

Levosulpiride-induced Movement Disorders

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Abstract

We reported a series of patients who presented with LSP-induced movement disorders specifically, dyskinesic movements. We have presented one case of LSP-induced parkinsonism and summarized ten cases of LSP-induced dyskinesia. The causality of the adverse drug reaction was assessed systematically using a validated rating system, and we extensively qualified the clinical presentation of each case of dyskinesia using a clinical rating scale. We described an unusual case of acute onset LSP-induced parkinsonism in a 56-year-aged female. The mean age of ten patients of LSP-induced dyskinesia was 65.3 years (standard deviation 10.4), and 25% of patients were female. They were consuming suspected medication for a median duration of 13 months (range 1–60 months). We noted LSP-induced dyskinesia was challenging to treat as its resolution is often incomplete even with adequate treatment.

Keywords: Adverse drug reaction, antipsychotic, dyskinesia, levosulpiride, movement disorders, parkinsonism

INTRODUCTION

Levosulpiride, (LSP) the levorotatory enantiomer of sulpiride, is an atypical antipsychotic drug likely to act by blocking the presynaptic dopaminergic autoreceptors in low doses and the postsynaptic dopaminergic receptors in higher doses.^[1] 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, gastroesophageal reflux disorder, nonulcer 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 gastrointestinal diseases on a long-term basis.^[2]

D2 receptor antagonists (antipsychotic drugs) are known to cause extrapyramidal syndrome (EPS) that includes acute muscular dystonia, neuroleptic malignant syndrome, dyskinesia, and Parkinson's disease (PD).^[3] One of such kinds of drug is LSP with additional serotonin receptor affinity. The incidence of EPS caused due to LSP should be lower than the typical antipsychotics owing to its atypical antipsychotic

profile.^[4] In addition to these, weight gain, increase in plasma prolactin level, postural hypotension, and elevated liver transaminase were reported as adverse effects of LSP.^[2]

Since there are only a few published reports of LSP-induced EPS, especially dyskinesia, we intended to compile a detailed review of ten clinically suspected cases of LSP-induced dyskinesia with or without accompanying Parkinsonian features.^[5-7] The features of drug (antipsychotics/D2 antagonists)-induced dyskinesia can be either orofacial dyskinesia or limb and trunk movements. The specific movements involved in orofacial dyskinesia can be one or combination of the following movements, for example, protrusion or twisting of the tongue, smacking and pursing of the lips, puffing of the cheeks, chewing movements of the jaw, and grimacing movements of the face. Whereas, limb and trunk

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movements include purposeless, jerky, choreiform movements, athetosis of the extremities, limb and axial dystonias, gait abnormalities, lordosis, shoulder shrugging, and rotatory movements of the pelvis.^[8] LSP-induced parkinsonism was considered as the presence of bradykinesia and at least one of following signs: tremor, rigidity, and postural instability.^[5]

In addition to summarizing cases with dyskinesia, we also described one unusual case of LSP-induced parkinsonism. The nature of the movement disorders, its pattern and severity (using validated clinical scales), drug intake details, and causality assessment of the suspected adverse reaction using validated causality assessment scale has been undertaken in this case series.

CASE SERIES

We have documented the narrative of a case of acute onset LSP-induced parkinsonism, followed by a summary of additional ten patients with clinically suspected LSP-induced dyskinesia. The cases were diagnosed at the movement disorder outpatient and inpatient departments of a tertiary care neuroscience referral hospital. All patients had documentary evidence of LSP intake in combination with PPI for functional dyspepsia or related disorders. Medical history and detailed drug history including dose, frequency, duration, indication for use, and concomitant medications were noted. Patients were clinically evaluated by a movement disorder specialist. The character of dyskinesia was noted using a validated clinical rating scale and Abnormal Involuntary Movement Scale.^[9] Approval of the institutional ethics committee obtained. Video recording of the movement disorder was done with prior written informed consent to be filmed for publication on line. A study-specific case report form was designed, and the collected data were transcribed onto a computerized database.

The clinical diagnosis of “LSP-induced dyskinesia” was based on the clinical profile, temporality of the adverse effect with drug intake, plausible explanation based on the pharmacological effects of the drug, outcome following drug dechallenge, and exclusion of other causes. Other causes of drug-induced dyskinesia were ruled out by history and various diagnostic tests like computed tomography (CT) scan/magnetic resonance imaging scan of the brain, etc. The causality assessment for the adverse drug effect was done using Naranjo Causality Assessment Scale^[10] which is an objective method to estimate the association of adverse drug reaction (ADR) with the suspected drug. The maximum possible score for this scale was 13. However, score ≥ 9 was indicative of “definitive” association; 5–8 as “probable;” 1–4 as “possible;” and ≤ 0 as “doubtful” causal association.

