**Metoclopramide-Induced Acute Dystonia**  
*Data From a Pediatric Emergency Unit*

**Coskun Yarar, MD,* Ayten Yakut, MD,* Kursat Bora Carman, MD,* Sabiha Sahin, MD,† Ozan Kocak, MD,‡ Serhat Ozkan, MD,§ and Cengiz Bal, PhD||

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**Objectives:** Metoclopramide is a commonly used medication in pediatric practice, and dystonia is a common adverse effect of it. The present study aims to evaluate the clinical characteristics of metoclopramide-induced acute dystonic reactions (MIADRs) in pediatric patients admitted to the pediatric emergency unit.

**Methods:** Twenty-eight patients were admitted with MIADRs between June 2004 and April 2016; they were enrolled into the study retrospectively.

**Results:** The study group was composed of 13 females and 15 males with the mean ± SD age of the females higher than that of the males, 12.3 ± 4.5 and 7.8 ± 4.3 years, respectively. Only 9 (32.1%) of the patients were diagnosed as MIADRs at the time of admission. Seventeen patients (60.7%) received over the recommended daily dose of metoclopramide. Dystonia was focal in most of the patients, with the most affected parts consisting of the neck, eyes, and orolingual regions. In 9 of the patients, the dystonia was episodic in nature. Pharmacological treatment was used for 18 patients. No patients died, and none suffered long-term injury related to MIADRs.

**Conclusions:** Metoclopramide administration may be associated with the occurrence of acute dystonic reaction. Metoclopramide-induced acute dystonic reactions may be misdiagnosed, so detailed medical history gathering and a high index of suspicion are warranted. Our data suggest that MIADRs may be dose related and that there may be age- and sex-related differences in the epidemiology of MIADRs.

**Key Words:** metoclopramide, dystonia, antiemetic agents, off-label drugs

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Metoclopramide is a recommended and approved agent for prophylaxis of nausea and vomiting related to chemotherapy or postoperation. However, it is one of the most prescribed off-label drugs for vomiting due to acute gastroenteritis in children under 18 years old, diagnosis of acute dystonic reaction, and other effects due to metoclopramide administration and dystonia. In this study, we evaluated 28 pediatric patients who developed acute dystonic reactions as a result of metoclopramide used for antiemetic purposes.

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**Methods**

In this descriptive cohort study, we retrospectively evaluated 28 consecutive pediatric patients (13 females and 15 males), with the diagnosis of acute dystonic reaction after metoclopramide therapy, who were admitted to the Pediatric Emergency Unit of Eskisehir Osmangazi University Hospital with MIADRs between June 2004 and April 2016. The total number of pediatric emergency unit admissions during this time was 130,743.

**Study Subjects**

1. Subjects were eligible for inclusion in the study as follows: children under 18 years old, diagnosis of acute dystonic reaction, and documented therapeutic use of metoclopramide for antiemetic purpose. Subjects were excluded if clinical records for the subject were unavailable.

2. Methods for case ascertainment: all patients were evaluated according to their final diagnosis. Two main sources were used to identify patients. For this purpose, *dystonia* and *drug side effects* codes were investigated according to the *International Statistical Classification of Disease, 10th Revision*, codes from electronical database of the hospital, and 46 patients were identified. In addition, dystonia-diagnosed patients were searched from outpatient records, and 34 patients were identified. Of the 80 cases identified in initial chart retrieval, 23 did not meet the inclusion criteria owing to misdiagnosis and/or miscoding, 11 did not meet the inclusion criteria because they had no documented metoclopramide administration, and 6 failed inclusion owing to exposure through suicide attempt or accidental exposure. Of the 40 subjects eligible for inclusion, 12 (30%) were excluded owing to missing or incomplete data. Ultimately, 28 children were included in the final analysis (Fig. 1).

