Case Report

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Persistent High Fever After Metchloropramide Treatment; Neuroleptic Malignant Syndrome

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Abstract

Neuroleptic Malignant Syndrome (NMS) is a state neurotransmitter levels fluctuate subsequent to administration of neuroleptic agents. Etiology of NMS is unclear. It's a neurological emergency includes symptoms like altered mental status, rigidity, fever and dysautonomia. Our aim in here is to mention the side effects of metoclopramide, which is commonly used in Emergency Departments (ED). In our case, subsequent to intravenous admission of metoclopramide, patients clinic worsened with NMS symptoms and this was quite unexpected and unwanted for ED doctors. By this case report it is wanted to raise awareness against, side effects of metoclopramide and NMS. Subsequent to intravenous administration of single dose metoclopramide to relieve abdominal pain into 21 years old male with no history of chronical diseases, symptoms of fever, muscle rigidity, confusion and fluctuating blood pressure levels quickly emerged along with leukocytosis and high levels of creatine phosphokinase. ED Doctors suspected NMS. Further laboratory and imaging studies has excluded other central nervous system pathologies and infections. Eventually, patient's clinic got better with symptomatic therapy and he was discharged fully recovered. NMS due to metoclopramide is quite rare, but usage of therapies includes metoclopramide at ED's are quite often. Subsequent to administration of this drug, if patients clinical state worsens with fever, confusion and muscle rigidity, physicians should keep NMS in mind.

Keywords: Adverse reactions, metoclopramide, neuroleptic malignant syndrome

Introduction

Neuroleptic Malignant Syndrome (NMS) is associated with anti-psychotic (neuroleptic) agents. It's a life threating neurologic emergency with altered mental status, muscle rigidity, fever and autonomic dysfunction. Dysautonomic symptoms and systemic complications are direct causes of mortality (1).

NMS, a disease of young and adult males, widely accepted as a situation of the fluctuating neurotransmitter levels subsequent to administration of tranquilizing and anti-psychotic agents but there are also other reasons and it's etiology remains unclear. When associated drugs analyzed, medications (Table 1) formerly known as neuroleptic agents which are first generation of anti-psychotics with high (haloperidol) and low potencies (chlorpromazine), second generation of anti-psychotics (clozapine, risperidone, olanzapine) and anti-emetic drugs (metoclopramide) mostly have blamed as a cause (2, 3).

Patients of NMS may show symptoms and sings of hyperthermia, muscle rigidity, autonomic dysfunction

Table 1: Medications Associated with Neuroleptic Malignant Syndrome

Typical Neuroleptics	Atypical Neuroleptics	Antiemetics	Others	Dopaminergic Agents (withdrawal)
Haloperidol	Clozapine	Droperidol	Tetrabenazine	Levodopa
Chlorpromazine	Risperidone	Domperidone	Reserpine	Amantadine
Fluphenazine	Quetiapine	Metoclopramide	Amoxapine	Tolcapone
Thioridazine	Ziprasidone	Promethazine	Diatrizoate	Dopamine agonists
Trifluordazine	Aripiprazole	Prochlorperazine	Lithium	
Thiothixene	Zotepine	Droperidol	Phenelzine	
Loxapine	Amisulpride		Dosulepin	
Bromperidol	Olanzapine		Trimipramine	
Promazine			Desipramine	
Clopenthixol				

*This table was created using data from Reference 4.

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Table 2: The DSM-V Criteria for Diagnosing Neuroleptic Malignant Syndrome are as Follows

Major Criteria (all required)	Other Criteria (at least two required)
Exposure to dopamine-blocking agent	Diaphoresis
Severe muscle rigidity	Dysphagia
Fever	Tremor
	Incontinence
	Altered level of consciousness
	Mutism
	Tachycardia
	Elevated or labile blood pressure
	Leukocytosis
	Elevated creatine phosphokinase

*This table was created using data from Reference 4.

(such as sweating, dysphagia, sialorrhea, pallor, urinary incontinence), tachycardia, tachypnea, hypertension or postural hypertension and altered mental status. High levels of creatine phosphokinase (CK) and white blood cell (WBC) can be found. Other diagnostic criteria must be assessed too. For differential diagnosis infectious diseases (encephalitis, meningitidis, brain abscess, rabies, tetanus, sepsis etc.), endocrine diseases (pheochromocytoma, thyrotoxicosis etc.), intoxications (drug abuse, heavy metal poisoning, lithium, salicylates) and other pharmacologic syndromes (serotonin syndrome, malignant hyperthermia, drug withdrawal or drug overdose) should keep in mind (3, 5).

Many patients apply to ED with fever. Causes from quite a wide range can be the trigger of fever and before deciding the therapy, doctors need to find the origin of fever, which can be very hard sometimes. For instance, just like in our case, when a patient with no fever quickly suffered from fever after drug therapy, ED doctors should immediately consider drug side effects and drug interactions for fever's origin. Some of drugs shown at Table-1 are oftenly use in EDs, therefore when a situation like our case emerged, ED doctors should consider NMS as a possible fever origin. In our case, the occurrence of NMS after a single dose of metoclopramide is unexpected and undesirable situation for emergency physicians. Thereafter with our case report we wanted to point out NMS which may be cause of the fever. It's rare, nevertheless it is a neurological emergency that every physician should keep in mind.

