American Journal of Emergency Medicine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Cholinergic symptoms and QTc prolongation following donepezil overdose

A. Pourmand [a,*], C. Shay [a], W. Redha [a,b,c], A. Aalam [a,b,c], M. Mazer-Amirshahi [d,e]

[a] Department of Emergency Medicine, The George Washington University School of Medicine and Health Sciences, Washington, DC, United States
[b] Department of Emergency, Faculty of Medicine, King Abdul Aziz University, Jeddah, Saudi Arabia
[c] Department of Emergency Medicine, The George Washington University School of Medicine and Health Sciences, Washington, DC, United States
[d] Department of Emergency Medicine, MedStar Washington Hospital Center, Washington, DC, United States
[e] Georgetown University School of Medicine, Washington, DC, United States

ARTICLE INFO

Article history:
Received 9 April 2017
Received in revised form 21 June 2017
Accepted 21 June 2017
Available online xxxx

Keywords:
Donepezil
Alzheimer's disease
QTc
Bradycardia

ABSTRACT

Donepezil is the most commonly prescribed acetylcholinesterase inhibitor for the treatment of Alzheimer's disease, an ailment that affects millions of older adult patients. By inhibiting the breakdown of acetylcholine in the central nervous system, donepezil has been shown to slow cognitive decline and improve patients' functional status. While donepezil is well-tolerated and generally considered safe at therapeutic doses, taking more than the prescribed dose could result in adverse cholinergic effects that range from mild gastrointestinal distress to serious cardiac dysrhythmias. We present a case of an 84-year-old man who developed gastrointestinal and cardiac disturbances after ingesting seven-times his daily dose of donepezil. As no specific antidote is available for donepezil overdose, this case highlights the importance of supportive care with particular attention to the management of cardiac dysrhythmias in patients displaying signs of toxicity.

1. Introduction

Donepezil (Aricept®) is a reversible, piperidine-based acetylcholinesterase (AChE) inhibitor used to slow the cognitive deterioration in patients with Alzheimer's disease (AD). It is approved to treat both mild to moderate AD and, at higher doses, to treat moderate to severe AD [1]. AD is the most common cause of dementia in the older adult population [2]. It is projected that by 2050, there will be 13.8 million people in the United States who suffer from the disorder [3]. Donepezil is the most commonly prescribed treatment for AD [4]. It increases concentrations of acetylcholine in the central nervous system by blocking the enzyme that breaks it down, acetylcholinesterase (AChE) [5]. Use of donepezil in patients with AD has been associated with improved daily functioning, decreased cognitive decline, and a greater delay in the need for admission to a nursing home [4]. More recently, its efficacy has also been proven for use in patients with vascular dementia [6]. Other AChE inhibitors that are approved by the US Food and Drug Administration (FDA) for the treatment of AD include rivastigmine and galantamine [7].

Donepezil is generally well tolerated at therapeutic dosages [6]. Although data are limited to case reports, the most commonly reported adverse effects in overdose include gastrointestinal disturbances, lethargy, and bradycardia. While donepezil acts preferentially on central AChE, these adverse effects demonstrate that the drug increases cholinergic activity in the peripheral nervous system as well. Of particular concern is the effect of donepezil on the cardiovascular system [8,9,10]. We report a case of donepezil overdose in a patient who presented to the emergency department (ED) with diarrhea, increased oral secretions, bradycardia, and prolonged QTc.

