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

Upinder Kaur, Sankha Shubhra Chakrabarti, Indrajeet Singh Gambhir
Division of Geriatrics, Department of General Medicine Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005, UP.

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. Neuroleptic malignant syndrome (NMS) is a rare but catastrophic reaction seen in approximately 2% patients on antipsychotics. 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. 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. 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 Table 1.

<table>
<thead>
<tr>
<th>Table 1: Laboratory findings of the patient</th>
<th>1st admission</th>
<th>Re admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2 (mmHg)</td>
<td>63.5</td>
<td>73</td>
</tr>
<tr>
<td>SO2 (%)</td>
<td>93.3</td>
<td>93</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>12.2</td>
<td>12.2</td>
</tr>
<tr>
<td>serum creatinine (mg/dL)</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>blood urea (mg/dL)</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>SGOT/SGPT</td>
<td>17/15</td>
<td>48/24</td>
</tr>
<tr>
<td>TLC (no./µL)</td>
<td>7800(N70L22)</td>
<td>9500(N79L14)</td>
</tr>
<tr>
<td>Na/K (meq/L)</td>
<td>136/5</td>
<td>139/4</td>
</tr>
<tr>
<td>RBS(mg/dL)</td>
<td>85</td>
<td>118</td>
</tr>
<tr>
<td>Ca/Po2 (mg/dL)</td>
<td>7.1/3.4</td>
<td>10.7/3.9</td>
</tr>
<tr>
<td>CPK(IU/L)</td>
<td>Not done</td>
<td>598</td>
</tr>
</tbody>
</table>

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The patient was nebulized with levosalbutamol-
iratropium-budesonide and oxygen was administered. At
the same time she was started on parenteral
Ampicillin 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. Trihexphenidyl 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
trihexphenidyl for 1 week more. After 10 days patient
reported almost complete recovery from rigidity but
presented with altered sensorium for which trihexphenidyl 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 V M. 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 103°F. 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.

<table>
<thead>
<tr>
<th>Criteria A</th>
<th>Criteria B</th>
<th>Criteria C</th>
<th>Criteria D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle rigidity</td>
<td>Diaphoresis</td>
<td>Not due to other cause(Viral encephalitis)</td>
<td>Not due to mental disorder</td>
</tr>
<tr>
<td>Fever</td>
<td>Dysphagia</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
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<tr>
<td>Yes</td>
<td>Incontinence</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>Altered consciousness</td>
<td></td>
<td></td>
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<td></td>
<td>Mutism</td>
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<td></td>
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<td></td>
<td>Tachycardia</td>
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<td></td>
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<tr>
<td></td>
<td>Elevated or Labile BP</td>
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<td></td>
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<td></td>
<td>Leucocytosis</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Lab evidence of muscle injury</td>
<td></td>
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</table>

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.

REFERENCES:

Cite this article as: