Long term effect of apraclonidine

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Abstract

Aims—To evaluate the effect of the chronic use of apraclonidine 0.5% on the intraocular pressure (IOP) of patients with glaucoma; also, to study the side effect profile of this drug when used chronically.

Methods—All patients who had uncontrolled IOP, who were either already on glaucoma medications, or who were intolerant of other glaucoma medications were enrolled. A total of 185 patients were started on apraclonidine 0.5% two to three times a day in one eye.

Results—Follow up extended to 35 weeks. The mean difference in IOP between treated and control eyes was 2.1 (SD 5.0) mm Hg. A similar IOP lowering effect was obtained comparing IOP difference from baseline in the treated eye only.

Conclusion—By the end of the follow up period, 46% of patients were still on the medication. The drug was stopped in 23% of patients because of side effects and in 31% of patients because of failure to lower IOP significantly.

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Apraclonidine hydrochloride (Iopidine, Alcon Laboratories, Fort Worth, TX, USA) is a topical, relatively selective α_2 adrenergic agonist that seems to lower the intraocular pressure (IOP) through a decrease in aqueous production.¹ This effect is most probably via a decrease in cAMP production resulting in a decreased Na-K ATPase activity of the ciliary body epithelium which results in a decrease in aqueous production.² Apraclonidine is an analogue of clonidine, which is a potent hypotensive agent. Because apraclonidine may exhibit such hypotensive properties, it may decrease blood flow to the ciliary body and, via a drop in metabolic activity of the ciliary epithelium, result in a decrease of aqueous production by a second mechanism.³ However, because apraclonidine is more hydrophilic than clonidine, it is less likely to penetrate lipid barriers such as the blood-brain barrier or the cornea⁴ and thus it may produce fewer systemic side effects. In the past, apraclonidine has proved safe and effective for single dose use to lessen the IOP increase after argon laser trabeculoplasty, argon laser iridotomy, and YAG laser capsulotomy.^{5–11} Because the chronic use of apraclonidine is now becoming widespread, we initiated this study to determine its effectiveness and safety in glaucoma patients with uncontrolled IOP requiring long term treatment.

Materials and methods

Beginning in October 1993, all of our patients who were started on chronic apraclonidine usage were enrolled into this study. These patients included those who were felt to have uncontrolled IOP and needed more aggressive treatment. All patients were either already on other glaucoma medications or had previously proved to be intolerant of other glaucoma medications and wished to avoid surgery. At the initiation of treatment, the IOP was measured in each eye. The patient was then started on apraclonidine 0.5% in one eye only and was instructed in punctal occlusion techniques. The patient was asked to take the medication two or three times a day at the discretion of the treating physician. The frequency of follow up examination was scheduled at the discretion of the treating physician according to the glaucoma status of the individual patient. Each examination included a Snellen visual acuity, slit-lamp examination, and IOP measurement with Goldmann applanation tonometry. At each visit, the patient was asked specifically about the development of any ocular or systemic side effects.

In an effort to determine the true effect of apraclonidine on IOP in a heterogeneous patient population, we calculated the difference in IOP between the treated (the eye receiving apraclonidine) and control (the other eye of the same patient) eye in each patient on each follow up visit. This IOP difference is that between the IOP measured at each follow up visit relative to the baseline IOP obtained at the initiation of treatment. This can be summarised:

$$\text{IOP C} = \text{IOP}_{\text{bas}} \text{ C} - \text{IOP}_{\text{fu}} \text{ C}$$

$$\text{IOP T} = \text{IOP}_{\text{bas}} \text{ T} - \text{IOP}_{\text{fu}} \text{ T}$$

$$\text{Diff} = \text{IOP C} - \text{IOP T}$$

where C=control eye

T=treated eye

IOP_{fu} =IOP on that follow up visit

IOP_{bas} =IOP at baseline

Diff=difference in IOP between treated and control eye

In addition, we also calculated the IOP difference from baseline in the treated eye only at each follow up.

If a change in therapy for either the treated eye or the control eye was required, that patient's IOP was not recorded for the study. Nor did we include patients whom the treating physician felt needed to be started on apraclonidine in both eyes at the same time. From 185 patients initially enrolled in the study, 157 met the long term follow up requirements. The others were dropped from the study owing to the development of intolerable side effects or a change in therapy.

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Table 1 Classification of glaucoma

Type of glaucoma	No of patient (%)
Primary open angle glaucoma	147 (80)
Primary angle closure glaucoma	14 (8)
Secondary open angle glaucoma	7 (4)
Secondary angle closure glaucoma	6 (3)
Low tension glaucoma	6 (3)
Congenital glaucoma	4 (2)

Results

One hundred and eighty five patients were enrolled in this study. Table 1 reveals the distribution of glaucoma types exhibited within this population. Apraclonidine was instilled twice a day in 81% of the patients and three times a day in 19%. The mean age for this population was 69 (SD 14) years, ranging from 13 to 96 years old; 58% were female and 42% male. Fifty one per cent of these patients had undergone previous argon laser trabeculoplasty and 29% had had previous glaucoma filtration surgery. Eighty four per cent of these patients were already on one or two glaucoma medications before starting apraclonidine. β Blockers were the most common medications, being used in 88% of the patients on medication. Miotics were used in 48%, carbonic anhydrase inhibitors in 18%, and adrenergic agents in 14% of the patients taking medication.

