

Ipratropium-Bromide-Induced Acute Anisocoria in the Intensive Care Setting Due to Ill-Fitting Face Masks

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Introduction

Anisocoria, or unequal pupil size, may be an early sign of an impending neurologic emergency in any patient.¹ Acute unilateral mydriasis is often suggestive of a life-threatening condition affecting cranial nerve function, such as tumor compression, intracranial hypertension with impending uncal herniation, expanding intracranial aneurysm, or hemorrhage. Benign mydriasis can be due to prior trauma, medication effects, and congenital abnormalities. Determining the cause of anisocoria can be challenging in critical care settings because patients often are sedated, paralyzed, intubated, or have a baseline altered mental status that makes full neurologic examination difficult. The workup of acute anisocoria frequently involves costly and/or invasive procedures, including computed tomography (CT), magnetic resonance imaging, electroencephalography, lumbar puncture, and neurologic consultations before ruling out the most serious causes.

We report 2 cases of anisocoria in elderly intensive care unit (ICU) patients, that were probably due to inadvertent ocular exposure to ipratropium caused by ill-fitting face masks. The unilateral mydriasis resolved spontaneously after life-threatening causes were excluded, and when the masks were removed or better fitted. Cases of ipratropium-bromide-induced anisocoria have rarely been reported, and we include a review of the English-language literature.¹⁻¹² Ipratropium bromide-induced anisocoria may be seen more frequently with the increased use of aerosolized anticholinergics and noninvasive positive-pressure ventilation in the management of respiratory insufficiency.

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Case Report 1

A 78-year-old woman with acute myelogenous leukemia, atrial fibrillation, and coronary-artery disease was admitted to our ICU with respiratory insufficiency following induction chemotherapy. Noninvasive positive-pressure ventilation delivered via oronasal mask was used to support oxygenation and alveolar ventilation. Nebulized levalbuterol and ipratropium bromide were administered for wheezing noted on physical examination. On ICU day 2 (hospital day 18), the patient had an acute mental-status change. A noncontrast head CT revealed no mass effect, nor intracranial hemorrhage. On ICU day 4, a magnetic resonance image of the brain revealed posterior reversible encephalopathy syndrome (an area of low attenuation involving the bilateral parieto-occipital lobes, seen in some post-chemotherapy patients).¹³ There was no evidence of acute infarct, space-occupying or enhancing mass lesion, or venous thrombosis. Neurologic examination was essentially nonfocal, but the patient remained delirious. On ICU day 6, the patient was noted to have a fixed, dilated right pupil, 7 mm in diameter. There was no history of recent trauma, and the patient denied headache or visual changes. The vital signs were stable and a neurologic examination remained without other focal neurologic findings. An urgent CT examination of the head failed to show any acute or new changes. During the workup it was noted that the mask was leaking predominantly toward the right side of the face. Nebulized levalbuterol and ipratropium bromide treatments had been given prior to the discovery of the pupillary change. The patient's respiratory status continued to improve, and she was switched to a nonrebreather face mask. On ICU day 7, the patient's pupils were equal in size and reactive to light. The patient was subsequently transferred from the ICU without recurrence of pupillary changes.

Case Report 2

A 64-year-old man with acute lymphoblastic leukemia was admitted to our ICU with pneumonia, altered mental status, and acute renal failure. A ventriculo-peritoneal shunt

with Ommaya reservoir had been previously placed for hydrocephalus, and to facilitate intrathecal chemotherapy. Neurologic examination on arrival to the ICU was notable only for delirium. A magnetic resonance image of the brain obtained shortly after ICU admission revealed a small infarction of the right mid-frontal lobe, without hemorrhage. Extensive periventricular and deep-white-matter changes involving the corpus callosum were present, suggesting microvascular disease or demyelination. Endotracheal intubation and mechanical ventilation were instituted for progressive hypoxemic respiratory failure. Levalbuterol and ipratropium bromide nebulized treatments were provided every 6 hours. The pneumonia improved with antimicrobial therapy, and the patient was extubated without problem. Supplemental oxygen was provided via simple face mask. Nebulized bronchodilator therapy was continued. On physical examination the following day, the patient's left pupil was noted to be fixed and dilated to 7 mm; there were no other focal findings. An urgent non-contrast head CT revealed no new changes. The vital signs and neurologic examination remained otherwise unchanged. During a review of the patient's medical chart it was noted that a nebulized treatment with levalbuterol and ipratropium bromide had been given via face mask 20 min before the change in the left pupil. Further investigation revealed that the face mask had been loose-fitting, which allowed nebulizer "mist" to leak toward the left eye. The unilateral left mydriasis resolved spontaneously over the next several hours. On the next ICU day, anisocoria was again noted. This time, the right pupil was fixed and dilated to 6 mm. Investigation revealed that the face mask had allowed "mist" to escape toward the right side of the face during bronchodilator therapy. Again, there were no other focal neurologic findings. No additional imaging was performed. The mydriasis resolved within several hours.

