Case Report / Olgu Sunumu

DOI: 10.4274/cayd.galenos.2021.32032
J Pediatr Emerg Intensive Care Med 2022;9:59-63

Delirium due to Anticholinergic Intoxication and Use of Physostigmine in Pediatric Emergency Room

Çocuk Acilde Antikolinerjik Zehirlenmeye Bağlı Deliryum ve Tedavide Fizostigmin Kullanımı

Alper Çiçek[1], Pelin Elibol[1], Şefika Bardak[1], Oğuz Demiroğlu[2], Gülşah Demir[1], Tuğçe Nalbant[1], Gamze Gökalp[3], Emel Berksoy[1]

[1]University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital, Clinic of Pediatric Emergency Medicine, İzmir, Turkey
[2]University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital, Clinic of Pediatrics, İzmir, Turkey
[3]İzmir Katip Çelebi University Faculty of Medicine, Department of Pediatric Emergency Medicine, İzmir, Turkey

Abstract

Anticholinergics are substances that antagonize the activity of the neurotransmitter acetylcholine. Anticholinergic syndrome (AS) occurs following a suicidal overdose, accidental drug intake, drug incompatibilities, and intake of multiple drugs simultaneously. Herein, we present two patients who were brought to the emergency room in a delirium state and were diagnosed with AS, presented other symptoms of anticholinergic toxidrome, and were treated with physostigmine.

Keywords: Anticholinergic syndrome, delirium, physostigmine

Öz

Antikolinerjikler, bir nörotransmitter olan asetilkolinin etkinliğini antagonize eden maddelerdir. Antikolinerjik sendrom (AS), özkıyım amaçlı aşırı doz alımlarında, kaza ile alımlarda, ilaç 5 uyumsuzluklarında ve birden fazla ilaç kullanan kişilerde meydana gelmektedir. Yazımızda, acil servise deliryum tablosu ile başvurup antikolinerjik toksidromun diğer belirtileri ile AS tanısı konularak fizostigmin tedavisi uygulanan iki olgu sunulmaktadır.

Anahtar Kelimeler: Antikolinerjik sendrom, deliryum, fizostigmin

Introduction

Anticholinergic syndrome (AS) is frequently encountered in emergency rooms. Over 600 compounds such as antihistamines, tricyclic antidepressants, sleeping pills, scopolamine, and opiates have anticholinergic effects (Table 1). In addition, atropine, a belladonna alkaloid, is an anticholinergic drug widely used for the treatment of bradyarrhythmias and organophosphate poisoning.[1]

Anticholinergic agents competitively inhibit the binding of acetylcholine to muscarinic acetylcholine receptors and are often referred to as "antimuscarinic agents." Muscarinic receptors are found in the central nervous system (CNS), heart, and peripheral postganglionic cholinergic nerves in smooth muscles (such as in the intestines and bronchus), glands (saliva and sweat), and the ciliary portion of the eye.[1]

The classical definition of AS is well known: Rredness of the skin due to cutaneous vasodilation (red-like beet), dryness of the skin because of impaired sweat gland functions ("dry as bone"), hyperthermia because of interference with heat dissipation mechanisms ("hot as a hare"), mydriasis, and blurred vision ("blind as a bat"). CNS symptoms included anxiety, agitation, dysarthria, confusion, disorientation, visual hallucinations, bizarre behavior, delirium, psychosis (usually paranoia), coma, and seizures ("mad as a hatter"). Other symptoms include urinary retention due to decreased

Address for Correspondence/Yazışma Adresi: Alper Çiçek, University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital, Clinic of Pediatric Emergency Medicine, İzmir, Turkey
E-mail: dr_alper_cicek@hotmail.com **ORCID ID:** orcid.org/0000-0001-5017-4525
Received/Geliş Tarihi: 02.10.2020 **Accepted/Kabul Tarihi:** 30.04.2021

contraction of the detrusor muscle of the bladder, blockage of the normal opening of the urethral sphincter ("full as a bottle"), tachycardia, and decreased or absent bowel sounds.[2] The management of the poisoned patient should always begin with the stabilization of the airway, breathing, and circulation. Patients should have intravenous access, supplemental oxygen, cardiac monitoring, and continuous pulse oximetry. Sodium bicarbonate should be used in the treatment of prolonged QRS intervals or for arrhythmias related to anticholinergic poisoning.[1,3] Physostigmine, an acetylcholinesterase inhibitor, may be required in cases of significant hypertension, uncontrolled hyperthermia, convulsions, delirium, and coma.[4]

Herein, we describe the cases of two patients who presented to the pediatric emergency room in a delirium state and were diagnosed with anticholinergic intoxication to draw attention to the clinical characteristics of AS and share their antidote (physostigmine) treatment experience.