Abnormal Involuntary Movement Scale

This validated clinical rating scale was designed to record the occurrence of drug-induced dyskinesia.^[9] It is a 12-item scale administered by the clinician. Severity of orofacial, limb, and truncal dyskinesia was estimated separately using 5-point Likert scale while the past two were binary option questions.

This assessment was reconfirmed from review of the video recording of the movement disorders.

Case: Acute onset levosulpiride-induced parkinsonism

Fifty-six-year-aged female presented to the emergency room of our hospital with rapidly progressive, acute onset tremor of lips, jaw, and all four limbs for past 3 days. She was also suffering from slurring of speech, headache, and involuntary movements of the tongue for the same duration. The tremor was confined to the lips, jaw, tongue, and all four limbs. It was a low-frequency tremor of Parkinsonian type.^[11] She was a known case of hypertension, diabetes mellitus type 2 (DM 2), and hypothyroidism on medication. She was alert, conscious at presentation with no history of convulsion, vomiting, blurring of vision, and diplopia. Her sensorium and pupillary reaction to light were normal. Sensory examination was normal. Deep tendon reflexes and superficial reflexes were within normal limits. There was evidence of asymmetrical bradykinesia (left > right) on finger-tapping test and rigidity over forearm muscles. CT scan head of the patient was essentially normal for the age. Serum sodium and potassium were within normal limits, and glycosylated hemoglobin was 6.2%. X-ray L-S spine (done for her low back pain) revealed spondylotic changes with loss of lumbar lordosis. She was on stable dose (for the past 3 months) of losartan (100 mg), hydrochlorothiazide (12.5 mg), and cilnidipine (10 mg) for hypertension. She was also taking levothyroxine (50 mcg) as a replacement for hypothyroidism, glimepiride (1 mg) for DM 2, aspirin (75 mg) and atorvastatin (20 mg) as a prophylaxis for stroke. Clonazepam 0.25 mg was another concomitant medication used once a day as sedative. She visited general physician 10 days before hospitalization for low back pain and was treated with nonsteroidal anti-inflammatory drug and fixed dose combination of omeprazole and LSP as a gastroprotective agent. On admission, she was considered as a case of “LSP-induced parkinsonism,” and the FDC (omeprazole + LSP) was withdrawn. In addition to dechallenge, she was treated with propranolol 20 mg. Gradually, the tremor subsided in next 3 days and she was discharged from hospital. On further causality assessment, strong temporal association was noted and the symptoms ameliorated following withdrawal of LSP. This symptom could not be explained by any other concomitant drug usage or comorbidity. We considered it as a probable case of LSP-induced parkinsonism. In a large case series of LSP-induced parkinsonism, the mean interval between taking LSP and onset of symptoms was 10.1 months (range 0.25–92 months). They reported that tremor was absent in 34.1% of LSP-induced parkinsonism.^[5] This case stands out because it was acute in onset and was rapidly progressive in nature and subsequently required hospitalization (video showing tremor of this patient, before and after withdrawal of LSP) [Videos 1 and 2].

Summary of the dyskinesia cases

The mean age of the 10 patients was 65.3 years (standard deviation 10.4), and 25% of patients were female. The daily

oral dose of LSP was 75 mg/day except for one patient who received 150 mg/day. The indication for drug use was nonulcer dyspepsia in all cases.

The median duration of symptom onset was 13 months (range 1–60 months). Three patients had reduced severity of dyskinesia after withdrawal of the drug, although none recovered completely. Table 1 presents the demographic and clinical profile of the patients. Three out of 10 patients of dyskinesia had “probable” and rest revealed “possible” association with LSP.

Clinical characteristics of LSP-induced dyskinesia were presented in Table 2. All of them had involuntary movements of orofacial area, with the most frequent presentation being abnormal jaw movement. Dyskinesia involving the lips and perioral area was observed in seven patients and in the tongue in six patients. Two patients had “darting” movement (tongue protrusion dyskinesia), and rest were having choreathetoid movement of the tongue. None of the patients had dyskinesia of the extremities and trunk. However, three patients had tremor and bradykinesia of the upper extremities. Three patients were incapacitated due to orofacial dyskinesia with serious problems while taking food.

