Original Article

Levosulpiride-Induced Neurological Adverse Effects: A Prospective Study from a Tertiary Care Center

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Abstract

Background: Levosulpiride (LS) is a prokinetic drug increasingly used for the gastric motility disorders. Despite its common use for the gastric motility disorder, the tendency to cause parkinsonism and acute dystonias are under-recognized as the major adverse effects. This study was aimed to evaluate the adverse effects of this drug in patients attending neurology clinics. **Methods:** Patients presenting with new-onset extrapyramidal symptoms with respect to LS therapy were selected for the study. A detailed history had been taken using a questionnaire. All the patients were tested for neurological manifestations. The number of cases was then statistically analyzed. **Results:** A total of 30 patients were diagnosed with LS-induced movement disorders. The average age of patients was 65 ± 12 years with 17 males and remaining females. Major presentations were tremor, stiffness, dystonia, neck or back pain, dysarthria, and abnormal feelings. Stiffness, tremor, or both were among the most common signs. A statistically significant ($P = 0.0154$) positive correlation ($r = 0.8295$) was found between the duration of LS treatment and incidence of tremor/stiffness. Among them, 19 patients were started with dopaminergic drugs and five were given symptomatic measures. Six patients had no follow-up. **Conclusion:** The LS treatment was found to produce adverse effects such as tremor and stiffness. Early recognition of this condition is essential for its complete cure and better prognosis. Therefore, one should be cautious about the LS as one of the etiologies for acute recent-onset extrapyramidal syndromes while working up patients.

Keywords: Dopaminergic, dyskinesia, dystonia, extrapyramidal, levosulpiride, Parkinsonism

Introduction

Levosulpiride (LS) is a substituted benzamide antipsychotic drug which has a selective antagonism on central dopamine receptors. The main mechanism consists of selective blockade of enteric D2 dopaminergic receptors and serotonin 5HT(4) receptor agonist. The blockade of D2 dopaminergic receptors preferentially located on the presynaptic membranes in the dopaminergic pathways of the brain produce its adverse effect.[1] It is indicated as antiemetic, antidyspeptic drug, as well as used for the management of premature ejaculation. Furthermore, LS is a mood elevator, which claimed its use in the treatment of psychoses such as schizophrenia, anxiety disorders, vertigo, and peptic ulceration.[2] Chronic administration of LS for 6 months was found to be effective in the maintenance of glycemic control in diabetic patients with gastroparesis.[3,4]

Despite its most popular application usually with a proton-pump inhibitor for the gastric motility disorder, a typical scenario which has been manifested in the middle-aged people were the development of upper limb tremors in a few weeks after initiating the medication.[5] Reports indicated that LS induces movement disorders.[6] Furthermore, weight gain, postural hypotension, increase in plasma prolactin level, and elevated liver transaminase activity were reported as the adverse effects.[7] More than 54.8% of healthy volunteers experienced one or more adverse events including diarrhea, constipation, drowsiness, extrapyramidal reactions, and skin rash from the LS therapy. Although a few studies with small sample size has been reported such movement disorders, a large population-based study is necessary to explore its adverse effect. Early recognition of this condition is essential for its complete cure and better prognosis. However, a little is known about LS-induced movement disorders in the Indian population. The drug bioavailability and metabolism was also found to vary in population. Hence, this study was aimed to evaluate the clinical presentations of adverse effect in patients with LS therapy.

Methods

A prospective study was conducted in patients who were under treatment for motor disorders of the upper gastrointestinal tract using LS and presented with movement disorders to the Neurology outpatient clinic, between March 2016 and January 2018. Patients who presented with Parkinson's disease and other movement disorders before LS intake were excluded from the study. The study was approved by the Institutional

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ethics committee and compiling the standards of the declaration of Helsinki. A detailed clinical history has been taken using a questionnaire. All the patients were tested for the motor, sensory, and extrapyramidal systems.

