DOI: 10.5350/BTDMJB201612202

Medication Related Dystonic Reactions Especially in Children on Risperidone: A Description of Eleven Cases and Review of the Literature

Emel Ataş Berksoy[1], Ünsal Yılmaz[2], Tanju Çelik[1], Hüseyin Anıl Korkmaz[3], Selçuk Yazıcı[4], Rahmi Özdemir[5], Özlem Bekem Soylu[1]

Dr. Behçet Uz Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesi, [1]Çocuk Acil Servisi, [2]Çocuk Nöroloji Bölümü, [3]Çocuk Endokrinoloji Bölümü, [5]Çocuk Kardiyoloji Bölümü, İzmir
[4]Balıkesir Üniversitesi Sağlık Uygulama ve Aaraştırma Hastanesi, Çocuk Acil Servisi, Balıkesir

ÖZET

İlaca bağlı distonik reaksiyon özellikle risperidon kullanan çocuklarda: 11 olgunun tanımlanması ve literatürün gözden geçirilmesi

Amaç: Bu çalışmada ilaca bağlı akut distoni nedeniyle özellikle risperidon tedavisi sonrası çocuk acil ünitesine başvuran çocukların klinik özellikleri değerlendirildi.

Gereç ve Yöntem: Ocak-Aralık 2013 tarihleri arasında acil ünitesinde ilaca bağlı akut distonik reaksiyon tanısı alan on bir hastanın (3-16 yaş) dosya bilgileri geriye dönük olarak değerlendirildi.

Bulgular: Hastaların 6'sı risperidon kullanmıştı. Bunlardan biri bilinmeyen miktarda kazara alım diğerleri ise dikkat eksikliği hiperaktivite veya davranım bozukluğu nedeniyle ≤6 mg/gün ağızdan kullanmaktaydı. İki hasta teröpetik dozlarda ağızdan metoklopramid almışlardı. Bu hastalardan biri intihar girişimi amaçlı diğeri de gastroenterit nedeni ile idi. Bir hasta soğuk algınlığı nedeniyle 4 mg (1 tablet) klorfeniramin maleat, bir hasta Syndenham kore nedeniyle 0,2 mg/gün haloperidol damla almış , bir hasta da bilinmeyen bir ot yemişti. Bilinmeyen ot yeme öyküsü olan hasta kliniğimize konvülziyon ve ensefalit ön tanıları ile sevk edilmişti. Risperidon kullanımı olan hastaların 3'ünde de ön tanı konvülziyon idi. Tüm hastalar ilaç kullanım öyküleri ve tedaviye iyi yanıt vermeleri nedeniyle klinik olarak akut distonik reaksiyon tanısı aldılar. Tüm hastalara biperiden laktat parenteral olarak uygulandı. Tüm belirti ve bulgular 30-45 dakika içinde tamamen kayboldu.

Sonuç: Akut distonik reaksiyon diğer pek çok klinik durumla karışabilen çocuklarda nadir görülen klinik bir durumdur. İlaç alım öyküsü bulunup hareket bozukluğu gelişen hastalarda akut distonik reaksiyon düşünülmelidir.

Anahtar kelimeler: Çocuk, distoni, ilaç

ABSTRACT

Medication related dystonic reactions especially in children on risperidone: a description of eleven cases and review of the literature

Objective: In this study, we evaluated the clinical characteristics of children who had admitted to the pediatric emergency unit due to drug- induced acute dystonia, particularly following risperidone treatment.

Material and Methods: The hospital records of eleven patients (range 3- 16 years age) who had been diagnosed as acute dystonic reaction in our emergency unit, between January and December 2013, were retrospectively reviewed.