Case Report

21 years old male with no medical history applied the ED with abdominal and dorsal pain. His pain had started 3-4 hours ago and it was getting more painful. There was no personal or family history of known disease and drug usage. During his physical examination, he's current situation was good, he was oriented and cooperated, no neurological pathologic signs had found. His vitals were, blood pressure: 126/68, fever: 36.7°C, pulse: 76 per minute, sO2: 95%. There was a minimal tenderness at left lower quadrant of abdomen but no signs of defense, rebound or costovertebral angle tenderness. His electrocardiography (ECG) was normal sinus rhythm. His radiologic imagines were normal except for distension due to intestinal gas. Blood and urinary samples had taken from patient and to relieve his symptoms intravenous metoclopramide, proton pump inhibitor and hyoscine-n-butyl bromide medications had began. Then he was taken to observation room.

Not long after, ED doctors were informed that patient was shivering and patient was re-assessed quickly. His body temperature was 40°C. Muscle rigidity and minimal neck stiffness had emerged quickly. Intravenous hydration and anti-pyretic therapy had began. Infection markers and CK levels had studied. Despite the efforts, his fever was persistent. His laboratory studies were, WBC: 8.9, Alanine aminotransferase (ALT): 20, Aspartate Aminotransferase (AST): 20, Creatinine: 0.95, Troponin: <0.01, CK: 225, C-reactive protein (CRP): 6.4. At the same time, he was being confused and blood pressure levels were getting lower. His pupillary light reflex was +/+, pupils were isochoric, deep tendon reflexes and muscle strength were normal. ED doctors had suspected NMS and referred him to neurologist for further investigation and therapy. His central nervous system (CNS) imagines were reported normal and neurological consultant report was stating that NMS can not be excluded but other CNS pathologies and infections were excluded. Approximately 1000 cc of saline was applied intravenously to the patient in the first hour and 1000 cc of saline was given as maintenance. After enough clinical observing and symptomatic therapy, his clinic got better and his CK levels decreased to 215. Blood tests were re-evaluated at approximately 4-hour intervals and urine output was more than 1 ml/kg/hour in the follow-up. He was discharged from the hospital fully recovered after 6-8 hours of observation.

Discussion

The incidence of NMS changes between 0.02% and 3%. Majority of NMS cases are young and adult males. It's mortality rate has reduced to 10%, which is still too high but better than former situation. About this reduction, growing awareness against NMS could be an important factor (1, 5). The case we presented is also supports scientific studies about NMS.

It's main trigger is oftenly first generation of anti-psychotics with high potencies but anti-psychotics with low potencies, atypical anti-psychotics, anti-emetics, tricyclic anti-depressants and lithium can also be a trigger

(3, 6). In our case, NMS emerged after administration of metoclopramide. Metoclopramide mostly causes tardive dyskinesia, dystonia and parkinsonism due to dopamine antagonism. But some studies reported that, it can cause NMS rarely, especially in older population. According to studies, NMS can be triggered either subsequent to single dose of metoclopramide or following administrations (3, 7).

In most of the cases altered mental status, muscle rigidity, hyperthermia and autonomic dysfunction are four major components of NMS. Those symptoms can emerge in 3 days, after drug administration (1, 4, 5). In our case, after intravenous administration of metoclopramide fever, muscle rigidity, altered mental status and fluctuating blood pressure levels emerged in 30-60 minutes.

NMS is a diagnosis of exclusion. Serotonin syndrome, malignant hyperthermia, malignant catatonia, other syndromes related with drug use and central nervous system infections must be excluded. In laboratory studies leukocytosis and high levels of CK, electrolyte imbalance due to possible renal failure can be expected (1, 5, 8). In our case leukocytosis and high levels of CK has been observed. For differential diagnosis central nervous system imaging and lumber puncture may be needed.

When approaching to patients who diagnosed with NMS, first of all administration of the drug which triggered NMS must be stopped. After that intensive care observation may be needed. Anti-pyretic therapy and external cooling methods can be used. Patient must be observed about cardiorespiratory failure, renal failure, aspiration pneumonia and coagulopathy. Even though there are different opinions, dantrolene, bromocriptine, amantadine and benzodiazepines can be administered into patient. For some cases, electroconvulsive therapy may helpful (1, 5, 9). Despite studies reported some cases that intensive care unit observation and mechanical ventilation are needed, with early diagnosis and therapy most of the cases can fully recover without any complication, just like our case (7, 8).

Conclusion

NMS related to metoclopramide is quite rare, but usage of metoclopramide is very often in EDs. When considered, if single dose of metoclopramide is enough to trigger NMS, patients who received metoclopramide therapy must be observed about emergence of NMS symptoms. If imaging and laboratory studies are not suitable for differential diagnosis, patient should be transferred to a more comprehensive center.

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