Levosulpiride associated neuroleptic malignant syndrome in an elderly patient: A tale of confusing brand names

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March 30, 2022

Abstract

Neuroleptic malignant syndrome(NMS) is a lethal idiosyncratic reaction characterized by fever, rigidity, altered sensorium and autonomic disturbances. Antidopaminergic drugs such as haloperidol, dopamine depletors like reserpine and atypical antipsychotics such as risperidone, are the major drugs implicated in NMS. Levosulpiride belongs to the benzamide class of antiemetics and is a blocker of dopamine(D2) receptors. The drug is available in India, Korea and some European countries. Here we present an interesting case of Levosulpiride associated neuroleptic malignant syndrome in an elderly female. The case also reflects how a minor difference in the brand names can produce a major debilitating cascade in geriatric patients.

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Word count : 1000

Table count : 1, Supplementary table: 1

Keywords: Geriatric pharmacovigilance, Levosulpiride, extrapyramidal, neuroleptic malignant syndrome, D2 blocker.

What is already known about this subject : NMS is common with D2 blockers but rarely reported with Levosulpiride

What this study adds : NMS can occur with Levosulpiride. Drugs with confusing brand names can be hazardous for elderly patients and should be scrutinized.

Dear Editor,

An 80-year-old female presented with generalised weakness, poor speech and intermittent movements of bilateral hands and peri-oral area of 10 days duration, and fever for 2 days. She had been bedridden for the past 10 days. The patient had a background history of hypertension, type 2 diabetes mellitus, hypothyroidism, and chronic bronchitis. She was receiving cilnidipine 10mg b.i.d, thyroxine 50µg o.d, zolpidem 5mg o.d, glimepride 2mg o.d, metformin 1000mg o.d, metered dose inhaler(MDI) of salmeterol- fluticasone and an over-the-counter analgesic of unclear identity on as needed basis for osteoarthritis of the knees. She was febrile, well oriented at the time of admission, with stable vitals. Chest examination revealed bilateral crackles. Bilateral upper limb tremors were present with generalised rigidity. After routine investigations (**Table 1**), a provisional diagnosis of urinary tract infection resulting in sepsis and acute kidney injury was made. Meropenem was initiated at the dose of 500mg 8-hourly and linezolid at the dose of 600mg 12-hourly. Prophylaxis for deep vein thrombosis was initiated.

On day-3 of admission, the patient had one episode of generalized tonic clonic seizures (GTCS) and became delirious. Injectable phenytoin 100mg was given 8-hourly along with oral carbamazepine 200mg b.i.d and clobazam 10mg o.d. Magnetic resonance imaging (MRI) of the brain done on day-4 of hospital stay was normal. Electroencephalogram (EEG) done on day-5 of hospital stay was non-specific with features of metabolic encephalopathy. Cerebrospinal fluid examination was planned but withheld as consent could not be obtained. The patient's blood pressure and heart rate were normal in the first few days of hospitalization but showed marked fluctuations thereafter during continuous monitoring, requiring multiple drug and dose modifications. As her general condition including tremors failed to improve, a provisional diagnosis of neuroleptic malignant syndrome was made, and bromocriptine was started at the dose of 2.5mg BD on day-12. Marked improvement in tremors and general condition was seen within 24 hours of starting bromocriptine. Carbamazepine was tapered and stopped over the next few days. Since the patient developed excessive sedation with bromocriptine, it was replaced by levodopa-carbidopa 62.5 mg t.i.d. This was well tolerated by the patient. A repeat MRI of the brain was again non-contributory, and the patient was discharged on day-20.

