

Metoclopramide-induced Serotonin Syndrome

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Abstract

A 40-year-old woman with bipolar disorder who was taking mirtazapine presented with mydriasis, abnormal diaphoresis, myoclonus and muscle rigidity after taking metoclopramide. Her medical history, which included the use of serotonergic agents, and the presence of symptoms including myoclonus and muscle rigidity were consistent with a diagnosis of serotonin syndrome (SS) according to the Hunter criteria. The symptoms diminished following three days of treatment with oral lorazepam and cyproheptadine and a reduced dose of mirtazapine. Metoclopramide is frequently used to various gastric symptom. Metoclopramide is not widely known to induce SS. This potentially fatal condition should be avoided by exercising care in the use of drugs that have the potential to cause drug-drug interactions.

Key words: serotonin syndrome, metoclopramide

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Introduction

The amount of serotonergic agents that are prescribed has recently been increasing. One of the adverse events associated with serotonergic agents is serotonin syndrome (SS). The development of SS can be caused not only by an overdose of serotonergic agents but also through an interaction with other drugs (1, 2). It has been reported that more than 85% of physicians are not aware of SS (3). We encountered a patient who was treated with noradrenergic and specific serotonergic antidepressants (NaSSAs), who developed SS after receiving an intramuscular injection of metoclopramide, which was administered to alleviate nausea.

Case Report

A 40-year-old woman with bipolar disorder who was taking mirtazapine, lamotrigine, aripiprazole, and lorazepam presented to the clinic with a chief complaint of nausea, and was treated with an intramuscular injection of metoclopramide. Following this treatment, the patient was brought to the emergency department by her family who described her condition as being unusual, lethargic and unresponsive. On physical examination, no abnormalities were observed, other than diaphoresis and muscle rigidity. A neurological exami-

nation revealed that her Glasgow Coma Scale (GCS) was E4V5M6, conversation was established without any issue, slight mydriasis of the pupils was noted (5/5); the other cranial nerve, motor and sensory findings were all normal. Overall increased tendon reflexes, negative pathological reflex, and occasional myoclonus in the legs were observed. The results of blood tests revealed no significant abnormalities other than a creatine phosphokinase level of 362 IU/L. The intake of serotonergic agents followed by myoclonus symptoms and muscle rigidity were consistent with a diagnosis of SS, according to the Hunter criteria. The symptoms improved after 3 days of treatment with an increased dose of lorazepam and a decreased dose of mirtazapine, along with the administration of cyproheptadine (24 mg, per day).

Discussion

The patient in the present case was a 40-year-old woman who took both serotonergic agents and antipsychotics and who developed acute symptoms that were related to autonomic hyperactivity, such as mydriasis and abnormal diaphoresis, as well as myoclonus and muscle rigidity.

It is always necessary to keep SS in mind when patients taking serotonergic agents demonstrate acute changes in their mental status, autonomic hyperactivity, neuromuscular abnormalities or other relevant conditions. The symptoms of

Table. The Distinctions between Serotonin Syndrome (SS) and Neuroleptic Malignant Syndrome (NMS) (1-2).

Characteristic	SS	NMS
Onset	sudden	gradual
Symptoms present within	24 hours	7 days
Core symptoms	agitation, diarrhea	dysphagia, hypersalivation, incontinence
Neuromuscular findings	mydriasis, hyperreflexia, clonus	bradyreflexia, severe muscular rigidity
Class of drug	Serotonin agent	Dopamin antagonist