2. Case report

An 84-year-old man with a past medical history of AD, hypertension, prior stroke, and benign prostatic hyperplasia inadvertently ingested 35 mg (7 doses of his daily 5 mg tablets) of donepezil. He was presented to the ED 6–7 h after the ingestion. Upon arrival, the patient was complaining of nausea, vomiting, diarrhea, fatigue, and excessive sweating. His initial vital signs were: blood pressure 131/58 mmHg, heart rate 50 beats/min, respiratory rate 16 breaths/min, oxygen saturation 98% on room air, and temperature 98.2 °F. He was awake and alert but confused, making it difficult to differentiate from his baseline dementia. His pupils were miotic bilaterally but reactive to light. He also had increased oral secretions causing him to spit frequently. His lungs were clear to auscultation bilaterally and bowel sounds were normal. His electrocardiogram (ECG) showed sinus rhythm at a rate of 70 beats/min with premature atrial contractions, and a prolonged QTc at 502 ms. (Fig. 1) The patient had no prior history of QTc prolongation and was not on any other medications known to cause QTc prolongation. During the ED stay, his heart rate fluctuated between 50 and 60 beats/min. His complete blood count and comprehensive metabolic panel were normal.

* Corresponding author at: Department of Emergency Medicine, George Washington University, Medical Center, 2120 L St., Washington, DC 20037, United States.
E-mail addresses: pourmand@email.gwu.edu (A. Pourmand), pourmand@gwu.edu (M. Mazer-Amirshahi).

http://dx.doi.org/10.1016/j.ajem.2017.06.044
0735-6757/

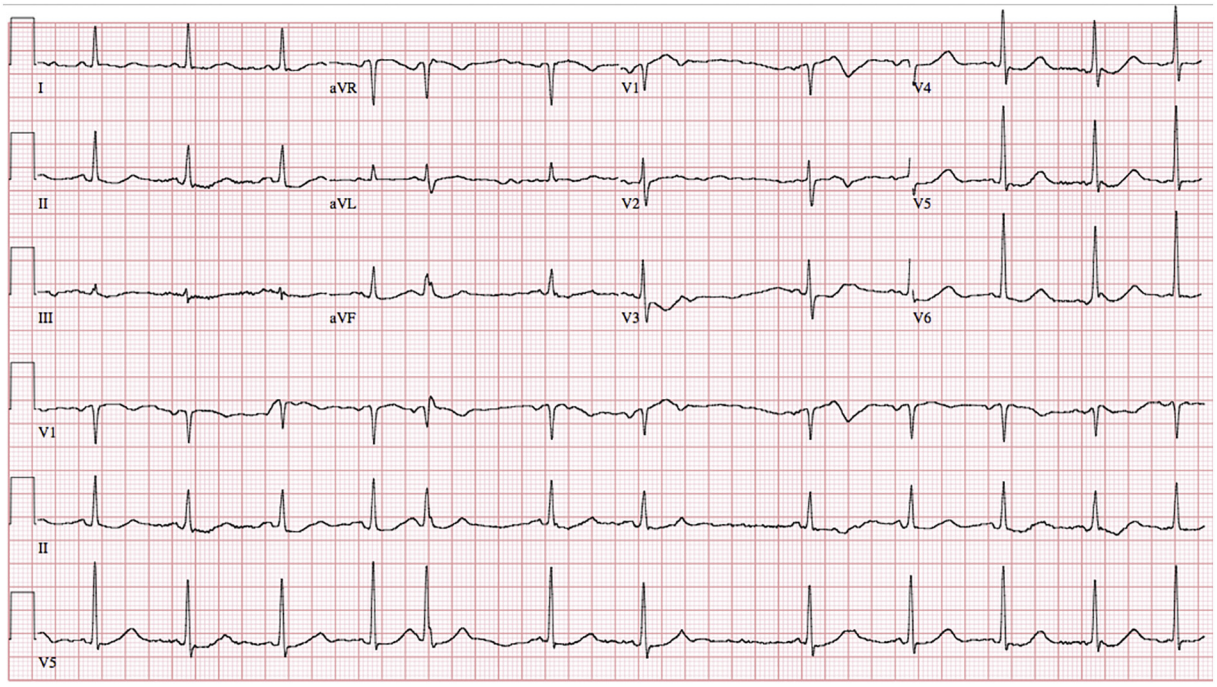

Fig. 1. Electrocardiogram with premature atrial contractions, and prolonged QT.

