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CASE STUDY

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A case of levosulpiride-induced tardive dyskinesia

Abstract

Levosulpiride is chemically a substituted benzamide which acts as an atypical antipsychotic and prokinetic agent. There is dearth of study and limited research on levosulpiride-induced tardive dyskinesia (TD) and its abuse potential till date. Levosulpiride can cause TD which is related to an apparent dopaminergic hyperactivity after long-term blockade of presynaptic dopaminergic D2 receptors. So, detailed drug history should be taken to detect the rare cases of levosulpiride-induced TD and physicians should be cautious in using levosulpiride, particularly in elderly patients.

Keywords: Benzamide. Antipsychotic. Prokinetic. Dopamine. Elderly.

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INTRODUCTION

Levosulpiride is chemically a substituted benzamide used for the management of dyspepsia and emesis. It is one of the molecules introduced in Indian market with indications for application in schizophrenia and somatoform disorders. It also has antidepressant and anxiolytic properties.[1] It is a selective antagonist of dopamine D2 receptor on both central and peripheral levels. It is an atypical antipsychotic and prokinetic agent. Though amenorrhoea, gynaecomastia, galactorrhoea are the most commonly reported side effects of levosulpiride, very little is known about levosulpiride-induced movement disorders (LIM) till date.

Tardive dyskinesia (TD) is now a less commonly encountered problem than in previous decades,[2] probably because of the introduction and widespread use of second generation antipsychotics. TD is often difficult to treat; so prevention, early detection, and early treatment are essential. TD is associated with greater cognitive impairment,[3] more severe psychopathology,[4] and higher mortality.[5] TD can also occur following the use of other dopamine antagonists, such as metoclopramide.[6] Risk of TD may be related to the extent of D2 receptor occupancy (higher occupancy imposes higher risk).[7]

CASE

Mr. X, 42 years old Hindu male from a rural and lower-middle socioeconomic background, educated up to tenth standard, married for last 16 years was diagnosed as a case of generalized anxiety disorder as per the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10)[8] criteria at Psychiatry outpatient department (OPD) of Assam Medical College Hospital, Dibrugarh, Assam, India in September 2008. Hamilton anxiety rating scale (HAM-A)[9] score was 27 (severe anxiety). The patient was treated with tablet clonazepam 0.75 mg daily in three divided doses and tablet levosulpiride 100 mg daily in two divided doses for three weeks, and advised to come for follow-up after three weeks. He stopped tablet clonazepam after three weeks. But, he never came for follow-up visit and started to abuse tablet levosulpiride in the same dose till May 2017. On 1 May 2017, he attended Psychiatry OPD with history of problem in chewing food and difficulty in mastication on both sides of jaw as well as difficulty in gurgling for last three months. On examination, there was sudden opening of mouth at times along with involuntary movement around mouth and bilateral jaw region. He was diagnosed as TD (orofacial TD in muscles of mastication in bilateral jaw area). Abnormal Involuntary Movement Scale (AIMS)[10] score was 13. Mild anxiety symptoms were also present on mental status examination. Tablet levosulpiride was stopped and tablet escitalopram 5 mg at bedtime was started along with tablet clonazepam 1.5 mg in three divided doses. During his follow-up visit on 24 May 2017, there was improvement of the involuntary movement around mouth and jaw region, and mastication was found to be better. AIMS score was decreased than before (AIMS=seven). TD improved but sleep problem started after stoppage of tablet levosulpiride. The patient was admitted in the Psychiatry Department with the complaint of difficulty in sleeping both in the initiation and maintenance phase. He was prescribed tablet lorazepam 2 mg and tablet mirtazapine 15 mg at bedtime, and kept under observation. Sleep problem improved over a period

of two weeks. There was a past history of flickering of eyelid in 2008 (three months after starting of tablet levosulpiride) which responded to clonazepam 2 mg in three divided doses.

DISCUSSION

Very few authors reported cases of different types of LIM separately in different journals over many a years. Shin *et al.*[11] found levosulpiride-induced parkinsonism (LIP) (93.4%) to be the most common LIM followed by TD (9.9%) and isolated tremor (3.3%). 85.7% patients were aged above 60 years. The oro-lingual area was the only body part that was involved in case of TD. Levosulpiride-induced TD persisted after withdrawal of levosulpiride in 66.7% patients with dyskinesia tremor. In our patient, oro-lingual dyskinesia (OLD) was found and it persisted (though in a lesser severity) even after withdrawal of levosulpiride which is similar to the above finding; but, our patient is much younger than reported earlier.

Sharma *et al.*[12] reported three cases of LIM of which two were symmetric parkinsonism and one with truncal akathisia. Average age of the patients was 75.33 years which was again higher than our patient. The longest duration of levosulpiride exposure was one year at a dose of 75 mg/day. But, our patient abused levosulpiride for a long period of almost nine years. The onset of movement disorder was sub-acute in two patients (similar to our finding) and acute in one patient. Kim *et al.*[13] also reported levosulpiride-induced resting oro-lingual tremor. Sometimes, levosulpiride can give rise to potentially life-threatening side effects like neuroleptic malignant syndrome. López de Munain *et al.*[14] reported OLD and tardive akathisia due to sulpiride in a 56-year-old woman who suffered from parkinsonism. Diwan[15] reported a case series of LIM in three female patients aged above 60 years. They presented with tongue protrusion dyskinesia and right leg tremors; symmetric parkinsonism, bradykinesia, rigidity, stooped posture, mask face, and 4-5 Hz perioral tremors along with lingual dystonia respectively. Naskar and Nath[16] reported rapid onset resistant dystonia with low dose of levosulpiride (25 mg for four months) in a 40 years old Indian female patient. Mathew *et al.*[17] reported six patients of drug-induced parkinsonism of which four were male and two were female. The mean age of the patients was 68.67 years (standard deviation [SD] 5.5) which was much higher than our patient. All the six patients had dyspepsia and were started on a combination of levosulpiride and proton pump inhibitors. Almost all patients developed parkinsonian features within one week of exposure to levosulpiride. In another study from Texas by Miller and Jankovic,[18] out of 125 patients who presented with drug-induced movement disorders, 26% were prescribed neuroleptics for gastrointestinal distress.

The main mechanism of action of levosulpiride consists of blocking the D2 dopaminergic receptors, located on the presynaptic membranes in the dopaminergic pathways of the brain. TD seems to be related with an apparent dopaminergic hyperactivity and it has to be differentiated from other neuroleptic-induced movement disorders, such as restless legs syndrome, to ensure appropriate treatment. Levosulpiride is also claimed to have mood elevating properties which explains its abuse potential to some extent.

Conclusion

Levosulpiride is a benzamide derivative which can cause movement disorders, presenting mainly with LIP followed by lower face dyskinesia as it exerts its pharmacologic activity mainly by blocking dopaminergic D2 receptors. The symptoms are often severe and irreversible even after the withdrawal of levosulpiride. It also has abuse potential due to its mood elevating property. Therefore, physicians should be cautious in using levosulpiride, particularly in elderly patients. Careful drug history and examination are of utmost importance to discover the rare cases of levosulpiride-induced TD.

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