SS: serotonin syndrome, NMS: neuroleptic malignant syndrome

SS are divided into the following three categories: 1) changes in mental condition (anxiety, agitated delirium, restlessness, and disorientation); 2) autonomic hyperactivity (diaphoresis, tachycardia, hyperthermia, hypertension, vomiting, and diarrhea); and 3) neuromuscular abnormalities (tremor, muscle rigidity, myoclonus, hyperreflexia, and bilateral Babinski sign) (1). The neuromuscular abnormalities are more likely to be observed within the lower extremities (4). The Hunter criteria, which display 84% sensitivity and 97% specificity in the diagnosis of SS, are the preferred diagnostic criteria (5). The Hunter criteria are satisfied in a patient who meets one of the following conditions (in the setting of administration of serotonergic agents): spontaneous clonus, inducible clonus and agitation or diaphoresis, ocular clonus and agitation or diaphoresis, tremor and hyperreflexia, hypertonia, a body temperature of $>38^{\circ}\text{C}$ and ocular clonus or inducible clonus. The blood serotonin concentration is not relevant to the diagnosis (4). The treatment of SS includes the discontinuation of serotonergic agents, supportive care with the stabilization of body temperature, and the administration of benzodiazepines to control agitation and autonomic instability as well as the administration of cyproheptadine (a histamine-1 receptor antagonist with nonspecific 5-HT_{1A} and 5-HT_{2A} antagonistic properties). Patients with a temperature of $>41.1^{\circ}\text{C}$ require immediate sedation with paralysis with nondepolarizing agents such as vecuronium, as well as endotracheal intubation; the use of antipyretic agents such as acetaminophen should be avoided (1).

Since the patient's medical history included the use of antipsychotics in addition to serotonergic agents, neuroleptic malignant syndrome (NMS) was a potential differential diagnosis. Both NMS and SS are associated with fever, consciousness disturbance, autonomic symptoms, muscular rigidity, and increased creatine phosphokinase levels, which sometimes makes it difficult to arrive at a differential diagnosis. The following three points are useful in distinguishing SS from NMS (Table). First, there are differences in the medications that induce the symptoms. SS is associated with the administration of serotonergic agents, while NMS is associated with antipsychotics. The second point is the course of the onset of symptoms. The majority of patients with SS present within 24 hours, with most presenting within six hours, after a change in dose or the initiation of a drug. On

the other hand, NMS develops within a few days to a few weeks after the initiation of a drug. The third point involves the neuromuscular symptoms. Symptoms such as myoclonus and increased tendon reflexes are observed in patients with SS, but not in patients with NMS (6).

In addition to NMS, anticholinergic poisoning, sympathetic nervous system poisoning, encephalitis, meningitis, malignant hyperthermia, intoxication from sympathomimetic agents and sedative-hypnotic withdrawal are the main differential diagnoses of SS; these conditions have recently been termed "cluster" diseases (7).

Frequently used drugs, including metoclopramide, can also cause SS. It is important to avoid prescribing drugs that have the potential to cause the development of SS to patients receiving serotonergic agents. In previous reports on SS caused by metoclopramide, two cases were caused by the additional administration of a single dose of metoclopramide (10 mg) to patients who were taking serotonergic agents. There are no reported cases in which SS was caused by metoclopramide alone (8, 9). NaSSAs inhibit the alpha 2, 5-HT₂ and 5-HT₃ receptors, thereby reinforcing the effects of noradrenaline and serotonin. Accordingly, NaSSAs enhance the release of norepinephrine and 5-HT_{1A}-mediated serotonergic transmission. With regard to the mechanism, it has been reported that metoclopramide has a 5-HT₃ receptor blocking effect; although this effect is weak, it may influence the development of SS (10).

Drugs that are frequently used in the daily medical care setting can also cause SS. Tramadol, triptan, fentanyl, pentazocine, valproate, carbamazepine, sumatriptan, linezolid, dextromethorphan, lithium, monoamine oxidase inhibitors, ondansetron, levodopa, carbidopa-levodopa and various drugs are listed as having the potential to cause SS (1).

Although SS is a rare disease that can lead to serious consequences, it is preventable. Clinicians should recognize this potentially fatal medical condition and be careful of avoiding drugs that may interact to cause SS.

The authors state that they have no Conflict of Interest (COI).

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