Case Reports

Case 1

A 4.5-year-old boy, who had no previous health problems and had normal neuromotor development, was brought to the emergency room because of uncontrollable movements and agitation just before admission. On admission, the patient had tossing-style movements of the hands and involuntary movements, did not answer verbal questions and calls, and made aimless, unpredictable, and strange movements accompanied by meaningless glances. History revealed that nearly an hour before the onset of symptoms, he drank a clear liquid in a plastic bottle that he saw under a tree while he was in the park with his family. He had no history of medication, trauma, or infection. He was diagnosed with asthma but did not use any medication, and his father was diagnosed with schizophrenia. Initial assessment revealed a body temperature of 38.1 °C, blood pressure of 115/80 mmHg, and heart rate of 168/min. Mild redness was seen on the cheeks. Systemic physical examination findings were normal, except for the absence of bowel sounds. He was agitated and did not respond to questions, only looking in the direction of the voice. Bilateral light reflexes were positive, and pupils were mydriatic. Pathological reflexes were not detected. Other neurological examination findings could not be evaluated because of agitation. On pre-diagnosis, the dystonic reaction was considered a movement disorder because of purposeless and involuntary hand and arm movements. Biperiden 0.04 mg/kg was administered intravenously (IV) for treatment and diagnostic purposes. However, his clinical status did not improve; his mouth was dry, with whole-body redness (flushing) and increased body temperature. AS was considered based on anamnesis, clinical findings, and intermittent delirium status. Activated charcoal could not be given because of the patient's agitation, fluctuations in consciousness, and risk of aspiration. A urinary catheter was inserted, and the bladder was emptied. The patient had no urine output and developed a mild globe vesicle. Blood gas, serum biochemistry, and complete blood count, and electrocardiography (ECG) findings were normal. The urine drug kit could not be obtained, so it could not be assessed. Meanwhile, 20 mL/kg of 0.9% NaCl solution was given to the patient, maintenance fluid was started,

Table 1. Compounds that may cause anticholinergic syndrome

Class of compound	Drugs or herbs
Antihistamines	H1 receptor antagonists (domperidone and loperamide)
Antiparkinsonian	Benztropine and trihexyphenidyl
Antimuscarinic, genitourinary system	Darifenacin, fesoterodine, flavoxate, oxybutynin, solifenacin, tolterodine, and trospium
Antimuscarinic, spasmolytics	Atropine, belladonna, clidinium-chlordiazepoxide, dicyclomine, hyoscyamine, glycopyrrolate, propantheline, and scopolamine
Antimuscarinic, inhaled bronchodilator	Ipratropium and tiotropium
Antimuscarinic, ophthalmic drugs (mydriatic/cycloplegic)	Atropine, cyclopentolate, homatropine, and scopolamine
Gastrointestinal drugs	Antiemetics (hydroxyzine, meclizine, and promethazine)
Muscle relaxants	Cyclobenzaprine, orphenadrine, and tizanidine
Psychotropic agents	Chlorpromazine, fluphenazine, loxapine, methotrimeprazine, thioridazine, trifluoperazine, clonazepam, tricyclic antidepressants, haloperidol, perphenazine, olanzapine, quetiapine, iloperidone, and risperidone
Herbs	Angel's trumpet (Brugmansia species), deadly nightshade (atropa belladonna), henbane, *Datura stramonium, Mandragora officinarum, Datura inoxia*, clitocybe, inocybe, amanita, entoloma, and mycena
Analgesics	Opiates: Ccodeine, hydrocodone, fentanyl, meperidine, methadone, morphine, and tramadol

and cooling was applied to the whole body. Physostigmine was considered to reverse the symptoms because of the delirium state, which is a sign of neurological involvement due to anticholinergic intoxication. Close vital signs follow-up and monitoring of the patient were performed during the cooling process until the medication was given. The tachycardia continued, but the patient's agitation decreased slightly during the cooling process. Physostigmine 0.02 mg/kg (0.4 mg) was administered IV for 1-2 min. The delirium status completely regressed, body temperature decreased, and flushing partially disappeared, but the dilation of the pupils continued within 15 min after the administration of the medication. Approximately 45 min later, the second dose of physostigmine was administered, as delirium recurred. The third dose of physostigmine was administered 4 h after the second dose, as the delirium recurred, but no additional symptoms were noted. Physostigmine did not show any side effects. All symptoms of the patient regressed, except pupil dilatation. The patient was followed up for 24-36 h asymptomatically and was discharged with full recovery.

