

Self-assumed Neurologic Related Condition Deviated Metoclopramide-Induced Acute Dystonic of Oculogyric Crisis in a Woman of Childbearing Age: A Case Report

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Abstract

A 26-year-old Malaysian woman (childbearing age) attended a private primary care clinic with a known case of gastroesophageal reflux disease (GERD) and complained of persistent nausea and a few episodes of vomiting. She had no known drug allergy, no surgical history, no hospitalization in the last two years, was a non-smoker, and no history of drug or alcohol abuse. The patient was prescribed Tab metoclopramide 10 mg TDS and Tab ranitidine 150 mg BD for five days. About 30 min after oral administration of both medicines, her eyes rolled involuntary upward, leading to lateral deviation of the eyes, and mouth jaws clenched as if “dislocated jaws.” The patient was immediately brought into an emergency department (ED) of a public tertiary care hospital. A drug challenge test was done which resulted in the withdrawal of metoclopramide. The accompanied sister later disclosed that the patient had taken metoclopramide and ranitidine from a private clinic earlier in the day. The patient self-assumed to have a sudden seizure, due to excessive hot weather and dehydration. A slow intravenous infusion of 50 mg/mL diphenhydramine hydrochloride in 0.9% w/v NaCl 100 mL was administered stat. Consequently, the symptoms vanished after approximately 30 min of the therapy, devoid of relapse. The patient was discharged from ED post 8 hours of monitoring with complete recovery. Physicians frequently prescribe metoclopramide to treat nausea and vomiting, which may cause adverse drug reaction of acute dystonic oculogyric crisis (OGC). Due to its unwanted and unpredictable extrapyramidal symptoms, metoclopramide should be prescribed and dispensed with caution. Thorough history taking at ED is imperative for correct early diagnosis and treatment, as metoclopramide-induced dystonic OGC has a high probability of confusion with other causes of dystonia such as conversion and seizures, encephalitis, tetanus, and hypercalcemic tetany.

Keywords

Metoclopramide, Adverse drug reaction, Oculogyric crisis, Dystonic reactions, Patient safety, Drug safety, Medical care

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Introduction

Metoclopramide is affordable, hence generally prescribed as prophylactic drug to prevent nausea and vomiting allied with chemotherapy or radiotherapy, symptomatic management of

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nausea and vomiting, and for postoperative gastrointestinal upset, including nausea and vomiting in adults. It alleviates nausea and vomiting in people with gastroesophageal reflux disease (GERD) or diabetic gastroparesis by escalating gastric motility.¹⁻³ It produces prokinetic and antiemetic effects by central and peripheral dopamine D₂ receptors antagonism in the medullary chemoreceptor trigger zone in the area postrema of the brain.⁴ The antagonism actions of metoclopramide on dopamine receptors in the basal ganglia trigger a modification in the dopaminergic-cholinergic balance, inducing a deficit in central dopamine transmission, henceforth surplus release of acetylcholine over dopamine.⁵⁻⁷ The onset of action of metoclopramide is 1–3 min following an IV dose, 10–15 min after an intramuscular (IM) dose, and 30–60 min after an oral dose; the pharmacological effects remain for 1–2 hours.⁸ The lipophilicity of metoclopramide produces a large half-life (4.5–8.8 hours) and volume of distribution (3.5 l/kg).⁹ Since metoclopramide crosses the blood–brain barrier, acute extrapyramidal symptoms like acute dyskinesias and dystonic reactions involving contractions of the facial, trapezius, and dorsal levator scapulae, and rhomboid muscles, opisthotonos, dystonic oculogyric crisis (OGC), dysarthria, torticollis, trismus, rhythmic protrusion of the tongue, bulbar type of speech, tardive dyskinesia, Parkinsonism, akinesia, akathisia, and neuroleptic malignant syndrome are common unwanted side effects of metoclopramide, and rarely laryngospasm causing stridor and dyspnoea^{5,10}; all these require immediate intervention.^{11,12}

OGC is an uncontrolled acute dystonic reaction described by shorter frequent spasms of extraocular muscles leading to bilateral involuntary tonic eye deviation, the generally persistent upward elevation of visual gaze with hyperextension of the neck and jaw opening, with each spasm lasting from seconds to several hours, and the whole episode may last from days to weeks.¹³⁻¹⁵ The spasm may be accompanied or preceded by distressing psychiatric symptoms as such anxiety, restlessness, compulsive thinking, sensations of augmented brightness, or alterations of visual background.¹⁶ This case report is to alert the adverse reaction of metoclopramide-induced dystonic (MID) OGC that occurred in a patient of childbearing age being treated for known GERD, with the purpose that metoclopramide should be prescribed and dispensed with caution by physicians and pharmacists. Detailed physical assessment and medication history must be conducted in patients with acute attacks of dystonic OGC to guide for accurate, rapid diagnostic assessment leading to the necessary use of resources, appropriate treatment, a suitable length of emergency department (ED) stay or hospitalization and counselling.

