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Poison Information Center Data about Drug-Induced Acute Dystonic Reactions

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ÖZET:

Zehir danışma merkezi verileri, ilaca bağlı akut distonik reaksiyonlar

Amaç: Çalışmamızın amacı, Ocak 1993-Aralık 2008 tarihleri arasında Dokuz Eylül Üniversitesi Tıp Fakültesi İlaç ve Zehir Danışma Merkezi (ZDM)'ne danışılan ilaçlara bağlı gelişen distonik reaksiyonların geriye yönelik değerlendirilmesidir.
Yöntem: Çalışmamızda, 1993 Ocak ve 2008 Aralık arasında ZDM'ne bildirilen ilaçlara bağlı gelişen distonik reaksiyon olgularının dağılımı, hangi ilaçlara bağlı olarak geliştikleri değerlendirildi. Verilerin istatistiksel analizinde ki-kare testi kullanıldı.
Bulgular: Distonik reaksiyon geliştiği bildirilen olguların %81.1'i çocukdu. Çocuklarda ve erişkinlerde kadın/erkek oranı ise sırasıyla 1.5 ve 1.0 idi. Çocuklarda, 0-12 yaş arasında yan etkiye bağlı olarak distonik reaksiyon gelişimi anlamlı oranda yüksekti (%87.5)(χ2= 11,285, p= 0.0008). İlaçlara bağlı gelişen distonik reaksiyonlarda alınan ilaç miktarı %57.7 hastada nontoksik, %22.3 hastada bilinmeyen, %20.0 hastada ise toksik idi. Distonik reaksiyon gelişen olgularda etken maddeler sırasıyla metoklopramid (%44.4, n=40), haloperidol (%35.6, n=32), risperidon (%15.6, n=14), trifluoperazin (%2.2, n=2), flufenazin (%1.1, n=1) ve klorpromazindi (%1.1, n=1). Çocuklarda distonik reaksiyon gelişimine neden olan en sık etken metoklopramid (%47.9, n=35) iken erişkinlerde haloperidol (%47.0, n=8) idi. Çocuklarda, 0-12 yaş grubunda metoklopramide bağlı distonik reaksiyon gelişimi yüksekti (χ2= 12,949, p=0.0003). Aynı yaş grubunda distonik reaksiyon gelişiminin anlamlı oranda nontoksik miktarda ilaç alımına bağlı olduğu saptandı (χ2= 5,882, p=0.0153).
Sonuç: En fazla distonik reaksiyona neden olan ilaçlar metoklopramid, haloperidol ve risperidondur. Hekimler, çocuklara metoklopramid, yetişkinlere haloperidol reçete ederken hastalara ve ailelerine tedavi dozlarında bile distonik reaksiyon gözlenebileceği konusunda uyarıda bulunmalıdır.

Anahtar sözcükler: Akut distonik reaksiyon, ilaç ve zehir danışma merkezi

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ABSTRACT:

Poison information center data about drug-induced acute dystonic reactions

Aim: To examine and describe the frequency of cases with drug-induced acute dystonic reactions (ADRs) based on the Data of Dokuz Eylul University Drug and Poison Information Center (DPIC).
Method: We analysed drug-induced ADRs and the distribution of the drugs which caused these ADRs reported to Dokuz Eylul University DPIC between January 1993 and December 2008. Statistical analysis was performed using the chi-square test.
Results: Of the reported drug-induced ADRs, 81.1% were in children. The female/male ratios were 1.5 and 1.0 in children and adults, respectively. Acute dystonic reactions occurring as side effects of drugs were found to be higher in children between 0 and 12 years of age (87.5%, χ2=11,285, p= 0.0008). The doses of the drugs to which the patients were exposed were found to be nontoxic (57.7%), unknown (22.3%) or toxic (20.0%). Metoclopramide (44.4%, n=40), haloperidol (35.6%, n=32), risperidone (15.6%, n=14), trifluoperazine (2.2%, n=2), fluphenazine (1%, n=1), and chlorpromazine (1%, n=1) were the drugs that caused the acute dystonic reactions. Metoclopramide (47.9%, n=35) and haloperidol (47.1%, n=8) were the most frequent drugs that caused dystonic reactions in children and adults, respectively. ADRs related to metoclopramide were higher in children between 0 and 12 years of age (χ2=12,949, p=0.0003). Drug-induced ADRs, that related to nontoxic amount of drugs, were higher in the same age group (χ2=5,882, p=0.0153).
Conclusion: Metoclopramide, haloperidol and risperidone were the most frequent causes of drug-induced ADRs. Physicians should inform patients and their families, when they prescribe haloperidol for adults and metoclopramide for children, about the possibility of drug-induced ADRs even in therapeutic doses.