**Clinical Data**

The study used clinical monitoring data on patient demographic characteristics, medical history, presenting complaints, physical examination findings, reasons for using the metoclopramide, daily dosages, and development periods of dystonia, initial diagnosis, final diagnosis, misdiagnosis, treatment, and outcome. The data were derived from the electronic and paper-based patient files and/or records. The diagnosis of MIADRs was made either by the emergency physician or by the consultant physician based on the history, physical and neurological examination of the patients, and/or their response to treatment. In some patients, video recording was helpful in the diagnosis of dystonia. The diagnoses were divided into 2 groups: initial diagnosis and final diagnosis. Misdiagnosis was detected by comparing the initial diagnosis with the final diagnosis. Time-to-onset of MIADRs refers to the time between the first dose of metoclopramide and onset of MIADRs. Duration of MIADRs refers to the time between the onset and termination of a MIADRs period. Types of dystonia: if dystonia affects a single area of the body defined as a focal, the contiguous area or adjacent body regions defined as segmental, or most to all of the body defined as generalized.

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*From the Departments of *Pediatric Neurology, and †Pediatric Emergency, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir; ‡Department of Pediatric Neurology, Samsun Education and Research Hospital, Samsun; Departments of ‡Neurology, and §Biostatistics, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey.

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Reprints: Coskun Yarar, MD, Department of Pediatric Neurology, Faculty of Medicine, Eskisehir Osmangazi University, Meselik, Eskisehir, Turkey (e-mail: coskunyaran@hotmail.com)

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Ethics
This study was approved by the local ethical committee of Eskisehir Osmangazi University in Eskisehir, Turkey.

RESULTS
A total of 28 patients, 13 females and 15 males, aged between 4 months and 17.3 years, were included in the study. The mean ± SD age of the whole sample was 9.8 ± 4.9 years (median, 10.3 years). The mean ± SD age of males was 7.8 ± 4.3 years, whereas the mean ± SD age of females was 12.3 ± 4.5 years (Table 1; Fig. 2). Nine (69.2%) of the females and 6 (40.0%) of the males were in the adolescence period (Table 1).

Metoclopramide was prescribed as an antiemetic in all patients. Of the sample, 17 patients were using multiple drugs, such as antibiotics and analgesics. Hyoscyamine-N-butylbromide, used by 2 patients, and trimebutine maleate, used by 1 patient, have anticholinergic properties.

The most common type of dystonia was the focal type, followed by the segmental and generalized types. Dystonia appeared most frequently in the neck, eyes, and orolingual region (Table 2; Fig. 3). The most common symptom accompanying dystonia was the alteration of consciousness in 12 patients (42.9%), and paresthesia was reported by 3 patients (10.7%). Physical examination findings other than dystonia included upper respiratory tract infections in 7 patients (25.0%), neck stiffness in 4 patients (14.3%), and obesity in 1 patient (3.6%).

TABLE 1. Comparison of Patients According to Sex and Treatment Characteristics

|                        | Female     | Male       |
|------------------------|------------|------------|
| Age, mean ± SD, y      | 12.3 ± 4.5 | 7.8 ± 4.3  |
| Adolescence period, n (%) | 9/13 (69.2) | 6/15 (40.0) |
| Metoclopramide dosage  |            |            |
| mg/kg/dose, median (min-max) | 0.45 (0.19–2.00) | 0.32 (0.10–1.54) |
| mg/kg/d, median (min-max)  | 0.69 (0.20–2.00) | 0.64 (0.10–1.54) |
| mg/d, median (min-max)   | 30.00 (15.00–60.00) | 15.00 (1.60–40.00) |
| Time-to-onset of MIADRs, median (min-max), h | 24.00 (2.00–96.00) | 2.00 (0.17–48.00) |
| Duration of MIADRs, median (min-max), h  | 0.50 (0.25–3.00) | 1.25 (0.03–5.50) |
| Over recommended daily dose, n (%) | 9/13 (69.23) | 8/15 (53.33) |
| Recovery time of MIADRs, median (min-max), min | 22.5 (1.8–720) | 37.5 (1.8–600) |

