J. Med. Toxicol. (2011) 7:57–59
DOI 10.1007/s13181-010-0112-8

TOXICOLOGY OBSERVATION

Cevimeline (Evoxac ®) Overdose

Berenika Voskoboynik · Kavita Babu · Jason B. Hack

Published online: 24 September 2010

Abstract Cevimeline (Evoxac ®) is an oral muscarinic agent that has been recently approved for the treatment of xerostomia in the setting of Sjogren's syndrome. Its toxicity in overdose has not been reported in the medical literature to date. We report a previously healthy patient who intentionally ingested approximately 10 mg/kg of cevimeline and presented with symptoms of muscarinic excess and mental status depression. The patient recovered uneventfully after receiving activated charcoal and supportive care. This report describes the first documented cevimeline overdose.

Keywords Cevimeline · Muscarinic agonist · Novel overdose

Introduction

Sjogren syndrome is a systemic chronic inflammatory disorder characterized by xerostomia, anhidrosis, and conjunctivitis sicca due to lymphocytic infiltration of exocrine organs, such as salivary, sweat, and lacrimal glands. Cevimeline is a recently approved, orally administered muscarinic agonist that directly stimulates M3 receptors in the salivary glands and is indicated for the treatment of dry mouth symptoms in patients with Sjogren's syndrome. Cevimeline is distributed under the brand name Evoxac ® by Daiichi Sankyo (Tokyo, Japan) in the USA, Japan, and Taiwan. Similar to pilocarpine, cevimeline works by increasing salivary secretion through direct stimulation of peripheral muscarinic receptors in salivary glands. However, the salivary secretion induced by cevimeline is longer lasting, 5 h versus less than 3 h for pilocarpine. Common reported side effects of this drug include nausea, headache, rhinorrhea, diarrhea, abdominal pain, and diaphoresis [1, 2].

B. Voskoboynik (✉)
Department of Pediatric Emergency Medicine,
Hasbro Children's Hospital, Alpert Medical School,
Brown University,
Providence, RI, USA
e-mail: wingednika@yahoo.com

K. Babu · J. B. Hack
Department of Emergency Medicine, Alpert Medical School,
Brown University,
Providence, RI, USA

Case Report

A 47-year-old female presented to the emergency department (ED) with the chief complaints of nausea and vomiting. Her medical history was significant for depression, treated with citalopram. She admitted to ingesting 20 30-mg cevimeline tablets (10 mg/kg) 1 h prior to arrival to the ED. She had also taken two 0.5-mg tablets of lorazepam earlier in the day and drank some alcohol. The patient obtained cevimeline from her friend, for whom it was prescribed. The patient had no prior history of suicide attempts.

On presentation to the ED, the patient's weight was 60 kg, and her vital signs revealed a heart rate of 94 bpm, blood pressure of 102/60 mmHg, respiratory rate of 20 breaths/min, temperature 98.6, and oxygen saturation on room air of 98%. She was somnolent, but arousable to voice and commands, and answered questions appropriately. She was extremely diaphoretic and nauseous, with several episodes of emesis in the ED. Her pupils were 4 mm and reactive to light bilaterally; she had no sialorrhea, lacrimation, or bladder or bowel incontinence. The patient's

cardiovascular, respiratory, and abdominal exams were otherwise unremarkable. Her neurologic examination was normal.

The patient's laboratory indices were significant only for a mild leukocytosis of (12.5×10^9 cells/L) and hypokalemia (2.6 m Eq/L). Her glucose was 125 mg/dL. Her blood alcohol level was 103 mg/dL. Her salicylic acid and acetaminophen levels were undetectable. Her urine toxicology screen for common drugs of abuse was negative. The patient's electrocardiogram demonstrated a normal sinus rhythm, normal axis, and normal QRS width, with a borderline QTc interval of 456 ms. A chest radiograph was unremarkable.

