

CASE REPORT

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Nebulized Ipratropium Bromide-induced Anisocoria: Why Is Anisocoria Observed?

Oksan Derinoz-Guleryuz, İlknur Fidanci, and Yasemin Men-Atmaca

*Department of Pediatrics, Division of Pediatric Emergency, Faculty of Medicine,
Gazi University, Ankara, Turkey*

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ABSTRACT

Pharmacological anisocoria is a rare but benign condition. This paper presents an eleven-year-old patient with asthma who developed ipratropium bromide-associated anisocoria during nebulizer treatment. Hypotheses regarding the possible causes of anisocoria are discussed and precautions to be taken during treatment are presented. To prevent the development of anisocoria, it was found that it is important to use the appropriate mask during nebulizer treatment, to place the mask on the face properly, and, if possible, to administer drugs by closing the eyes. Further, it is recommended that patients undergo an ophthalmological examination before discharge and that they and their families be informed that the condition is temporary.

Keywords: Anisocoria; Child; Ipratropium bromide; Pediatric emergency medicine

INTRODUCTION

Anisocoria may develop alongside life-threatening clinical conditions (such as an intracranial mass, hemorrhages, and herniation) or as a result of a normal, physiological condition. Pharmacological (i.e. drug-induced) anisocoria is a rare yet benign form of anisocoria. While drug-induced mydriasis causes bilateral mydriasis, eye drops (such as cyclopentolate) and anticholinergic drugs (such as ipratropium bromide) administered by aerosol cause unilateral mydriasis.^{1,2}

There are several hypotheses in the literature about ipratropium bromide-induced mydriasis.¹⁻³ However, its exact cause is still unknown.

This paper discusses the mechanisms which may have caused unilateral mydriasis to develop after aerosol drug administration to a patient who then developed ipratropium bromide-induced anisocoria. The purpose is to bring attention to consideration for the effective treatment of patients in line with these mechanisms.

Case Presentation

An eleven-year-old male patient, who had been treated for asthma for six years prior, was admitted for experiencing phlegmy cough at night and shortness of breath on exertion for three days. Written informed consent was obtained from the parents of the patient for the publication of the patient data and photographs. He did not have a fever. His medical history indicated that he had been followed-up due to asthma; however, he had not been using his medication regularly for the past two years. His family history did not show anything

Corresponding Author: Oksan Derinoz-Guleryuz, MD;
Department of Pediatrics, Division of Pediatric Emergency, Faculty
of Medicine, Gazi University, Ankara, Turkey. Tel: (+90 31) 2202
4212, E-mail: oderinoz@gazi.edu.tr, oksanderinoz@gmail.com

relating to his symptoms. His family did not know whether the patient had received ipratropium bromide treatment before. Also, they did not remember that such a side effect developed during the treatment. The initial assessment presented an overall good condition without any toxic presentation. He had tachypnea (respiratory rate: 38/min) and was hypoxic (SPO₂: 91%, at room air). A physical examination showed bilateral extensive rhonchi and bilateral subcostal retraction in the respiratory system. Capillary refill time was normal. He did not have cyanosis. Another system examination was unremarkable.

The patient was considered to have respiratory distress due to an asthma attack and was referred to the pediatric emergency observation unit. Hydration, oxygen, salbutamol sulfate nebulizer (Ronkotol 2.5 mg/2.5 mL), ipratropium bromide (Ipratrom 500 mcg/2 ml), budesonide (BudecortSteri-Neb 0.5 mg/mL) and systemic steroid (Prednol-L 40 mg) therapies were started. At the fourth hour of the treatment, a second examination was conducted. The patient's tachypnea had regressed; however, hypoxia was still present. The

physical examination identified mydriasis in the left eye, which had not been detected during the initial examination (Figure 1). Another round of neurological examinations showed normal eye movement in all directions with no ptosis; however, the left eye did not show reflex to light. Other cranial nerves and neurological examinations were normal. No focal neurological signs were found. Because the patient had no history of trauma, the ophthalmology department was consulted. "Right eye light reflex +/+, left eye light reflex -/-, right pupil normal, left pupil dilated, anisocoria present. No papilledema, right and left optical discs, and the macula are normal." A cranial tomography scan was performed to eliminate a possible intracranial condition and the results were normal. The anisocoria was linked to drug therapies that were being administered. The treatment was discontinued. The patient, whose clinical picture had improved, left the hospital voluntarily. The anisocoria was completely better when the patient came in for an examination 48 hours later (Figure 2).



Figure 1. Mydriasis of the left eye following nebulizer ipratropium bromide therapy



Figure 2. Regression of mydriasis of the right eye after the discontinuation of ipratropium bromide therapy and evening up of both pupils' diameters

DISCUSSION

Pharmacological anisocoria is a clinical condition that develops with the mucosal absorption of drugs after the topical use of eye drops, including atropine and cyclopentolate, or nebulized use of drugs such as ipratropium bromide. Pharmacological anisocoria, which is a benign cause of anisocoria, causes mydriasis by stimulating the sympathetic innervations of the dilator pupil or by inhibiting the parasympathetic innervations of the sphincter pupil.³ However, the developing anisocoria is usually unilateral, primarily affecting the left eye.⁴⁻⁶ While several hypotheses have been put forward in the literature, the pathogenesis of anisocoria remains inconclusive because most of these studies are based on case reports.

