Levosulpiride-Induced Dystonia: 7 Cases

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Abstract

Levosulpiride is a newer prokinetic agent with increasingly extensive use in India by general physicians. Levosulpiride selectively inhibits gut and central D2 receptors and is associated with various movement disorders like- tremor, Parkinsonism, dyskinesias and rarely dystonia. We report 7 cases of levosulpiride-induced dystonia at our institute. Though all patient had at least 50% improvement after discontinuation of levosulpiride, none had complete recovery at mean follow up of 5.5 months. Through this article we want to highlight extrapyramidal side effects of levosulpiride, need of its awareness among physicians.

Introduction

Levosulpiride (LVS), a known prokinetic agent, is a benzamide derivative with selective inhibition on central and enteral D2 receptors.[1] This drug is a preferred choice for treatment of functional dyspepsia in many countries and lack life threatening side effects.[2-4] However LVS use is associated with various movement disorder including tremor, dyskinesia and Parkinsonism[5-7] causing significant disability. Apart from a few case reports/ short case series, data on LVS induced movement disorders (LIM), particularly LVS induced dystonia are limited. In this article we report 7 cases of LVS induced dystonia presented to neurology department of our institute.

Case 1

A 67-year-old female patient presented with abnormal involuntary movements of tongue and lower lip of 4 years duration. She also complained of feeling of discomfort and urges to move her lower limbs constantly for last 8 months along with increase in intensity of orolingual symptoms for past 8 months. There was no abnormal posturing of limbs or neck, rest tremor, rigidity or bradykinesia. She was a known diabetic and hypertensive for 20 years with a fair glycemic and blood pressure control. She was on multiple medications for symptoms of dyspepsia for past 4 years with mild improvement of symptoms. Her medicines contained LVS, which was started 4 years back with a dose of 25 mg/day. Her dystonic movement started after about 1 month of onset of LVS. For past 8 months she has been taking LVS 75mg/day temporally correlating with worsening of her neurological symptoms. There was no past or current history of any previous antipsychotic use.

Examination revealed oro-lingual dystonia and akathesia. Her brain imaging showed chronic ischemic changes only. Considering close correlation of onset of drug and dystonia, provisional diagnosis of LIM was made and offending drug was stopped. She was treated with tetrabenazine (TBZ) 25mg-75mg/day and clonazepam (CLZ) 0.5-1.0 mg/day. At 3 months follow up; there was 30-40% improvement in symptoms that further improved to 80-90% at 10 months follow up.

Profile of other cases with LVS-induced dystonia is detailed in Table 1.

Discussion

LVS is a newer prokinetic drug with increasing extensive use in India by general physicians. It selectively inhibits presynaptic dopamine D2 receptors with sodium dependent functions, in gut and central nervous system. There has been an increase in the prescription of LVS in recent years and consequently an increase in the incidence of LIM.

We observed 7 patients with LVS-induced dystonia (age 48-75 years, male/female 3/4). All seven patients had extrapyramidal side effect at a dose of 25 mg / day and time to onset of symptoms ranging from 3 days to ≤ 1month. Three patients had jaw opening dystonia, 3 had oro-lingual dystonia (OLD) and 1 presented with cranio-cervical dystonia. Drug Induced akathesia and Parkinsonism (DIP) was seen in one patient each. All our patients had at least 50% improvement (global subjective assessment) of symptoms on stopping LVS. All of them were prescribed tetrabenazine and clonazepam, 4 patients received additional baclofen (details in table1). The patient with OLD received 28 IU of injection botulinum toxin in

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Received: 26.12.2017; Accepted: 13.04.2018

Table 1: Profile of patients with LVS-induced dystonia

Case	Age/sex	Duration of symptoms, (in months)	Dose of LVS at onset / Maximum dose /day (in mg)	Time to onset of symptoms after initiation of LVS (in weeks)	Distribution of movement disorder	Treatment given/ day (in mg)	Outcome at last follow up
1	67/F	48	25/ 75	<4	OLD, akathesia	TBZ 75 CLZ 1.0	80-90% recovery/ 10 months
2	66/M	5	25	2	OLD	TBZ 75 CLZ 2.0 BACL 20	60-70% recovery / 3 months
3	65/F	1.5	25	1	OMD (Jaw opening) dystonia	TBZ 37.5 CLZ 0.75 BACL 40	40-50 % recovery/3 months
4	75/M	1 week	25	3 days	OMD (Jaw opening) dystonia, DIP	TBZ 75 CLZ 1 BACL 20	70-80% recovery/1 month
5	65/M	6	25	<4	OLD	TBZ 75 CLZ 1.5 + Inj Btx	70-80% recovery/1 month
6	54/F	3	25/50	<4	OMD (Jaw opening) dystonia	TBZ 75 CLZ 1	50-60% recovery / 2 months/
7	48/F	48	25	1	Cervical + cranial dystonia	TBZ 75 CLZ 0.75 BACL 40 + Inj Btx	60-70% recovery/ 20 months

LVS= levosulpiride, OLD= Oro lingual dystonia, OMD- Oro mandibular Dystonia, DIP- Drug induced Parkinsonism, Tetrabenazine=TBZ, Clonazepam=CLZ, BACL=Baclofen, Inj Btx= Injection botulinum toxin, IU= international units

addition to drugs and reported 70% recovery at 1 month follow up. The patient with cranio-cervical dystonia also received botulinum injection twice (bilateral trapezius 40 IU each and left sternocleidomastoid 30 IU) with 60-70% improvement in symptoms that lasted for 6 months. At follow up of 1-20 months (mean 5.5 months) none of the patients had complete recovery. High frequency of LIM observed in elderly population may be due to more frequent dyspepsia and use of prokinetic. Increased susceptibility of elderly brain to LIM because of age related change is another possible explanation.[8]

Shin et al. identified 91 patients with LIM over a period of 6 years (2002-2008), 78 patients (85.1%) aged more than 60 years. The most common LIM in their study was Parkinsonism (93.4%) followed by tardive dyskinesia (9.9%) and isolated tremor (3.3%).[6] Oro-lingual area was the most common part affected by tardive dyskinesia. Even after withdrawal of LVS, 48 % patients with Parkinsonism and 67% with tardive dyskinesia had persistent symptoms. The mean dose of LVS causing DIP was 74.1 6 ± 19.2 mg. The mean dose of LVS at which our patients developed extrapyramidal side effects was 25mg. We might assume that higher dose of LVS is associated with Parkinsonism and lower doses with dystonia.

LVS induced dystonia is reported very rarely. Gupta S et al. observed acute muscular dystonia of hands, leg tongue muscles and akathesia in one of his patients taking LVS.[9] Diwan AG reported a 70-year-old female patient with early onset dystonia (after 3 days of 25 mg/day dose of LVS). She had complete recovery of symptoms on withdrawal of drug.[10] Naskar S and Kamal Nath reported upper trunk and neck dystonia in a forty-year-old female after intake of LVS 25mg/day for 4 months. They highlighted development of early onset treatment resistant dystonia even with low dose of LVS.[11]

Our article invite attention on LIM, a disabling condition caused by drugs used for relatively minor condition. We want to highlight the long latency in diagnosing LIM, a potentially treatable condition. Though, in our patents none had completely improved after mean follow up of 5.5 months on treatment. This warrants the need for awareness about extrapyramidal side effects of LVS among physicians. The offending drug to be stopped at slightest suspicion of LIM. A warning label about extra pyramidal side effects of LVS on drug envelope is highly recommended.

Acknowledgment

We express our heartfelt gratitude to all our patients and their family

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