Statistical analysis

Data were expressed as mean and standard deviation for quantitative variables. Categorical variables are provided as numbers or percentages. Spearman correlation test (SPSS, 16v, IBM, Chicago, Illinois, USA) was done to find the correlation between the duration of LS treatment and incidence of clinical symptoms. $P < 0.05$ was considered as statistically significant.

Results

A total of 30 patients who presented with movement disorders after the LS were enrolled in this study. The average age of patients was 65 ± 12 years with 17 males and remaining females. Among the total cases, LS alone treated in seven patients, LS plus rabeprazole treated in 15 patients, LS plus esomeprazole treated in 6 patients and LS plus pantoprazole treated in two patients. Most of the patients were presented with tremors, stiffness in the limbs, dystonia, neck or back pain, dysarthria, and some had abnormal feelings mostly tightness of whole body, tingling, numbness, and restlessness. Extrapyramidal examination revealed a mild tremor at rest in the upper limbs and abnormal gait. Stiffness, tremor or both was the major signs in 26/30 cases (86.66%) during the examination. Only 13.33% of patients (4/30) had no tremor or stiffness. Both stiffness and tremor were presented in 30%, stiffness alone was observed in 32.14%, and tremor alone was observed in 28.57% of cases. Careful assessment of the cases revealed that the motor symptoms had started few days after initiating the LS. Distribution of clinical presentations among the patients treated with LS alone and in combination with proton pump inhibitors is depicted in Figure 1. Among the 9 cases who had a history of LS treatment <2 weeks, nine cases had no tremor/stiffness. However, they presented with abnormal feeling and dysarthria. Patients, 15/30 were treated for 3–5 weeks duration had a clinical presentation of tremor (8/15), stiffness (2/15), and both (5/15). Only five patients presented with a history of treatment duration of >6 months. Among them, three cases had stiffness and remaining had tremor along with stiffness. There was a positive correlation ($r = 0.8295$) between the duration of LS treatment and incidence of tremor/stiffness. The two-tailed $P = 0.0154$ was found statistically significant.

Since the symptoms persisted even after the withdrawal of LS, patients (19/30) were treated with medications. Among them, 14/19 was started with dopaminergic drugs and 5/30 were treated for symptomatic measures. Remaining (6/30) had no follow-up. Only 1/19 patient had complete recovery after 3 months of dopaminergic therapy.

Discussion

The results of the present study revealed that LS could induce parkinsonian features such as resting tremor, dystonia, neck or back pain, and dysarthria irrespective of the duration of LS treatment. The other major symptoms manifested were dysgraphia, abnormal gait. Although most of the patients in our study presented with the clinical features after 3–5 weeks of treatment, a few presented within 4 days to 1 week after beginning the therapy. We could not find any significant difference in the presentations of clinical symptoms among the patients with LS alone or LS in combination with other proton pump inhibitors such as esomeprazole, pantoprazole, or rabeprazole.

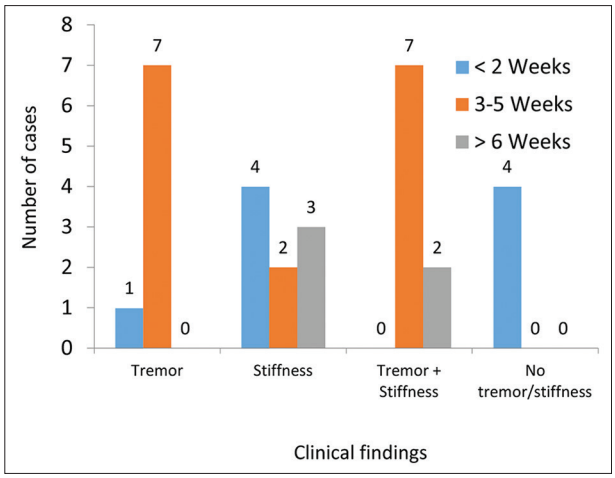

Figure 1: Distribution of duration and major clinical presentations of cases treated with levosulpiride