FIGURE 1. Flow diagram detailing the patients search and selection process.
The most common initial diagnoses on admission were seizures, drug reactions, myalgia, and encephalitis, in that order (Table 3). Thirteen (46.4%) of the patients were hospitalized with dystonic reactions and/or accompanying diseases. The laboratory investigation did not detect any electrolyte or acid-based imbalances. The routes of metoclopramide administration were oral in 22 patients (78.6%), intravenous infusion in 3 patients (10.7%), intramuscular in 2 patients (7.1%), and both oral and intravenous in 1 patient (3.6%). Eight patients were given more than 1 dose of metoclopramide. Dystonic reactions occurred following an average of 22.2 ± 2.4 hours (0.2–96.0 hours; median, 24.0 hours) after metoclopramide therapy was initiated. Dystonia was periodic (episodic) in 9 patients. One of the patients had an experience of dystonic reaction attributed to metoclopramide previously. The mean ± SD metoclopramide dose was 0.7 ± 0.5 mg/kg per day, ranging from 0.1 to 2.0 mg/kg per day (median, 0.7 mg/kg per day). Seventeen patients (60.7%) received over the recommended daily dose of 0.5 mg/kg per day of metoclopramide, and 13 (76.5%) of these patients were administered metoclopramide only via the oral route.

In the treatment of MIADRs, metoclopramide was initially discontinued in all patients, and then intravenous biperiden lactate at 1.2 mg/m² per dose (maximum [max] 4 times in 30-minute intervals), and/or oral diphenhydramine hydrochloride at 37.5 mg/m² per dose (max 300 mg/d), or intravenous diazepam at 0.3 mg/kg (max 10 mg) was administered. Intravenous rehydration therapy was used for 2 patients, and no medication was given in 6 patients. In 8 of the patients, dystonic reactions were resolved within 22.5 minutes (median) when biperiden lactate was administered, and in 6 of the patients, dystonic reactions were resolved spontaneously within 37.5 minutes (median) (Table 1). All patients in our study fully recovered without any sequelae (Table 4).

**DISCUSSION**

Metoclopramide is an approved agent in children for the chemotherapy-induced or postoperative nausea and vomiting, delayed gastric emptying, and facilitating intestinal small bowel intubation. In some countries, it is contraindicated for children younger than 1 year old, and care is advised in children under the age of 5 years as well as the duration of use more than 5 days. Limiting metoclopramide use in children is owing to the immaturity of the blood-brain barrier in infants, decreased metoclopramide clearance in children, the efficacy of metoclopramide relative to other available therapies, and reports of adverse effects of metoclopramide. Still, metoclopramide is one of the most frequently used off-label antiemetic agents in children. Reported adverse effects of metoclopramide include, most commonly, extrapyramidal symptoms, sedation, and diarrhea. Acute extrapyramidal symptoms induced by dopamine blocking agents may occur in the forms of dystonia, akathisia, and parkinsonism. Children and adolescent girls have high risks of developing MIADRs. In this study, about two thirds of patients were not diagnosed at the time of admission, and MIADRs appeared in

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**TABLE 2. Type and Localization of MIADRs in the Patients (N = 28)**

| Type                        | No. Patients, n (%) |
|-----------------------------|---------------------|
| Focal                       | 12 (42.9)           |
| Segmental                   | 9 (32.1)            |
| Generalized                 | 7 (25.0)            |
| Localization*               |                     |
| Neck (torticollis, retrocollis) | 18 (64.3)       |
| Eyes (oculogric crisis, tonic deviation) | 12 (42.9)    |
| Orolingual                  | 6 (21.4)            |
| Chin                        | 5 (17.9)            |
| Hand                        | 2 (7.1)             |

*In some patients, more than 1 localization was affected.
females at a later age than males. A higher than recommended dose of metoclopramide was used in most of the patients. Drug-related dystonic mechanisms are generally explained by impaired dopamine and acetylcholine balance in the striatum. The effects of metoclopramide occur with different mechanisms. It increases peripheral cholinergic activity and has prokinetic properties. In the central nervous system, it blocks the dopamine, particularly the D2 subtype, which is associated with an antiemetic effect, dystonia, and elevated prolactin levels. Metoclopramide also has weak serotonin receptor antagonistic properties. In England, from 1967 to 1982, 15.9 million metoclopramide prescriptions were written by general practitioners, and cases of dystonia and dyskinesias were reported in 479 of those prescribed (190.7 reports/million prescriptions). In the same study, dystonia frequency was reported as significantly higher in females aged 12 to 19 years than dystonia rates in other age groups, whereas parkinsonism symptoms were significantly more frequent in the elderly. In the present study, MIADRs were more common in adolescent girls, similar to results reported by Bateman et al. In contrast to this study, neither Cézard et al. nor Faridi and Gandhi found any relationship between sex and MIADRs. It is still unknown why MIADRs appear more common in adolescent girls. Our findings may be explained by the fact that dopamine receptors vary with age and sex, and the effects of sex steroids and prolactin levels on dopamine receptors may also have an influence. Bateman et al. suggested that the rate of adolescent girls receiving an overdose of metoclopramide for suicidal purposes may explain this statistic, but we excluded this possibility because the use of metoclopramide for suicidal purposes was an exclusion criterion in our study. The genetic predisposition has also been reported to be effective in MIADRs. However, we did not evaluate the genetic characteristics of the patients in our study. Despite the fact that metoclopramide is not allowed to be used in children under 1 year, in this study, 2 patients under 1 year were given metoclopramide. This may be owing to a lack of mentioned information.