Key words: Acute Dystonic reactions (ADRs), Drug and Poison Information Center (DPIC).

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INTRODUCTION

Dystonia is a neurological movement disorder in which sustained muscle contractions cause twisting and repetitive movements or abnormal postures of the neck (torticollis, retrocollis), the jaw, the tongue or the entire body (opisthotonus). Upward or lateral movement of the eyes (rolling or deviated gaze), dysphagia, dysarthria, and difficult breathing may also happen in acute dystonic reactions (ADRs). Although the the rapid blockage of dopaminergic receptors in the nigrostriatal tract is believed to be the reason for occurrence of ADRs, some questions remain about the exact mechanism (1,2).

Dystonic reactions are clinical signs and symptoms that are observed in some neurological diseases such as Huntington's chorea, Parkinson's disease, Wilson's disease, as well as being due to trauma, tumors, basal ganglia strokes, seizures, idiopathic causes, and medications. Drug-induced ADRs commonly occur after the initiation of antipsychotic therapy not only with therapeutic doses but also with overdoses (3). In addition to the antipsychotics, opioids (alfentanil), antiarrhythmics (flecainide), anticonvulsants (carbamazepine, phenytoin), tricyclic antidepressants (amitriptyline, amoxapine), selective serotonin re-uptake inhibitors (fluvoxamine, paroxetine), monoamine-oxidase inhibitors (phenelzine, tranylcypromine), and antiemetics (metoclopramide, domperidone) are some other drugs which cause ADRs (4-7).

High potency antipsychotic use, young age, male gender, primary psychotic disorders, family history, and prior dystonic reactions have been reported to be risk factors for the development of drug-induced ADRs (8,9). Because of the risk of sudden death related to difficulty breathing due to ADRs, immediate treatment is important for patients who have impaired respiration (1,10). Anticholinergic drugs such as biperiden and diphenhydramine are the main treatment agents for drug-induced ADRs (10).

Although there are some case reports citing various drugs such as metoclopramide, haloperidol, and cetirizine as causes of drug-induced ADRs, data about the distribution of drug-induced ADRs are limited. In this study, we conducted a retrospective review of drug-induced acute dystonic reactions reported to the Dokuz Eylul University Drug and Poison Information Center during the period from 1993 through 2008. Our goal was to examine and describe the frequency of cases with drug-induced acute dystonic reactions and classify the drugs that cause these ADRs.

METHOD

This study was approved by the Institutional Ethics Committee of Dokuz Eylul University, School of Medicine. The poisoning exposure cases related to drug-induced acute dystonic reactions (ADRs) reported to Dokuz Eylul University Drug and Poison Information Center (DPIC) between January 1, 1993 and December 31, 2008 were evaluated retrospectively. An ADR diagnosis reflects the physician's opinion given during a telephone consultation. For all of the drug-induced acute dystonic reaction cases, age, gender, exposure time, exposure reason (accidental, intentional, side-effect, and unknown) amount (toxic, non-toxic, and unknown) of exposed drug, the name of the drug and recommended treatments were registered into Statistical Package for the Social Sciences (SPSS) for Windows Release 15.0.1. Thomson, Micromedex Healthcare CD's data were used to classify the amounts of the drugs as toxic or non-toxic. Unknown amount was used generally for the intentional exposures. Ages of the children were categorized as ≤6 years, 7 to 12 and 13 to 18 years old.

The gender and age distribution of drug-induced ADRs and the percentages of drug-induced acute dystonic reactions in children and adults were evaluated by crosstabs. Statistical analysis was performed by a chi-square test. P values of <0.05 were considered to be statistically significant.

RESULTS

Dokuz Eylul University Drug and Poison Information Center received 90 phone calls involving drug-induced ADRs between January1993 and December 2008. Of the 90 cases with ADRs, 55.6% (n=50) were female and 40.0% (n=36) were male and 81.1% (n=73) of them were children. Female/male ratios were 1.5 and 1.0 in children and adults, respectively (Table 1). The mean ages of the children and adults were 9.02±5.2 and 26.5±8.8 years, respectively. Most of the calls occurred in the evening hours between 18:00 and 23:59 hours (60.0%).

