JPPT | Case Report

Ophthalmic Atropine: A Typical Anticholinergic Toxidrome From an Atypical Old Culprit

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Included on the World Health Organization Model Lists of Essential Medicines, atropine remains a cornerstone medication that is used for a myriad of clinical indications. Systemically, atropine carries indications for the treatment of asymptomatic and symptomatic bradycardia, reduction of salivation and bronchial secretions prior to surgery, and as an antidote for a variety of poisoning agents (i.e., carbamate or organophosphate insecticides, nerve agents, muscarine-containing mushrooms). Topically, atropine is administered via the ophthalmic route for the treatment of cycloplegia, mydriasis, and amblyopia or may be administered sublingually to treat chronic sialorrhea. As an anticholinergic, supratherapeutic concentrations of atropine result in a toxidrome typical of other anticholinergic medication overdoses. However, it is easy to overlook atropine as the causative agent when being administered topically, potentially resulting in an unnecessarily extensive and complicated workup. This case report describes the systemic absorption of atropine administered through the ophthalmic route at normal doses, resulting in stroke-like symptoms in an adolescent male. Upon identifying that the patient was being treated with atropine ophthalmic drops prior to hospital arrival, a dose of intravenous physostigmine was administered, resulting in complete reversal of all toxidrome symptoms.

ABBREVIATIONS CT, computed tomography; ED, emergency department; LP, lumbar puncture; MRI, magnetic resonance imaging

KEYWORDS atropine; delirium; ophthalmic; physostigmine; stroke-like; toxicity

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Introduction

As a reversible, competitive antagonist of acetylcholine at muscarinic receptors, atropine falls into the anticholinergic class of medications.[1] As such, supratherapeutic concentrations of atropine may result in a toxidrome similar to that seen in overdoses of other medications that possess anticholinergic properties, such as diphenhydramine, an antihistamine that demonstrates anticholinergic side effects with increased doses.[2] The acute presentation of patients experiencing anticholinergic overdoses may include flushing of the skin, dry mouth and skin, mydriasis resulting in vision disturbances, hallucinations and delirium, elevated temperature, and urinary retention.

Although uncommon, the occurrence of toxicities related to ophthalmic atropine use have been documented in case reports in the past.[3–9] However, it should be noted that these cases all report toxicities secondary to supratherapeutic doses of ophthalmic atropine. Unlike other anticholinergics that possess a charged quaternary amine group in their chemical structures that inhibits penetration of the blood-brain barrier, atropine's tertiary amine structure allows it to cross the blood-brain barrier. This results in an increased risk of central nervous system toxicity such as stroke-like symptoms or altered mental status, even when the medication is administered topically via the ophthalmic route.[10,11] Although these toxicities are typically self-limiting and resolve over time, they are nonspecific and mimic more concerning acute disease states, requiring prompt assessment and workup.

Case Report

A 12-year-old African American male (30 kg) reported to be previously healthy, presented to an outside urgent care clinic with symptoms of nausea and vomiting, left upper extremity weakness, and altered mental status including confusion and agitation. The family reported an abrupt onset of symptoms, with arrival to the urgent care within 2 hours of symptom onset. Owing to concerns of a stroke, the patient was transferred to our institution's emergency department (ED) for additional imaging and a diagnostic workup. Upon arrival, the patient was found to be tachycardic, with a heart rate of 154 beats per minute, and febrile, with an oral temperature of 38.3°C. He was moving all extremities, including his left upper extremity, but was not responding appropriately to commands or questions. Owing to his neurologic status and continued concern for stroke, the stroke protocol was activated and the patient was taken

for a computed tomography (CT) scan and a magnetic resonance imaging (MRI) scan. A lumbar puncture (LP) was performed to rule out meningitis.