The extrapyramidal examination showed tremor as well as cogwheel rigidity in most of the cases. Most of the antipsychotic drugs are known to cause extrapyramidal syndromes such as acute Parkinson's disease, dystonia, and dyskinesia.[8] The adverse effect such as galactorrhoea and menstrual abnormalities in females were also observed in LS therapy. The effect is mediated through hyperprolactinemia from the blockade of dopaminergic type 2 receptors.[9]

Our results are consistent with the previous case series reported by Choudhury *et al.* that LS can induce parkinsonism and dyskinesia in most of the elder patient.[9,10] In our study, most of the patients were >54 years. However, no correlation between the age and treatment was evidenced in this study. Among the total cases, a 38-year-old male was presented with some "abnormal feelings" even 4 days after starting the LS therapy. Some of the patient had complaints of tremor and abnormal gait in extreme cases. Patients were brought in the nonambulant state with dysarthria where the adverse effect was limiting their capacity to communicate. The de novo tremor was observed as localized to face, chin apart from the common site which is upper and lower limbs. A few of the patients complained about neck or back pain after the LS therapy for a short duration. This was associated with spasm in the muscles of the back. Radhakrishnan and Goyal recently reported a series of cases in which the onset of symptoms appeared 3 days to ≤1 month after the initiation of the 25 mg/day LS therapy.[11] Choudhury *et al.* reported that LS therapy at 75 mg/day produced dyskinesia

with a median duration of symptom onset was 13 months and female dominance.[10]

The exact mechanism of the adverse effect of LS has not yet been elucidated. However, various mechanisms were suggested for the adverse effect while using this prokinetic medication. One of the early experimental evidence in rats by Nielsen and Lyon concluded that long-term treatment with neuroleptic drug losses cells in the corpus striatum.[12] While the latter study by Elkashef and Wyatt demonstrated the role of free radicals in the pathogenesis of tardive dyskinesia.[13] Study on the pharmacokinetic properties of LS in healthy Indian participants is not available. However, a study in Chinese volunteers indicated that it could exhibit a linear pharmacokinetic property over the oral dose range of 25 to 100 mg which is similar to the intramuscular (IM) dose range of 25 to 75 mg. However, the bioavailability after oral administration was poor, and the rate of absorption was slower than that of IM administration. The plasma half-life was reported as 6.8–7 h.[14] Hence, the chance for adverse effect will be more in the parenteral therapy. This new prokinetic drug is being increasingly used, its tendency to cause Parkinsonian features should be born in mind while dealing patients with acute-onset Parkinsonism or other involuntary movements like dystonias.

A recent report on six patients with the adverse effect such as rigidity and tremor in four patients after LS treatment of 1–12 weeks and the symptoms were fully improved/subsided after stopping the drug.[15] Radhakrishnan and Goyal showed that at least 50% improvement of symptoms on stopping the LS.[11] In this study, none of the patients improved in their symptoms after the stopping the medicine. Our study is consistent with this observation to Sharma *et al*. in which they reported persisted akathisia in most of the patients even after withdrawal of LS.[6] The symptoms are often severe and irreversible and were managed with levodopa and pramipexole. Dopaminergic drugs such as carbidopa-levodopa (100/10 mg) or pramipexole, dopamine agonist (0.5 mg) are the common treatment given for the adverse incidence. This is the first study reported from south India in 30 patients who presented with the adverse effect of LS. A small sample size and short duration of follow-up are the major limitations of this study. Therefore, a large prospective study from a multicenter with more cases is warranted.

Conclusion

The LS treatment produces adverse effects such as tremor and stiffness. Therefore, early recognition of this condition is essential for its complete cure and better prognosis. Physicians should be cautious about the adverse effects of LS therapy, especially when one comes across an acute recent onset extrapyramidal syndrome. Early recognition would probably improve the prognosis.

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Conflicts of interest

There are no conflicts of interest.

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