A Single Dose of Metoclopramide Associated with Extrapyramidal Symptoms in a Child: A Case Report

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Abstract
A case of postoperative extrapyramidal symptoms is reported. A healthy 10-year-old boy was admitted to our hospital due to tonsillitis and adenoid hypertrophy pending tonsillectomy and adenoidectomy. A single dose of metoclopramide was given following an episode of vomit that occurred approximately 20 hours postoperatively. One hour subsequent to the administration of metoclopramide the patient developed fever, facial flushing, diaphoresis, headache, increased muscle rigidity, autonomic instability and altered level of consciousness. The clinical manifestations were present for approximately 22 hours. The patient received naloxone and symptomatic therapy and after 24 hours was fully recovered without complication. The ability of dopamine antagonist agents, including metoclopramide to precipitate extrapyramidal symptoms and drugs induced movement disorder is discussed [1]. These extrapyramidal and autonomic symptoms will be discussed as the early recognition of dystonia and/or akathisia by anesthetic personnel following the administration of metoclopramide is of great value for the punctual treatment of these conditions.

Keywords: Extrapyramidal symptoms; Metoclopramide; Neuroleptic malignant syndrome

Introduction
The European Medicines Agency’s Committee on Medicinal Products for Human Use (CHMP) and North America have recommended restricted use of metoclopramide in pediatric patients to minimize the known risk of potentially serious neurological side effects [2]. Extrapyramidal symptoms also known as extrapyramidal side effects, are forms of abnormal movement disorders caused by a blockage of normal dopamine function in the brain or depletion in the basal ganglia [3]. The four main types of extrapyramidal symptoms are parkinsonian symptoms, tardive dyskinesia, dystonia and akathisia [4]. While the former two (parkinsonian symptoms and tardive dyskinesia) is generally observed after long term use, the latter two can develop just after a single dose of dopamine antagonist agent such as metoclopramide [5]. The incidence of extrapyramidal symptoms associated with the administration of metoclopramide has been reported to be approximately 0.2% [6,7].

Metoclopramide, a procainamide derivative, a fruitful anesthetic adjuvant, is the most commonly used selective D2 receptor antagonist used for antiemetic prophylaxis, primarily for PONV and chemotherapy associated with low emetogenic risk [8]. Its antiemetic effects are as a result of antagonizing central and peripheral dopamine receptors [9]. Metoclopramide can precipitate extrapyramidal symptoms (movements disorder or parkinsonism) [9]. The underlying mechanism that causes extrapyramidal symptoms is not yet clear but a striatal dopamine D2 receptor blockade causing a dopamine-cholinergic imbalance is believe to be the fundamental cause [3,10].

Subsequently to metoclopramide administration, symptoms can appear within 24-72 hours [9]. The incidence of these adverse effects has greater risk in people at the extreme age spectrum, 6 times higher in children than adults, and it can be up to 25% even at the recommended dose and are usually in form of involuntary limb movement, facial grimacing, torticollis, trismus, and rarely in severe form such as neuroleptic malignant syndrome [7,9,11].

Neuroleptic malignant syndrome (NMS) is an idiosyncratic disorder that seems to be precipitated by administration of neuroleptics that block dopamine in the nigrostriatal pathway, mesocortical pathway, hypothalamic nucleus or withdrawal of dopaminergic agents. It is an infrequent but potentially life-threatening neurologic emergency [12,13].

Antipsychotics commonly referred to as neuroleptics or major tranquilizers such as butyrophenones, phenothiazine, and thioxanthenes, are commonly used to treat neuropsychiatric disorders and nonneuroleptic agents such as Metoclopramide. The administration of one or both of these drugs can potentially trigger neuroleptic malignant syndrome because of their dopamine receptor-blocking properties [14,15].
The classical clinical features of NMS comprise of muscular rigidity, fluctuating mental state, hyperpyrexia, autonomic instability, diaphoresis. Characteristic laboratory findings seen in NMS include an elevated level of creatinine phosphokinase (CPK) due to rhabdomyolysis and leukocytosis but are not specific for the syndrome nor present in all cases [12,15].

These two similar syndromes initial treatment should be aimed at immediate cessation of all neuroleptic agents and non-neuroleptics agents with antidopaminergic activity. The next key step is supportive therapy aimed at decreasing hyperthermia, hydration, metabolic abnormality may need to be corrected and restoration of dopamine balance. In more severe cases of NMS, various authors have recommended treatment with various medications such as benzodiazepines, dantrolene, bromocriptine, amantadine hydrochloride and other dopaminergic agents [12]. The two most frequently used medications are bromocriptine, a dopamine agonist and dantrolene sodium, a muscle relaxant. Although NMS has a low incidence rate of approximately 0.2%, mortality rate may be as high as 30% mainly as a result of complications such as rhabdomyolysis or cardiovascular collapse making early recognition and institution of circulatory and respiratory therapy if needed life saving [6,7].

Case Report

Chief complain
Snoring and Rhinorrhea

History

A healthy 10 years old Male (weight 25kg) that started with snoring and rhinorrhea onset 6 years ago, that worsen gradually in the last 2 years, the same is accompanied by mouth breathing that increases in the presence of a cold infection. No other accompanying symptom was recorded. The patient was admitted to hospital with the diagnosis of tonsillitis and adenoid hypertrophy pending surgery. He was seen by the anesthesiology team on the day prior to surgery and was deemed fit for surgery with ASA 1. A family history of problem with anesthesia was denied. Chest x-ray and all complementary blood analysis done were normal.

