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Therapeutic Dose of Metoclopramide Induced Dystonic Reacton in Children

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ABSTRACT

Metoclopramide is a dopamine antagonist that is used in gastro esophageal disease and enteritis in adults and pediatric. The major side effects are extrapyramidal symptoms. They appear as dystonic movements. These are more common in children and young adults, especially in females. This retrospective descriptive study was conducted in Misurata Medical Center. It is aimed to draw attention to the frequent occurrence of metoclopramide-induced side-reactions. We studied the files of 45 patients who had been exposed to this reaction between the years of 2006 to 2008. Different dosage form of metoclopramide found to induced this acute reaction. Dystonia was occurred in 18 (40%) children who received drops, 10 (22%) patients received injection, and 6 (13.33%) children received syrup, while one patient received a tablet. The other children had received two dosage forms as injection with drops, syrup or suppository. All 45 children were treated intravenously with a single dose of diazepam. Young children especially females are more susceptible to dystonic reactions form metoclopramide. Our study indicates that diazepam is effective drug to abolish this adverse reaction.

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Introduction

Metoclopramide is a dopamine-receptor antagonist, used as antiemetic, and a stimulant of the upper gastrointestinal (GI) motility [1-3]. Its chemical name is 4-Amino-5-chloro-N-(2-diethylaminoethyl)-2-methoxybenzamide, and its generic name is plasil®, and its molecular formula of is CH2, CIN, O_2 =299.8 [4].

Metoclopramide mechanisms of action are complex involve; 5-HT4-receptor antagonism, vagal and central 5-HT3- antagonism, and possible sensitization of muscarinic receptors on smooth muscle, in addition to dopamine receptor antagonism. Metoclopramide is one of the oldest true prokinetic agents; its administration results in coordinated contractions of upper GI muscles, that enhance transit relief of GI motility disorder. Its effects are confined largely to the upper digestive tract, where it increases lower esophageal sphincter tone and stimulates antral and small intestinal contractions. Despite having in vitro effects on the contractility of colonic smooth muscle, metoclopramide has no clinically significant effects on large-bowel motility. Metoclopramide has been used as therapeutic agent in variety of GI disorders but principally for the management of GI motility disorders especially for the management of gastroesophageal reflux disease to produce symptomatic relief of symptoms, but not healing of associated esophagitis. It is clearly less effective than modern acid-suppressive medications, such as proton pump inhibitors or histamine H2-receptor antagonists, and now rarely is used in this setting.

Metoclopramide is indicated more often in symptomatic patients with gastroparesis, in whom it may cause mild to modest improvements of gastric emptying. In general, its greatest utility lies in its ability to ameliorate the nausea and vomiting that often accompany GI dysmotility syndromes [5]. It is found to be effective for the prevention of cancer chemotherapy-induced nausea and vomiting, and for the prevention of postoperative nausea and vomiting when nasogastric suction is considered undesirable [2,3,6].

Metoclopramide has been used for treatment of migraine. IM metoclopramide may be considered as adjunctive therapy for control of nausea in patients with acute migraine attacks and that the intravenous administration of the drug may be considered as monotherapy for relief of migraine pain [7].

The precise mechanism of antiemetic action of metoclopramide is unclear, but the drug has been shown to directly affect the medullary chemoreceptor trigger zone (CTZ) in the area postrema, apparently by blocking dopamine receptors in the CTZ [1,6]. Metoclopramide

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increases the CTZ threshold and decreases the sensitivity of visceral nerves that transmit afferent impulses from the GI tract to the vomiting center in the lateral reticular formation. The drug also enhances gastric emptying, which is believed to minimize stasis that precedes vomiting [1]. It also has been suggested that inhibition of serotonin receptors, at least when relatively high doses of metoclopramide are used, may contribute to the antiemetic action of the drug [8]. At least when relatively high doses of metoclopramide inhibit the central and peripheral emetic effects of apomorphine, hydergine, and levodopa [1]. Metoclopramide dosage forms include: tablets; each tablet contains metoclopramide HCL 10 mg, syrup; each teaspoonful (5ml) contains metoclopramide HCL 5 mg, suppositories; each suppository contains metoclopramide HCL 5mg, 10mg or 20mg, drops; each 1ml contains metoclopramide 4mg (16 drops), ampoules; each ampoule (2ml) contains metoclopramide HCL 10mg. The safety profile of metoclopramide in adults cannot be extrapolated to pediatric patients and should be used with caution in pediatric patient, since the incidence of extrapyramidal reaction is increased in these patients. Following oral or IV administration of metoclopramide in infants and children, pharmacodynamics of the drug is highly variable, and a relationship between drug plasma concentrations and pharmacodynamic effects has not been established.