Results: Six of the patients had used risperidone. One of these was accidental ingestion of an unknown amount. The others had taken risperidone <6 mg/day orally for conduct disorder or attention deficiency hyperactivity disorder (ADHD). Two children had taken metoclopromide orally at therapeutic dosages. One of these was as an attempt for suicide; the other was for acute gastroenteritis. One patient had taken a 4 mg chlorpheniramine maleate tablet for common cold, another had used haloperidol gutt (0.2 mg/day) for Sydenham chorea, and there was one case of unknown weed ingestion. The patient who had a history of unknown weed ingestion was referred to our clinic with the initial diagnosis of convulsion and encephalitis. Convulsion was the initial diagnosis in three of the cases of risperidone use also. All the patients were clinically diagnosed as acute dystonic reaction with the history of drug usage and a good response to treatment. Biperidene lactate was administered in all cases. All the signs and symptoms of the patients had disappeared within 30-45 minutes.

Conclusion: Acute dystonic reaction is a rare clinical condition in children, which can easily be mistaken for other conditions. Acute dystonic reaction should be considered in patients who develop movement disorders and whose history includes the intake of a variety of medicines.

Key words: Child, drug, dystonia

Bakırköy Tıp Dergisi 2016;12:64-69

Yazışma adresi / *Address reprint requests to:* Dr. Emel Ataş Berksoy, Dr. Behçet Uz Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesi, Çocuk Acil Servisi, İzmir

Elektronik posta adresi / *E-mail address:* emelberksoy@hotmail.com

Geliş tarihi / *Date of receipt:* 19 Ocak 2015 / January 19, 2015

Kabul tarihi / *Date of acceptance:* 14 Ocak 2016 / January 14, 2016

INTRODUCTION

Acute dystonic reactions are defined as involuntary, slow, and sustained contractions of muscle groups, which may result in twisting, repetitive movements, and abnormal posturing. Drug-induced acute dystonic reactions are commonly encountered in the emergency units. They may occur in patients who have been medicated with antipsychotics, antidepressants, anti-emetics, antimalarials and antiepileptic drugs (1,2). They occur frequently (0.5-1%) in patients to whom metoclopramide is administered as an anti-emetic (3). The clinical presentation of acute dystonia can be variable, such as trismus, torticollis, dysarthria, oculogyric crises, swallowing disorders, and blepharospasms. Dystonic reactions are generally mistaken for tetany and convulsions, and because of that, the diagnosis may be incorrect (4).

This study reports eleven pediatric patients admitted to our emergency unit with dystonic reactions. The cases reported here demonstrate the emergency presentation of drug- induced dystonic reactions. We emphasize that these reactions may be confused with other disorders and mistreated. We also aim to highlight the fact that dystonia can be a side effect of risperidone even if it is used at low doses, which is commonly used by child psychiatrists in our country.

MATERIAL AND METHODS

The hospital records of eleven patients, who had admitted to the pediatric emergency unit of our hospital due to acute dystonia between January and December 2013, were retrospectively reviewed. Patients were excluded from the study if they had been previously diagnosed with primary or secondary dystonia. Dystonia was defined as abnormal movements and/or postures caused by sustained, repetitive involuntary contractions. The age and gender of the patients, initial diagnosis, diagnosis, etiologic factor of dystonia, drug dosage, development period of dystonia, symptoms and treatment were noted from the records. The study was approved by the local ethical committee.

Statistical Analyses

Data analyses were performed using SPSS for Windows, version 15.0 (SPSS Inc., Chicago, USA). Means ± standard deviations were calculated for measurable variables.

