RESEARCH ARTICLE

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Domperidone induced neuroleptic malignant syndrome: an uncommon toxicity of a common drug.

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ABSTRACT

Domperidone is commonly used as an antiemetic and prokinetic drug. Its safety profile is presumed to be good and serious side effects are seldom associated with it. The elderly population in general is more susceptible to adverse drug reactions owing to altered pharmacokinetics and pharmacodynamics. Here we present a case of neuroleptic malignant syndrome in an elderly lady who was prescribed domperidone.

Key-words: Neuroleptic malignant syndrome, domperidone, geriatric pharmacology, pharmacovigilance

Introduction

Domperidone, a dopaminergic D2 receptor blocker, is used clinically as an antiemetic and a prokinetic in a spectrum of disorders affecting the gastrointestinal system. Domperidone is unable to cross the blood brain barrier and hence devoid of side effects affecting the central nervous system.[1] Neuroleptic malignant syndrome (NMS) is a rare but catastrophic reaction seen in approximately 2% patients on antipsychotics.[2] It is characterized by rigidity, hyperthermia, altered mental status and elevated serum creatine phospho kinase (CPK). In majority of cases, symptoms are seen to occur within 1-4 weeks of use of neuroleptic but risk of developing NMS persists even after 10-20 days of discontinuation of the drug. Symptoms of NMS can persist for 1-44 days and death is generally due to respiratory failure.[3] On advanced search using Pubmed in the month of November 2014, using keywords "Domperidone" and "Neuroleptic malignant syndrome" in title/abstract, we found only one case report of NMS by domperidone in an adult female with a positive family history of malignant hyperthermia.[4] Here we report a case of NMS after domperidone administration in an elderly female.

Case History

An elderly lady of age 70 years with a background of COPD was admitted to the geriatric ward with productive cough, fever and dyspnea of 5 days duration. There was no history of chest pain, orthopnea, palpitations or syncope. Her sensorium was clear. On examination, patient was febrile and tachypneic (RR-30/min) with stable blood pressure. Chest examination revealed bilateral coarse crepitations. Chest X Ray showed bilateral patchy infiltrates and a diagnosis of pneumonitis leading to acute exacerbation of COPD was made. Other lab findings are shown in Table1.

Table 1: Laboratory findings of the patient

	1st admission	Re admission
PaO_2 (mmHg)	63.5	73
SO_2 %	93.3	93
Hb (g/dL)	12.2	12.2
serum creatinine (mg/dL)	0.9	0.9
blood urea (mg/dL)	29	29
SGOT/SGPT	17/15	48/24
TLC(no./µL)	7800(N70L22)	9500(N79L14)
Na/K (meq/L)	136/5	139/4
RBS(mg/dl)	85	118
Ca/Po_4(mg/dL)	7.1/3.4	10.7/3.9
CPK(IU/L)	Not done	598

The patient was nebulized with levosalbutamol-ipratropium-budesonide and oxygen was administered. At the same time she was started on parenteral Amoxiclav 1.2g 8 hourly and oral azithromycin 500 mg daily. Oral Rabeprazole-domperidone combination (20mg Rabeprazole and 10 mg domperidone) was administered as a counter measure to stress gastritis. On 3rd day of hospital stay, she developed bilaterally symmetric rigidity of upper and lower limbs, bilateral hand tremors, insomnia and dysphagia. There was no postural hypotension or other signs of autonomic dysfunction. MRI Brain was done which showed only age related cerebral atrophy. There were no features suggesting sensory, cranial nerve or cerebellar involvement. Bilateral plantars were downgoing and upper and lower limb reflexes were normal ruling out upper motor neuron involvement. Domperidone was thought to be responsible for rigidity and therefore stopped. Trihexiphenidyl was started at a dose of 2mg tid and improvement was noticed on day 8. Patient was discharged on day 14 and advised continuation of trihexiphenidyl for 1 week more. After 10 days patient reported almost complete recovery from rigidity but presented with altered sensorium for which trihexiphenidyl was stopped. However, after 2 weeks, patient was readmitted with chief complaint of severe rigidity and altered mental status. Her Glasgow Coma score was 5 with $E_1V_1M_3$. In between, there was no history of trauma/seizure/vomiting/exposure to high temperature/dryness of mouth or skin. Her heart rate was 100/min, respiratory rate - 32/min and axillary temperature was 101^0F. The patient had a BP of 110/80mm Hg with a postural fall of 30 mmHg systolic and 10 mmHg diastolic, suggesting autonomic dysfunction. There was no neck rigidity or choreiform movement. Examination revealed severe rigidity of the entire body and bilateral crepitations in chest. Reports of cerebrospinal fluid examination, serum troponin I, serum B-type natriuretic peptide and thyroid function test were normal. Suspecting NMS, CPK level was measured on the 4th day of hospital stay and was found to be elevated (597 IU/L). Diagnosis of NMS was made and bromocriptine along with levodopa-carbidopa were started but condition of patient deteriorated and she died of cardiorespiratory arrest on 6th day of hospital stay.

Discussion

A clinical diagnosis of NMS was made in this case. NMS is treatable but easily overlooked owing to variations in the clinical presentation and the absence of a standard diagnostic criteria. Although international consensus was recently arrived at, further validation is needed before implementing the new criteria in clinical practice.[5] We used the DSM –IV criteria for NMS diagnosis.[3] Table 2 shows the NMS criteria and those fulfilled in our patient.

Table2 : DSM – IV criteria for NMS

	Criteria fulfilled in our patient
Criteria A	
Muscle rigidity	Yes
Fever	Yes
Criteria B	
Diaphoresis	--
Dysphagia	--
Tremors	Yes
Incontinenece	--
Altered consciousness	Yes
Mutism	--
Tachycardia	Yes
Elevated or Labile BP	Yes
Leucocytosis	--
Lab evidence of muscle injury	Yes
Criteria C	
Not due to other cause(Viral encephalitis)	Yes
Criteria D	
Not due to mental disorder	Yes

The degree of CPK elevation was moderate and might be non-specific for NMS in this case, but on careful search of literature we found multiple case reports of NMS with no or minor elevation of CPK. [6-7] After applying Naranjo Scale for causality of reaction to domperidone, score of 6 was obtained, putting the case in the 'Probable' category.[8] Further the reaction was rated to be 'severe' on Hartwig's severity assessment scale. [8] NMS is often confused with conditions like viral encephalitis but normal CSF and MRI findings suffice to rule out the possibility of any viral infection in our patient. Another condition with similar presentation is lethal catatonia but neither there was any history of development of abnormal behavioral pattern over previous weeks nor did the patient show any stereotypic movements or waxy flexibility during the entire course of her illness.

Domperidone is considered to be one of the safest antiemetic/ prokinetic since it is unable to cross the blood brain barrier. The development of NMS can be attributed to the direct muscle toxicity of the drug or alternatively the altered permeability of blood brain barrier in the elderly. Enhanced penetration of domperidone into the central nervous system could have resulted in its deposition in the striatum or hypothalamus. Further studies are needed to know the exact mechanism of action. Dantrolene is the drug of choice for NMS but was not used in this case because of availability issues. [2-3]

In our knowledge, this is the first case report of NMS in elderly after domperidone administration and that too at

lowest dose possible. The case emphasizes the need to exercise caution while using domperidone or any drug with anti-dopaminergic properties in the elderly patient, especially those with acute illnesses which may alter the blood-brain barrier function. A further point of note is that domperidone is widely used in conjunction with Levodopa to counteract its emetogenic potential. The current case report also raises concerns regarding the use of domperidone in patients of Parkinsonism.

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