Acute Angle-Closure Glaucoma as a Complication of Combined β-Agonist and Ipratropium Bromide Therapy in the Emergency Department

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Acute angle-closure glaucoma is an uncommon complication of inhaled ipratropium bromide therapy for asthma. All previously reported cases have occurred in hospitalized patients receiving continuing nebulized therapy. A 66-year-old woman with asthma returned to the emergency department with bilateral acute angle-closure glaucoma less than 48 hours after successful treatment with nebulized albuterol sulfate and ipratropium bromide given by metered-dose inhaler. Acute angle-closure glaucoma occurring after ipratropium bromide use is believed to result from local ophthalmic effects attributable to topical absorption instead of systemic action. Greater awareness of this complication and suggested preventive measures may lessen morbidity.

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INTRODUCTION

Acute angle-closure glaucoma (AACG) occurs in 0.10% to 0.17% of the population 40 years and older and increases in frequency with advancing age.[1] The risk of exacerbating pre-existing or as yet undiagnosed narrow-angle glaucoma in older patients who receive inhalation therapy with β-adrenergic agents and ipratropium bromide for obstructive airway disease is well documented and may increase with the aging of the population.[2-5] With initial symptoms that include both sudden decrease in visual acuity in the affected eye associated with photophobia and ipsilateral headache in the distribution of the trigeminal division of the ophthalmic nerve, the onset of AACG may occur one hour to nine days after inhalation therapy is initiated.[2] Timely diagnosis is essential to prevent persistent glaucomatous ocular changes and visual field defects.

Although AACG has been reported in association with ipratropium bromide alone,[3,5] experimental and clinical case reports suggest that an additive effect of combined therapy with the nebulized β-adrenergic agent salbutamol

(albuterol sulfate) and ipratropium bromide is responsible for precipitating AACG in those predisposed to it.[2,4,5] When these agents are administered together, pretreatment screening is suggested to identify such patients, as is using protective eyewear and tube-device delivery systems instead of face masks.

CASE REPORT

A 66-year-old woman arrived at the emergency department complaining of headache and diminished visual acuity of both eyes, especially the left, beginning eight hours earlier. She reported a gritty, sandpaper-like sensation in both eyes. The headache was most severe behind and around the left eye. She was nauseated but had not vomited.

Thirty-six hours before the onset of symptoms, she had been treated in the ED for exacerbation of asthma and was discharged home. During the ED visit, she had received four 0.6-mL (3.0 mg) doses of nebulized albuterol sulfate by face mask and 125 mg methylprednisolone sodium succinate intravenously. Each nebulized treatment was followed by four puffs (72 μg) of ipratropium bromide given by metered-dose inhaler. She was discharged free of wheezing and started on a 12-day tapered regimen of prednisone in addition to her other medications.

The patient's medical history included nasal polyposis and a prior episode of AACG of the left eye. Seven months before, the patient had had laser iridotomy of the left eye with documented decrease in intraocular pressure from 28 mm Hg to 20 mm Hg one month later. Patency of the iridotomy at that time, however, was uncertain. She had done well without ophthalmologic medications. She had no history of diabetes mellitus, hypertension, or cardiac disease. Her current medications included theophylline, an oral decongestant, conjugated estrogen, beclomethasone nasal spray, and triamcinolone acetonide and albuterol sulfate taken by metered-dose inhaler, in addition to the tapered prednisone begun the day before. She was allergic to salicylate, penicillin, and sulfa.

On physical examination, she was alert and oriented but anxious. Vital signs were blood pressure, 254/122 mm Hg; pulse, 94; respirations, 20; and temperature, 37.0°C. The neck was supple. Both lung fields were clear. Ocular examination results revealed photophobia. The patient was able to count fingers at 3 ft using the right eye but could only detect hand motion with the left eye. The right pupil was round and reactive, and the anterior chamber was clear. The left pupil was at midposition and fixed with corneal clouding. Schiotz tonometry of the left eye using the 7.5-g weight revealed a pressure of more than 59 mm Hg. Funduscopic examination results revealed that the right eye was clear, but the left fundus was obscured by corneal clouding.

After IV access was established and 10 mg nifedipine was administered by mouth for blood pressure control, an emergency ophthalmology consultation was obtained. Gonioscopic examination of the left eye by the ophthalmologist revealed a 360-degree closure of the angle and a nonpatent peripheral iridotomy. Ocular pressures, measured by applanation tonometry, were 40 mm Hg OD and 65 mm Hg OS, consistent with bilateral AACG.