The patient was admitted to the hospital in a telemetry bed, and observed for the next 48 h. He received intravenous fluids and his daily dose of donepezil was withheld. The patient received one dose of atropine 0.5 mg intravenously for bradycardia with a heart rate below 50 beats/min. During the hospital course, his QTc interval decreased to normal range. His bradycardia resolved and his repeat ECG revealed a normal sinus rhythm with a rate of 75 beats/min. At this juncture, case management provided the patient with services for a home health aide to assist with medications and follow up with his primary care physician.

3. Discussion

Acetylcholinesterase inhibitors are considered first-line agents for the treatment of AD because they slow cognitive decline and improve functional status [11]. Donepezil is the only AChE inhibitor approved for use in all stages of the disease [11]. The most frequently reported adverse effects of donepezil at therapeutic doses include nausea, vomiting, diarrhea, and sedation [4]. These adverse effects can be attributed to the drug's inadvertent inhibition of peripheral AChE, which can lead to cholinergic crisis.

There have been several published case studies of donepezil toxicity in the elderly since the drug's approval in 1996. Greene et al. reported a case of a 74-year-old female who developed nausea, vomiting, drowsiness, flushing and diarrhea after she ingested 45 mg of donepezil. She returned to baseline after a day of observation at home [8]. Shepherd et al. reported a case of a 79-year-old nursing home patient who accidentally ingested 50 mg of donepezil, a tenfold increase in her usual 5-mg dose, which resulted in persistent bradycardia as well as nausea and vomiting. She required a total of 3 mg of atropine in order for her heartrate to return to baseline, and she returned home on day 2 after ingestion [9].

Even at therapeutic doses, the cholinergic actions of donepezil appear to induce adverse side effects on the cardiovascular system. Tanaka et al. reported 2 cases of bradycardia and QTc prolongation in patients who ingested therapeutic doses of 5–10 mg/day. The first patient, a 90-year-old male, experienced 2:1 atrioventicular block and complete right bundle-branch block, while the other patient, an 87 year-old female, experienced torsade de pointes leading to ventricular fibrillation. These cardiac disturbances completely resolved upon discontinuation of the drug. In both cases, donepezil had not been used in combination with other drugs that might have affected the QTc interval; however, it was unclear whether or not these patients may have had prior cardiac conduction disturbances [12]. Takaya et al. reported an 83-year-old female with a documented history of myocardial infarction who was being treated for two years with 5 mg donepezil for AD and experienced an episode of vomiting and syncope and was admitted to the hospital, where she experienced two further episodes of syncope with ECG-confirmed torsades de pointes. This patient required treatment with potassium chloride, magnesium sulfate, and lidocaine [13]. Given the occurrence of QTc prolongation in patients who are taking therapeutic doses of donepezil, it can be suggested that certain populations are particularly sensitive to the cardiac effects of AChE inhibitors, and these populations may have an underlying cardiac predisposition to QTc-prolongation and/or syncope.

Other cholinesterase inhibitors approved for first-line therapy for the treatment of mild-to-moderate AD include galantamine and rivastigmine. Donepezil may be relatively safer in overdose compared to other cholinesterase inhibitors [14]. It has a high degree of selectivity for the central nervous system, making peripheral cholinergic crisis less likely to occur. A longer half-life may have the benefit of easier dosing, but it also means that the cholinergic adverse effects are longer lasting. This is particularly true for pediatric populations. In one report by Garlich et al. a 14-month boy ingested one of his grandfather's 10 mg donepezil tablets and subsequently experienced somnolence and intermittent episodes of asymptomatic bradycardia [10]. He required observation in the pediatric intensive care unit for a total of five days before returning to baseline. These authors concluded that the excess cholinergic activity enhanced the toddler's sensitivity to vagal tone, leading to transient bradycardia. This patient's clinical course parallels that of elderly patients who experienced brady-dysrhythmias, suggesting that donepezil affects vagal tone.