Discussion

The first report of ipratropium-bromide-induced anisocoria was published in 1986,² but this condition has rarely been reported in the general medical literature. Most reported cases occurred in pediatric patients, because maintaining proper face mask fit during respiratory treatments is particularly difficult in that population.¹⁴

Ipratropium bromide is an anticholinergic drug, frequently used in aerosol form for its bronchodilatory and antisecretory properties in patients exhibiting respiratory compromise. Ipratropium, like other anticholinergics, antagonizes the actions of acetylcholine at cholinergic receptors. However, inhaled ipratropium can have unintended anticholinergic effects, especially if locally or systemically absorbed. These include mydriasis, cycloplegia, blurred vision, dry mucous membranes, dry eyes, tachycardia, decreased gastric emptying, and urinary retention. With a

malpositioned or poorly fitting aerosol mask, direct exposure to the eyes may cause unilateral or bilateral mydriasis.³⁻⁵

Ipratropium-bromide-induced anisocoria has been reported in the pediatric,^{3,6,7} internal medicine,^{2,4,5,8} and ophthalmology literature,¹ but not in the neurosurgical adult critical care or anesthesiology literature. Drug-induced anisocoria has also been reported to occur after the application of scopolamine patches for treatment of nausea in cancer patients.¹⁵ The unilateral mydriasis was noted on the same side on which the patch was applied. Like ipratropium bromide, scopolamine has anticholinergic effects.

Other causes of anisocoria include compression or destruction of cranial nerve III by increased intracranial pressure from tumor, thrombus, edema, aneurysm, or hemorrhage.^{1,4} Horner syndrome has also been associated with anisocoria. This is most often associated with tumor invasion or post-surgical resection in the area of the cervical sympathetic chain.⁶ Ocular trauma can damage the pupillary sphincter muscles, causing anisocoria.

While brain imaging remains the most effective method to rule out structural causes of acute anisocoria, 1% pilocarpine eye drops may be used to differentiate anticholinergic drug effects from other causes.^{6,9} In ipratropium-induced mydriasis, the affected eye will be unresponsive to pilocarpine, while the unaffected eye will constrict.^{1,4} Increased intraocular pressure or damage to the sphincter muscle may also cause the pupil to be unreactive to pilocarpine, but a history of trauma should be readily elicited to rule out that diagnosis.⁴ In mydriasis caused by increased intracranial pressure causing cranial-nerve-III compression or damage, the pupil will still constrict with pilocarpine, since the sphincter muscle is still intact and responsive to cholinergic stimulation.⁹ However, pilocarpine may also cause undesirable effects. Miosis, ciliary spasm, blurred vision, and photophobia have been reported.⁶ Thus, it is prudent to consider the risk/benefit relationship prior to instilling pilocarpine eye drops.

In our cases, a unilateral mydriatic pupil developed in 2 leukemia patients with respiratory compromise who had received nebulized ipratropium. Each patient had coexistent altered mental status. Concern for structural neurologic causes led to neurologic imaging, which revealed normal or unchanged results. In each case, the anisocoria resolved without apparent residual effect. The anisocoria and the subsequent imaging studies may have been avoided by assuring that a properly fitted face mask had been applied.⁶ Although a leak-free mask fit is perhaps an unreasonable expectation, assurance that respiratory gases are not leaking toward the eyes should reduce the incidence of bronchodilator-induced anisocoria.

Although anisocoria is not a dangerous adverse effect of ipratropium bromide, the condition may be misinterpreted as a severe neurologic emergency in patients with altered

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consciousness. Ipratropium bromide should be considered in the differential diagnosis of patients with anisocoria when no structural explanation can be found with a brain CT.

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