Is the combination of domperidone and metoclopramide increasing the risk of developing serotonin syndrome?: a case report

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Abstract

Metoclopramide and domperidone are dopamine antagonists that can cause an acute dystonic reaction. Metoclopramide is a rare but major contributor to serotonin syndrome, particularly when used with other serotonergic agents. Serotonin syndrome is a rare, potentially life-threatening adverse reaction characterized by a triad of altered mental status, autonomic dysfunction, and neuromuscular hyperactivity that typically results from exposure to serotonergic agents. Herein, we report a previously healthy 9-year-old girl who was brought to the emergency department with an alteration in the level of conscious and involuntary repetitive movements after approximately 24 hours of receiving a therapeutic dose of metoclopramide and domperidone. Physical examination showed tachycardia, hyperthermia, and a Glasgow Coma Scale score of 11, as well as mydriasis and hyperreflexia. In addition to resolving the symptoms after administering midazolam and diphenhydramine, the diagnosis of serotonin syndrome was made based on the classical symptoms and signs, which met the Hunter criteria. This case indicates the need for clinical awareness of the life-threatening syndrome and caution with medications having potential interactions with metoclopramide.

Key words: Domperidone; Dystonia; Metoclopramide; Pediatrics; Serotonin Syndrome

Introduction

Metoclopramide is a common antiemetic medication that inhibits serotonin reuptake and may cause acute dystonic reactions or serotonin syndrome in rare instances, particularly when used with other serotonergic medications (1,2). Domperidone is a neuroleptic antiemetic, a dopamine receptor antagonist. Like metoclopramide, it can induce dystonic and extrapyramidal symptoms (EPSs), with a higher likelihood in children (3). While evidence emphasizing the possible synergistic effects between metoclopramide and domperidone is limited, combining these 2 medications might theoretically increase the risk of adverse effects (AEs) related to their dopaminergic actions (4). Serotonin syndrome, a rare and potentially life-threatening adverse reaction of such drugs, results from excessive serotonergic activity in the central nervous system (CNS), which can arise from inadvertent drug interactions, intentional overdoses, or the consequences of therapeutic use (1). The syndrome can affect patients of all ages and typically presents with a triad of altered mental status, autonomic dysfunction, and neuromuscular hyperactivity (5). The diagnosis remains challenging since it depends on a clinical diagnosis without laboratory criteria.

Herein, we describe a 9-year-old girl who was diagnosed with serotonin syndrome based on the Hunter diagnostic criteria. This case report may
increase clinical awareness and improve patient care of the potentially life-threatening condition.

Case

A previously healthy 9-year-old girl was brought to the emergency department (ED) for evaluation of her altered mental status and abnormal movements. Two days earlier, she experienced recurrent vomiting and was administered domperidone 10 mg every 8 hours (0.8 mg/kg/day) for 1 day with no improvement, and subsequently a single dose of intravenous (IV) metoclopramide 2.5 mg (0.07 mg/kg) at other institutions. Approximately 24 hours after the single administration of metoclopramide, she became increasingly agitated, confused, and lethargic with involuntary repetitive movements. The movements encompassed the widely opened mouth with rhythmic tongue protrusion, oculogyric crisis, torticollis, opisthotonos, and generalized myoclonus. Furthermore, her temperature rose up to 39 °C after around 36 hours of the use of metoclopramide. She did not undergo a recent infection or take another medication. There was no past or family history of psychiatric disorders.

The initial vital signs at the ED were as follows: blood pressure, 110/75 mmHg; heart rate, 160 beats/minute; respiratory rate, 27 breaths/minute; temperature, 37.3 °C; oxygen saturation, 95% on room air; and a Glasgow Coma Scale score, 11 (eye opening, 4; verbal response, 2; and motor response, 5). At the presentation, she was agitated, confused, and disoriented. A complete neurological assessment showed bilateral mydriasis with sluggish reactivity, myoclonic movements, and muscle rigidity of the upper and lower extremities including the neck muscles. Reflexes were 2+ and 3+ in the upper and lower extremities, respectively, with bilateral plantar extensor responses. Otherwise, no focal or lateralizing deficits were observed.

The girl was hospitalized to treat the case of presumed serotonin syndrome or neuroleptic malignant syndrome (NMS), and to rule out other serious conditions, such as CNS infection. A brain computed tomography was conducted immediately afterward, proving the absence of acute cerebral lesions. We saw unremarkable findings of complete blood count, electrolytes, hepatic and renal function tests, toxicology, erythrocyte sedimentation rate, C-reactive protein, creatine phosphokinase, cerebrospinal fluid analysis, and urinalysis. Given the abovementioned use of metoclopramide, the diagnosis of serotonin syndrome was made based on the clinical manifestation that met the Hunter criteria (4). In addition to supportive measures, the girl received single doses of IV midazolam and per os diphenhydramine, resulting in the cessation of the abnormal movements. Subsequently, she received per os diphenhydramine every 8 hours for 1 day. Over the following 36 hours, she returned to her baseline and was observed for 24 hours. Finally, approximately 72 hours after the presentation to the ED, she was discharged uneventfully and advised to avoid metoclopramide and other medications that can induce serotonin syndrome.

