Journal of Research in Clinical Medicine

J Res Clin Med, 2024, 12: 2
doi: 10.34172/jrcm.2024.32207
https://jrcm.tbzmed.ac.ir

TUOMS PRESS

Case Report

Donepezil overdose and its atypical clinical presentations: A case report

Mohammad Delirrad[1], Habib Ahmadi[2], Nader Aghakhani[3*]

[1]Department of Forensic Medicine, School of Medicine, Food and Beverages Safety Research Center, Taleghani Hospital, Urmia University of Medical Sciences, Urmia, Iran
[2]Fellowship in Toxicology, Kermanshah Urmia University of Medical Sciences, Kermanshah, Iran
[3]Food and Beverages Safety Research Center, Urmia University of Medical Sciences, Urmia, Iran

Article info

Article History:
Received: February 12, 2022
Accepted: February 23, 2023
ePublished: January 9, 2024

Keywords:
Donepezil, Overdose, Atypical, Clinical presentations, Case report

Abstract

Donepezil [Aricept®] is a centrally acting reversible acetylcholinesterase inhibitor. We are reporting an unusual case of a 49-year-old male patient with a history of gastric bypass surgery who mistakenly ingested 200 mg of donepezil. During the hospital stay, atypical presentations such as tachycardia, disorientation, mydriasis, and ophthalmic myoclonus were diagnosed. He had experienced convulsions several times and developed rhabdomyolysis. The patient gradually improved under supportive management and was discharged from the hospital after seven days. The authors hope that reporting this case will provide both context for clinicians to be aware of its overdose that may be presented by atypical manifestations or side effects, along with the main muscarinic anticholinergic presentations.

Introduction

Donepezil hydrochloride [Aricept®], a centrally acting reversible acetylcholinesterase inhibitor, has been used since 1996 after approval by the US Food and Drug Administration (FDA) to treat mild to moderately severe Alzheimer and cognitive impairment

The recommended starting dose of donepezil is 5 mg/d, increasing after four weeks by 10 mg/d and the maximum recommended daily dose is reported as 10 mg or 23 mg in the literature.[1]

There have been a few reports of donepezil overdose, most of which have occurred in Alzheimer's patients or children.[2] To the best of our knowledge, all reported cases of donepezil overdose have described muscarinic cholinergic symptoms.[3] Here, we report a case of accidental poisoning by Donepezil with atypical nicotinic presentations, review the related literature, and advocate for its application in similar clinical scenarios.

Case Report

In 2018, a 49-year-old man was admitted to our poisoning emergency department (ED) two hours after ingestion of twenty 10-mg tablets (totally, 200 mg) of donepezil hydrochloride. On admission, the patient was very toxic, agitated, and had significant tremors in the extremities and throughout the body. In physical examination, he was confused, hypertensive (BP = 180/110 mm Hg), and had bilateral mydriatic pupils. Other vital signs were normal (HR = 80 bpm, RR = 22/min, T = 37.1 °C).

After venous access, he received 500 mL of D5W intravenously (IV), diazepam 5 mg IV, ranitidine 50 mg IV, ondansetron 4 mg IV, and midazolam 2.5 + 2.5 mg IV. Concurrently, continuous cardiac monitoring and pulse oximetry were started. An electrocardiogram (ECG) was taken, and appropriate blood samples were collected for laboratory tests.

After determining the relative hemodynamic stability of the patient, an exact history was taken from his wife. The patient had a history of psychotic problems from some years ago. He had also undergone gastric bypass surgery six years ago. Regarding the drug history, the wife showed us two blank blisters of donepezil tablets and also a bag containing the patient's medications, including acetyl salicylic acid (80 mg), valsartan (40 mg tab), and atorvastatin (40 mg tab). She also stated that her husband had overdosed on benzodiazepines in the past. In the current poisoning, he asked a pharmacy for a strong sleep pill and mistakenly received donepezil tablets, which he then ingested instead of sleep pills. In the ED, IV nitroglycerin (NG) infusion was started to control hypertension. The patient's blood glucose was measured at 171 mg/dL with a glucometer. He also received 5 mg IV biperiden hydrochloride (Akineton®) with a doubt of extrapyramidal symptoms. We requested an intensivist

***Corresponding Author:** Nader Aghakhani, Email: nader1453@umsu.ac.ir

consultation for admitting the patient to the intensive care unit (ICU). Unfortunately, there was no empty bed in the ICUs, and the patient was inevitably transferred to the poisoning ward after about two hours in the ED.

