Case in Point

Anticholinergic Toxicity in a Patient With Sialorrhea

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This case examines the adverse effects associated with atropine ophthalmic drops when used orally for the treatment of sialorrhea.

Sialorrhea, or excessive drooling, is a significant problem in patients with neurologic disabilities that impair orofacial control. In 2010, the Veteran's Affairs (VA) health care system reported that 19,200 to 44,400 patients with Parkinson disease had experienced sialorrhea.[1,2] Because these patients are often unable to manage their oral secretions, they are at increased risk of local skin maceration, perioral infections, aspiration, and dehydration.[3,4]

Many treatments are available for sialorrhea, such as botulinum toxin and anticholinergic medications (eg, glycopyrrolate, scopolamine, and benztropine), but there is currently no gold standard of therapy. Although not supported by randomized controlled trials, sublingual administration of atropine ophthalmic drops has been reported to be successful in reducing sialorrhea.[3-6]

Atropine is an anticholinergic drug that competitively blocks the muscarinic actions of acetylcholine, both centrally and peripherally, at the end-organ sites of the parasympathetic nervous system.[5] Atropine does not prevent the release of acetylcholine but antagonizes the effect of the neurotransmitter on effector cells.[5,7] For this reason, atropine may be used as an approach to control excessive drooling and is recommended by the National Institute of Health and Clinical Excellence (NICE) Parkinson disease clinical guidelines for the treatment of sialorrhea in patients with Parkinson disease.[8]

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CASE REPORT

An 81-year-old white man with a focused medical history of Parkinson disease, stroke with residual dysphagia, chronic renal insufficiency, diabetes mellitus, and anemia presented with an altered level of consciousness and agitation to the emergency department (ED) at the Malcom Randall VA Medical Center in Gainesville, Florida. Prior to presenting to the ED, emergency medical services had responded to a 9-1-1 call from the patient's home because of bilateral lower extremity weakness and acute mental status changes that included agitation, confusion, and combative behavior. Emergency medical services declared the patient a possible stroke alert, and he was instantly transported to the nearest stroke center for further evaluation.

On arrival at the stroke center, the patient's vital signs were remarkable for a mild tachycardia and a temperature of 101°F. Blood pressure (BP) and respiratory rate were normal. The examination was remarkable for an alert, but agitated patient, and the report showed he was unable and unwilling to answer questions or follow commands. He was able to move all 4 extremities and had a nonfocal examination. Laboratory data results were obtained and were unremarkable. A complete blood count showed a normal white blood cell (WBC) count and differential and mild anemia without change. A metabolic panel showed renal insufficiency without worsening and otherwise normal values. Glucose was 123 mg/dL and the anion gap was within the normal range. A urinalysis had no evidence of infection. An electrocardiogram (ECG) revealed a sinus tachycardia without widening of the ventricular complex or prolongation of the QT interval. A chest x-ray and a computed tomography image of the head showed no acute abnormalities. Troponin and creatine kinase MB (CK-MB) were normal. Alcohol, aspirin, and acetaminophen levels were undetectable. Blood and urine cultures were sent for suspicion of infection. A neurologist was consulted and recommended an MRI of the brain with and without contrast, an electroencephalogram, blood cultures, lumbar puncture, and infective dose consultation.

After a full neurologic examination, stroke was ruled out. Because the patient was a veteran, he was transferred in stable condition to our VA Medical Center ED for admission and further workup of his continued mental status abnormality.

The patient was alert with eyes open when he arrived in the ED. He was mildly agitated when stimulated and would not answer questions or follow commands. A detailed neurologic examination was impossible due to the patient's mental status, but no focal deficit was seen in his cranial nerves or on peripheral nervous system examination. Vital signs revealed a 100.5°F temperature, BP of 122/71 mm Hg, heart rate of 89 beats per minute, respiratory rate of 18 breaths per minute, and oxygen saturation of 100%. A physical examination revealed pupils that were dilated to 5-mm round, symmetrical, and minimally reactive to light; mouth showed very dry mucous membranes; lungs were clear to auscultation without respiratory distress; a cardiac examination showed a regular rate and rhythm; abdomen was soft and nontender; skin was dry and warm with a red discoloration to the arms.

A review of the patient's medications revealed he was taking the following oral medications: aspirin 25 mg/dipyridamole 200 mg twice daily, aspirin 81 mg once daily, atropine 1% ophthalmic solution 2 to 4 drops orally 3 to 4 times daily as needed, ferrous sulfate 325 mg once daily, folic acid 1 mg once daily, tramadol 50 mg 3 times daily as needed (reported occasional use), and a once-a-day multivitamin. The patient had started carbidopa 25 mg/levodopa 100 mg 3 weeks prior; however, the medication was discontinued after 2 doses because of hypotension and somnolence. In addition, the patient's neurologist had recently prescribed onabotulinumtoxinA (25 units into bilateral parotids and 12.5 units into bilateral submandibular administered 8 days prior) and atropine 1% ophthalmic drops to be administered orally for treatment of chronic sialorrhea due to Parkinson disease and previous stroke. The patient's wife reported that 4 drops of 1% atropine ophthalmic solution had been administered orally (atropine 1% ophthalmic solution = 10 mg/mL; 4 drops = 0.2 mL; total dose of atropine = 2 mg) for the first time 4 hours prior to the onset of symptoms. He did not have a history of known allergies or adverse reactions to any drugs.