Table 1: The gender and age distribution of drug-induced dystonic reactions

	Children		Adults		Total	
	No	%	No	%	No	%
Male	28	77.8	8	22.2	36	100.0
Female	42	84.0	8	16.0	50	100.0
Unknown	3	75.0	1	25.0	4	100.0
Total	73	81.1	17	18.9	90	100.0
Age						
Mean±SD	9.02±5.2		26.5±8.8		12.31±9.1	
Range	(0.5-18.0)		(20.0-50.0)		(0.5-50.0)	

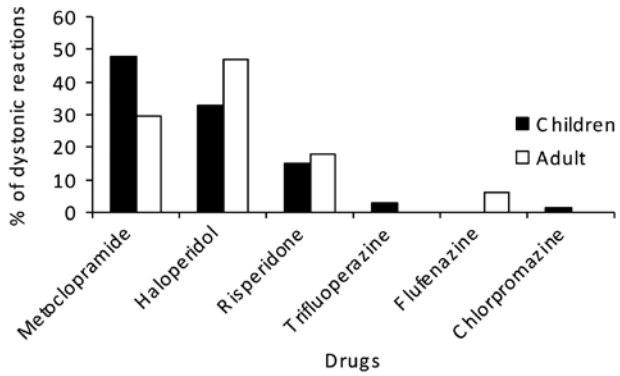

Figure 1: Percentages of drug-induced dystonic reactions in children and adults

Table 2: Reasons for drug-induced dystonic reactions according to age groups

	Reason for drug-induced dystonic reactions								Total	
Age group	**Accidental**		**Intentional**		**Side effect**		**Unknown**			
	No	**%**	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**
0-6	8	33.3	0	0.0	16	66.7	0	0.0	24	100.0
7-12	2	7.4	3	11.1	19	70.4	3	11.1	27	100.0
13-18	1	4.5	13	59.1	5	22.8	3	13.6	22	100.0
	11	15.1	16	21.9	40	54.8	6	8.2	73	100.0
19-29	1	7.2	10	71.4	3	21.4			14	100.0
30-39	0		1	100.0	0				1	100.0
40-49	0		0		1	100.0			1	100.0
50-59	0		0		1	100.0			1	100.0
≥60	0		0		0				0	
	1	5.9	11	64.7	5	29.4	0		17	100.0
Total	12	13.3	27	30.0	45	50.0	6	6.7	90	100.0

The rates of occurrence of side effect related drug-induced ADRs were 54.8% (n=40) and 29.4% (n=5) in children and adults, respectively. Intentional drug exposures were more common in adults than in children (64,7%, $\chi 2$= 10,070, p= 0.0015). Side effect related ADRs were higher in children between 0 and 12 years of age (87.5%, $\chi 2$= 11,285, p= 0.0008) (Table 2).

The amounts of the drugs to which the patients were exposed were found to be nontoxic in 57.7% (n=52), unknown in 22.3% (n=20) and toxic in 20.0% (n=18) of the cases. The majority of the ADRs in children developed from non-toxic amounts of drug exposures (60.3%, n=44), as compared with adults (47.1%, n=8). Side effect related acute dystonic reactions were higher in patients exposed to nontoxic amounts of drugs ($\chi 2$= 21,01, p<0.0001) . Most of the drug-induced ADRs (79.1%) were reported within 24 hours, and the remainder were reported within 72 hours of exposure. ADRs related to nontoxic drug exposures were reported more frequently in the first 24 hours in children ($\chi 2$= 3,996, p=0,0456).

Metoclopramide (44.4%,n=40), haloperidol (35.6%, n=32), risperidone (15.6%, n=14), trifluoperazine (2.2%, n=2), fluphenazine (1%, n=1), and chlorpromazine (1%, n=1) were the reported causes of drug-induced ADRs. Metoclopramide (47.9%, n=35) and haloperidol (47.1%, n=8) were the most frequent causes of ADRs in children and in adults, respectively (Figure 1). Most of the metoclopramide-induced ADRs were due to nontoxic amounts of exposure (85.0%, $\chi 2$= 13,670, p=0.0002). ADRs related to metoclopramide exposure were higher in children between 0 and 12 years of age ($\chi 2$= 12,949, p=0.0003) as opposed to those due to other drugs. Drug-induced ADRs related to nontoxic amounts of drugs were higher in the same age group ($\chi 2$= 5,882, p=0.0153) (Table 3).