IV fluid therapy and NG infusions were continued in the ward. The patient maintained nil per os (NPO) and received oxygen using a nasal cannula. One hour after admission in the ward, the vital signs were 110/70 mm Hg, PR = 55/min, RR = 26/min, and T = 37 °C. A half-hour later, he experienced prominent bradycardia (HR = 45), which was alleviated using 1 mg IV atropine. He also received 10 mg of IV diazepam two times to control convulsions during the night.

Next morning, in physical examinations, he had dilated pupils, diaphoresis, hyperthermia, agitation, hallucinations, and tremor-like movements in the whole body. The patient also had many disturbing bilateral myoclonic jerks in the entire body. Sodium valproate was prescribed in doses of 500 mg IV initially and then 200 mg every 12 hours.

In the evening, he had another convulsive movement, which was controlled by diazepam 10 mg IV. The patient also received 1 g of IV acetaminophen (Apotel®). In the second night shift, he also had convulsions and received phenytoin (Dilantin®) 1 g IV stat in 200 mL of NS, then 125 mg every eight hours, and acetaminophen 1 g IV. At last, the patient recovered.

Table 1 shows the laboratory findings of the patient on admission. A urine toxicology screen revealed the presence of barbiturate and benzodiazepine. Also, the patient's creatine phosphokinase (CPK) level was raised to 2441 on the second day and 5,162 on the third day of admission, indicating rhabdomyolysis. Both IV fluids and sodium bicarbonate were used to treat rhabdomyolysis, and the CPK level decreased to 418 on day five.

Thyroid function tests and cholinesterase activities (RBC and plasma) were normal on day four after admission. The patient gradually improved and was discharged from the hospital on day seven after admission, without any complications.

Table 1. Laboratory findings of the patient (49-year-old, male) who overdosed 200 mg donepezil by mistake

Test	Result	Normal values	Unit
CBC/Diff			
WBC	11.2	4.4-11.3	$\times 10^3$ µL
Neutrophils	88.0	45-73	%
Lymphocytes	10.5	20-45	%
Mixed (Monocytes + Eosinophils + Basophils)	1.5	6-15	%
RBC	4.85	4.5-5.9	$\times 10^6$ µL
Hemoglobin	15.3	12.5-15.5	g/dL
Hematocrit	44.1	36-45	%
MCV	90.9	80-96	fL
MCH	34.7	26.5-32.5	pg
MCHC	34.7	33-36	g/dL
Platelets	203	150-450	$\times 10^3$ µL
Biochemistry			
Plasma sodium	136	135-145	mEq/L
Plasma potassium	3.8	3.5-5.3	mEq/L
Plasma calcium [Total]	9.2	8.5-10.5	mg/dL
Plasma magnesium	2.5	1.7-2.7	mg/dl
Blood glucose	113	-	mg/dL
Urea	**13**	17-50	mg/dL
Creatinine	1.2	Up to 1.5	mg/dL
AST	18	5-40	U/L
ALT	13	5-40	U/L
ALP	**350**	80-306	U/L
Bilirubin [Total]	1.0	0.3-1.3	mg/dL
Bilirubin [Direct]	0.3	0-0.3	mg/dL
CPK [Total]	**259**	Up to 190	U/L
Coagulation tests			
PT	11.7	11-13	Sec
PTT	25.1	25-35	Sec
INR	0.96	-	-
Arterial blood gas analysis			
pH	**7.48**	7.35-7.45	
PCO_2	35.6	35-45	mm Hg
HCO_3^-	26.5	22-26	mEq/L
PO_2	71.2	75-100	mm Hg
O_2 saturation	95.4	95-100	%
Cholinesterase activity			
RBC acetylcholinesterase	5.2	>4.2	U/mL
S-ChE [Butyrylcholinesterase]	8510	4000-12000	U/L