In the clinical course of donepezil overdose, a few recommendations can be made in terms of management; although the optimal management is poorly defined due to limited data. Asymptomatic individuals with small, unintentional ingestions can be cleared in the ED with ECG

Please cite this article as: Pourmand A, et al, Cholinergic symptoms and QTc prolongation following donepezil overdose, American Journal of Emergency Medicine (2016), http://dx.doi.org/10.1016/j.ajem.2017.06.044

and cardiac monitoring. Physicians should consider hospitalization when signs of altered mental status or excessive peripheral cholinergic symptoms are observed. Symptomatic individuals and those with intentional ingestions necessitate observation and may require supportive measures to compensate for fluid loss and to correct electrolyte imbalances. For patients who present early within an hour of ingestion of larger toxic doses, activated charcoal can be considered in order to prevent drug absorption in patients with an intact airway. Atropine should be administered based on standard protocols for clinically significant symptoms of cholinergic toxicity such as symptomatic bradycardia and respiratory secretions. Transcutaneous cardiac pacing may also be required if patient is hemodynamically unstable secondary to bradycardia. In light of the adverse cardiac effects of the drug, continuous cardiac monitoring should be considered. Particular attention should be paid to patients with predisposing factors for QTc-prolongation and torsades de pointes, as it is still unclear as to whether or not donepezil ingestion is related to these events.

Author disclosure statement

No competing financial interests exist.

References

[1] Aricept (donepezil hydrochloride) [label]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020690s035.021720s008.022568s005lbl.pdf; 2012 [Accessed 4 April 2017].
[2] Birks J, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev 2006;1:CD001190.
[3] Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. Neurology 2013;80(19):1778–83.
[4] Cacabelos Ramon. Donepezil in Alzheimer's disease: from conventional trials to pharmacogenetics. Neuropsychiatr Dis Treat 2007;3(3):303–33.
[5] Wilkinson DG, Francis PT, Schwam E, Payne-Parrish J. Cholinesterase inhibitors used in the treatment of Alzheimer's disease: the relationship between pharmacological effects and clinical efficacy. Drugs Aging 2004;21(7):453–78.
[6] Birks J, Malouf Reem. Donepezil for vascular cognitive impairment. Cochrane Database Syst Rev 2004;1:CD004395.
[7] Birks JS. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev 2006;1:CD005593.
[8] Greene YM, Noviasky J, Tariot PN. Donepezil overdose. J Clin Psychiatry 1999;60(1):56–7.
[9] Shepherd G, Klein-Schwartz W, Edwards R. Donepezil overdose: a tenfold dosing error. Ann Pharmacother 1999;33(7–8):812–5.
[10] Garlich FM, Balakrishnan K, Shah SK, Howland MA, Fong J, Nelson LS. Prolonged altered mental status and bradycardia following pediatric donepezil ingestion. Clin Toxicol (Phila) 2014;52(4):291–4.
[11] Winslow B, Onysko M, Stob C, Hazlewood K. Treatment of Alzheimer disease. Am Fam Physician 2011;83(12):1403–12.
[12] Tanaka A, Koga S, Hiramatsu Y. Donepezil-induced adverse side effects of cardiac rhythm: 2 cases report of atrioventricular block and Torsade de Pointes. Intern Med 2009;48(14):1219–23.
[13] Takaya T, Okamoto M, Yodoi K, Hata K, Kijima Y, Nakajima H, et al. Torsades de Pointes with QT prolongation related to donepezil use. J Cardiol 2009;54(3):507–11.
[14] Yiannopoulou KG, Papageorgiou SG. Current and future treatments for Alzheimer's disease. Ther Adv Neurol Disord 2013;6(1):19–33.

Please cite this article as: Pourmand A, et al, Cholinergic symptoms and QTc prolongation following donepezil overdose, American Journal of Emergency Medicine (2016), http://dx.doi.org/10.1016/j.ajem.2017.06.044