Two patients out of ten were taking L-dopa concomitantly before the onset of dyskinesia. None of them was on

antipsychotics, which were likely to produce similar symptoms. Two patients were prescribed clozapine 25 mg one tablet per day to treat this condition. Two patients received tetrabenazine 25 mg and 75 mg daily dose as a treatment. Patients were also taking propranolol, trihexyphenidyl, and amantadine either to treat the dyskinesia or to improve associated symptoms such as bradykinesia/tremor. Selected drug history was presented in Table 3. LSP was prescribed initially by general physicians in five out of ten cases and in three cases by specialists.

DISCUSSION

Antipsychotic drug-induced dyskinesia is a frequently noticed ADR in a movement disorder or psychiatry clinic, yet often a challenging task for a clinician to identify it and treat. An understanding of basic pharmacology and updated knowledge of newly reported ADR might help clinicians to suspect and subsequently diagnose it correctly. The mechanism of antipsychotic-induced dyskinesia is not completely understood, but several hypotheses have been postulated by investigators. Classically, it was explained as a phenomenon resulted due to upregulation and supersensitization of postsynaptic striatal dopaminergic receptors induced by antipsychotics on prolonged administration.^[12] Scientists also claimed a loss of GABAergic neurons, confined to ventrolateral striatum in response to

Table 1: Demography and disease profile of levosulpiride-induced dyskinesia

Patient	Age	Gender	DM2	HTN	Total daily dose (mg)	Interval between taking levosulpiride and onset of symptoms (months)	Causality
K-C	53	Male	No	No	150	13	Probable
C-C	64	Female	Yes	No	75	3	Possible
B-J	73	Male	Yes	Yes	75	15	Probable
J-C	50	Male	Yes	Yes	75	1	Possible
S-K-M	70	Male	No	Yes	150	13	Possible
B-M	80	Male	No	Yes	75	6	Possible
S-D	60	Female	Yes	Yes	75	60	Probable
B-K-M	72	Male	Yes	Yes	75	24	Possible
J-B	67	Female	No	Yes	75	3	Possible
S-R-G	72	Female	No	Yes	75	16	Possible

DM2=Diabetes mellitus Type 2, HTN=Hypertension

Table 2: Clinical characteristics of levosulpiride-induced dyskinesia

Patient	Lips and perioral area	Jaw	Tongue	Upper extremities	Lower extremities	Incapacitation due to abnormal movements	Movement during sleep
K-C	Yes	Yes	No	No	No	No	No
C-C	Yes	Yes	Yes	No	No	No	No
B-J	Yes	Yes	No	No	No	No	Yes
J-C	No	Yes	Yes	No	No	Yes	Yes
S-K-M	Yes	Yes	Yes	No	No	Yes	Yes
B-M	No	Yes	No	No	No	Yes	Yes
S-D	Yes	Yes	No	No	No	No	Yes
B-K-M	Yes	Yes	Yes	No	No	No	Yes
J-B	Yes	Yes	Yes	No	No	No	Yes
S-R-G	Yes	Yes	No	No	No	Yes	No

Table 3: Medications details of patients with levosulpiride-induced dyskinesia

Patients' name	Use of clozapine	Use of tetrabenazine	Use of trihexyphenidyl	Use of levodopa	Use of amantadine	Use of propranolol
K-C	Yes	Yes	No	No	No	Yes
C-C	No	Yes	Yes	No	No	No
B-J	No	No	Yes	No	No	No
J-C	No	No	No	No	No	No
S-K-M	Yes	No	Yes	Yes	Yes	No
B-M	No	No	Yes	Yes	No	No
S-D	No	No	No	No	No	No
B-K-M	No	Yes	No	Yes	No	No
J-B	No	Yes	No	No	No	Yes
S-R-G	No	Yes	No	No	No	No

prolonged usage of antipsychotics.^[13] Excitotoxicity, free radical-mediated damage to neuronal membranes and role of nondopaminergic neurotransmitters in the development of this symptom were other possible mechanisms.^[14,15] Nondopaminergic hypothesis became prominent following multiple reported cases of dyskinesia induced by atypical antipsychotics with low dopaminergic action. Subsequently, the involvement of nondopaminergic neurotransmitters like serotonin, noradrenalin, substance P, etc. in the toxicogenesis has been substantiated.^[16]

