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Effect of Nebulized Ipratropium Bromide on Intraocular Pressures in Children*

Wade T. A. Watson, M.D.; E. Paul Shuckett, M.D.; Allan B. Becker, M.D.; and F. Estelle R. Simons, M.D.

Study objective: To evaluate the effects of nebulized ipratropium bromide on intraocular pressures and pupillary responses in children with asthma.

Design: A double-blind, randomized, crossover study.

Setting: Children’s Hospital of Winnipeg, University of Manitoba.

Patients or participants: Age 6 to 17 years with asthma.

Intervention: Nebulized ipratropium bromide added to albuterol sulfate, albuterol alone, or saline solution was given by face mask and nebulizer. Before and 0.5 h after nebulization, intraocular pressures (mm Hg), pupillary size (mm), and pupillary responses were measured. In a subsequent open study, patients who had been admitted to hospital with acute asthma who were treated with nebulized ipratropium bromide were recruited for measurement of intraocular pressures, pupillary size, and pupillary responses.

Measurements and results: Twenty patients completed the double-blind study, and 26 patients completed the open study. There were no changes in intraocular pressures, pupillary size, or pupillary response after any treatment on any study day in either the double-blind or the open studies.

Conclusion: In children with asthma, who have no pre-existing ocular abnormalities, the risk of an adverse reaction to nebulized ipratropium bromide delivered by face mask inadvertently absorbed in the eye is extremely small.

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Ipratropium bromide, a topically active quaternary derivative of n-isopropylnoratropine, is widely used as a nonselective muscarinic receptor antagonist. For treatment of acute bronchospasm in adults and children, it is administered with a β2-adrenergic agonist.1-5

Administration of ipratropium bromide by nebulizer and face mask has been reported to be associated with acute angle-closure glaucoma6-11 and unilateral fixed dilated pupil.12-14 In the reports of glaucoma, patients complained of blurring of vision and ocular pain within minutes of ipratropium administration. The increased intraocular pressures responded to appropriate treatment with intravenous or oral acetazolamide, topical pilocarpine, and analgesia. Patients with a unilateral dilated pupil also reported symptoms within minutes of ipratropium bromide administration, with resolution over 6 to 8 h.

These adverse effects have been attributed to ipratropium bromide escaping from the face mask and being absorbed locally in the eye.13,14 Approximately 90 percent of the medication delivered by face mask and nebulizer escapes into the air or is left in the nebulizer. Some hospitals now recommend ipratropium bromide be delivered only by metered-dose inhaler or by mouthpiece with a nebulizer, and not by face mask; however, children may not cooperate with the use of mouthpieces.

To date, and to our knowledge, there are no data on the effect of nebulized ipratropium bromide on intraocular pressure or pupillary responses in children. It is not known if children are at risk for ocular complications from ipratropium bromide. We hypothesized that nebulized ipratropium bromide, when combined with a β2-adrenergic agonist, would not significantly affect intraocular pressures, pupillary size, or change in pupillary responses in children. We performed a double-blind, placebo-controlled, crossover study of nebulized ipratropium bromide and albuterol alone, and saline solution to assess this hypothesis.

METHODS

The study was approved by the Faculty Committee on the Use of Human Subjects in Research at the University of Manitoba. All patients and/or parents gave written informed consent before study entry. Patients were eligible for study if they were aged 6 to 17 years, had moderate to severe asthma, and had previously used ipratropium bromide during asthma exacerbations. Patients were excluded from study if they had a history of severe eye injury or congenital eye disorders, including congenital glaucoma.

All patients arrived at the Pediatric Allergy Laboratory in the Health Sciences Clinical Research Centre at 7:30 AM, having used no bronchodilator medications by face mask and nebulizer within the previous 12 h. Baseline intraocular pressures were measured using a Goldmann applanation tonometer (Haag-Streit, Bern, Switzerland), attached to a slit lamp for ophthalmologic examinations. Before each measurement, proparacaine hydrochloride 0.5 percent, 1 drop, was instilled in each eye for local anesthesia.

In a double-blind, randomized three-way crossover fashion, patients received nebulized ipratropium bromide, 250 μg if they...
weighed <40 kg, and 500 μg if they weighted >40 kg, added to albuterol sulfate, 0.1 mg/kg (maximum dose, 5.0 mg), albuterol alone, or saline solution alone via face mask and nebulizer. The medications were delivered by a jet nebulizer (Bennett Twin) driven by 5 L of oxygen per minute via a loose-fitting face mask. The nebulization was continued until all medication was delivered. At the end of the nebulization, patients were questioned with regards to possible adverse effects, including dry mouth, bad taste, blurred vision, palpatations, or tremor. Before and 0.5 h after completion of the nebulization, intraocular pressure (mm Hg), pupillary size (mm), and pupillary response were measured. Pupillary size was expressed as the diameter in millimeters using light from the slit lamp as the only light source. Pupillary response was assessed in a darkened room after shining a beam of light into the eye. Patients returned to the Health Sciences Clinical Research Centre on two additional occasions to receive the alternate medications by face mask nebulizer. All visits occurred at least 48 h apart. An intraocular pressure increase of 3 mm Hg or more was considered to be significant.15 Results were expressed as mean ± SD and analyzed using analysis of variance and paired t-tests. For adverse effects, results were analyzed using McNemar’s test for correlated proportions. A p value of <0.05 was considered statistically significant.