RESULTS

The mean age of the patients was 10.59±3.77 years (3- 16 years), nine of whom were male (Table 1). Mean time of dystonia development after medication was 47 hours (3 hour- 2 weeks). Two patients had been referred to our hospital with the initial diagnosis of seizure and rectal diazepam had been applied by a family physician. All of the other patients had been directly admitted to our emergency room. The pre-diagnosis was seizure in four cases, and one was diagnosed as having encephalitis also. This patient had a history of unknown weed ingestion. Risperidone had been taken by six of the cases. Five of them were using this medication for the treatment of conduct disorder. One child had taken this medicine accidentally and the amount taken was unknown. He had a diagnosis of cerebral palsy and mental retardation. Of these six cases, only one patient developed dystonia after the initial dose, whereas four of the patients developed dystonia after the dose titration. Metoclopramide was taken by one patient who had attempted suicide. The other one had received metoclopramide orally for acute gastroenteritis, and developed dystonia after the initial dose. One patient had taken a single dose of 4 mg chlorpheniramine maleate tablet for common cold and another one had a history of unknown weed ingestion. One patient with Syndenham chorea had been taking haloperidol gutt 2 ml/day bid orally for two days. He had also symptoms of tardive dyskinesia. None of the patients took these medicines in combination with other drugs with known neurological side effects. Symptoms and signs were contraction of the legs in three patients, tongue protrusion in two patients, torticollis in three patients, and oculogyric crises in three patients. In addition to these, opisthotonus was observed in two cases and trismus in one case. Acute dystonic reaction was diagnosed in all cases, based on physical examination and history of potential drug ingestion. Complete blood count, blood chemistry and blood gas analysis were normal in all patients. Biperidene lactate (0.04 mg/kg/dose, intramuscular) was administered in all cases. All the symptoms and signs disappeared within 30-45 minutes after the treatment. Risperidone and

Table 1: The features of the patients with acute dystonic reactions

Case	Age (year)	Gender	Pre-diagnosis	Development of dystonia after the initial dose	Etiology (dose)	Onset of symptoms (hours)	Signs
1	6.5	female	Seizure+ encephalitis		Unknown weed ingestion	4	Oculogyric crises
2	11	male	Convulsion	+	Risperidone 0.5 mg /day p.o (first dose) for conduct disorder	24 hours	Oculogyric crises+ opisthotonus
3	13	male	Epileptic seizure×	+	Accidental risperidone intake (dose?)	12 hours	Torticollis+ tongue protrusion
4	11	male	Dystonia×		Risperidone usage for one year 2 mg /day bid p.o, titrated to 4mg/day for 2 days for conduct disorder	48 hours	Contractions + trismus
5	3	female	convulsion×		Risperidone (0.2 mg/day p.o for 2 weeks for ADHD	2 weeks	hypertonicity of legs+ oculogyric crises
6	7	male	Dystonia×		1 mg/day risperidone [for 2 months] titrated to 2 mg/day p.o(first titrated dose) for ADHD	10 hours	Torticollis+ opisthothonus
7	16	male	Dystonia×	+	3 metoclopramide tablets p.o for suicidal attempt	8 hours	Oculogyric crises
8	11	male	Dystonia×	+	Chlorpheniramine maleate 4 mg. (1 tablet) p.o for common cold	3 hours	Tortikollis+ contraction of legs + tongue protrusion
9	15	male	Dystonia×		Haloperidol (2mg/20ml) 2ml /day p.o for Sydenham chorea	2 days	Torticollis+ oculogyric crises+ dysphagia+ diffuculty in speech+ tardive dyskinesia
10	14	male	Dystonia×		Risperidone (1 mg/day for 4 weeks) after titration to 2 mg/day p.o.for conduct dısorder of autism	16 hours	Oculogyric crises+ opisthotonus
11	9	female	Dystonia×	+	(10 mg) one tablet of metoclopramide p.o for acute gastroenteritis	10 hours	Oculogyric crises+ opisthothonus

ADHD : attencion deficit-hyperactivity disorder, × : cases who admitted directly to the emergency department

haloperidol were discontinued and all the patients were observed for 24 hours. Within this time the symptoms did not reappear. The specific features of each of the patients are outlined in Table 1.

