Ocular Effects of Apraclonidine in Horner Syndrome

Jose Morales, MD; Sandra M. Brown, MD; Aziz S. Abdul-Rahim, MD; Craig E. Crosson, PhD

Objective: To determine the location of action of apraclonidine, an α-adrenergic receptor agonist that reduces aqueous production and lowers intraocular pressure (IOP).

Methods: The study cohort consisted of 6 patients with Horner syndrome (decreased or absent sympathetic innervation of 1 eye). We instilled 1% apraclonidine into the affected eye, and the changes in IOP and pupil diameter (PD) of both eyes were measured over 4 hours. In a separate session, apraclonidine was instilled into the normal eye and the measurements were repeated.

Results: The average baseline IOP was 16.3 mm Hg for affected eyes and 16.7 mm Hg for normal eyes. The average maximum ipsilateral reduction in IOP was 5.8 mm Hg in affected eyes and 5.2 mm Hg in normal eyes; this difference was not statistically significant. The average baseline PDs for affected and normal eyes were 3.2 mm and 4.2 mm, respectively. Instillation of apraclonidine into affected eyes produced mydriasis of 1.0 to 4.5 mm; baseline anisocoria reversed in all patients. There was no significant change in the PD of normal eyes after ipsilateral instillation of apraclonidine.

Conclusions: Apraclonidine's major site of pharmacologic action for reduction of aqueous production is on postjunctional α2 receptors in the ciliary body. The up-regulation of α receptors that occurs with sympathetic denervation unmasks apraclonidine's α1 effect, which clinically causes pupil dilation. Apraclonidine may be a useful medication for the diagnosis of Horner syndrome.


Apraclonidine (Iopidine; Alcon, Fort Worth, Tex) is an adrenergic receptor agonist that is approved for the treatment of elevated intraocular pressure (IOP) following argon laser trabeculoplasty.1 It lowers IOP primarily by reducing aqueous production through its effect on α2 receptors.2 Apraclonidine's α1 activity does not affect aqueous production, but it causes the conjunctival vasoconstriction often noted with its use. Although several α2 agonists are used clinically as ocular hypotensive agents, their site(s) of action is not completely understood. Animal studies have provided evidence that α2 agonists can lower IOP by acting on prejunctional and postjunctional receptors in the eye as well as on α2 receptors in the central nervous system.3-5

Patients with Horner syndrome (HS) (disruption of sympathetic innervation to the eye and adnexa) provide a unique opportunity to study the relative contributions of the peripheral and central actions of α2 agonists in lowering IOP. They also provide an opportunity for the evaluation of the α1 effect, without the influence of normal sympathetic tone. Our study examines the change in IOP and pupil diameter (PD) after instillation of 1% apraclonidine in the affected and normal eyes of patients with HS.

RESULTS

The baseline IOPs for affected and normal eyes were 16.3 ± 1.5 and 16.7 ± 1.0 mm Hg, respectively. Figure 1 shows the IOP response to unilateral apraclonidine administration. Apraclonidine produced a significant reduction in ipsilateral IOP in both affected and normal eyes. The maximum reductions for affected and normal eyes were 5.8 ± 1.0 and 5.2 ± 0.8 mm Hg, respectively. In contrast, a significant contralateral reduction in IOP was observed only in normal eyes.

The average baseline PDs for affected and normal eyes with room lights on were 3.2 mm and 4.2 mm, respectively. Figure 2 shows the PD response following apraclonidine administration. In

From the Department of Ophthalmology and Visual Sciences, Texas Tech University Health Sciences Center, Lubbock. Dr Crosson is currently affiliated with the Medical University of South Carolina, Storm Eye Institute, Charleston.
MATERIALS AND METHODS

Eleven patients with unilateral HS were identified from the records of the study facility between 1989 and 1994. Six agreed to participate in the investigation, which was approved by the institutional review board. The diagnosis of HS was made on clinical grounds alone if the patient had ptosis of no more than 2 mm, ipsilateral miosis, and ipsilateral dilation lag to sudden darkness. Horner syndrome was confirmed in patient 6, who had more than 2 mm of ptosis, when the ipsilateral miotic pupil failed to dilate after instillation of 1 drop of 10% cocaine. Instillation of 1% hydroxyamphetamine was used to localize HS as either preganglionic or postganglionic in 5 of the 6 patients. In patient 3, localization was presumed to be postganglionic because of intact facial sweating and an established diagnosis of cluster headaches. Two patients had preganglionic lesions and 4 had postganglionic lesions.

