

CASE REPORT

Occurrence of acute cholinergic syndrome in an infant due to donepezil ingestion

Mahdieh Sadeghi¹ | Zakaria Zakariaei^{2,3}  | Mostafa Soleymani³ |
Abdollah Malakian⁴

¹Mazandaran University of Medical Sciences, Sari, Iran

²Toxicology and Forensic Medicine Division, Orthopedic Research Center, Imam Khomeini Hospital, Mazandaran University of Medical Sciences, Sari, Iran

³Toxoplasmosis Research Center, Communicable Diseases Institute, Iranian National Registry Center for Lophomoniasis and Toxoplasmosis, Mazandaran University of Medical Sciences, Sari, Iran

⁴Faculty of Medicine, Department of Emergency Medicine, Mazandaran University of Medical Sciences, Sari, Iran

Correspondence

Zakaria Zakariaei, Toxicology and Forensic Medicine Division, Orthopedic Research Center, Imam Khomeini Hospital, Mazandaran University of Medical Sciences, Sari 48166-33131, Iran.
Email: ali.zakariaei@yahoo.com

Funding information

None

Abstract

Donepezil and acetyl cholinesterase inhibitors are the most commonly prescribed medications for the treatment of Alzheimer's disease. We describe a 2-year-old infant who was referred to the emergency department after developing cholinergic syndrome 6 hours after ingesting 10 mg of his grandmother's donepezil tablets and was finally discharged in stable condition.

KEYWORDS

acetyl cholinesterase inhibitor, cholinergic syndrome, donepezil

1 | INTRODUCTION

Acute cholinergic syndrome (ACS) is caused by excess cholinergic response in the body with symptoms of muscarinic, nicotine, and central muscarinic such as pupil miosis, sinus bradycardia, excessive secretions (diarrhea, bronchorrhea, and sialorrhea as symptoms), wheezing (by bronchospasm), increased bowel sounds, muscle weakness and fasciculation, and central nervous system (CNS) toxicity and coma, which can be life-threatening.^{1,2}

Donepezil, as the most commonly prescribed treatment for Alzheimer's disease (AD), is well absorbed orally, has a half-life of 70 hours,³ and is metabolized in the liver by the enzymes CYP3A4 and partly CYP2D6. It has a

significant protein binding capacity (95.6%) and in cases where serum protein levels are reduced, increased free levels of donepezil can lead to ACS despite no increase in serum levels of donepezil. Also, donepezil is a centrally acting, reversible acetyl cholinesterase inhibitor (AChE) of the piperidine class and is one of the medications used to treat or slow the progression of mild to severe AD.^{4,5} Common side effects of therapeutic doses include fatigue, insomnia, nausea, and diarrhea, but the important concern is that donepezil, like other AChE inhibitors, may cause ACS if ingested in excess.⁶

Although it is used to treat autism or attention deficit hyperactivity disorder (ADHD) in children, to date, little is known about the side effects of exposure to young

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *Clinical Case Reports* published by John Wiley & Sons Ltd.

children. However, retrospective analysis of toxin center data shows that most children exposed to it have minimal or no clinical findings.^{7,8} Herein, we report the case of a 2-year-old boy with a previous healthy history who developed ACS following the oral consumption of a 10 mg pill of donepezil.

2 | CASE PRESENTATION

In June 2020, a 2-year-old boy was brought to the pediatric emergency room of our medical center by his parents with drowsiness. On examination, the child was lethargic; the pupils were miotic (diameter: 2 mm) and reactive to light. The baby's skin was moist due to excessive sweating and had tearing, urinary incontinence, bronchorrhea, and sialorrhea. His vital signs were as follows: blood pressure, 80/50 mmHg (which is in the normal range based on BP levels for boys according to age and height for Iranian children⁹); heart rate, 140 beats/minutes; respiratory rate, 18/minutes; oxygen saturation (SpO₂), 80% on room air; and temperature, 37°C. Generalized rales and wheezing were also heard in the lungs. His complete blood cell count and comprehensive metabolic panel were normal.

The child weighed 10 kg and was 85 cm tall. In the history taken from the parents, they did not mention the history of the underlying disease or the use of any particular medicine. No insecticides, pesticides, or organophosphates were kept at home, but the grandmother of the family, who had AD and was being treated with donepezil (10 mg tablets), was living with them, so, immediately after suspecting acute cholinergic syndrome following the ingestion of donepezil, standard treatment was started, and the child was admitted to the pediatric intensive care unit (PICU) with a possible diagnosis of donepezil poisoning.

In treatment, one ampoule of 0.5 mg atropine (0.05 mg/kg) was injected intravenously (IV), and 5 minutes later, the next ampoule of atropine was injected IV, liquid therapy with normal saline was administered at 100 cc/kg over 24 hours. After the patient's symptoms subsided with the second dose of atropine, treatment was continued with 0.25 mg of atropine per hour by IV infusion.