DISCUSSION

Acute dystonic reactions have been reported secondary to various medications, including neuroleptic and antiemetic drugs (haloperidol, chlorpromazine, olanzapine, risperidone, prochlorperazine), calcium channel blockers, stimulants (amphetamine, cocaine, ergot alkaloids), anticonvulsants (carbamazepine, phenytoin) that change the dopaminergic tone in the basal ganglia or antagonize dopamine D2 receptors (1-9). A variety of forms of dystonia is observed clinically, such as torticollis, trismus, grimacing, dysarthria, oculogyric crisis, swallowing difficulties and blepharospasm. The pathogenesis remains unclear, but it is believed to be due to a deficit in central dopamine transmission, resulting in hyperactive striatal acetylcholine release (1,5). This is reversed with the use of anticholinergic medications.

Acute dystonic reaction in the emergency unit may be a serious condition because of the high probability of misdiagnosis (10,11). When there is a dystonia, the possibilities of tetanus, convulsion, hypocalcemia, other electrolyte imbalances and encephalitis should be included in the differential diagnosis, which may delay intervention and result in fatal outcome due to tongue protrusion and laryngeal spasm (12). In our series, case 1, 2, 3 and case 5 illustrates this point. Case 1 had been referred to our clinic with the pre-diagnoses of encephalitis and convulsion and had been treated with diazepam. He was clinically diagnosed as acute dystonic reaction secondary to unknown weed ingestion. The other 3 patients were also diagnosed as convulsion first at our emergency unit. Diazepam had been administered to all of them but clinical signs (extrapyramidal reactions) had not resolved within 30 minutes. The patients were diagnosed as secondary dystonic reaction with the history of risperidone usage and weed ingestion, because they had no progressive symptoms, and a good response to biperidene lactate. This misdiagnosing situation resulted in loss of time and treatment with an unnecessary medication like diazepam.

Risperidone, a second generation antipsychotic drug is increasingly prescribed in children and adolescents with conduct disorder, especially in young children with normal intelligence (13). Antipsychotic–induced acute dystonic reaction is defined as sustained abnormal postures or muscle spasms that develop within seven days of starting, or after rapidly raising the dose of medication (14). The exact pathophysiology remains unknown but probably involves the blockade of dopamine D2 receptors in the striatum (15,16). The risk of risperidone-induced dystonia is increased if the patient is young, male, has experienced previous incidences of acute dystonia, or has used psychoactive substances, and rapid titration (1). As previous other case report in the literature had indicated, our results showed that not only titrated high doses but also initial low doses of risperidone may induce dystonia in children (17). In our series, case 2 highlights this point. He was 11 years of age and had received 0.5 mg risperidon orally as an initial dose. He developed dystonia which was confused with convulsion after 24 hours of risperidone intake. As a second generation antipsychotic, risperidone is increasingly prescribed off- label in its indication. Especially in our country it is commonly used in very young children with ADHD because of adverse affects of stimulant medications in children less than 6 years old. One of our cases of risperidone reaction was in a 3-years-old female. She was medicated with low dose of risperidone for 2 weeks to improve the symptoms of ADHD. She had neither prior medical problems nor history of other drug administration. Consistent with previous reports(1), only one of the six patients in our series with risperidone induced dystonia was female. Two patients developed dystonia after a titration risperidone dosage, and dystonic reaction developed rapidly soon after the initial therapeutic risperidone dose. Although the incidence of dystonic reaction associated with therapeutic risperidone usage is low in adults, its occurrence in children is less defined. Acute dystonia in children is frightening for the parents and it can lead to serious complications and even death. However, it can be prevented by using new atypical antipsychotics or by reducing the relevant dosage, and it can be reversed with anticholinergics. The multicentre retrospective study, which included atypical antipsychotics intoxication in children younger than 6 years, reported that extrapyramidal motor symptoms were observed in one case (1%) after the ingestion of risperidone (18). Another study, describing the clinical features of a

risperidone overdose (>6 mg) including the frequency of dystonic reactions in adults, showed that 11% of patients developed acute dystonic reactions (19). We aimed to point out that risperidone induced acute dystonic reactions can occur even with therapeutic doses, so it should be prescribed for correct indication and further prospective studies are needed for efficacy and tolerability of risperidone especially in children younger than 6 years with ADHD.