While awaiting the results of the imaging, the ED team had the opportunity to gather the patient's medication history. Further questioning with family revealed that prior to arrival the patient was prescribed and receiving prednisolone 1% ophthalmic drops, 1 drop into the left eye 4 times daily, and atropine 1% ophthalmic drops, 1 drop into his left eye twice daily for the previous 10 days. The patient was treated with this regimen intermittently over the past several years for a self-reported previous eye injury as a young child, but additional details regarding the injury were unavailable from the family or from outside records, although compliance was also confirmed with the family. A calculated adverse drug reaction score (Naranjo scale; see Supplemental Table) of 4 indicated a possible adverse drug reaction to the atropine eye drops. With the newly identified information and the patient's presentation that included symptoms of an anticholinergic overdose, the decision was made to administer physostigmine. This decision was reinforced by the results of the CT and MRI scans being found to be unremarkable, along with a normal opening pressure during the LP and clear cerebrospinal fluid from the LP sample. A single dose of 0.5 mg of physostigmine was administered intravenously as an undiluted push over a 5-minute period approximately 1.5 hours from the initial arrival to our ED. The patient began responding appropriately and answering questions within 3 minutes of completing the administration of the dose. Owing to the rapid and complete response to the dose of physostigmine, antibiotic therapy was not pursued for the initial concern of potential meningitis.

Shortly thereafter, the patient was admitted to the hospital for observation. An electroencephalogram study and overnight monitoring did not reveal any seizure activity and the patient remained neurologically appropriate overnight. No further doses of physostigmine were indicated. He was discharged from the hospital the following afternoon at baseline neurologic and physical status.

Discussion

This case report is similar to previous reports published decades ago in which patients presented with nonspecific neurologic symptoms following ophthalmic atropine administration.[3–11] A unique aspect to our case compared with many of the previously published reports is that our patient presented with a severe toxidrome following recommended therapeutic dosing of atropine via the ophthalmic route. During a follow-up conversation with family, it was uncovered that the patient had been on atropine ophthalmic drops intermittently nearly his entire life for a previous eye injury, although additional details were unavailable. The patient's family was familiar with dosing and administration, minimizing concerns for an administration error.

Atropine is absorbed systemically after intraocular administration through direct absorption via the conjunctiva and transmission through lacrimal drainage system into the sinuses.[12] Punctal occlusion, a process in which fingertip pressure is applied to the nasal lacrimal sac, is a method to decrease systemic absorption of medications administered via the intraocular route by limiting the flow of medication through the nasolacrimal duct into the back of the nasal cavity where it may be absorbed systemically. Additionally, it has been postulated that there may be a direct access route for atropine to the brain when administered by the ophthalmic route.[13] This theory has significant implications, because it identifies the risk of central nervous toxicities at normal dosing of ophthalmic atropine drops in susceptible patients, similar to what we experienced in this case.

Also unique to this case is that the patient was simultaneously being treated intermittently with prednisolone ophthalmic drops for multiple courses over the past several years. The package insert for prednisolone acetate ophthalmic suspension cautions that long-term use of topical corticosteroids has been known to cause corneal and scleral thinning.[14] The potential thinning of the cornea and sclera may have led to increased absorption directly through these sites, especially when considering the lipophilicity of atropine.[15]

Unfortunately, the risk of systemic absorption via the ophthalmic route in pediatrics is not limited to atropine. Farkouh et al[15] identified potential adverse effects in a variety of drug classes with medications that are administered into the eye, including antibiotics, corticosteroids, sympathomimetics, beta-receptor blockers, and others. The authors also identify reasons why pediatric patients have a higher risk of absorption and side effects associated with ophthalmic medications, even when administering the doses correctly. Interestingly, despite our patient also being treated with prednisolone eye drops prior to arrival, he did not present with any adverse events associated with this medication.

Physostigmine was used to reverse the patient's neurologic symptoms in our case. Physostigmine is a reversible cholinesterase inhibitor that increases the concentration of synaptic acetylcholine, opposing the anticholinergic effects of atropine.[16] General use of physostigmine has fallen out of favor over time because of reports of seizures and asystole secondary to its use.[17] However, the risks associated with the use of the medication may be outweighed by its utility in the setting of acute, severe atropine overdose.[11,18] This case demonstrates the immediate therapeutic potential of physostigmine following ophthalmic administration of atropine.

Conclusion

This case revisits the risk of systemic absorption with ophthalmic atropine administration and potential adverse reactions that may occur. While uncommon, awareness of the potential for systemic absorption of ophthalmic atropine and its associated toxicities may assist in expediting its diagnosis and treatment initiation. Further, this case demonstrates the potential role of physostigmine as a diagnostic aid and treatment of acute, severe neurologic symptoms believed to be caused by systemic absorption of ophthalmic atropine.

Article Information

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation. Given the nature of this study, approval by Children's Minnesota Institutional Review Board was not required. However, informed assent was obtained from the patient and informed consent was obtained from the patient's caregivers.

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