonly used to treat these conditions, its potential to cause Parkinsonism and acute dystonia as significant adverse effects is often under-recognized.[1] Levosulpiride is an enantiomer of sulpiride with anti-dopaminergic activity at D2 receptors and agonistic activity at 5HT4 receptors. By inhibiting D2 receptors in the gastrointestinal system, it increases gastric and gallbladder motility and enhances the tone of the lower oesophageal sphincter. Its central action on the area postrema also makes it a potent antiemetic. Levosulpiride is used to treat dyspepsia, gastroparesis, burning mouth syndrome, cataplexy, acute labyrinthine dysfunction, and premature ejaculation. It is also recommended for psychiatric illnesses such as depressive disorders, somatoform disorder, and both positive and negative symptoms of schizophrenia. The drug remains un metabolized and is excreted in urine unchanged, which reduces the potential for drug interactions. Animal studies have not found any teratogenic, mutagenic or oncogenic potential, but no studies have confidently assessed its use during pregnancy. As levosulpiride is excreted in breast milk, its use is highly advised against in lactating mothers.[2] Here we present a case involving a 45year-old man who developed levosulpride induced parkinsonism, highlighting a rare side effect of levosulpiride that is documented in medical literature. Upon the discontinuation of levosulpiride, the symptoms resolved.

KEYWORDS: Levosulpiride, parkinsonism, acute dystonia, prokinetic drug.

INTRODUCTION

Levosulpiride, (LSP) the levorotatory enantiomer of sulpiride, is an atypical antipsychotic drug likely to act by blocking the presynaptic dopaminergic auto receptors in low doses and the postsynaptic dopaminergic receptors in higher doses. In addition to its use for psychosis and associated psychiatric disorders, it is currently being increasingly used for various gastrointestinal disorders such as irritable bowel syndrome, gastro esophageal reflux disorder, non-ulcer dyspepsia and as a prokinetic agent. Fixed dose combination (FDC) products of LSP with proton-pump inhibitors (PPIs) are being prescribed in India and other parts of the world for various gastro intestinal diseases on a long-term basis.[3] The safety profile of sulpiride is similar to other typical antipsychotics. Its common adverse effects (<10% by the Council for International Organizations of Medical Sciences (CIOMS) frequency rating) include sedation, drowsiness, insomnia, weight gain, increased hepatic enzymes, constipation, maculo-papular rash, hyperprolactinemia, breast pain, galactorrhea and extra pyramidal disorder. Extra pyramidal manifestations caused by sulpiride include dystonia, akathisia, parkinsonism and tremors.[3]

Drugs that block dopamine (DA) receptors or deplete DA storage create a functional dopaminergic deficient state, causing clinical symptoms that mimic idiopathic Parkinson's disease (PD). It soon became evident that there was a relationship between parkinsonian symptoms and DA deficiency in patients treated with neuroleptics. This observation led to the significant discovery that markedly depleted DA, one of the catecholamines, is a key factor in the pathogenesis of PD.[4]

CASE DESCRIPTION

A 45-year-old male has presented to the emergency department (ED) at 11.45 pm on 04/03/24 presenting with both upper limb and lower limb weakness, slurring of speech since afternoon, difficulty walking and a history of increased muscle tone. His medical history included chronic kidney disease (CKD), hypertension (HTN) and coronary artery disease (CAD), Insomnia. His medication regimen included T. Arkamin (Clonidine) 100 mcg three times daily, T. Isolazine (Isosorbide dinitrate 10 mg + Hydralazine hydrochloride

37.5 mg) three times daily, T. Betaloc 50 mg twice daily, T. Pantodac 40 mg twice daily, T. Unienzyme once daily and T. Petril Beta (Clonazepam 0.25 mg + Propranolol 10 mg) once daily, along with thrice-weekly dialysis. He had been taking Rabonik Plus (Rabeprazole 40 mg + Levosulpiride 75 mg) once daily for two months to manage gastric issues.