To identify the cause of NMS, drug review was repeated, and the caregivers were asked to bring the over-the-counter analgesic which the patient had been taking. The OTC analgesic prescribed one-month back was PANADOL (paracetamol 500mg). Instead, the patient started consuming PANIDO-L (pantoprazole 40mg- Levosulpiride 75mg). This had been prescribed to the patient by her family physician 5 months back, probably for dyspepsia. The exact amount of consumption of PANIDO-L could not be ascertained, but the caregivers gave a history of once to twice daily dosing of the drug for the past 20 days before she got admitted. At present with uneventful follow up of more than 1 year, the patient is maintained on thyroxine, nifedipine, chlorthalidone and MDI of salmeterol-fluticasone.

Neuroleptic malignant syndrome(NMS) is a lethal idiosyncratic reaction characterized by fever, rigidity, altered sensorium and autonomic disturbances.[1]NMS carries a mortality rate of 10-20% if untreated. The aetiopathogenesis of NMS is still unclear but dopamine blockade in hypothalamus, meso cortical system and striatum has been linked to fever, altered sensorium and Parkinsonian features, respectively. Increased sympathoadrenal activity and abnormal regulation of calcium in skeletal myocytes are thought to produce autonomic disturbances and muscle rigidity.[1] In many cases, the typical features of NMS are preceded by the development of Parkinsonian features, as was in our case. Here, we reported a case of levosulpiride associated NMS with normal CPK in an elderly female with moderate renal dysfunction. CPK is raised in many cases

of NMS but it is no longer uncommon to find NMS with normal CPK.[1,2]Levosulpiride, S(-) enantiomer of sulpiride, belongs to the benzamide class of antiemetics and is a blocker of dopamine (D2) receptors. The drug is available in India, Korea, and some European countries. It is used for gastrointestinal disorders at the dose of 25 mg thrice daily while a higher dose of 200-400 mg is advised for the management of psychiatric illnesses. Since the primary route of elimination of levosulpiride is renal, toxicity can occur even when the drug is used at therapeutic dose in patients with renal derangement. On Naranjo scale, the reaction shared a 'probable' association with levosulpiride and was rated as 'severe' in Hartwig's severity assessment scale.

The common differential diagnoses of NMS include viral encephalitis, serotonin syndrome, lethal catatonia and nonconvulsive status epilepticus and were reasonably excluded in our patient (**Supplementary table 1**).[1] Lack of clinical improvement with reasonable course of antibiotics and antiepileptics and marked improvement within 24 hours of bromocriptine administration are the major features supportive of NMS. On PubMed search, we found only one published case of levosulpiride associated NMS. The case occurred in a 53-year-old female of rheumatoid arthritis and type 2 diabetes mellitus with adrenal insufficiency who developed acute renal injury secondary to gentamycin injections and then developed nausea and vomiting for which she received parenteral levosulpiride. NMS like features developed soon after.[3] Another drug suspected to contribute to our patient's condition was cilnidipine. Though we could not find any relevant reports of possible association of NMS with cilnidipine, a possibility of drug interaction between levosulpiride and cilnidipine cannot be excluded. Cilnidipine belongs to the class of L type calcium channel blockers and some members of this class have been linked with Parkinsonian syndrome complex.[4]

The present case highlights two major points. First, NMS can occur with levosulpiride at the recommended therapeutic dose, particularly in the presence of renal dysfunction. Discontinuation of the offending drug, prompt symptomatic therapy and institution of bromocriptine are the life saving measures which make NMS treatable. Second, the case also highlights how a minor difference in the brand names of two drugs can lead to inadvertent administration of a wrong drug and produce undesired consequences, especially in elderly patients. Such easily available over the counter medications with confusing brand names need to be under stricter scrutiny of regulatory bodies.

Acknowledgment: None

Conflict of interest: None

Funding: None

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Table 1 : Biochemical, hematological, and radiological investigations of the patient.

Supplementary table 1: Differential diagnoses of neuroleptic malignant syndrome and salient features.

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`Table 1 (1).docx` available at https://authorea.com/users/323229/articles/562160-levosulpiride-associated-neuroleptic-malignant-syndrome-in-an-elderly-patient-a-tale-of-confusing-brand-names