Clinical profile of acute drug-induced dystonia in children

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ABSTRACT

Background: Acute dystonic reactions are the most common type of extrapyramidal reactions associated with the use of certain drugs. Drug-induced dystonic reactions (DIDRs) are diagnosed based on the detailed history and physical examination. **Objective:** The objective of the study was to describe the clinical profile, identify the drugs causing dystonic reactions and outcomes in a cohort of children with DIDRs. **Materials and Methods:** This study is a prospective observational study conducted in patients with DIDRs between February 2019 and January 2020 aged <15 years. DIDRs were diagnosed on the basis of history and physical examination. **Results:** During the proposed study period, 12 children with DIDRs were identified with a mean age of 50.8 months and eight patients (67%) were boys. The most common cause of DIDRs was with antipsychotics in eight patients (67%) and with antiemetics in four patients (33%). All patients with DIDRs due to antiemetics were infants and received the drug with overdose. These infants needed more diagnostic investigations. Most of the children responded with stoppage of causative drug and administration of benzodiazepine and diphenhydramine. On follow-up, there was no recurrence. **Conclusion:** DIDRs were common with antiemetics and antipsychotics either with therapeutic dose or overdose. Benzodiazepines and diphenhydramine were more effective drugs in the treatment of DIDRs.

Key words: *Antiemetics, Antipsychotics, Drug induced, Dystonia, History, Physical examination*

Dystonia is defined as a movement disorder, characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. It is often initiated or worsened by voluntary action and associated with overflow muscle activation [1]. Dystonia in childhood has numerous etiologies. Dystonia can be the only sign of a disease or one of the several manifestations of a clinical syndrome caused by acquired brain lesions, degenerative disorders, drugs, or a psychogenic problem.

Drug-induced dystonic reactions (DIDRs) occur due to the many drugs within therapeutic dose or overdose within minutes, hours, or even days of exposure to an inciting drug. Antipsychotics, anticonvulsants, tricyclic antidepressants, and antiemetics are common drugs causing DIDRs [2]. The mechanism of acute dystonia is still unclear. It is proposed that dystonic movements may be due to the imbalance between cholinergic and dopaminergic stimulation [3,4]. Thus, blockade of these receptors by drugs causes the disappearance of the inhibiting effect of dopamine on acetylcholine, and as a result, cholinergic system becomes relatively more dominant and leads to the development of extrapyramidal movement disorders, such as dystonia [5].

There are limited data about the causes, clinical features, and outcomes of DIDRs in childhood. The aim of this study was to examine and describe patients with DIDRs, to identify their complaints at admission, to determine the drugs that cause DIDRs, and the treatment options.

MATERIALS AND METHODS

This study was a prospective observational study, conducted at a tertiary hospital of South India during a period of 12 months (from February 2019 to January 2020). The inclusion criteria included children <15 years, who presented to the pediatric emergency department with acute dystonia and with a history of drug ingestion. The exclusion criteria included children with chronic dystonia, cerebral palsy, and any neurodegenerative disorders.

This study was approved by the institutional ethical committee. A written informed consent was obtained from parents of enrolled children. Data for all the patients such as age, gender, complaints at admission, causative drug for DIDRs, duration of drug intake, dosage of the drug (therapeutic dose, overdose, and unknown dose), class of the drug, recommended treatment, and follow-up were recorded. The data were presented as number and percentages.

RESULTS

During the study period, a total of 12 patients with mean age of 50.8 months (range 4–108 months), were admitted with DIDRs.

The most frequent causes of DIDRs were antipsychotics (67%) and antiemetics (33%). Risperidone was the most commonly used drug within antipsychotics in this study. The diagnosis of patients, who had taken antipsychotic drugs, was attention deficient hyperactivity disorder (ADHD) (4/8), and autism spectrum disorder (ASD) (4/8). All patients with DIDRs due to antiemetics were infants and were prescribed for vomiting and gastroesophageal reflux disease (GERD). Among 12 patients, two patients received combination of two drugs (Table 1). Among these, two patients' one received tetrabenazine with trihexyphenidyl and other one received tetrabenazine with haloperidol.

In eight patients (67.6%), dystonic reactions emerged due to drugs that were prescribed by a pediatrician and psychiatrist. However, 33.3% of the patients obtained the drugs as over the counter (OTC) drugs. Routine blood investigations (complete blood count, serum electrolytes, creatinine, and liver function test) were normal in all children. Electroencephalogram (EEG) was done in seven patients and all had normal findings. Neuroimaging was done in two infants who were normal in both.

All the patients were treated with benzodiazepine in emergency department. A total of eight patients received oral diphenhydramine for 3 days. The follow-up period ranged from 4 to 8 months and there was no recurrence of dystonia at the last follow-up.

Table 1: Clinical profile of drug-induced dystonic reactions in children

Characteristics	Value
Age: Mean age (range)	50.8 mo (4–108 mo)
<1 year	4 (33.3%)
1–5 years	3 (25%)
6–15 years	7 (41.6%)
Sex: Males	8 (67%)
Types of drugs	
Antiemetics	
Domperidone	4 (33.3%)
Antipsychotics	
Risperidone	4 (33.3%)
Haloperidol	1 (8.3%)
Aripiprazole	1 (8.3%)
Methylphenidate	1 (8.3%)
Others	
Tetrabenazine	2 (16.6%)
Polypharmacy	2 (16.6%)
Types of dystonia	
Opisthotonus	1 (8.3%)
Abnormal posturing of head and neck	7 (58.3%)
Abnormal posturing of head, neck, and extremities	4 (33.3%)
Dosage	
Therapeutic dose	5 (41.7%)
Overdose	7 (58.3%)
Duration of drug use	
<12 h	4 (33.3%)
12–48 h	4 (33.3%)
2–7 days	4 (33.3%)

DISCUSSION

Acute dystonic reaction is a common problem encountered when using antipsychotic drugs or certain other drugs. Dopaminergic receptors in the nigrostriatal pathway have a significant role in initiation and control of the movement. Thus, blockade of these receptors by drugs causes the disappearance of the inhibiting effect of dopamine on acetylcholine, and as a result, cholinergic system becomes relatively more dominant and leads to the development of extrapyramidal movement disorders, such as dystonia [5].