Pilocarpine 2% drops were instilled in both eyes hourly, and 300 mL of 20% IV mannitol solution was infused over one hour. Because of the history of allergy to sulfa, acetazolamide (a sulfonamide derivative) was not given. Topical β-adrenergic receptor–blocking agents were withheld because of the history of asthma.

The patient was taken to the eye clinic and, after partial clearing of the left cornea, the ophthalmologist performed peripheral iridotomy and iridoplasty on both eyes using a neodymium:YAG (yttrium-aluminum-garnet) laser. The patient was returned to the ED and discharged in good condition ten hours after initially being seen. She was given 3% pilocarpine and 1% prednisolone acetate eye drops in addition to her previous medications. The diagnosis at discharge was AACG with plateau iris of both eyes.

At a follow-up clinic visit one month later, the patient was doing well. Visual acuity was 20/40 OU, and she had intraocular pressures of 22 mm Hg OD and 24 mm Hg OS.

DISCUSSION

Ipratropium bromide is a synthetic, quaternary ammonium compound with anticholinergic bronchodilator properties. Because of the poor systemic absorption of ipratropium bromide from the tracheobronchial tree after inhalation, initial studies minimized the potential adverse effects of this agent compared with those of inhaled atropine in patients with glaucoma.[6,7] Since then, ten cases of AACG after administration of nebulized ipratropium bromide have been reported.[2-5] Eight have occurred after combined use of nebulized ipratropium bromide and salbutamol (albuterol sulfate). Seven of the ten cases of AACG were bilateral, and four of the five cases for which gender was cited occurred in female patients,[3-5] consistent with the female preponderance of AACG in the general population.

All ten cases occurred in either Great Britain or New Zealand, where ipratropium bromide is available for nebulization in a solution form. Boehringer-Ingelheim, the

manufacturer of ipratropium bromide, may soon market a nebulization solution for use in the United States.

Currently, ipratropium bromide is available in the United States only in a metered-dose inhaler. This case report of AACG is the first known in the United States to occur after giving ipratropium bromide and is the first related to its use when given by metered-dose inhaler. This case report of AACG also is the first known to occur in an outpatient previously treated with ipratropium bromide in the ED and discharged after successful resolution of obstructive airway disease. All previous case reports[2-5] described patients hospitalized for continuing treatment of chronic obstructive pulmonary disease.

Acute angle-closure glaucoma occurs with one quarter the frequency of primary open-angle glaucoma.[8] Risk factors include advancing age, female gender, hyperopia, shallow anterior chamber, increased lens thickness, and family history of glaucoma.[9] White women are affected three times more frequently than white men, whereas the female/male incidence ratio is 1:1 among blacks.[10]

As one ages, increased lens thickness results in relative pupillary block.[11] AACG occurs when pupillary dilation then blocks the outflow of aqueous humor from the posterior to the anterior chamber, resulting in a blockage of the trabecular meshwork and increased intraocular pressure. Conditions that predispose to mydriasis, such as low ambient light, emotional stimulation, and sympathomimetic and anticholinergic parasympatholytic medication, are all known to precipitate AACG.[9]

In several large, retrospective studies of postoperative patients, AACG has been attributed to parenteral anticholinergic administration.[12-14] AACG also has been associated with aerosolized atropine used to treat chronic obstructive pulmonary disease.[9] More recently, AACG has occurred after ipratropium bromide administration, as in this case report. Two cases of AACG caused by nebulized ipratropium bromide alone have been reported,[3,5] whereas all other reported cases have occurred after combined use of nebulized salbutamol (albuterol sulfate) and ipratropium bromide.[2,4,5] Kalra and Bone[15] have postulated that adding β-agonist stimulation of aqueous humor secretion from the ciliary body to the pupillary dilation brought on by ipratropium bromide's topical parasympatholytic effect elevates intraocular pressure and precipitates AACG.