RESULTS

Twenty patients, mean age 12.5 ± 1.7 years, completed the double-blind study. Baseline intraocular pressures (mm Hg) were 13.1 ± 2.3 in the right eye and 12.6 ± 2.3 in the left eye. Measurements of baseline intraocular pressure were not significantly different on each study day (Table 1). No increase in intraocular pressure were seen after any medications on any day. Pupillary size and pupillary response were unchanged on any of the study days. No patient spontaneously complained of adverse effects. On direct questioning, significantly more patients complained of tremor after albuterol than after placebo (p <0.05). Slightly more patients complained of tremor and palpitations after nebulized ipratropium/albuterol than after placebo (p <0.08) (Table 2). Four patients complained of blurred vision after ipratropium/albuterol. No change in pupillary size or response was noted in these patients. An additional 26 patients (16 male), mean age 10.8 ± 2.4 years, were recruited in the open arm of the study. No change in pupillary size, pupillary response, or intraocular pressures was seen after administration of nebulized ipratropium bromide and albuterol.

DISCUSSION

Nebulized ipratropium bromide, combined with albuterol, did not significantly increase intraocular pressures or affect pupillary size or pupillary response in young patients with asthma.

Acute angle-closure glaucoma is very rare in childhood. In an adult, dilation of the iris can cause a sudden attack of angle-closure glaucoma. As the lens matures, it thickens and causes the anterior chamber to become shallow. When the iris dilates, the out-flow track for fluid closes and angle-closure develops. Under age 17 years, with few exceptions, the lens is not thick enough to induce angle-closure glaucoma. These exceptions would include congenital abnormalities of the eye (eg, iridocorneal dysgenesis, aniridia, Sturge-Weber syndrome) or other ocular abnormalities (eg, uveitis, aphakia, traumatic hyphema). Absolute contraindication for the use of nebulized ipratropium bromide would include those with blindness and significant retinal detachment secondary to retinopathy of prematurity, infantile or childhood glaucoma, traumatic cataracts, or dislocation of the lens.16 Slippage of face masks in adults may relate to drowsiness or confusion related to impaired consciousness due to hypoxia, hypercapnia, or other factors that may be less relevant in children.

Frequently, parents, nurses, or respiratory therapists must hold a child while administering ipratropium bromide via face mask. There have been no reports of angle-closure glaucoma in adults in this

Table 1—Ocular Measurements on Each Study Day

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Placebo</th>
<th>Albuterol</th>
<th>Ipratropium/Albuterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraocular pressure</td>
<td>OD</td>
<td>13.1±2.3</td>
<td>12.3±2.4</td>
<td>12.9±2.7</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>12.6±2.3</td>
<td>12.5±2.2</td>
<td>12.5±2.8</td>
</tr>
<tr>
<td>Pupillary size, (mm)</td>
<td>OD</td>
<td>4.4±0.8</td>
<td>4.3±0.8</td>
<td>4.2±0.6</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>4.4±0.8</td>
<td>4.3±0.9</td>
<td>4.2±0.8</td>
</tr>
<tr>
<td>Pupillary response</td>
<td>OD</td>
<td>2.0±0.0</td>
<td>2.0±0.0</td>
<td>2.0±0.0</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>2.0±0.0</td>
<td>2.0±0.0</td>
<td>2.0±0.0</td>
</tr>
</tbody>
</table>

*Results are expressed as mean ± SD. Pupillary responses were graded as follows: 0=no response; 1=sluggish; 2=brisk response. OD=right eye; OS=left eye.

Table 2—Adverse Effects Reported by Patients After Receiving Nebulized Medications

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Albuterol</th>
<th>Ipratropium/Albuterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>6</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Bad taste</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Tremor</td>
<td>2</td>
<td>8*</td>
<td>7†</td>
</tr>
<tr>
<td>Palpitations</td>
<td>2</td>
<td>5</td>
<td>8†</td>
</tr>
</tbody>
</table>

*p <0.05 compared with placebo.  †p <0.08 compared with placebo.
situation, and the concentration of ipratropium bromide in the air would be significantly less than if the medicine were administered directly by face mask and nebulizer.

In children with asthma and no preexisting ocular abnormalities, the risk of an adverse reaction to nebulized ipratropium bromide inadvertently absorbed in the eye is extremely small. Further studies in larger numbers of children will be necessary to confirm these findings.

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REFERENCES

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