Whereas 11 patients were treated only with metoclopramide, 17 patients received additional medication as well. Twelve patients received antibiotics, and 10 patients received analgesic treatment. Two patients received hyoscine-N-butylbromide, 1 patient received an anticholinergic drug containing trimebutine maleate, and 1 patient received a sympathomimetic drug containing pseudoephedrine. These medicines do not present a high risk of causing acute dystonic reactions.

In this study, the most common type of dystonia was the focal type, and neck and eyes were the most frequently affected localizations. Low and Goel reported that opisthotonos and torticollis are the most common extrapyramidal symptoms observed in children receiving metoclopramide for therapeutic purposes.

On admission, only one third of the patients were considered drug reactions, suggesting that diagnosing metoclopramide-related dystonic reactions in children may be difficult. This finding is consistent with other studies and case reports. In this study, the presence of adverse effects such as nuchal rigidity and oculogyric crisis may have caused misdiagnoses of encephalitis or seize. Prediagnoses of encephalitis and tetanus that were subsequently diagnosed with MIADRs have been reported in some pediatric cases. A thorough case history and suspicion are important for the correct diagnosis of MIADRs.

The etiology of emesis and vomiting was evaluated in relation to acute gastroenteritis and upper respiratory tract infections in half of the patients in this study. Although infection and high fever have been reported to be associated with dystonia in children, in this study, each infection or fever was not accompanied by...
dystonia, and dystonic reactions improved with the termination of metoclopramide therapy, suggesting that the dystonic reactions were associated with metoclopramide. Concomitant infection and/or fever with dystonia may cause difficulty in initial diagnosis at the admission as it was in the present study.

Dystonic reactions occurred after an average of 22.2 ± 2.4 hours after metoclopramide therapy. The similar finding has been reported by other authors. The mean elimination half-life of metoclopramide is 4.1 to 4.4 hours in childhood, with up to 96 hours. The long half-life observed may suggest accumulation or may be evidence of the switch from first order to zero order elimination kinetics. In this study, time of onset of MIADRs was seen up to 96 hours. Metoclopramide-induced acute dystonic reactions may occur in single or multiple doses, therapeutic doses, or high doses in children. In this study, MIADRs were associated with multiple-dose administration of metoclopramide in eight patients. Allen et al concluded that a metoclopramide dose below 2 mg/kg is safe and also that the administration of metoclopramide at the admission as it was in the present study.

There were some limitations in this study. The main limitations of the study were that the data were based on the statements of parents/carers and the retrospective nature of the study design. In addition, 30% of the potentially eligible subjects had to be excluded owing to missing or incomplete data, and this could introduce bias into the data set. The genetic predisposition of our patients to dystonia was unknown. In future studies, it may be useful to investigate the relationship between the acute dystonia occurring at therapeutic doses of metoclopramide and genetic susceptibility. The strength of this study is that it is one of the studies with the largest number of cases investigating the clinical features of MIADRs in children.

CONCLUSIONS

Use of metoclopramide with approved indications and adjusted doses may prevent MIADRs in children. Acute dystonia-related metoclopramide can be easily confused with other diagnoses, but treatment is simple and the prognosis is good. In our study, MIADRs tended to be older ages in females. Correct diagnosis is important to decrease anxiety surrounding the patient for the family and doctor and also to prevent unnecessary testing and treatments.

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