Case 2

An 11-year-old male teen with normal neurologic development and no known illness and drug use was brought to the pediatric emergency room by emergency medical services for 3 h of meaningless speech, impulsive movements, and visual hallucinations. His family recalled that he spent the whole day at home with his mother and siblings and did not take any unknown food or medicine. Although the impulsive movements of the patient could be calmed at the admission, his visual delusions continued. He also had auditory delusions. Further assessment revealed that the patient was given an oral antipyretic at home due to a suspicion of fever and he did not take anything else. On physical examination, the patient was not oriented to place and time. Both pupils were mydriatic. On oral and oropharynx examination, the tongue and mucous membranes appeared dry. There was noticeable flushing on the face. Results of other systemic examinations were normal. The patient's mother was asked about intake of foreign substances insistently. The family stated that they consumed the same food all day, and none of the family members had any complaints. The trauma history was not clear. AS was considered based on the current history and physical examination findings. On detailed anamnesis, they ate arugula, parsley-like herbs with the meal, and did not pay attention to whether there was a different herb among them. Complete blood count, kidney and liver function tests, and blood electrolyte levels were normal. Blood gas analysis and ECG were normal. Because the patient was delirious, physostigmine was administered as 0.5 mg IV. His delusional behavior and visual and auditory hallucinations regressed 10-15 min after the medication was administered. The 10-drug test in which narcotic substance metabolites were examined in urine was negative. During follow-up, the patient was cooperative and oriented. He had normal responses to external stimuli. No side effects of physostigmine were recorded. No mass or space-occupying lesion was found in the non-contrast brain tomography performed to exclude organic causes due to suspicious trauma history. No anticholinergic neurological finding was detected during the follow-up, and we did not give an additional dose of physostigmine. After the asymptomatic 24-36-h observation period, the patient was discharged to home with full recovery.

Discussion

Atropine and other anticholinergic alkaloids cause symptoms by competitively blocking the effect of acetylcholine on central and peripheral muscarinic receptors.[5] Symptoms usually start 30-60 min after oral intake and may continue for 24-48 h because the active ingredients slow down gastrointestinal (GI) motility.[6] In the presented cases, acute effects started approximately 1 h after ingestion of the substance. Classical anticholinergic symptoms are mydriasis, red-dry skin, hallucinations, agitation, hyperthermia, urinary retention, decreased bowel motility, delirium, confusion, impaired speech, hypertension, nausea, abdominal pain, headache, syncope, chest pain, erythema, ataxia, and fasciculations. The most serious finding is delirium and agitation.[7] Consistent with the literature, both cases presented with inappropriate speech, mydriasis, high fever, flushed skin, and delirium. Since no toxicological imaging or laboratory test can be used for diagnosis, AS should be considered if anticholinergic findings are detected in the physical examination after the patient's condition was stable. Typical anticholinergic drug, substance, or herb intake was not detected in the history from the patients' family members. Only in the first case delirium was observed 1 h after drinking the clear, odorless, and tasteless liquid in a burned-off pet bottle, suggesting that the agent might be a volatile or liquid illicit drug. In the second case, although the substance, medicine, or herb was not defined, Atropa belladonna can be mixed mistakenly with arugula and parsley, which was eaten only by the child. Besides, since most people exposed to the active ingredient are brought to the emergency rooms because of hallucinations and delirium, the anamnesis is not useful in some cases.[8] Delirium is the most common mental disorder in hospital admissions of anticholinergic intoxications.[9] Both patients were brought to the pediatric emergency department with delirium. Since many conditions such as infections, substance abuse and withdrawal, metabolic disorders, toxins, neurological problems, endocrine disorders, and drug use can cause this clinical picture, these

should be considered in the differential diagnosis.[10] In both patients, delirium was accompanied by dry mouth and skin, flushing, mydriasis, tachycardia, and high fever, suggesting AS. Although poisoning with sympathomimetic agents causes a similar clinical picture, absence of bowel sounds has been an important finding of AS. GI decontamination, which decreases absorption, should be performed depending on the venom, route, and timing of exposure. We did not use activated charcoal in both patients because of their agitation and changes in consciousness. To tachyarrhythmia that occurs during follow-up, propranolol can be used as 0.01-0.1 mg/kg (maximum 1 mg) in children.[11] The tachycardia observed in our patients was controlled with high fever treatment and antidote therapy. In the case of hyperpyrexia, external cooling and intravenous fluid therapy may be required.[12] In both cases, high fever and partial delirium conditions were controlled with external cooling and fluid treatments.