Data are insufficient to determine whether the pharmacokinetics of the drug in children is similar to that in adults [2]. The drug should be administered with caution to neonates because decreased clearance may result in increased serum concentrations of the drug. In addition, since neonates have NADH methemoglobin reductase deficiency, they may be more susceptible to methemoglobinemia. The manufacturers currently recommend that metoclopramide may be used in children only to facilitate intubation of the small intestine [2].

Metoclopramide has been effective for the management of gastric stasis and gastroesophageal reflux in infants and children [9,10]. The drug has also been used in children for evacuation of the stomach prior to administration of anesthesia for emergency surgery [11].

Adverse reaction to metoclopramide generally involves the central nervous system (CNS) and GI tract. and are usually mild, transient, and reversible following discontinuance of the drug [1,2,6]. Evidence from clinical trials in patients receiving metoclopramide dosage of 40-80 mg daily for 4-12 weeks suggests that the incidence of metoclopramide-induce adverse effects is related to dosage and duration of therapy [2].

The major side effects include extrapyramidal symptoms. Dystonic acute reactions include involuntary movements of limbs, torticollis, facial spasms, protrusions of the tongue, opisthotonos and oculogyric crisis, those are more common in children and young adults, especially in female. They are apparently mediated via blockage of central dopaminergic receptor involved in motor function [12]. These symptoms generally occur within 24-48 hours after taken the drug and usually subside within 24 hours following discontinuation of the drug [1,2]. There is no specific antidote for metoclopramide intoxication however, most patients respond rapidly to treatment with diazepam or other agents with central anticholinergic activity such as diphenhydramine or benzotropine [13].

Parkinsonism and tardive dyskinesia have occasionally occurred, usually during prolonged treatment in elderly patients. Other adverse effects include restlessness, drowsiness, diarrhea, hypotension, hypertension, dizziness, headache, and depression. There are isolated reports of blood disorders, hypersensitivity reaction, and neuroleptic malignant syndrome. Disorders of cardiac conduction have been reported with intravenous metoclopramide. Long term use of the drug stimulates prolactin secretion and may cause galactorrhoea. Transient increases in plasma-aldosterone concentrations have been reported [4)].

Tardive akathisia refers to akathisia that occurs after long-term medication use, and may become permanent. Tardive dystonia develops after several years of medication use, which may be irreversible (2). The current study was conducted to report cases of dystonic reactions in pediatric patients related to the use of metoclopramide as anti-emetic and to remind practitioners of the potential hazard of the use of this agent in pediatric age group. It also aimed to determine the prevalence of dystonic reaction associated to metoclopramide use in children and to draw attention to the frequent occurrence of metoclopramide-induced dystonic reaction in children.

Methods

Study design and setting

This was a retrospective descriptive study, conducted in Misurata Medical Center. Forty-five children admitted to the pediatric department between the years (2006 to 2008) due to metoclopramide adverse effects, their files in the archive of the hospital were studied carefully.

Inclusion and exclusion criteria

All pediatric patients (<1 year to 12 years) receiving metoclopramide and have extrapyramidal symptoms was included in this study. Patients aged above of 12 years was excluded.

Data collection

Patient data was collected from the patient's file from the archive room. The collected data includes gender and age, dosage form of metoclopramide, manifestation of adverse effects, onset of adverse effects, emergency treatment, duration of admission.

Results

The total number of cases admitted to the pediatric department due to metoclopramide adverse effects, were 45 patients from the total admission (6100 cases), during the study period. Dystonia symptoms associated with metoclopramide were occurred in 26 females (57.8%) and in 19 males (42.2%), female to male ratio 1.4:1.

Metoclopramide was prescribed to children as plasil, most of them were young, 36 cases (80%) were under one year of age, three cases (6.7%) between one and three years, two cases (4.5%) were between four and seven years, and

four cases (8.8%) were above seven years. All patients had manifested with various dystonic symptoms that occurred 15 minutes after injection to about one hour after ingestion of one or two doses of metoclopramide (Table 1).

Table 1. Relation of metoclopramide-dystonic reaction with age.

Age (year)	< 1	1-3	4-7	> 7	Total
No.	36	3	2	4	45
%	80	6.7	4.5	8.8	100

The dose of metoclopramide ranged from 1 mg to 10 mg given once or twice daily.

Drops were prescribed in 18 case (40%), 10 cases (22%) received injection, 6 cases (13.33%) received syrup, and one case (2.22%) received tablets. Injection with syrup, drops or suppository were prescribed for 10 patients (22%) (Table 2).

Table 2. Metoclopramide dosage form and dystonic reactions

Dose form	No.	%
Drops	18	40
Syrup	6	13.33
Tablet	1	2.22
Injection	10	22
Injection + other	10	22

The most prominent clinical symptom was oculogyric crisis, occurred in 31 cases (68.9%), fourteen patients (31.1%) showed tonic-clonic convulsion, torticollis was manifested in twelve cases (26.7%), opisthotonos children and facial grimacing were in nine patients (20%) and one case (22.2%) respectively, all symptoms occurred singly or in combination (Table 3).