In the present study, most of the children had DIDRs between 4 and 8 years of age group. The probable reason could be diagnosis of the primary disease and treatment with antipsychotic drugs or an increase in the number of dopaminergic receptors along with the increase in age [6]. Derinoz and Caglar and Park *et al*. reported similar finding in their studies [7-9].

In the present study, common drugs causing DIDRs were identified as antiemetics and antipsychotics. Among antiemetic drugs, metoclopramide is well recognized for extrapyramidal symptoms, but domperidone can also cause DIDRs, which is used for the treatment of GERD in infants [10-13]. Pellegrino *et al*. and Franckx and Noel also reported domperidone-induced extrapyramidal symptoms especially dystonia [14,15]. Dhakal *et al*. reported a case of 13-year-old boy with severe extrapyramidal features by domperidone even with therapeutic dose [16]. In the present study, DIDRs due to domperidone were observed in four infants and they used the drug with overdose because of improper prescription and OTC availability. These children developed dystonia after taking multiple doses within 48 h. These children underwent EEG to rule out the seizures; however, all had normal EEG. Magnetic resonance imaging (MRI) brain was done in two infants and both were normal.

Antipsychotic drugs were well recognized as another class of drugs to cause DIDRs [17-20]. In the present study, most of the patients received antipsychotic drugs for their primary disease such as ASD and/or ADHD. Among these, risperidone was the most common cause even with therapeutic dose. However, with therapeutic dose, they developed dystonia 2–7 days after drug initiation. With risperidone overdose, the patients developed dystonia within 12 h of duration. Derinoz *et al.* and Park *et al.* reported the similar cause of DDIRs in children [7,9]. In the present study, one patient developed dystonia after tetrabenazine ingestion with overdose. Reches *et al*. and Kenney *et al*. also reported similar findings [21,22].

There is variable anatomical distribution of the muscle involvement related to DIDRs [18]. Most commonly cranial, pharyngeal, cervical, and axial muscles are affected, but only extremities may be affected sometimes. Eventually, various forms of dystonia, such as torticollis, trismus, grimacing, dysarthria, oculogyric crisis, blepharospasm, and swallowing difficulties might be seen. However, the severity of symptoms is variable [1]. Acute dystonia may occur as opisthotonos form, which is a painful and distressing condition. Some clinical conditions may be life threatening, such as laryngospasm, and

immediate treatment is important for patients who have impaired respiration [21,22]. In this study, the most commonly observed presentations were involvement of head and neck region and only one child had opisthotonus posturing.

In this study, dystonia occurred in 48% of patients who took drugs in therapeutic dosage. Most of the patients developed dystonia within 48 h after drug ingestion with overdose which was similar to other studies. Dystonia developed within 3–7 days after drug ingestion with therapeutic dose. The studies by Derinoz and Caglar, Park *et al.,* and Yis *et al*. [11] revealed that dystonia is usually seen within the first 24–72 h of drug exposure [7,9]. When physicians prescribe a drug that has a risk of DIDRs, they should inform the patients about possible late complications. A follow-up of the patient after 3 days to check for the progression and occurrence of DIDR may be suggested.

Acute dystonia may be confused with different conditions such as partial seizure, encephalitis, tetany, GERD, and electrolyte imbalances [7-9,17]. In this study, infants had more thorough evaluation such as MRI brain, EEG, and serum electrolytes than the older groups. These findings may be associated with the physician's unawareness of DIDR and fear of misdiagnosis, particularly in younger children. Thus, physicians should have a high index of suspicion and knowledge of DIDRs to avoid unnecessary investigations.

Recognizing signs and symptoms of DIDRs after the administration of a drug are the first step of the diagnosis and the treatment is the discontinuation of the drug immediately. DIDRs can be treated with various medications depending on the availability such as biperiden, benztropine, trihexyphenidyl, or diphenhydramine [23-25]. In our study, all the cases were treated with an intravenous midazolam in emergency department. All these patients had relief from dystonia, suggesting that parenteral benzodiazepines can be used for DIDRs in emergency. A total of eight patients were treated with oral diphenhydramine for 3–5 days.

To the best of our knowledge, this is the first study and the largest cohort to examine DIDRS in children from India using parenteral benzodiazepine and oral diphenhydramine, which is safe, easily available, and cheap. This study had several limitations. First, this was a single center study. Second, our small sample size could not represent all pediatric DIDR patients.

CONCLUSION

DIDRs can develop commonly as treatment side effect with therapeutic doses or with overdoses of antiemetics and antipsychotics. In children, DIDR responded well to benzodiazepines and diphenhydramine. Proper diagnosis through taking of accurate drug history would avoid unnecessary investigations. However, prospective multicenter studies are needed to confirm these features of pediatric DIDRs.

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