ALT, Alanine aminotransferase; ALP, Alkaline phosphatase; AST, Aspartate aminotransferase; CBC/Diff, Complete blood count with differential; CPK, Creatine phosphokinase; MCH, mean corpuscular hemoglobin; MCHC, Mean corpuscular hemoglobin concentration; MCV, Mean corpuscular volume; RBC, Red blood cells; WBC, White blood cells.
Note: Tests were performed on admission.

Discussion

About 47 million people around the world are affected by Alzheimer's disease or another type of dementia. Two other medications in this group are rivastigmine (since 1997) and galantamine (since 2000); however, donepezil is the most commonly used drug.[4] Except for rivastigmine, which has been available as a transdermal application since 2007, all three drugs are taken orally.[3] Donepezil is a well-tolerated medicine that is generally safe, even in patients with multiple co-morbidities receiving polypharmacy.[2]

The most common side effects of donepezil include nausea, vomiting, diarrhea, anorexia, fatigue, dizziness, insomnia, agitation, minor weight loss, sinus bradycardia, Q-T interval prolongation, torsade de pointes, muscle cramps, rhabdomyolysis, and abnormal liver function

tests[5]. All these common side effects are expected outcomes of cholinergic augmentation.[6] Donepezil and the other two cholinomimetics may also have some potential to cause generalized convulsions.[1]

Rarely, donepezil may induce delirium, encephalopathy, acute cognitive effects, or the neuroleptic malignant syndrome.[7] Also, the drug was associated with a higher risk of hospital admission with rhabdomyolysis compared with rivastigmine or galantamine.

Donepezil overdose (up to 50 mg/d) results in a cholinergic crisis, characterized by severe vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse, and convulsions.[1] The first case of donepezil overdose was reported by Shepherd et al, that reported the first case of donepezil overdose in a 79-year-old woman with Alzheimer's disease who had been mistakenly given ten times the usual dose (50 mg).[4] Our patient, who presented to the emergency department 75 minutes after an overdose, was lethargic; she had vomiting and sinus bradycardia (HR = 56). She was admitted to the ICU after receiving an initial dose of atropine and was found to have crackles at the base of both lungs. She recovered during the next 18 hours using 3 mg of IV atropine. The authors concluded that appropriate treatment for donepezil overdose included gastrointestinal decontamination using activated charcoal, supportive care, and atropine if necessary for the treatment of bradycardia and/or increased pulmonary secretions.[4]

Also, Mottram and ter Haar[8] reported a 53-year-old man with memory loss who had been treated with donepezil for six months and had accidentally taken 200 mg (twenty 10-mg tablets), which is 20 to 40 times the recommended daily dosage. This patient had perspiration, confusion, somnolence, and sinus bradycardia (HR: 30-50 bpm) 30 to 60 minutes after ingestion. He was admitted to the intensive care unit for three days and was given atropine.

Thornton and Clark reported a 67-year-old man with dementia and hypertension who came to the ED one hour after eating 290 mg of donepezil. The patient had vomiting diaphoresis and a regular heart rate (HR = 82 bpm). He received ondansetron and activated charcoal and developed bradycardia [HR = 59 bpm] and systolic hypertension (BP = 168/77 mm Hg). The blood concentration of donepezil on admission and 3.5 hours later was 240 and 130 ng/mL, respectively. The patient was admitted and had no episodes of bradycardia, but suffered complications such as delirium and ileus during hospitalization and was discharged after 40 days.[2]

Bougea et al also reported generalized myoclonus induced in a patient with AD after receiving 30 mg of Donepezil daily for about 25 days.[1]

Here, we report a case of donepezil overdose with atypical nicotinic presentations. To the best of our knowledge, there was no similar report in the literature. Our patient has no AD and has mistakenly taken donepezil instead of sleeping pills. Whether the observed nicotinic signs (hypertension, mydriasis, agitation, tremors, myoclonus, and multiple convulsions) were caused by donepezil overdose per se or were drug interactions remained unclear. One of our limitations was the inability of our hospital to measure serum donepezil concentration.