Testing with apraclonidine was divided into 2 sessions. In session 1, baseline pupil diameter measured in normal room illumination and with room lights off and IOP by Goldmann applanation were recorded for each eye. Pupil diameter was determined to the nearest 0.5 mm using the pupil gauge on the Rosenbaum pocket vision screener. One drop of 1% apraclonidine was applied to the eye with HS. Pupillary and IOP measurements were repeated at 1, 2, 3, and 4 hours after instillation. During session 2 on a separate day, the same data were recorded; however, apraclonidine was instilled into the normal eye. The 2 sessions were separated by 4 to 11 days.

For analysis of IOP and PD data, eyes with both preganglionic and postganglionic HS lesions were grouped as “affected eyes,” owing to the low number of patients with preganglionic HS lesions identified. Values were expressed as means and SEs. Data from affected eyes were compared with those from normal eyes by means of the paired t test. P ≤ .05 was considered significant.

The HS eyes, the administration of apraclonidine produced a rapid increase in ipsilateral PD of 1.0 to 4.5 mm (Table). This increase in PD was maintained throughout the 4-hour study period, and a reversal of the baseline anisocoria was observed in all subjects. In contrast, the administration of apraclonidine to the normal eyes by means of the paired t test.

COMMENT

Horner syndrome is caused by interruption of the serial 3-neuron sympathetic outflow path to the eye and adnexa. Lesions that affect the neurons that travel from the brainstem to the spine, or from the spine to the superior cervical ganglion, are termed preganglionic. Lesions that affect efferent fibers from the superior cervical ganglion are termed postganglionic. Although sympathetic outflow is greatly reduced with preganglionic lesions, there is still a small, tonic release of norepinephrine from the intact postganglionic nerve terminals into the junctional spaces of the ciliary epithelium. In contrast, lesions that affect the postganglionic efferent neurons from the superior cervical ganglion cause total depletion of norepinephrine at the target tissues. Associated with the reduced or absent sympathetic drive is an up-regulation of postjunctional α receptors in the eye and ocular adnexa.

Ocular α2 receptors exist prejunctionally on the sympathetic nerve terminals and postjunctionally on the ciliary epithelium and the trabecular meshwork cells. In addition, α2 receptors are present on nerve fibers of the sympathetic chain in the central nervous system. In postganglionic HS, prejunctional α2 receptors are absent. Because 1% apraclonidine caused an equal decrease in IOP in normal eyes and in eyes with postganglionic HS, the activation of postjunctional α2 receptors is sufficient to account for apraclonidine’s effect on IOP. The small contralateral response measured in normal eyes but not in affected eyes suggests that the activation of prejunctional or central receptors can also lower IOP to a small extent.

Apcraronidine can also stimulate α1 adrenergic receptors. The most pronounced clinical effect in normal patients is conjunctival vasoconstriction. A finding of this study was that 1 drop of 1% apraclonidine dilated the abnormal miotic pupil of the patients with HS, often dra-
matically. This response was seen in eyes with preganglionic or postganglionic lesions. In control eyes, mydriasis of 0.5 mm was noted in only 1 patient at 1 time point. Others have investigated the effects of apraclonidine on the pupils of patients with ocular hypertension and of normal volunteers. In some reports, dilation of approximately 0.5 mm was observed in a small proportion of the subjects\(^1,^0-^1^2\) while in other studies\(^1^3,^1^4\) no significant dilation was observed. Our results confirm the finding that in normally innervated eyes, 1% apraclonidine produces little or no pupil dilation. Paradoxically, Jampel et al\(^1^5\) noted miosis in response to 0.25% apraclonidine. This may be due to selective activation of prejunctional \(\alpha_2\) receptors at lower concentrations, leading to decreased release of norepinephrine; this effect would be more pronounced in individuals with greater resting sympathetic tone and absent in patients with HS. We postulate that the mydriatic response we observed in eyes with HS was due to denervation supersensitivity of the \(\alpha_1\) receptors on the iris dilator muscle, as has been demonstrated with epinephrine bitartrate and phenylephrine hydrochloride.\(^1^5,^1^6\)