A common hypothesis in the literature is that anisocoria is caused by the mucosal absorption of drugs when the mask is improperly fit, particularly in elderly patients receiving inhaler therapy.¹ In pediatric cases, several factors lead to anisocoria, including difficulties in mask and drug use; the fact that children do not want to keep the mask on or cooperate during the therapy; and loose or improper mask fit, which results in particles leaking from the edges of the mask during drug aerosolization and accumulating on the face and eyes of the patient. For effective treatment, children must often receive therapy while sitting on the lap of a parent who holds the mask and places it on the face of the child with his/her right hand. While this prevents the mask from sitting on the face too tightly, it often results in the drugs having more contact with the left eye. (Since the hand that is holding the mask is partially closing the right eye, that eye is affected less.) This is why anisocoria is often observed in the left eye.

Other hypotheses are related to the type of mask used during treatment. The standard masks that are used to administer bronchodilator drugs leak air from the sides. When the mask is not properly placed on the face, drug particles may escape from the sides of the mask and accumulate on the face leading to anisocoria. In contrast with this hypothesis, another study reported that masks with air leakage may be preferable since tight-fitting masks lead to drug accumulation. Furthermore, it was also reported that drug accumulation is less in systems where they are aerosolized into small particles; that each drug accumulated differently in eyes; and that, therefore,

masks should be chosen according to the drug to be administered.⁷

Our hypothesis is related to hand preference and eye dominance. We believe that unilateral anisocoria develops due to dominant hand choice and eye dominance while applying the mask; this is because the child uses his dominant eye much more. However, as with others, this hypothesis needs to be proven by further studies.

Rosenbach was the first to identify the dominant eye and develop a test to determine it.⁸ This test is performed by having a person keep both eyes open and focused on a distant object, then superimposing their index finger on and looking at a distant object. (It is important to make sure that they superimpose the index finger on the distant object and that they are following the same line). When the image of the index finger falls out of Panum's area, the finger is seen double. To determine the dominant eye, the person first looks at this object with both eyes open. When the index finger and the distant object overlap, the person alternately closes one eye at a time without moving their head. The eye that keeps the index finger directly in front of the object while the other eye is closed is the dominant eye. When looking with the other eye, the index finger seems to move away from the object. Even though the relationship between hand choice and the dominant eye is not yet certain, many studies are being carried out on this subject.⁹ In our case, we have not been able to identify eye dominance. However, we think that this may be one cause of unilateral anisocoria in cases receiving nebulizer drug therapy.

The presence of anisocoria in a patient requires that they be examined for life-threatening conditions. To this end, imaging methods are often used to exclude the presence of an intracranial event. In a patient with normal images, causes for pharmacological or physiological anisocoria are then explored. The patient in our case did not have any prior complaints, trauma history, signs of increased intracranial pressure, or focal neurological deficit. Imaging examinations were performed to eliminate life-threatening conditions. Literature shows that cranial imaging has been performed on nearly all cases even though anisocoria was thought to have developed due to a benign cause, as in our case study.^{1-3,5,6} Our suggested approach for similar cases (when anisocoria is not thought to be a result of a life-threatening condition) is to wait for the

drugs to complete their half-lives to minimize unnecessary radiation exposure. During this time, it is best to monitor the clinical condition of the patient to decide on which imaging method to use. Ipratropium bromide is an anticholinergic, atropine-derived drug that is administered by inhalation whereby it antagonizes acetylcholine in muscarinic cholinergic receptors. It is a Bronchodilator that works by blocking the muscarinic receptors of bronchial smooth muscles and by reducing vagal tone; it is most often used in combination with salbutamol therapy in children with asthma. Its half-life is six to eight hours. When accidentally administered to the eye, it affects muscarinic receptors and causes mydriasis.⁴ For this reason, it would be appropriate to monitor patients for at least six to eight hours when ipratropium bromide-associated anisocoria is present and then decide on an imaging method.

Another important characteristic of ipratropium bromide-associated anisocoria cases in literature is that nearly all of the reported cases were of patients with fair skin and blue/green-eyes, just like in our case.^{1,3,10} Although we have not been able to review the literature to determine whether light eye color has any effect on drug absorption, one reason might be that allergic individuals—who are often fair-skinned—use these drugs more often, causing anisocoria to be more easily detected and reported in these individuals as compared to dark-eyed individuals. It is hard to pinpoint the actual number of cases since anisocoria is very difficult to detect in other eye colors. For this reason, it is important to monitor all cases receiving nebulizer drug therapy.

In conclusion, ipratropium bromide-associated anisocoria is a benign condition and its causes are still hypotheses. To prevent this side effect of the drug—as well as unnecessary tests—it is important to properly place the appropriate mask on the face during nebulizer drug therapy, to administer the drug with eyes closed, and, if necessary and possible, to conduct an ophthalmological examination before discharge. Patients and their families should also be informed that the condition is temporary.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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