Study Highlights

What is current knowledge?

- Donepezil overdose is a rare condition mostly occurs in Alzheimer's patients or children. To the best of our knowledge, all reported cases of donepezil overdose have described muscarinic cholinergic symptoms.

What is new here?

- Here, we report a case of accidental poisoning by Donepezil with atypical nicotinic presentations, review the related literature, and advocate for its application in similar clinical scenarios.

Conclusion

We suspected that the patient's unusual symptoms were due to either the rapid absorption of donepezil during gastric bypass surgery or drug interactions. Therefore, it is important for medical toxicologists and emergency medicine specialists to be aware that a donepezil overdose may present with atypical nicotinic manifestations and other side effects in addition to the main muscarinic anticholinergic presentations. Further research needed to provide a more comprehensive understanding of pathological picture associated with of these atypical clinical presentations of this type of overdose.

Acknowledgements

Authors would like to acknowledge and thank the patient for his agreement with the publication of this report. We would also like to thank the staffs of toxicology emergency department of Emam Reza hospital in Mashhad for their kind cooperation.

Authors' Contribution

Conceptualization: Nader Aghakhani, Mohammad Delirad.
Investigation: Mohammad Delirrad, Habib Ahmadi.
Resources: Mohammad Delirrad.
Writing–original draft: Mohammad Delirrad.
Writing–review & editing: Nader Aghakhani.

Competing Interests

The authors have no conflicts of interests to declare.

Consent for Publication

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

Ethical Approval

In this manuscript, confidentiality and non-disclosure of secrets were observed. Patient's consent was obtained, and all ethical principles were followed. Manuscript was prepared based on

JRCM's recommendations for the conduct, reporting, editing and publication of scholarly work in medical journals.

Funding
This study did not require any funding.

References

1. Bougea A, Gerakoulis S, Anagnostou E, Paraskevas G, Kapaki E, Kararizou E. Donepezil-induced myoclonus in a patient with Alzheimer disease. Ann Pharmacother. 2014;48(12):1659-61. doi: 10.1177/1060028014550334.
2. Thornton SL, Clark RF. Encephalopathy from unintentional donepezil and memantine ingestion. Pediatr Emerg Care. 2014;30(9):649-50. doi: 10.1097/pec.0000000000000216 .
3. Hanazawa T, Kamijo Y, Yoshizawa T, Fujita Y, Usui K, Haga Y. Acute cholinergic syndrome in a patient taking the prescribed dose of donepezil for Alzheimer's disease. Psychogeriatrics. 2020;20(4):538-9. doi: 10.1111/psyg.12531.
4. Shepherd G, Klein-Schwartz W, Edwards R. Donepezil overdose: a tenfold dosing error. Ann Pharmacother. 1999;33(7-8):812-5. doi: 10.1345/aph.18273.
5. Colović MB, Krstić DZ, Lazarević-Pašti TD, Bondžić AM, Vasić VM. Acetylcholinesterase inhibitors: pharmacology and toxicology. Curr Neuropharmacol. 2013;11(3):315-35. doi: 10.2174/1570159x11311030006.
6. Dunn NR, Pearce GL, Shakir SA. Adverse effects associated with the use of donepezil in general practice in England. J Psychopharmacol. 2000;14(4):406-8. doi: 10.1177/026988110001400410.
7. Matsumoto T, Kawanishi C, Isojima D, Iseki E, Kishida I, Kosaka K. Neuroleptic malignant syndrome induced by donepezil. Int J Neuropsychopharmacol. 2004;7(1):101-3. doi: 10.1017/s1461145703003857.
8. Mottram AR, ter Haar E. Donepezil overdose-trending levels and symptoms. Case Rep Intern Med. 2014;1(2):80-2. doi: 10.5430/crim.v1n2p80.