In this case series, we presented ten cases of LSP-induced dyskinesia and one case of LSP-induced parkinsonism from the eastern part of India. The largest study published till date is from South Korea where nine cases of LSP-induced dyskinesia have been reported. The time interval between taking LSP and onset of symptoms was 17.1 months for dyskinesia, whereas in our study, it was 13 months. Similar to their observation, we also noticed majority of the patients were over 60 years. The increased susceptibility of the elderly brain due to age-related changes in striatal system might have precipitated dyskinesia. The chance of frequent intake of LSP by elderly people is also higher as the prevalence of functional dyspepsia is greater among them. In our study, 71.4% of LSP-induced dyskinesia patients were male, which is in line with the report by the Korean group who reported 66.6% of patients were male.

In contrast to the present study where we did not find complete resolution in any of the cases, the Shin *et al.*^[5] found that the symptom disappeared completely in 33.3% of patients after withdrawal of the medicine, although we did not follow-up the cases until resolution. The mean duration of dyskinesia in our study was 16.75 months in contrast to 8.2 months in Korean study. Similar to their findings, all patients had lower face dyskinesia in our study.

A group from India^[6] reported three LSP-induced PD and truncal akathisia cases where the symptoms of akathisia persisted even after withdrawal of drug. One case of LSP-induced “tongue protrusion dyskinesia” and another case with early onset “resistant dystonia” were also reported from India.^[7,17]

All of our reported cases were consuming LSP and PPI fixed dose combination. Hence, we searched the literature for possible pharmacokinetic compatibility of PPI and LSP. The plasma half-life for LSP was 6.8–7 h and that of esomeprazole was 1–1.5 h (other PPIs 0.6–1.9 h).^[18,19] Despite its lower half-life of PPI, it is known to have a prolonged duration of action. Hence, it can be regarded as a rational combination from its pharmacokinetic perspective. Furthermore, antacids might reduce the gastric absorption of LSP.^[2] Although the exact reason for reduced absorption of LSP is not known, we assume that it is due to the formation of calcium salts and not due to reduced pH as it is mainly absorbed from the intestine.^[20] There was no published literature of P450 enzyme interaction of LSP. Putting all these information together, we do not expect this adverse reaction had resulted due to pharmacokinetic interaction of PPI and LSP.

The first-generation antipsychotics (haloperidol) are commonly reported to produce extrapyramidal symptoms. Previously, it was thought, newer antipsychotics were essentially devoid of EPS. However, due to many fold increase in the usage of newer agents, it was further noticed that the antipsychotic-induced EPS was prevalent with newer agents too. In addition, the nonpsychiatric usage of this group had further made it essentially an over the counter drug in some parts of the world. The uptake of dopamine transporter ligand is asymmetrically reduced in PD, whereas it is normal in drug-induced parkinsonism. In this way, idiopathic PD and drug-induced parkinsonism can be differentiated using this method. However, due to unavailability of this tool, we had to rely only on clinical diagnosis. In the prescribing information of LSP, the risk of EPS was mentioned and the usage of this drug was recommended to restrict for a short duration (8 weeks), as reported by a South Korean group.^[5] Surprisingly, the risk of dyskinesia or related hyperkinetic movement disorders as possible ADR to LSP were not mentioned in the package inserts of available Indian brands of LSP and PPI combinations. It was stated that EPS develops in higher doses or in individuals who are susceptible of developing EPS. The maximum duration of drug usage was also not mentioned. We observed that the dyskinesia

is not related to drug dose as most of our patients were taking 75 mg (therapeutic doses) of LSP. To understand the susceptibility, genetic testing might be helpful, but it is not part of our routine practice.

CONCLUSION

The standard recommendation should be withdrawal of the suspected drug if EPS develops. However, the package inserts proposed to reduce (or withdraw) LSP, which might aggravate the condition (if continued in a reduced dose). Hence, we recommend reviewing and revise the package inserts of LSP + PPI fixed dose combinations. We think, even if the combination of PPI and LSP turns out to be effective in the treatment of functional dyspepsia, yet the concerns for safety should limit its prolonged usage. The generation of awareness regarding LSP-induced EPS, among doctors, pharmacists, and patients, is highly desired. The patients should be instructed carefully regarding the correct usage of the drug.

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Conflicts of interest

There are no conflicts of interest.

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