Case Presentation

A 26-year-old (childbearing age) female of Malay ethnicity consulted a physician at a private primary care clinic with the

chief complaint of persistent nausea and a few episodes of vomiting. In her known condition of GERD, she had no known drug allergy, surgical history, or hospitalization history for the past two years, was a non-smoker, and had no history of drug or alcohol abuse. Her family history was unremarkable. The physician prescribed Tab metoclopramide 10 mg TDS and Tab ranitidine 150 mg BD for five days. Approximately 30 min after oral administration of both tablets, the patient's eyes rolled involuntary upward, leading to lateral deviation of the eyes, and mouth jaws clenched as if “dislocated jaws.” She was then rushed immediately to the nearest ED of a public tertiary care hospital located 30 km away from her house.

The differential diagnosis was conversion disorder or seizure. During the initial clinical presentation, the patient was discerning her condition and was in severe distress. On neurological assessment, consciousness was clear with a Glasgow Coma Scale of 15/15. Cranial nerve examination was within normal limits. Her respiration rate was 20 breaths/min, blood pressure 125/85 mmHg, pulse rate 86 beats/min, oxygen saturation 98%, and body temperature of 37.3°C. Lab findings of complete blood count, liver and kidney function tests, and electrolytes were unremarkable. No signs of respiratory distress were shown. On ophthalmic examination by an on-call ophthalmologist, the patient exhibited isochoric pupils giving indirect and direct light reflexes. Intraocular pressure was normal. Ocular motility and visual acuity were not examined owing to her condition.

To determine and rule out the causative of her condition, she was administered IV metoclopramide since the patient was persistently nauseated. Less than 3 min post-administration, patient's eyes rolled up, mouth jaws clenched as in “dislocated jaws,” spasm of neck muscle and muscle at the back of the body, causing body “twisted” to the right direction. However, there was no hypersalivation, and she could swallow, yet struggling. Metoclopramide was then immediately stopped and removed from the treatment plan. Further history taken from the accompanied sister revealed both tablets of metoclopramide and ranitidine were received from a private clinic. The patient did not inform earlier as she thought of having a sudden seizure due to extreme hot weather and dehydration. She was then treated with a slow IV infusion of 50 mg/mL diphenhydramine hydrochloride in 0.9% w/v NaCl 100 mL. The dystonic OGC symptoms disappeared within approximately 30 min of therapy, free of relapse. The patient was discharged approximately after close monitoring of 8 hours post-hospitalization with complete recuperation. At the scheduled appointment with an internal medicine physician and an ophthalmologist one week later, her health status remained well.

The Naranjo Adverse Drug Reaction (ADR) Probability Scale scored 9 and compartmentalized it as a “definite” ADR. The pharmacy department of the respective hospital issued a red ADR card to the patient. She and her sister were counselled on the significance of divulging health-related information

upon query by physicians treating her to minimize inaccuracy in diagnosing processes so that actual treatment could be initiated to manage the condition. They were also counselled on contraindication to metoclopramide and to keep the red ADR card in her purse for future alarmed reference.

Discussion

A final diagnosis of ADR acute MID OGC was confirmed based on the detailed history, distinctive physical examination findings, and drug challenge test. OGC is an atypical non-life-threatening neurological manifestation described by persistent dystonic, conjugate, and characteristically upward deviation of the eyes enduring for seconds to hours.^{16,17} OGC may be caused by drug-induced disorders, disorders associated with focal brain lesions, and congenital neurometabolic disorders.^{18,19} The drug-induced dystonic OGC includes antiemetics, antimalarials, antipsychotics, antidepressants, and antiepileptics. Drugs from the aforementioned class may block the D₂ receptors of nigrostriatal dopamine, which results in modification of the dopaminergic-cholinergic balance in the nigrostriatum. However, these drug-induced ADRs are self-limiting, dose-independent, and rarely cause permanent damage.¹⁹

