

Clinical Note

Anisocoria with high dose ipratropium bromide inhaler

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Ipratropium bromide is an atropine derived anti-cholinergic bronchodilator used in obstructive lung diseases. Anisocoria mainly caused by the direct effect of nebulized ipratropium bromide via a leaking mask has been well described in the literature.^{1,2} However, anisocoria induced by systemic absorption after long-term use of high dose ipratropium inhaler is not well reported. We report a case of a 24-year old asthmatic, after consent was obtained who developed fixed dilated pupils due to the systemic effect of an ipratropium inhaler. The aim of the report is to draw clinicians' attention to this rare but possible anticholinergic systemic side effect of inhaled ipratropium bromide.

The patient is a 24-year-old female, known case of bronchial asthma for more than 10 years. Her asthma was categorized as severe and poorly controlled. Her medications were; ipratropium bromide via metered dose inhaler 20 mcg per puff, 16 puff/day without a spacer device (patient technique was ideal); montelukast 10 mg once daily; budesonide turbobhaler 200 mcg, 8 puffs per day; azithromycin 250 mg 3 times per week; fexofenadine 160 mg at night; esomeprazole 40 mg once daily; and diltiazem 90 mg once daily. Two months after the current dose of ipratropium, she started to complain of blurred vision, eye dryness, and photophobia. There was no headache, eye pain, loss of vision, or neurological symptoms. There was no history of trauma. Examination performed by a neuroophthalmologist showed bilateral dilated pupils, her right pupil was 7 mm and left pupil was 9 mm in size with sluggish reaction to light. Eye movements, optic disc, and fundi were normal with no visual deficit found. Neurologic examination including cranial nerves was normal, except the newly developed anisocoria. Her pupils failed to respond to local application of 1% pilocarpine eye drops after 30 minutes, and both pupils remained dilated. This was consistent with a pharmacological cause

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for dilation.² Discontinuation of the ipratropium lead to gradual resolution of anisocoria, and her pupils returned to their normal size of 3 mm within one week and reacted normally to light. To confirm the above-mentioned side effects to ipratropium, a re-challenge with the same dose of inhaler was prescribed after neuroophthalmologist approval, which showed recurrence of the anisocoria (Figure 1).

Anticholinergic, ipratropium bromide, is a quaternary ammonium derivative of atropine sulfate that blocks muscarinic (M) receptors on airway smooth muscle and submucosal gland cells leading to reductions in bronchomotor tone, and subsequently bronchodilation.³ Typical dosing is 2 puffs 4 times per day, but higher doses are recommended in patients with severer disease.³ Atropine-like side effects of ipratropium bromide are relatively few, since it is not sufficiently absorbed from mucosal surfaces to produce detectable blood levels, and hence systemic effects. Such agents produce anticholinergic effects at the site of deposition, as seen with the dilatation of the pupil if delivered to the eye or dilatation of the bronchi if inhaled. Nebulized ipratropium bromide has been previously reported to cause unilateral pharmaceutical mydriasis in hospitalized adults and children.^{1,2} This is thought to occur through direct contact of nebulized ipratropium with the eyes, due to a leaky mask. Theoretically, as an atropine derived compound, ipratropium bromide can cause atropine-like side effects if systemically absorbed. Extensive toxicological examinations revealed that with high doses, all typical symptoms of overdosing an anticholinergic drug, like dryness of the mucosa, hypertension, skin rashes, urinary retention, constipation, and headache may occur.³ However, mydriasis is also a described complication, but it is rare and there are only a few reported adult cases in



Figure 1 - Pupils before A) and after B) use of an anticholinergic showing significant dilatation, namely, anisocoria.

the literature.^{4,5} This is mostly unilateral and observed with nebulized rather than inhaled ipratropium bromide. Therefore, our case suggests that ipratropium inhaler can also achieve sufficient serum concentrations, to produce systemic side effects, including bilateral pupil size changes, as demonstrated in this reported case. Pharmaceutical pupils can be identified easily with 1% pilocarpine. The pilocarpine test can be applied to differentiate the diagnosis from other neurologic and ophthalmologic reasons. Pilocarpine has a parasympathomimetic effect and hence causes miosis. Application of diluted 1% pilocarpine causes constriction in normal pupils and dilated pupil due to third nerve paralysis and Adie pupil. If an agent like ipratropium bromide, which blocks the cholinergic stimulation of the sphincter muscle, is on board, constriction does not occur. The response to the test is expected within 20 minutes.² In retrospect, our patient was also found to have other anticholinergic effects along with anisocoria, such as tachycardia, tremor, dryness of mouth, and nausea.

In conclusion, atropine-like systemic side effects of ipratropium bromide inhaler can occur and clinicians must be aware of these complications. Our report highlights the potential systemic absorption of inhaled ipratropium leading to anisocoria and other anticholinergic effects.

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