In their controlled, double-blind, crossover British study,[15] 46 patients with a history of glaucoma were treated with nebulized ipratropium bromide and salbutamol for chronic bronchitis. No statistically significant rise in intraocular pressure or narrowing of anterior chamber angle was noted in any patient with open-angle or narrow-angle glaucoma or in the control subjects after they received either drug alone. Only when both nebulized agents were administered together did an increase in intraocular pressure (mean, 5.8 mm Hg ± 0.3 mm Hg) occur and only in those with a history of narrow-angle glaucoma, of whom five also had transient angle closure. Intraocular pressure changes and angle closure did not occur in patients receiving the combined treatment when protective eyewear (swimming goggles) was worn or when antiglaucoma treatment was continued. This finding suggests that the ocular changes induced by these agents occur as a result of the direct topical deposition of aerosolized drug in the conjunctival sac instead of as a systemic effect.[15]

The case reported here, in which AACG developed in the patient after nebulized albuterol sulfate was administered by face mask followed immediately by four puffs of ipratropium bromide, would seem to support the results of the study of Kalra and Bone.[15] The ipratropium bromide in our case was administered by metered-dose inhaler, probably using the open-mouth technique without a spacer device.

Several recommendations have been made in an attempt to minimize the risk of AACG in patients treated with nebulized ipratropium bromide for obstructive airway disease.[2-5,9] Before administering the drug, older patients, especially women, must be questioned regarding a history of AACG or abortive episodes of angle closure suggested by transient blurred vision, "halos," or red eye, associated with unilateral headache and nausea.[2-9] Using a hand-held penlight to estimate anterior chamber depth also may be helpful. By holding a penlight over the lateral canthus and directing it nasally, a shallow anterior chamber can be detected when the light does not illuminate the nasal portion of the iris because the iris bows forward.[9]

For patients requiring nebulized anticholinergic therapy and determined to be at increased risk for AACG, several approaches have been suggested. Berdy et al advised that an ophthalmologist examine those at risk before therapy is initiated.[9] Such examination may be appropriate in selected hospitalized patients but is probably impractical for the acutely ill patient in the ED.

Using masks that are both correctly fitted and positioned to minimize ocular deposition of nebulized drug[2,5] and, when possible, using a hand-held nebulizer instead of a face mask may decrease ocular absorption even further.[5] Because ipratropium bromide is currently available in the United States only in a metered-dose inhaler, a spacer device is recommended instead of the open-mouth technique probably used in our case. Protective eye wear such as swimming goggles[15] or even the disposable plastic glasses

now available in most EDs as part of universal precautions may offer the best protection for those at risk of glaucoma who are likely to benefit from inhaled anticholinergic therapy.

Avoiding simultaneous administration of nebulized β-adrenergic and anticholinergic agents may be another solution.[2,15] This recommendation may be difficult to follow because little evidence indicates the appropriate interval of separation,[18] in terms of both therapeutic and adverse effects. Used appropriately in acute asthma, ipratropium bromide provides a synergistic benefit when given with an inhaled β-adrenergic agent.[16-18] Also advised are pretreating at-risk patients with topical miotics such as 1% pilocarpine hydrochloride[9] and ensuring continuous antiglaucoma therapy during acute and chronic combination therapy with inhaled β-adrenergics and ipratropium bromide.[2,15]

A well-informed patient is also desirable. Whether patients are in the ED, hospital, or outpatient setting, informing them of the signs and symptoms of AACG and of the preventive measures described here is recommended. To prevent inadvertent autoinoculation, patients also must be cautioned specifically against rubbing the eyes after using ipratropium bromide.

Given the increasing acceptance of ipratropium bromide in the routine treatment of both asthma and chronic obstructive pulmonary disease and its impending availability in nebulized form in this country, heightened awareness of the potential for ipratropium bromide–related AACG is essential.

SUMMARY

Reported is a case of AACG in a 66-year-old female asthmatic patient treated less than 48 hours earlier with inhaled ipratropium bromide. Although only 12 case reports of AACG associated with inhaled anticholinergics are known to have appeared to date in the biomedical literature in English, and only ten of these were associated with ipratropium bromide, several factors would suggest a potential increase in the incidence of this complication. These include the increasing acceptance of inhaled anticholinergics, especially ipratropium bromide, combined with inhaled β-adrenergic agents in routine treatment of acute and chronic asthma; an aging population with increasing numbers susceptible to glaucomatous attacks; and the impending availability of ipratropium bromide as a nebulized solution in the United States.

Obtaining a screening history and performing an appropriately directed physical examination to identify those at risk for AACG are recommended. Using protective eyewear and tube-device delivery systems instead of face masks is advised. Both are reasonable measures for preventing AACG when combined β-agonist and ipratropium bromide therapy is anticipated.

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