Physostigmine is a specific antidote that suppresses anticholinesterase and crosses the blood–brain barrier. Physostigmine should be given in cases with uncontrolled tachycardia, convulsion, respiratory arrest, coma, and delirium.[12] Its effect is observed within 5-15 min, as its half-life is 15 min; another dose given 20-30 min after the first dose may be required.[13] Thornton et al.[14] reported an 11-year-old patient who manifested signs of anticholinergic intoxication, whose agitation could not be controlled with lorazepam and worsened after administration, but responded successfully with repeated doses of physostigmine. In truth, the first patient was given a second dose half an hour later and a third dose 4 h later because of delirium recurrence. Although the symptoms and signs guide the duration of physostigmine treatment, none of the 14 patients with anticholinergic toxicity needed additional physostigmine 6.5 h after the first dose in a retrospective study.[13] Our second patient did not need an additional dose after the first dose of physostigmine. After treatment and follow-up, most patients can be discharged with recommendations less than 48 h.[14] Consistent with the literature, we discharged both of our patients after being asymptomatic within 24-36 h of observation, but with persistent mydriasis.[15,16]

Conclusion

Recognizing the classical anticholinergic intoxication findings with a fully correct anamnesis from the patient or family enables the physician to determine the early and correct approach. Not only drugs and substances taken but also herbs eaten should be questioned in detail. Anticholinergic symptoms should be reviewed, especially in patients presenting with acute delirium.

Ethics

Informed Consent: Informed consents were obtained from patients' family.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Ç., Ş.B., O.D., G.D., G.G., Concept: A.Ç., O.D., T.N., E.B., Design: A.Ç., P.E., Ş.B., E.B., Data Collection or Processing: A.Ç., P.E., O.D., G.D., Analysis or Interpretation: A.Ç., P.E., T.N., E.B., Literature Search: A.Ç., T.N., G.G., E.B., Writing: A.Ç., P.E., O.D., E.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. O'Donnell KA, Osterhoudt KC, Burns MM, Calello DP, Henreting FM. Toxicologic Emergencies. In: Shaw KN, Bachur RG (Ed.):Fleisher & Ludwig's textbook of pediatric emergency medicine. Baltimore, Lippincott Williams & Wilkins; 2015;7:1061-111.
2. Demirhan A, Tekelioğlu ÜY, Yıldız İ, Korkmaz T, Bilgi M, et al. Anticholinergic Toxic Syndrome Caused by Atropa Belladonna Fruit (Deadly Nightshade): A Case Report. Turk J Anaesthesiol Reanim. 2013;41:226-8.
3. Sharma AN, Hexdall AH, Chang EK, Nelson LS, Hoffman RS. Diphenhydramine-induced wide complex dysrhythmia responds to treatment with sodium bicarbonate. Am J Emerg Med. 2003;21:212-5.
4. Katsanoulas K, Papaioannou A, Fraidakis O, Michaloudis D. Undiagnosed central anticholinergic syndrome may lead to dangerous complications. Eur J Anaesthesiol. 1999;16:803-9.
5. Brown JH, Laiken N. Chapter 9Muscarinic Receptor agonistsand antagonists. In: Brunton LL, Bruce AC, Bjorn CK (Eds.): Goodman &Gilman the pharmacologic basis of therapeutics. New York: McGraw-Hill, 2011;11:219-35.
6. Graziano S, Orsolini L, Rotolo MC, Tittarelli R, Schifano F, Pichini S. Herbal Highs: Review on Psychoactive Effects and Neuropharmacology. Curr Neuropharmacol. 2017;15:750-61.
7. Krenzelok EP, Leikin JB. Approach to the poisoned patient. Dis Mon. 1996;42:509-607.
8. Forrester MB. Jimsonweed (Datura stramonium) exposures in Texas, 1998-2004. J Toxicol Environ Health A. 2006;69:1757-62.
9. Kose R, Sahin OO, Abay E. A case of delirium due to datura stramonium intoxication. Anatol J Psychiatr. 2008;9:54-7.
10. Bayraktar E. Deliryum, demans, amnestik ve diğer kognitif bozukluklar. İçinde: Güleç C, Köroğlu E (ed.ler). Psikiyatri Temel Kitabı. 1. Baskı. Ankara, Hekimler Yayın Birliği. 1996;221-56.
11. Vanderhoff BT, Mosser KH. Jimson weed toxicity: Management of anticholinergic plant ingestion. Am Fam Physician. 1992;46:526-30.
12. Wolf LR. Anticholinergic toxicity. In: Tintinalli JE, Kellen GD, Stapezynski JS (Eds.). Emergency Medicine: A comprehensive study guide. 5th ed. New York: McGraw-Hill; 2000:1182-5.

13. Rosenbaum C, Bird SB. Timing and frequency of physostigmine redosing for antimuscarinic toxicity. J Med Toxicol. 2010;6:386-92.
14. Thornton SL, Farnaes L, Minns A. Prolonged antimuscarinic delirium in a child due to benztropine exposure treated with multiple doses of physostigmine. Pediatr Emerg Care. 2016;32:243-5.
15. Bryant S, Singer J. Management of toxic exposure in children. Emerg Med Clin North Am. 2003;21:101-19.
16. Savitt DL, Roberts JR, Siegel EG. Anisocoria From Jimsonweed. JAMA. 1986;255:1439-40.