Metoclopramide is a drug used to prevent nausea through dopamine receptor antagonism. The primary side effect of the drug is extrapyramidal symptoms that generally manifest as acute dystonic reactions with an incidence as high as 25% in children (4). Acute dystonia due to metoclopramide use has been observed in female patients more frequently than in males (4). In our series, one of the two patients who developed dystonia due to metoclopramide use was male. The other one was a female with acute gastroenteritis. The adverse effects of metoclopramide are idiosyncratic, and therefore acute dystonia may even appear with low doses within the first 24-72 hours of use (3,4,9,10). The literature reports that acute dystonic reaction may develop in fourteen days after taking metaclopromide (10,11,20). One patient in our series had taken 30 mg metoclopramide orally as a suicide attempt and was admitted to the clinic eight hours after drug ingestion, although the amount of the drug ingested was within the therapeutic range.

Mixtures containing antihistamines and decongestants, which are frequently used in daily pediatric practice, may cause acute dystonic reactions even if they are used at therapeutic dosages. There are case reports of acute dystonia in children medicated with cetirizine, dextromethorphan and antihistamine containing cough suppressant, and cold syrup (21-23). In one of our patients, acute dystonia developed after the ingestion of one 4 mg tablet of chlorpheniramine maleate, which had been taken for a common cold. To our knowledge, no chlorpheniramine maleate-induced dystonia had been reported previously in any of the literature relating to this subject.

It has been estimated that around 2.5% of all patients treated with neuroleptic drugs develop acute dystonia within 48 hours after starting therapy (24,25). Haloperidol interferes with the effects of neurotransmitters in the brain since it is a butyrophenone derivative, which blocks the dopamine and serotonin receptors, causing a higher incidence of extrapyramidal adverse effects than the other antipsychotics (5,9,24,25). In one patient, acute dystonia prominently manifested as oropharyngeal dystonia and grimacing, and developed after the administration of therapeutic doses of haloperidol.

Biperidene lactate (0.04 mg/kg, oral or parenteral, maximum four doses with 30 minutes interval), diphenhydramine hydrochloride (1.25 mg/kg/dose, oral or parenteral, maximum 300 mg /day with a six hour interval) were recommended in treatment of acute dystonia (3,26). In our study group, all patients were treated with biperidene lactate (single dose), and all of them responded to this treatment. This rapid recovery following a biperidene lactate injection supported the diagnosis of drug-induced dystonia and eliminated the need for any unnecessary diagnostic investigations. As previous studies had indicated, our results showed that not only titrated high doses but also initial low doses of risperidone may induce dystonia in children.

When patients are admitted with dystonic reactions, drug ingestion should be taken into account so that unnecessary investigations can be avoided. If dystonic movements are not recognized, misdiagnosis may occur. Therefore, it is advisable that if the diagnosis is suspected, an acute dystonic reaction can be treated in the first instance and then the situation can be evaluated further if there is no response. The training of physicians and pediatricians should include adverse reactions of the drugs and management of acute psychiatric emergencies such as acute dystonic reactions, which could be easily managed. In our country, there are predisposing factors for acute dystonias, especially drugs that are frequently used in daily pediatric practice and the increasing use of antipsychotics for ADHD in child psychiatry. These drugs should be used with caution for adverse effects on central nervous system especially in children before 6 years of age.

REFERENCES

1. van Harten PN, Hoek HW, Kahn RS. Acute dystonia induced by drug treatment. BMJ 1999; 319: 623-626.
2. Mihanović M, Bodor D, Kezić S, et al. Differential diagnosis of psychotropic side effects and symptoms and signs of psychiatric disorders. Psychiatr Danub 2009; 21: 570-574.

3. Bateman DN, Darling WM, Boys R ,et al. Extrapyramidal reactions to metoclopramide and prochlorperazine. Q J Med 1989; 71: 307-311.