The prevalence of MID OGC is approximately 0.2% even if metoclopramide is used at therapeutic dosages; nonetheless, it occurs more at higher doses, multiple doses, in females, pediatrics, adult patients <30 years of age, in patients having a family history of neurological disease treated with neuroleptics, as well as in patients having blood relatives that have a history of acute dystonic reactions to metoclopramide.^{6, 7, 20–25} This was also seen in those having genetic polymorphism in the CYP450D6 gene.^{21, 23, 26} It is still uncertain why females have a higher risk of developing dystonic reactions.²⁷ Guala et al.²⁸ and van der Padt et al.²² suggested withdrawal or cautious consumption of metoclopramide among family members in which ADR to metoclopramide is befallen in one of family members. Our patient is a female, childbearing age, less than 30-years old, and used a therapeutic dose of metoclopramide. She experienced acute dystonic OGC reactions that occurred within the first 24 hours, which aligns with the study of Bateman et al.,¹⁰ who reported that 63% of the patients experienced this unwanted effect within the first 24 hours, whereas in 94% of the cases, symptoms occurred during the first 72 hours. In addition, our patient experienced dystonic OGC after intake of a single dose of metoclopramide, which is similar to other findings.^{16, 29–31} Extrapyramidal side effects may be miscalculated with convulsions, tetanus, and seizure attributable to a scarcity of validated data and under-declaring cases of metoclopramide.^{6, 22, 32}

In Malaysia, the following directive from the Drug Control Authority (DCA) for manufacturers to revise metoclopramide package inserts to enhance medication safety. Under this directive, new information that should be added is the

contraindication of metoclopramide for patients aged < 1-year old, and restriction of use in patients aged 1–18 as a second-line option. Meanwhile, the Malaysia DCA's executive body also issued a safety issue notification to healthcare professionals in 2015.^{33,34} Till January 2022, a total of 897 reports with 1,591 suspected adverse events associated with metoclopramide were received by the Malaysian health authority. There were 361 adverse neurologic events reported, with higher incident of OGC ($n = 241$ (66.7%)).³⁵

Standard treatment management of MID OGC is to stop the dose of metoclopramide and administer the antihistaminic or anticholinergic drug (diphenhydramine, benztropine, biperiden). The route and dose of administration depend upon the severity and symptoms of the affected patient. Usually, IV administration is the most common route of choice as it can alleviate OGC within 10 min. IM route is an option over the IV route, although it requires a minimum of 30 min for the onset of action. Oral administration is the least selected as it involves first-pass biotransformation in the gastrointestinal tract leading to as low as 25% bioavailability with mean peak time of up to 4 hours.^{5, 13, 23, 32, 36–39} If there is a poor response, respective selected antidote therapy should be reiterated after 15 to 30 min. Administration of oral anticholinergics is recommended for 4 to 7 days to avoid recurrence of symptoms.^{19,20,39} Refractory cases respond to benzodiazepines such as lorazepam or diazepam.⁴⁰ In this present case, our patient was successfully managed with IV diphenhydramine hydrochloride without relapse.

Treatment management involving metoclopramide must be initiated at the lowest effective dose within the shortest duration of time. In the short term, it is effective, except its central nervous system side effects are incommensurate.⁴¹ In view of dystonic OGC and other multiple side effects/ADRs of metoclopramide, prior to prescribing this drug, the pharmacists and physicians should acquire informed consent from the patients and counsel on the odds of ADRs/side effects. If the patient possesses an adverse risk history, the pharmacist should recommend an alternative drug to the physician for suitable management of the condition. In the Malaysian setting, this interprofessional team approach is not within a private primary care setting as no pharmacist is stationed within a private primary care clinic, as well as mandatory prescription and dispensing separation is not yet lawfully in practice.

Conclusion

MID OGC must be made known among physicians and pharmacists for cautious prescribing, dispensing, and counselling. It is imperative to distinguish this dystonic OGC as in numerous incidents; it can occur within 72 hours post-initiation of metoclopramide therapy and particularly in younger females; in view of lack in detailing the patient history, dystonic OGC can be perplexed with other neurologic-related

maladies. Hence, early right diagnosis must be made to avoid delay in providing accurate treatment, unnecessary resources, long ED stay or hospitalization. Affected patients and caregivers could be anxious and traumatized, preceding to fatal consequences. Respective patients and caregivers must be counselled on the importance of disclosing health information accordingly, this contraindication to metoclopramide, and keep the issued ADR red card safely.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

Ethical Approval and Informed Consent

Our institution does not impose ethical approval for case reports. Nevertheless, written informed consent for the publication of this case report was obtained from the patient. The identification details of the patient were hidden as requested. The patient understands that any information which discloses her identification will not be published.

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