After counting the grandmother's pills by the parents, it was revealed that one pill was missing, and thus, our diagnosis was strengthened. In addition, the patient had no nicotine symptoms during hospitalization, and the serum level of the AChE enzyme was in the normal range.

Atropine was tapered 24 hours after the start of treatment, and after 4 days of hospitalization in PICU, he was transferred to the pediatric ward in good general condition with oral consumption tolerance, and after 72 hours of complete improvement of symptoms, he was discharged in good general condition without complications from the

hospital. Written informed consent was obtained from the patient's parents for the publication of this report. This study was conducted according to the Declaration of Helsinki Principles. Moreover, CARE guidelines and methodology were followed in this study.

3 | DISCUSSION

Cognitive and behavioral changes in AD, which is the most common cause of dementia in old age, are partly attributed to impaired cholinergic neurotransmission.⁵ Donepezil, rivastigmine, and galantamine are centrally acting, reversible AChE inhibitors that reduce cholinergic neurotransmission and are used to help reduce the symptoms of AD.¹⁰ These medications are also used to treat autism, ADHD, and other psychiatric conditions.⁸

Information on donepezil poisoning in children is scarce. However, there are concerns about the possibility of developing acute cholinergic syndrome (ACS) following ingestion of AChE inhibitors that lead to increased secretions (sialorrhea, diarrhea, and bronchorrhea), wheezing (by bronchospasm), CNS toxicity, muscle fasciculation, weakness, and lethargy.^{1,2,7,8}

Our patient was a 2-year-old boy who was brought to the emergency department with drowsiness and increased body secretions, and in trying to find the cause of these symptoms, it was found that the child accidentally swallowed a 10 mg pill of donepezil from his grandmother's medications. Therefore, with the diagnosis of ACS following the ingestion of donepezil, treatment with atropine and fluid was started for him, which responded well, and considering that in some studies, the half-life of donepezil was reported to be up to 70 hours,⁶ we hospitalized him for 4 days (until the atropine dose was tapered) in the PICU and then for 3 days in the pediatric ward, and finally, the child was discharged with complete remission of symptoms.

The research on pediatric donepezil exposure is scarce, limited to abstracts, and provides no information on how to treat donepezil ingestions in children. In an abstract, Daubert et al. describe the case of a two-and-a-half-year-old girl who ingested a 10 mg donepezil pill and subsequently suffered somnolence, urinary incontinence, miosis, drooling, rhinorrhea, fasciculations, and a coarse tremor. She did not develop bradycardia or any other abnormal vital signs. Her clinical symptoms, which included a combination of muscarinic and nicotinic cholinergic signs, resolved completely within 12 hours without atropine treatment.¹¹

Thornton et al. report in a paper that the case of a 2-year-old girl who, after taking 20 mg of donepezil and 10 mg of memantine, developed visual hallucinations

and seizure-like activity without showing any signs of cholinergic syndrome and was eventually treated without atropine.¹²

Drooling, also known as salivary hypersecretion (sialorrhea), is the unintentional loss of saliva and other oral secretions from the mouth, which can be caused by swallowing difficulties. Although drooling may be encountered in healthy children, it is commonly observed in neurologically impaired children (such as those with cerebral palsy, facial nerve palsy, myasthenia gravis, and polymyositis).¹³

Causes that are associated with increased oral secretions and cholinergic symptoms, which can be presented in the differential diagnosis of donepezil toxicity in children, include physiological causes (drooling is a common sign of teething), esophageal obstruction (such as may occur with esophageal stricture or a foreign body in the esophagus), drug causes (morphine, pilocarpine, methacholine, and haloperidol), and may also result from the ingestion of caustics or corrosive acids with injury to the esophagus. A history of choking, gagging, coughing, vomiting, and dyspnea suggest a foreign body in the esophagus. Oropharyngeal infections such as tonsillitis, peritonsillar or retropharyngeal abscess, epiglottitis, gingivostomatitis from herpes simplex virus or coxsackievirus may cause hypersecretion of saliva and muscarini symptoms.¹⁴

Also, according to research by Boskabadi et al¹⁵ on several cases of muscarinic symptoms following accidental consumption of *Conium maculatum*, donepezil poisoning should be considered in the differential diagnosis.

In a retrospective study, Thornton et al.¹⁶ report the management of 189 children who became symptomatic after ingesting AChE inhibitor medications, of whom 100 were managed at home and of the remaining 89 children treated in hospital, only one 1-year-old boy with drooling was treated with atropine 0.25 mg IV. Garlich et al.¹⁷ report that a 14-month-old boy developed drowsiness and drooling after taking a 10 mg pill of donepezil and had two episodes of non-bilious, non-bloody emesis, and diarrhea during hospitalization, managed without the need for atropine. Therefore, it seems that if the child has evidence in favor of ACS, treatment with atropine along with supportive therapy is necessary.