4. Yis U, Ozdemir D, Duman M, et al. Metoclopramide induced dystonia in children: two cases reports.Eur J Emerg Med 2005; 12: 117-119.

5. Van Harten PN, van Trier JC, Horwitz EH, et al. Cocain as a risk factor for neuroleptic-induced acute dystonia. J Clin Psychiatry 1998; 59: 128-130.

6. Aggarwal A, Jiloha RC. Olanzapin induced tardive dystonia. Indian J Pharmacother 1993; 27: 874-876.

7. Burstein AH,Fullerton T. Oculogyric crises possibly related to pentazocine. Ann Pharmacother 1993; 27: 874-876.

8. Carey MJ, Aitken ME. Diverse effects of antiemetics in children. N Z Med J 1994; 9: 452-453.

9. Vernon MG. Drug induced tardive movement disorders. J Neuroscience Nursing 1991; 23: 183-187.

10. Dingli K, Morgan R, Leen C. Acute dystonic reaction caused by metoclopramide, versus tetanus. BMJ 2007; 334: 899-900.

11. Ferrando SJ, Eisendrath SJ. Adverse neuropsychiatric effects of dopamine antagonist medications. Misdiagnosis in the medical setting. Psychosomatics 1991; 32: 426-432.

12. Munhoz RP, Moscovich M, Araujo PD, et al. Movement disorders emergencies. A review. Arq Neuropsiquiatr 2012; 70: 453-461.

13. Glennon J, Purper-Ouakil D, Bakker M, et al. Paediatric European Risperidone Studies (PERS): context, rationale, objectives, strategy, and challenges. Eur Child Adolesc Psychiatry 2014; 23: 1149-1160.

14. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition. Washington, DC: American Psychiatric Association; 1994.

15. Scott LJ, Dhillon S. Risperidone: a review of its use in the treatment of irritability associated with autistic disorder in children and adolescents. Paediatr Drugs 2007; 9: 343-554.

16. Fenton C, Scott LJ. Risperidone: a review of its use in the treatment of bipolar mania.CNS Drugs 2005; 19: 429-444.

17. Cheslik TA, Erramouspe J. Ann Pharmacother 1996; 30: 360-363.

18. Meli M, Rauber-Lüthy C, Hoffmann-Walbeck P, et al. Atypical antipsychotic poisoning in young children: a multicentre analysis of poisons centres data. Eur J Pediatr 2014; 173: 743-750.

19. Page CB, Calver LA, Isbister GK. Risperidone overdose causes extrapyramidal effects but not cardiac toxicity. J Clin Psychopharmacol 2010; 30: 387-390.

20. Işıkay S, Yılmaz K, Almacıoğlu M. Evaluation of patients with metoclopramide-induced acute dystonic reaction. J Academic Emerg Med 2013; 12: 80-84.

21. Esen I, Demirpence S, Yis U, et al. Cetirizine-induced dystonic reaction in a 6-year-old boy. Pediatr Emerg Care 2008; 24: 627-628.

22. Polizzi A, Incorpora G, Ruggieri M. Dystonia as acute adverse reaction to cough suppressant in a 3-year-old girl. Eur J Paediatr Neurol 2001; 5: 167-168.

23. Joseph MM, King WD. Dystonic reaction following recommended use of a cold syrup. Ann Emerg Med 1995; 26: 749-751.

24. Buldessarini RJ, Tarazi FI. Pharmacotherapy of psychosis and mania. In: Brunton LL, Lazo JS, Parker KL, Editors. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 11th Edition. New York: Mc-Graw Hill Company; 2005.

25. Ibrahim ZY, Brooks EF. Neuroleptic-induced bilateral temporomandibular joint dislocation. Am J Psychiatry 1996; 153: 293-294.

26. Fahn S. Systemic therapy of dystonia. Can J Neurol Sci 1987; 14: 528-532.