Table 3: Exposure amounts of the drugs

	Total							
Drugs	**Toxic**		**Non toxic**		**Unknown**		**Total**	
	No	%	No	%	No	%	No	%
Haloperidol	11	34.4	10	31.2	11	34.4	32	100.0
Metoclopromide	2	05.9	34	85.0	4	10.0	40	100.0
Risperidone	3	21.4	7	50.0	4	28.6	14	100.0
Trifluoperazine	1	50.0	0		1	50.0	2	100.0
Fluphenazine	0		1	100.0	0		1	100.0
Chlorpromazine	1	100.0			0		1	100.0
Total	18	20.0	52	57.7	20	22.3	90	100.0

DISCUSSION

Acute dystonic reaction, a movement disorder characterized by involuntary muscle spasms, is a common problem encountered when using antipsychotic drugs or certain other drugs even in therapeutic doses. Some diseases, trauma or tumours are other reasons for the development of ADRs. In the current study, we analysed drug-induced acute dystonic reactions (ADRs) reported to our Drug and Poison Information Center (DPIC) and we found that most of the ADRs occurred in therapeutic or nontoxic doses.

Drug-induced ADRs are frequently frightening because of their abrupt onset and life threatening nature. Diagnosis and treatment of drug-induced ADRs must occur quickly because of possible complications such as respiratory depression, joint dislocation, and death. Drug-induced ADRs are generally seen in young adults. Older patients rarely have this side effect (11,12). We found that children between 0 and 12 years of age were the most affected group of patients. Additionally, most of the adults with ADRs were young and there were only two patients older than 40 years of age in the present study. Although in some previous studies, male gender has been reported to be a risk factor for drug-induced ADRs, in our study female gender was dominant in children and no difference in gender dominance was present in adults. In a study from the United Kingdom (UK), 70% of patients with metoclopramide-induced acute dystonic reactions were female (8,9,13). Bateman et al. also reported female dominance in extrapyramidal reactions caused by metoclopramide (14).

Although antipsychotics and some other drugs such as flecainide and alfentanil can cause ADRs, high-potency antipsychotics such as haloperidol and fluphenazine have been reported to be the riskiest drugs for ADRs (15,16). Antipsychotics with a stronger anticholinergic potency tend to carry a lower risk for development of ADRs. Although the atypical antipsycotics present a very low risk for the occurence of ADRs, cases of ADRs have been reported to have been caused by clozapine, olanzapine, and quetiapine (17).

In our study, the older antipsychotic, haloperidol, was the most common cause of ADRs in adults, possibly due to dopaminergic receptor blockade and weak anticholinergic effects. An antiemetic and gastrointestinal stimulant drug, metoclopramide, was the most common cause of ADRs in children. The data about the safety and efficacy of haloperidol use in children are insufficient (18).

Metoclopramide, which blocks the dopaminergic D2 receptors located in the chemoreceptor trigger zone, is used for treating nausea, vomiting, and gastro-esophageal reflux disease (GERD) (19). In the present study, children with most of the ADRs related to metoclopramide use were between 0 and 12 years of age. They also were exposed to therapeutic doses of metoclopramide in our study. There is less evidence to support the use of metoclopramide in infants (20). In a national survey about antiemetic use in pediatric gastroenteritis by Kwon et al, akathisia and dystonia were observed in up to 25% of children receiving metoclopramide (21). The other causes of the drug-induced ADRs were risperidone, trifluoperazine, fluphenazine, and chlorpromazine in the current study. According to our DPIC data, most of the drug-induced ADRs resulted from nontoxic or therapeutic amounts of drug exposure.

ADRs in the emergency service are important events because of serious complications such as joint dislocation, airway compromise, and death (22,23). Differential diagnosis, and treatment of patients with drug-induced ADRs in the

emergency service, especially in the pediatric emergency service, are very important and could be life saving.

Limitations

The retrospective nature of the study prevented us from learning the outcomes of the patients.

We could not find the indication for use of the medications and other concomitant drugs, which might have increased the risk of dystonia and the occurrence of co-morbidities (renal failure). We also could not check other risk factors including alcohol and cocaine use. The number of the patients was low and finally we could not evaluate the duration and outcomes of the dystonic reactions.

CONCLUSIONS

- Physicians should be careful when prescribing metoclopramide for children up to the age of 12 to avoid metoclopramide-induced dystonic reactions even in therapeutic doses.
- Families must be educated about this frightening and abrupt onset adverse effect.
- Prospective studies including larger numbers of patients, using the newer antipsychotic drugs and including follow ups are needed.
- Patients must be informed and educated about ADRs when an antipsychotic drug such as haloperidol is prescribed.

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