The patient was placed on a monitor in the emergency department. She received ondansetron for nausea as well as 50 g of activated charcoal. She was admitted to telemetry, where she remained normotensive and never exhibited any dysrhythmias. The patient's QTc interval normalized on subsequent electrocardiograms. The patient's symptoms fully resolved during her inpatient hospitalization. She was subsequently transferred to an inpatient psychiatric ward for further evaluation of her suicidality. She did not exhibit any delayed effects of the ingestion.

Discussion

Cevimeline is a quinuclidine derivative of acetylcholine that directly stimulates muscarinic M3 receptors in the salivary glands [1]. Approved by the Food and Drug Administration in January of 2000 and available in the US, it is currently indicated for the treatment of symptoms of dry mouth in patients with Sjogren's syndrome. During development and testing, cevimeline induced an increase in salivary secretion in animal and human studies, with its effects lasting 2-fold longer than pilocarpine, the first secretagogue and muscarinic receptor agonist at M1–M5 [1]. Studies in rats also demonstrated stimulation of tear secretion. In animal studies, cevimeline doses sufficient to induce salivation generally did not affect the central nervous system (oral administration of 3–10 mg/kg), general behavior, cardiovascular, respiratory, gastrointestinal, or urinary systems [1, 3]. In human studies, while headache, dizziness, and nervousness were reported as adverse central nervous system events, they were not significantly different between the 60 mg three times daily (tid) patient group as compared to the placebo [4].

Cevimeline is metabolized by the cytochrome P450 isozymes CYP2D6 and CYP3A3/4 [5]. It is excreted primarily by the kidneys, with 86.8% of the dose recovered in the urine after a single-dose administration. No accumulation of cevimeline or its metabolites is observed after repeat administration. Its pharmacokinetic profile demonstrates time to a mean maximum plasma concentration (C_{max}) of 1.53 h, which is reduced by 17.3% with meal intake [5] and a mean elimination half-life of 3.3 h in healthy human subjects and 5.1 h in women with Sjogren's syndrome [1].

The recommended dose of cevimeline for the treatment of dry mouth symptoms of Sjogren's syndrome is 30 mg orally three times a day. The most frequently reported side effects associated with it included nausea, increased sweating, rhinitis, and diarrhea [2]. Hypothermia and bradycardia were observed in animal studies at 10-fold higher doses than those sufficient to induce salivation [1].

The clinical presentation in this case of cevimeline overdose is likely due to its direct stimulation of M3 muscarinic receptors located at effector organs of the parasympathetic system. The patient in our case report presented with a moderate muscarinic toxicity after intentionally ingesting about 10 mg/kg of cevimeline. Signs and symptoms of an acute intoxication will likely parallel other medications in this class, like pilocarpine, bethanechol, and methacholine. Muscarinic manifestations include vomiting, diarrhea, and abdominal cramping due to increased peristalsis, bronchorrhea, wheezing, excessive salivation, sweating, and urinary incontinence. Bradycardia, hypotension, bronchospasm, and miosis have also been observed. Because cevimeline has specificity for M3 muscarinic receptors on salivary glands, it is likely to exhibit fewer cardiac side effects, usually associated with M2 muscarinic receptors [6].

In addition to supportive therapy early in presentation, potential treatment for this class of medication includes glycopyrrolate and atropine. Both atropine and glycopyrrolate are parasympatholytic agents that competitively block the action of acetylcholine at muscarinic receptors, thereby reversing the effects of direct stimulation of the receptors by cevimeline. The administration of activated charcoal can also be considered in early presenters to limit drug absorption. Goals of therapy for treating muscarinic toxicity include decreasing salivary secretion; decreasing bronchorrhea and wheezing; decreasing peristalsis, increasing heart rate, and enhancing atrioventricular conduction [7].