Discussion

Metoclopramide is commonly used as both a prokinetic and an antiemetic to ease nausea, vomiting, and gastroesophageal reflux. Beyond its role as a dopamine receptor antagonist, metoclopramide also acts as an agonist of 5-hydroxytryptamine 4 receptors and as an antagonist of 5-hydroxytryptamine 3 receptors. Despite its therapeutic benefits, use of the drug can lead to a range of AEs, such as drowsiness, restlessness or agitation, headache, diarrhea or constipation, and muscle spasms or stiffness. Additionally, metoclopramide has been implicated in serotonin syndrome due to its inhibition of serotonin reuptake (1,2).

Both metoclopramide and domperidone primarily act as a dopamine receptor antagonist to increase the gastrointestinal motility. Domperidone does
not cross the blood–brain barrier as readily as metoclopramide. However, its EPSs, such as dystonia, akathisia, and tardive dyskinesia, have been observed in infants or young children due to the immature and more permeable blood–brain barrier (3,6). It is important to note that the AEs of both medications are dose-independent so that can develop even within therapeutic doses (7). While metoclopramide does have some influence on the serotonin receptors, it is generally not considered potently serotonergic. Although serotonin syndrome caused solely by metoclopramide has been rarely reported, it is notable that individual responses to medications can vary, and rare AEs like serotonin syndrome can still occur (8).

Concurrent use of metoclopramide with antipsychotics may increase the bioavailability of each drug and the risk of AEs, such as EPSs (9). This corroborates our hypothesis that the concurrent use of domperidone and metoclopramide could predispose children to serotonin syndrome. The diagnosis is challenging owing to the variable onset, evolving diagnostic criteria, nonspecific symptoms, a lack of awareness among clinicians, and substantial clinical overlap with other conditions (1). The incidence of serotonin syndrome is unknown due to its underreporting. In children, the incidence of metoclopramide–induced acute dystonia is estimated to be as high as 25%. Girls, young children, and long-term users are particularly at risk (7).

Clinical diagnosis of serotonin syndrome requires the use of serotonergic agents with a detailed medical history, a review of other medications, and careful physical examination. Despite the lack of laboratory criteria, some patients may show high concentrations of creatine phosphokinase, leukocytosis, and low bicarbonate. In severe cases, they may develop rhabdomyolysis and acute kidney injury (1). However, the case patient exhibited normal laboratory results. In approximately 90% of cases, symptoms manifest within the initial 24 hours following exposure to serotonergic drugs, with the remaining cases presenting within 72 hours (1,10). Our patient developed symptoms 24 hours after the metoclopramide injection. Patients with serotonin syndrome can present with varying degrees of mental status (agitated, disorientation, or delirium), autonomic dysfunction (mydriasis, hyperthermia, or tachycardia), and neuromuscular hyperactivity (myoclonus, tremor, muscle rigidity, or hyperreflexia). Mild symptoms may include intermittent tremors, myoclonus, tachycardia, and hyperreflexia (1,10,11).

Among the proposed diagnostic criteria for serotonin syndrome, the Hunter criteria are most accurate, with an 84% sensitivity and 97% specificity. The diagnosis requires one of the following conditions after exposure to serotonergic agents: spontaneous clonus; inducible clonus with agitation or diaphoresis; hypertonia and temperature above 38 °C with ocular or inducible clonus; or tremor and hyperreflexia (12). The presentation of the case patient was consistent with the syndrome given the receiving of metoclopramide along with the altered mental status (agitation, confusion, and lethargy), autonomic instability (an elevated temperature, tachycardia, vomiting, and mydriasis), and neuromuscular symptoms (tongue protrusion, oculogyric crisis, torticollis, opisthotonos, generalized myoclonus, hyperreflexia, and bilateral Babinski sign). In addition, the diagnosis was supported by excluding other causes after the completion of the laboratory assessment as well as the improvement in her symptoms following the administration of midazolam and diphenhydramine.