4 | CONCLUSION

To rule out other viral diseases, foreign body swallowing, contact with insecticides or cholinergic drugs (donepezil, rivastigmine), history, careful examination of the oral cavity and upper respiratory tract, and a chest X-ray should be considered in any infant without an underlying disease who has symptoms suggestive of acute cholinergic

syndrome such as diarrhea, vomiting, sialorrhea, and bronchorrhea.

ACKNOWLEDGEMENT

None declared.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

AUTHOR CONTRIBUTIONS

ZZ was involved in the interpretation and collecting of data and editing of the manuscript. AM and MS involved in writing, editing, and preparing the final version of the manuscript. MS is responsible for submitting the manuscript. All authors reviewed the paper and approved the final version of the manuscript.

ETHICAL APPROVAL

The study was approved by our local ethics committee.

CONSENT

Written informed consent was obtained from the patient's parents for publication of this report.

DATA AVAILABILITY STATEMENT

The data are available to the correspondent author and can be obtained upon request.

ORCID

Zakaria Zakariaei  <https://orcid.org/0000-0003-4835-9349>

REFERENCES

1. Hanazawa T, Kamijo Y, Yoshizawa T, et al. Acute cholinergic syndrome in a patient with Alzheimer's disease taking the prescribed dose of galantamine. *Psychogeriatrics*. 2018;18:434-435.
2. Garlich FM, Balakrishnan K, Shah SK, et al. Prolonged altered mental status and bradycardia following pediatric donepezil ingestion. *Clin Toxicol*. 2014;52(4):291-294.
3. Wilkinson DG. The pharmacology of donepezil: a new treatment of Alzheimer's disease. *Expert Opin Pharmacother*. 1999;1:121-135.
4. Hanazawa T, Kamijo Y, Yoshizawa T, et al. Acute cholinergic syndrome in a patient taking the prescribed dose of donepezil for Alzheimer's disease. *Psychogeriatrics*. 2020;20(4):538-539. doi:10.1111/psyg.12531. Epub 2020 Feb 17 PMID: 32065723.
5. Barner EL, Gray SL. Donepezil use in Alzheimer disease. *Ann Pharmacother*. 1998;32:70-77.
6. Dunn NR, Pearce GL, Shakir SA. Adverse effects associated with the use of donepezil in general practice in England. *J Psychopharmacol*. 2000;14:406-408.
7. Deitche A, Deitche W, Bebart V, et al. Clinical effects following acute donepezil (Aricept) ingestion by young children. *Clin Toxicol*. 2008;46:616-617.

8. Rossignol DA, Frye RE. The use of medications approved for Alzheimer's disease in autism spectrum disorder: a systematic review. *Front Pediatr*. 2014;2:87.
9. Ataei N, Hosseini M, Fayaz M, et al. Blood pressure percentiles by age and height for children and adolescents in Tehran, Iran. *J Hum Hypertens*. 2016;30(4):268-277.
10. Wilkinson DG, Francis PT, Schwam E, et al. Cholinesterase inhibitors used in the treatment of Alzheimer's disease: the relationship between pharmacological effects and clinical efficacy. *Drugs Aging*. 2004;21:453-478.
11. Daubert CP, Aaron C, Smolinske S. Acute pediatric donepezil overdose presenting as a cholinergic toxidrome. *J Toxicol*. 2005;43:483.
12. Thornton SL, Clark RF. Encephalopathy from unintentional donepezil and memantine ingestion. *Pediatr Emerg Care*. 2014;30(9):649-650.
13. McGeachan AJ, Mcdermott CJ. Management of oral secretions in neurological disease. *Pract Neurol*. 2017;17(2):96-103.
14. Lee JH. Foreign body ingestion in children. *Clin Endosc*. 2018;51(2):129.
15. Boskabadi J, Askari Z, Zakariaei Z, Fakhar M, Tabaripour R. Mild-to-severe poisoning due to *Conium maculatum* as toxic herb: a case series. *Clin Case Rep*. 2021;9(7):e04509.
16. Thornton SL, Pchelnikova JL, Cantrell FL. Characteristics of pediatric exposures to antidementia drugs reported to a poison control system. *J Pediatr*. 2016;172:147-150.
17. Garlich FM, Balakrishnan K, Shah SK, et al. Prolonged altered mental status and bradycardia following pediatric donepezil ingestion. *Clin Toxicol (Phila)*. 2014;52(4):291-294.

How to cite this article: Sadeghi M, Zakariaei Z, Soleymani M, Malakian A. Occurrence of acute cholinergic syndrome in an infant due to donepezil ingestion. *Clin Case Rep*. 2022;10:e05469. doi:[10.1002/ccr3.5469](https://doi.org/10.1002/ccr3.5469)