In light of the clinical findings on examination and proximity of atropine administration, it was determined that the patient was likely experiencing symptoms consistent with anticholinergic toxicity.

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The patient was admitted to internal medicine. The admitting team ordered an MRI of the brain, which revealed no acute abnormalities. Blood and urine cultures showed no bacteria growth. The patient had a gradual resolution of his symptoms with return to baseline within 48 hours, and he was discharged home. At 1-month follow-up, his mental status remained at baseline without further episodes since atropine had been discontinued.

DISCUSSION

The presentation of this patient is consistent with anticholinergic poisoning. Classic symptoms of anticholinergic intoxication were observed, including agitated delirium ("mad as a hatter"), flushing ("red as a beet"), dry mucous membranes and skin ("dry as a bone"), mydriasis ("blind as a bat"), febrile ("hot as a hare"), as well as tachycardia. These symptoms occurred a few hours following an initial dose of orally administered atropine ophthalmic drops prescribed for sialorrhea. Most patients with anticholinergic toxicity do well with supportive care alone.[9] Some patients may benefit from antidotal therapy with physostigmine; however, consultation with a medical toxicologist or regional poison center is recommended prior to the administration of physostigmine.[9]

Atropine has been suggested as an attractive treatment option for sialorrhea because of the presumption that the drug exerts primarily a local effect directly on the salivary glands, which may result in minimal systemic absorption and adverse events.[4,7] In addition, salivary secretions are generally inhibited with atropine at doses lower than those required to affect other organs.[7] However, potential adverse effects are still possible, in-

cluding peripheral anticholinergic effects, such as mydriasis, dry mucous membranes, flushed skin, tachycardia, urinary retention, and hypoactive bowel sounds.[4,5] Moreover, atropine is a tertiary amine that is able to cross the blood brain barrier and produce central nervous system effects like confusion, disorientation, ataxia, and hallucinations.[4,5,7]

According to the Naranjo probability scale, this case represents probable adverse drug events related to atropine. The Naranjo scale accounts for factors including previous reports of similar events and time relationship to event.[10] Although a rechallenge of the drug may have provided a stronger causal relationship, atropine was never restarted for control of sialorrhea in this patient.

Following oral administration, atropine typically is well absorbed, and peak plasma concentrations are seen within 1 hour. Atropine is metabolized in the liver to several metabolites. The initial half-life is about 2 to 3 hours, and the terminal half-life is about 12.5 hours. Atropine and its metabolites are primarily excreted renally and, to a lesser extent, by the pulmonary and fecal routes.[7] Although the manufacturer recommends using caution and reducing dosing in patients with renal insufficiency, no guidelines or recommendations are given on how this should be done.[7] Generally, atropine should be used with caution in geriatric patients (as the elderly are generally more sensitive to anticholinergic drugs) and those with medical conditions that may alter their response to anticholinergics.[7] It is unclear whether the patient's age or renal insufficiency played a role in the onset and duration of anticholinergic symptoms associated with atropine, but it is not unreasonable to suggest.

Several reports of orally administered atropine drops in the treatment of sialorrhea have had positive results. A small pilot study investigated an orally administered atropine eyedrop solution (1 drop of 500 mcg of drug from a 1% w/v solution) twice daily for the treatment of hypersalivation in 7 patients with Parkinson disease.[6] Patients demonstrated significant reductions in saliva production both subjectively and objectively, although 1 patient withdrew because of delirium and 2 patients experienced worsening of hallucinations from baseline.[6] Despite these promising reports, however, the effectiveness of sublingual atropine for sialorrhea remains unproven by randomized controlled trials.[11]

Advantages of orally administered atropine eyedrops include its low cost, availability as eyedrops, and reversibility.[6] However, the optimal dose of orally administered atropine drops for the treatment of sialorrhea has not been established, and patients or caregivers may have difficulty manipulating the dropper to ensure accurate dosing, potentially increasing the risk of an accidental overdose. In our case report, the patient received approximately 2 mg of atropine, but the possibility of inaccurate dosing using an ophthalmic dropper for oral administration cannot be excluded.

SUMMARY

We present a case report of anticholinergic toxicity induced by the oral administration of atropine 1% ophthalmic drops in an 81-year-old patient with Parkinson disease experiencing sialorrhea. To our knowledge, this is the first report of anticholinergic toxicity associated with atropine for the treatment of sialorrhea. Clinicians using atropine 1% ophthalmic drops should remain aware of the potential for anticholinergic toxicity when used for this indication, in particular in the elderly and those with underlying renal insufficiency. ●

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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