Upon admission, he was afebrile with an arterial blood pressure of 200/110 mmHg and a peripheric oxygen saturation of 98%. Neurological examination revealed bilateral rigidity, bradykinesia, bradyphrenia, tremors, paucity of movements all 4 limbs, plantar bilateral flexor. Increased muscle tone with a power of 3/5 was noted. His vital signs on admission were a temperature of 36 degree Celsius, a heart rate of 90 beats per minute, a respiratory rate of 20 breaths per minute, and oxygen saturation of 98% at room air. The initial laboratory work up identified normal levels of liver enzymes and electrolytes. Anemia (Hb-8.7g/dl), elevated serum creatinine (11.9mg/dl), Elevated ESR (59 mm/hr) were noted. Other laboratory findings were unremarkable. MRI brain imaging report shows no e/o ICH, no infarct. In the ward patient had a hypertensive crisis associated with saturation fall; he was shifted to intensive care unit (ICU) where he underwent intubation and mechanical ventilation. He was started on NTG infusion 0-3 ml/hr and tapered according to BP (keeping BP between 150-180 mm Hg).

A complete analysis of his cerebrospinal fluid (CSF) was normal. MRI of the brain revealed mild neuroparenchymal involutional changes, along with bilateral periventricular and frontoparietal deep white matter Fazekas grade 1 small vessel ischemic changes.

A diagnosis of levosulpride induced parkinsonism was made. Hence levosulpiride was discontinued. Treatment with Syndopa Plus, intravenous antibiotics, antihypertensives, and supportive care led to the resolution of his parkinsonism symptoms within two weeks He was gradually weaned off ventilator support, with subsequent improvement in his bradykinesia and bradyphrenia.

Therefore, Levosulpiride was identified as the likely causative agent.

DISCUSSION

Levosulpiride-induced parkinsonism is a rare but significant adverse effect of levosulpiride treatment. The exact mechanisms underlying this condition are not completely understood, but several pathophysiological processes have been proposed. A knowledge of basic pharmacology and updated knowledge of newly reported adverse drug reactions might help clinicians to suspect and subsequently diagnose it properly.

Dopamine receptor antagonism is thought to play a significant role in levosulpiride-induced parkinsonism. Dopamine neurotransmission is reduced when levosulpiride binds to dopamine receptors in the striatum. The onset of parkinsonian symptoms could be attributed to this imbalance in dopamine and acetylcholine.[5]

The first-generation antipsychotics such as Haloperidol are commonly reported to cause extrapyramidal symptoms. Previously, it was thought, newer antipsychotics were essentially devoid of EPS. However, due to many folds rise in the usage of newer drugs, it was noticed that the antipsychotic-induced EPS was prevalent with newer agents too.[6] Early rat experiments by Nielsen and Lyon concluded that long-term treatment with neuroleptic drug losses cells in the corpus striatum.[7] A recent study by Mathew Thomas Nadimpally on six patients developed adverse effect such as rigidity and tremor in four patients after taking Levosulpiride with proton pump inhibitors for 1–12 weeks and the symptoms were fully improved as well as subsided after stopping the drug.[8] Radhakrishnan and Goyal in their study conducted in 7 patients developed levosulpiride induced dystonia at 25mg/ day, with symptoms appearing within 1 month followed by at least 50% improvement of symptoms on stopping the Levosulpiride.[9]

Another study conducted by Supriyo Choudhury, Koustav Chatterjee on Levosulpiride induced movement disorders compared any possible pharmacokinetic interaction of PPI and LSP. The plasma half-life for levosulpiride was 6.8-7 hrs. And that of esomeprazole was 1-1.5 hrs. where as other PPIs 0.6-1.9 hrs. Thus observed ADR are not related to pharmacokinetic interaction of PPI and LSP.[2]

The symptoms were more severe and irreversible and were treated with levodopa and pramipexole. Dopaminergic drugs such as carbidopa-levodopa (100/10 mg) or pramipexole, dopamine agonist (0.5 mg) is the common treatment given for the adverse effects. In this case report symptoms were improved after discontinuation of the medicine and managed with Tab. Syndopa plus.

CONCLUSION

Levosulpiride is a prokinetic agent that is widely used in India by general physicians. Thus, clinicians should be aware of levosulpiride-induced atypical parkinsonism. The patients should be counselled carefully regarding the appropriate usage of the drug.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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