If excessive oral and GI tract secretions result in respiratory compromise or symptomatic bradycardia develops after cevimeline overdose, intravenous atropine may be useful in reversing these symptoms. Atropine is a nonselective central and peripheral muscarinic antagonist [8]. In adults, atropine is given at the initial dose of 1 to 2 mg IV for mild-to-moderate cholinergic poisoning and 3–5 mg IV for severe poisoning; the initial pediatric dose is and 0.02 mg/kg IV [9]. Repeated doses must be administered until satisfactory improvement of respiratory symptoms and increase in heart rate are achieved. Glycopyrrolate, a quaternary ammonium compound, is a

peripheral muscarinic antagonist with poor CNS penetration and fewer CNS side-effects used to reverse cholinergic toxicity [10]. Initial glycopyrrolate IV dose for adults is 1 to 2 mg and 0.025 mg/kg for children [7]. Beta-2 agonists or epinephrine may be indicated for the treatment of bronchospasm secondary to cevimeline in addition to atropine and glycopyrrolate due to their bronchodilatory effects.

This case presentation has several limitations. Serum and urine levels of cevimeline are unavailable in clinical laboratory settings, so confirmatory levels could not be obtained. It is possible that patient's sedation and decreased sensory responses to stimuli can be partially attributed to the presence of ethanol. Although the patient denied the ingestion, her nausea could be attributed to an undetected concomitant ingestion of citalopram, patient's prescription medication. In our institution, as in many others, levels of citalopram are not available for relevant clinical use in the emergency department. The etiology of hypokalemia in this patient's presentation is unclear as neither cevimeline nor citalopram cause hypokalemia with monotherapy. Excessive diaphoresis was most likely caused by the presence of a muscarinic agent since citalopram does not exhibit significant anticholinergic effects. We have been able to find no data, in vitro, animal, or human, to address whether or not there is a loss of M3 receptor specificity in overdose or toxicity.

Conclusion

We present the first case of cevimeline overdose resulting in significant muscarinic symptoms. Uses, side effects, and potential antidotal therapy for this overdose are discussed. Emergency physicians need to be aware of this medication, its toxicity, and treatments.

References

1. Weber J, Keating GM (2008) Cevimeline. In Drugs 68(12):1691–1698
2. Petrone D, Condemi JJ, Fife R et al (2002) A double-blind, randomized, placebo-controlled study of Cevimeline in Sjogren's syndrome patients with xerostomia and keratoconjunctivitissicca. Arthritis Rheum 46(3):748–754
3. Arisawa H, Imai E, Fujise N, Fukui K, Masunaga H (2002) General Pharmacological profile of the novel muscarinic receptor agonist SN1-2011, a drug for xerostomia in Sjogren's syndrome, 1 s communication. Arzneimittelforschung 52 (10):14–20
4. Fife R, Chase WF, Dore RK et al (2002) Cevimeline for the treatment of xerostomia in patients with Sjogren syndrome: a randomized trial. Arch Intern Med 162(11):1293–1300
5. Daiichi-Sankyo, Inc. (2009) Evoxac® capsules (cevimeline hydrochloride): US prescribing information [online]. Cited on: 5 Jan 2009. Cited at: http://www.evoxac.com/pdf/EVOXAC_PI.pdf
6. Hendrickson RG, Morocco AP, Greenberg MI (2004) Pilocarpine toxicity and the treatment of xerostomia. J Emerg Med 26 (4):429–432
7. Olson K (ed) (2004) Poisoning and drug overdose, 5th edn. McGraw-Hill, New York, pp 415–417
8. Eddleston M, Buckley NA, Eyer P, Dawson A (2008) Management of acute organophosphorus pesticide poisoning. Lancet 371:587–607
9. Howland MA (2006) Antidotes in depth: Atropine. In: Flomenbaum NA (ed) Goldfrank's toxicological emergencies, 8th edn. McGraw-Hill, New York, pp 1519–1522
10. Bardin PG, van Eden SF (1990) Organophosphate poisoning: grading the severity and comparing treatment between atropine and glycopyrrolate. Crit Care Med 18:956–960