Table 3. Dystonic symptoms among metoclopramide users

Symptom	No.	%
Oculogyric crisis	31	68.9
Tonic-clonic convulsion	14	31.1
Torticollis	12	26.7
Opisthotonos	9	20
Facial grimacing	1	2.22

All 45 children were treated intravenously with a single dose of diazepam. Dystonic symptoms were abolished few minutes after treatment.

All children were admitted and observed in pediatric department; five (11.11%) children were discharge home few hours after treatment, while 30 (66.7%) children admitted for one day, the other were stay 2 to 4 days in pediatric department due to gastroenteritis (Figure 1).

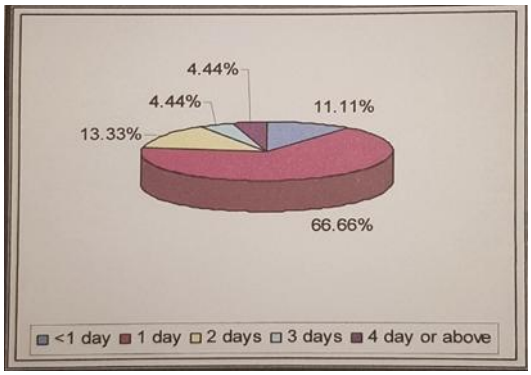

Figure 1. Duration of admission

Discussion

Metoclopramide, a dopamine-2 receptor antagonist that possesses central anti-emetic and peripheral gastrointestinal motility effects, is widely used. It has been used in the pediatric filed for the various indications, e.g., gastrointestinal reflux, chemotherapy- induced emesis, surgery-induced emesis and as anti-emetic for acute illness e.g., gastroenteritis [14].

Dystonia refers to a brief or sustained muscle spasm, often with slow abnormal movements. Although any group may be involved, it most commonly affects facial muscles. Dystonia seems to result from over activity in several areas of the brain, the basal ganglia, thalamus, cerebellum, and cerebral cortex.

In this retrospective study we report that administration of metoclopramide to 45 children via any route was associated with extrapyramidal-dystonic reactions. The results of the presented study show that the dystonic reaction occurs in 45 children, 57.8% were females and 42.2% were males, and 36 (80%) infants are more susceptible to this adverse effect than older one. Female children outnumbered male at a ratio of 1.8:1.3. Miller [15] reported that women outnumbered men 3 to 1.

Bateman et al. [16] reported that 445 cases of metoclopramide dystonia were occurred in United Kingdom in the period 1967-1982 due to 15.9 million prescriptions of metoclopramide. The relative risk of dystonia was 1.8 in females compared with male patients. In this research we found that dystonia from metoclopramide is dose and sex- independent and occurs few minutes after injection or rectal to several hours after ingestion of one or two doses of this drug. This result is in agreement with that reported by Cezard et al., [17] who found that metoclopramide shows the frequent occurrence of acute dystonia in children. Also, the result is compatible to that reported by Hansen [18] who found that dystonia and akathisia can occur after a single dose of metoclopramide. Furthermore, Yis Uluc [14] reported that the dystonic reaction caused by metoclopramide can be seen at normal dose.

Various types of dystonia symptoms form metoclopramide were reported in this study, the prominent sing in most children (31 out of 45 or 68.9%) was oculogyric crisis (spasm of extra-ocular muscles, forcing the eyes into upward or lateral gaze). This reaction is most commonly explained as an adverse effect of anti-emetic drugs such as prochlorperazine or metoclopramide [19].

The other types of dystonia were torticollis reported in 12 (26.7%) children and opisthotonos were manifested in 9 (20%) patients. The other form of metoclopramide-dystonic reaction is facial grimacing was reported in one case (2.22%). In addition, fourteen (31.1%) patients showed tonic and clonic convulsions, this reaction occurs especially in children with fever and who received oral with parenteral metoclopramide. Obviously dystonic symptoms are frightening to the patient and the parents' medical management was conducted by administration of diazepam intravenously in all cases. Pinder (20) reported that most patients affected by metoclopramide-dystonic reactions respond rapidly to treatment with diazepam or anticholinergic agents such as diphenhydramine.
Hospitalization due to metoclopramide-dystonic reaction was needed for all patients and ranging from less than one day 5 (11.11%) patients to 1 day for 30 (66.7%) children for observation because recurrent dystonia can occur. The others were stay 2 to 4 days in pediatric department due to gastroenteritis.

Conclusion

Administration of metoclopramide through any route is associated with significant dystonic reactions. Despite the fact that these adverse effects disappear spontaneously and completely after discontinuation this treatment, they create unnecessary anxiety for the patient, parents and health care personnel. Our study indicates that intravenous injection of diazepam or antihistaminic are effective drugs for the management of dystonic reactions due to metoclopramide.

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