Upon arrival to the anesthesia room standard monitoring device were applied. After preoxygenation anesthesia was induced with midazolam 1mg IV, propofol 80mg IV, rocuronium 40mg IV and was maintained with oxygen, inhaled sevoflurane maintained at 1-1.5 MAC, propofol 60mg/hr IV, and remifentanil 250μg/h IV in infusion, sufentanil 5μg was given twice.

Following completion of the surgical procedure, the patient was transferred to post-anesthesia care unit (PACU) with patient-controlled intravenous anesthesia PCA (Tramadol 125mg, droperidol 5mg, ondansetron 2.5mg and sufentanil 50μg mixed in 100ml normal saline) pumping rate at 1ml/hr to prevent postoperative pain, nausea and vomit.

In PACU, extubation was done when the patient responded to verbal command and showed adequate spontaneous respiration and muscle strength. Posterior to the removal of the tracheal tube Oxygen via face mask was applied and the patient was transferred to the ward after 30 minutes of normal vital signs.

Approximately 20 hours postoperatively, the patient vomited shortly after eating breakfast (egg and milk). The decision was made by the attending doctor to stop PCA and metoclopramide 5mg IM was given. One (1) hour subsequent to the administration of metoclopramide, the patient had a fever of 38.5 °C. Facial flushing, diaphoresis, headache, muscle tremor, rigidity of the extremities and unresponsive to verbal commands.

The anesthetist was asked to review patient and encountered the following on physical examination: clear bilateral breath sounds, RR18/min, HR:122/min SpO2 98%, bp:112/68mmHg, consciousness normal but unresponsive to interrogation, blank stare(eyes), pupil symmetric and bilateral light response normal, facial flushing, diaphoretic, muscle tremor and moderate rigidity of extremities. The reflex response was conserved, and No signs of central nervous system infection were observed.

Body temperature was decreased by a water-soaked blanket and Naloxone 0.5mg IM was given. One-hour posterior to the onset of sign and symptoms no significant clinical change was observed, as only the headache was alleviated, however, 24 hours later the patient had fully recovered and without complaints.

Discussion

The patient in this present case was a healthy 10-year-old boy who after receiving a single dose of metoclopramide, an antidopaminergic agent, for PONV following a tonsillectomy and adenoidectomy surgery and who developed acute symptoms that were related to neuromuscular hyperactivity and autonomic instability.

It is within the scope of knowledge that metoclopramide can cause extrapyramidal manifestations, such as dystonic-dyskinetic reactions, with an approximate report rate in the developed world of 1:500 patients [4,11].

This case presented a diagnostic challenge. Various possible diagnoses were entertained. Our patient had received total opioid of tramadol 125mg in PCA was given which first entertained the diagnosis of opioid toxicity for which naloxone 0.5mg IM was given to reverse narcotization. The failure of naloxone to improve the patient condition and the posterior progression of clinical manifestations suggest that his condition was not related to narcotization [16]. We entertained the diagnosis of extrapyramidal symptoms because of the rapid onset and offset of clinical manifestations which can appear at even standard dose treatment and children are more susceptible, presenting more frequently in form as face and extremities hyperesthesia, torticollis and opisthotonus. We thought the autonomous hyperactivity may be a further result of the side effects of metoclopramide. In spite of the relationship that exist between the occurrence of extrapyramidal symptoms and the administration of metoclopramide that may increase to

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25% in pediatrics and elderly patients, we cannot rule out NMS because of the presentation of rigidity, autonomic instability and hyperthermia observed after administering metoclopramide, a dopamine antagonist in conjunction with droperidol 5mg that was placed in the PCA which would mildly increase the antidiopaminergic potency but because of the frequent use of small dose of droperidol in PCA, the slow pumping rate of the PCA and the absence of any previous recorded case in our hospital we doubted such diagnosis.

Our patient improved after 24 hours of suspension of all medication and therefore no complimentary analysis such as Creatine Kinase (CK) was done to aid in a definite diagnosis.

Although metoclopramide can induce extrapyramidal symptoms and in worse form NMS, it should be taken into account that this drug is still widely used in clinical practice. In 2004 over 7 million prescriptions for metoclopramide were issued in USA alone [11]. Punctual recognition and discontinuation of the offensive agent is indispensable in preventing complication in these distressing disorders. It is of great importance that clinicians know to differentiate between the two syndromes since each condition is treated differently.

Observing causative agent and laboratory findings may help in making an accurate diagnosis [17].

In an effort to further prevent the acute neurological effects associated with the use of metoclopramide the European Medicine Agency’s Committee on Medicinal Products for Human Use (CHMP) recommendations about the use of metoclopramide in pediatric age are [18]:

- a) Metoclopramide use prohibited in children under one year of age and children over one-year metoclopramide should be use as a second-choice medication for prevention of nausea and vomit posterior to chemotherapy and PONV.
- b) Intravenous bolus of metoclopramide should be given in 3 minutes or more.
- c) Metoclopramide should only be prescribed for brief use (Maximum 5 days) with maximum dose per day 0.5mg per kg.

**Summary**

In summary, extrapyramidal symptoms and NMS are uncommon distressing disorder precipitated by dopamine antagonist including some commonly used by anesthetists. NMS is differentiated by more severe and prolonged period of clinical manifestations accompanied by alternations in complementary analysis. The mortality rate is significant. Currently, dantrolene, bromocriptine and amantadine in NMS and benzo diazepine in Extrapyramidal syndrome have been reported to be effective. Muscle relaxants are increasingly in use in severe patients [19-25]

**References**