Differential diagnoses include NMS, anticholinergic toxicity, and CNS infections, to name a few (1). Overlapped symptoms of serotonin syndrome and NMS make distinguishing the 2 entities challenging. Table 1 lists key points useful in distinguishing serotonin syndrome from NMS and anticholinergic toxicity (1,10,11,13). The 2 main distinguishing features are the rapidity of progression and the specific motor findings. Serotonin syndrome typically manifests within 24 hours, while NMS tends to develop gradually over a span.
of days to weeks (1,14,15). The majority of sero-
tonin syndrome cases resolve completely within 24 hours, whereas NMS typically necessitates an average recovery period of 9 days (1,14,15). Although anticholinergic toxicity can manifest symptoms similar to those seen in serotonin syndrome and NMS, the toxicity is distinguished by the mainte-
nance of normal muscle tone and reflexes (13). Acute dystonic reactions are usually rapid in onset and are characterized by torticollis, oculogyric crises, and opisthotonos. Compared with sero-
tonin syndrome, dystonic reactions have asymmetric muscle contractions and rapidly improve with diphenhydramine or benztropine (4). Malignant hyperthermia occurs in susceptible individuals exposed to succinylcholine or halogenated volatile anesthetics (16).

Supportive care is the cornerstone of manage-
ment. Most of the mild or moderate cases improved within 24 hours of discontinuing the serotonergic agents and supporting care (1). The care includes continuous cardiac monitoring, correction of vital signs, and administration of oxygen and IV flu-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Serotonin syndrome</th>
<th>Neuroleptic malignant syndrome</th>
<th>Anticholinergic toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causative agents</td>
<td>SSRI, SNRI, MAOI, tricyclic antidepressants, synthetic opioids, and illicit drugs</td>
<td>Antipsychotics, dopaminergic agents (withdrawal), and antiemetics</td>
<td>Antihistamines, antipsychotics, tricyclic antidepressants, and illicit drugs</td>
</tr>
<tr>
<td>Onset</td>
<td>Abrupt (≤ 24 h)</td>
<td>Gradual (≤ 7 d)</td>
<td>Abrupt (≤ 1-2 h)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Altered mental status, autonomic instabilities, and neuromuscular symptoms</td>
<td>Altered mental status, autonomic instabilities, and neuromuscular symptoms</td>
<td>Altered mental status, delirium, and visual hallucination</td>
</tr>
<tr>
<td>Core symptoms</td>
<td>Myoclonus, tremor, diarrhea, increased bowel sounds, and shivering</td>
<td>Hypersalivation, diaphoresis, dysphagia, and incontinence</td>
<td>Dry skin and mucus membrane, decrease bowel sounds, and urinary retention</td>
</tr>
<tr>
<td>Signs</td>
<td>Hyperthermia, raised BP, tachycardia, mydriasis, rigidity, hypersalivation, clonus, and Babinski sign</td>
<td>Hyperthermia, raised BP, tachycardia, “lead-pipe” rigidity, and hyporeflexia</td>
<td>Hyperthermia, raised BP, tachycardia, mydriasis, and normal muscle tone/proprioception</td>
</tr>
<tr>
<td>Main treatment</td>
<td>Stop serotonergic agent, IV fluid and cooling, Benzodiazepine, Cyproheptadine</td>
<td>Stop antipsychotics, IV fluid, Dantrolene, Bromocriptine</td>
<td>Stop anticholinergics, IV fluid and cooling, Benzdiazepine, Physostigmine</td>
</tr>
<tr>
<td>Recovery</td>
<td>≤ 24 h</td>
<td>≤ About 9 d</td>
<td>≤ Hours-days</td>
</tr>
</tbody>
</table>

may require antihypertensive agents, such as esmolol, and may be labile and challenging to treat. Hypotension can be treated conservatively with IV fluids alone, and if refractory to the fluids, norepinephrine, phenylephrine, and epinephrine (1,11). In cases of severe hyperthermia (>41.1 °C), increasing PCO₂, or severe rigidity might require soothing measures, including sedation, external cooling, muscle relaxation, or intubation with non-depolarizing neuromuscular blocking agents, such as vecuronium (11,17). Care should be taken to avoid succinylcholine due to the risk of hyperkalemia and worsening of rhabdomyolysis, as well as fentanyl, which can precipitate serotonin syndrome (11). Cyproheptadine is an antihistamine often used as an antidote for serotonin syndrome, particularly if BZDs and supportive care fail to correct vital signs and improve agitation (19). In certain cases, weakness and muscle pain can persist for several months. However, appropriate medical management of serotonin syndrome is generally associated with favorable outcomes (1).

Although serotonin syndrome is rare and preventable, it can lead to serious consequences. Clinicians should be aware of this life-threatening syndrome and be cautious with medications that have potential interactions with metoclopramide that may lead to serotonin syndrome.

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**Data availability**

All data presented in this manuscript are available from the corresponding author upon reasonable request.

**References**

Drugs induced serotonin syndrome


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