Observation of the pupils in our small series of patients leads us to propose that reversal of anisocoria after simultaneous instillation of 1 drop of 1% apraclonid-

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**Figure 2.** Pupil diameter (PD) response vs time after instillation of 1 drop of 1% apraclonidine into 1 eye. A, Ipsilateral PD response. B, Contralateral PD response. HS indicates Horner syndrome; asterisk, \(P < .05\).

**Figure 3.** All photographs were taken with room lights on. A, The patient at baseline, showing left ptosis and miosis; note the incidental elevated left upper eyelid fold consistent with levator aponeurosis dehiscence. B, Forty-five minutes after instillation of 10% cocaine to each eye. Failure of the left pupil to dilate indicates Horner syndrome. C, Several weeks later, appearance 1 hour after instillation of 1 drop of 1% apraclonidine to the left eye. Note reversal of baseline anisocoria.

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**Pupil Size at Baseline and 1 Hour After Instillation of 1% Apraclonidine to the Affected Eye of Patients With HS**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Laterality</th>
<th>Location</th>
<th>Ambient Illumination</th>
<th>Baseline</th>
<th>After Apraclonidine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R</td>
<td>L</td>
</tr>
<tr>
<td>1</td>
<td>L</td>
<td>Postganglionic</td>
<td>Dk</td>
<td>6.0</td>
<td>5.0</td>
</tr>
<tr>
<td>2</td>
<td>R</td>
<td>Preganglionic</td>
<td>Lt</td>
<td>4.0</td>
<td>3.0</td>
</tr>
<tr>
<td>3</td>
<td>R</td>
<td>Postganglionic</td>
<td>Lt</td>
<td>5.0</td>
<td>6.0</td>
</tr>
<tr>
<td>4</td>
<td>L</td>
<td>Postganglionic</td>
<td>Lt</td>
<td>3.5</td>
<td>3.0</td>
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<tr>
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<td>L</td>
<td>Preganglionic</td>
<td>Lt</td>
<td>3.0</td>
<td>3.5</td>
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<tr>
<td>6</td>
<td>L</td>
<td>Postganglionic</td>
<td>Lt</td>
<td>4.0</td>
<td>3.5</td>
</tr>
</tbody>
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* HS indicates Horner syndrome; R, right eye; L, left eye; Dk, room lights off; and Lt, room lights on.
dine in both eyes of a patient with possible HS may be a sensitive and specific test for this disorder. Topical 5% or 10% cocaine has been the standard medication for the pharmacologic diagnosis of HS for decades.16-18 Cocaine, a narcotic, is a controlled substance that must be prepared by individual pharmacies for local use. Topical apraclonidine has an advantage in that it is readily available and widely used, most commonly for the prevention of IOP elevation after laser capsulotomy. Additional studies comparing the sensitivity and specificity of these 2 drugs in diagnosing HS will be necessary to definitively demonstrate the diagnostic utility of apraclonidine.

In summary, our study provides evidence that the activation of ocular postjunctional α1 receptors is sufficient to lower IOP in humans. Therefore, efforts to reduce the systemic absorption of topical adrenergic agonist medications, such as closing the eyes and placing pressure over the lacrimal sacs, should reduce adverse effects without sacrificing the ocular hypotensive activity. The mydriatic effect of apraclonidine in eyes with HS supports the idea that α1 receptors are up-regulated in the uveal tissue of these eyes. Because 1% apraclonidine is easy to obtain, can be used as formulated by the manufacturer, and has no excessive regulatory controls, it represents an attractive alternative to other agents in the diagnosis of HS.

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Reprints: Sandra M. Brown, MD, Department of Ophthalmology and Visual Sciences, Texas Tech University Health Sciences Center, Sixth and Flint, Lubbock, TX 79430 (e-mail: eyesmb@ttuhsc.edu).

REFERENCES