Ocular Effects of Apraclonidine in Horner Syndrome

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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 upregulation 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.3,4

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
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. P ≤ .05 was considered significant.

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 H5, prejunctional α2 receptors are absent. Because 1% apraclonidine caused an equal decrease in IOP in normal eyes and in eyes with postganglionic H5, 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.

A recent 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\textsuperscript{1,9-12} while in other studies\textsuperscript{13,14} 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\textsuperscript{11} 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.\textsuperscript{15,16}

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% apraclonidin...
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.\textsuperscript{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 $\alpha_2$ 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 $\alpha_1$ 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.

Accepted for publication January 4, 2000.

This research was supported in part by grant EYO9741 from the National Institutes of Health, Bethesda, Md (Dr Crosson).

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