The mean follow up time was 10 (7) weeks, ranging from 1 day to 35 weeks. Eight patients (4%) had to discontinue apraclonidine within 3 weeks: one with low tension glaucoma noted a sudden decrease in visual acuity after the first drop which cleared after 24 hours. This symptom was presumed to be due to decreased perfusion in the short posterior ciliary arteries as this was noted on colour Doppler examination. Six of these patients developed conjunctival hyperaemia with itching and tearing which was presumably an early allergic conjunctivitis. One patient had severe subjective blurred vision and refused further apraclonidine drops. Another patient with low tension glaucoma had apraclonidine stopped after 6 weeks of use. He complained of seeing only one colour on waking in the morning. Decreased perfusion in the short posterior ciliary system was noted on colour Doppler imaging. In all, 39% of patients developed ocular or systemic side effects. In 23% of the total number of patients, the side effects were severe enough to require discontinuation of the apraclonidine treatment. Table 2 shows the frequency of each type of side effect that was exhibited with chronic apraclonidine usage. The average for onset of any of these side effects was at 10 (7)

Table 2 Side effects of chronic apraclonidine

Side effects	% Of total patients studied
Loss of acuity	20
Allergy	19
Blurred vision	8
Discomfort	6
Hyperaemia	5
Foreign body sensation	1
Dry mouth	1
Systemic complaints	2

Figure 1 Status of apraclonidine usage at end of study period.

weeks of therapy. The most common side effect was that of a documented loss of Snellen acuity. Of that group of patients, 62% lost one line on the Snellen chart, 27% lost 2 lines, 5% lost 3 lines, and 5% lost 4 lines. The side effect in Table 2 listed as blurred vision was simply a subjective response on the part of the patient and could not be documented by a decrease in Snellen acuity. The second most common side effect was the appearance of a fairly classic looking allergic conjunctivitis which occurred at 11 (9) weeks. Two per cent of patients reported systemic side effects which included upset stomach, dry mouth, coldness of the extremities, and throat irritation.

In 100 of the patients (54%), apraclonidine was stopped at a mean follow up time of 10 (7) weeks. The medication was stopped because of intolerable side effects in 43 of these patients (23%), and because it had an inadequate effect on IOP in 57 patients (31%) (Fig 1).

The IOP lowering effect of chronic apraclonidine usage is shown in Table 3. The overall change in the difference in the IOP between the treated and control eye was a decrease in the IOP of the treated eye of 2.1 (5.0) mm Hg ($p < 0.001$ paired t test). For each period of follow up, there is a different number of patients because the follow up interval was left to the discretion of the treating physician depending on the individual patient situation.

Table 4 lists the level of change, obtained with the use of apraclonidine. We separated, within each period of follow up, patients who had no decrease in IOP from those who had a decreased 1–3 mm Hg and those with a decrease of more than 3 mm Hg. The percentages are calculated in relation to the total number of patients who came to that specific follow up visit. We observed that at

Table 3 Hypotensive effect of chronic apraclonidine on treated eyes compared with control eyes

Follow up (weeks)	IOP (mean (SD))*	Total number of patients
3–6	2.7 (4.5)	88
7–8	1.7 (5.0)	30
9–12	3.1 (4.9)	29
13–16	2.4 (7.0)	16
17–20	1.8 (5.7)	9
21–24	0.7 (3.6)	10
≥25	3.3 (7.4)	9

*IOP=IOP control eye–IOP treated eye.

Table 4 Distribution of patients (%) according to level of change in IOP*

Follow up (weeks)	Decrease in IOP (mm Hg)			Total
	≤0	1-3	≥3	
3-6	24	34	42	88
7-8	57	7	36	30
9-12	28	27	45	29
13-16	31	13	56	16
17-20	33	22	45	9
21-24	60	20	20	10
≥25	33	11	56	9

*IOP=IOP control eye-IOP treated eye (mm Hg).

each follow up visit, at least 24% of the patients showed no apparent effect on IOP because of apraclonidine. Considering the maximal effect group (an IOP decrease of more than 3 mm Hg), 67% of patients with an IOP decrease in the later phases of the study had an IOP decrease of similar scale in the earlier period (3-6 weeks). Therefore, there did not seem to be an increasing effect with time in those patients who continued to obtain an effect from apraclonidine.

The IOP response in treated eyes only compared with baseline is shown in Table 5. There was no statistical difference in IOP lowering effect at any follow up when these numbers were compared with those obtained in Table 3, where IOP response was calculated by difference between control eye and treated eye.

To determine if there were any features that would help to differentiate patients with no treatment effect due to apraclonidine from those with sustained or maximal effect, we analysed different variables in these two groups. There was no statistical difference with regard to age, pretreatment IOP control, number of medications, number of previous surgeries, or lasers performed. The only statistical difference noted ($p=0.04$) was in terms of glaucoma diagnosis; there were a great number of patients with primary angle closure glaucoma among those patients who had had a good effect with apraclonidine.

An evaluation of twice a day compared with three times a day use of apraclonidine showed no statistical difference in terms of pressure control or side effects (in general and specifically regarding allergic reactions).

Discussion

We found a 39% rate of side effects in this patient population. Side effects developed as early as the application of the first drop or as late as 35 weeks. Several patients had more than one type of side effect. In 23% of patients, the side effects were severe enough to require discontinuation of treatment. The most common side effect was loss of Snellen acuity; in the majority of cases this was one line and was transitory, not requiring cessation of treatment. However, in four patients it led to suspension of treatment. Fourteen patients lost 2-4 lines of Snellen acuity. Of these, five patients continued using apraclonidine, three recovered baseline vision on the next follow up visit, and two did not improve. In the

remaining nine patients apraclonidine was stopped. In this group, three patients recovered baseline vision and four patients did not improve. Two patients underwent surgery, making an evaluation of visual acuity less valid. The precise time of recovery of baseline vision could not be determined because of the different intervals of follow up at which the patients were seen.

An allergic conjunctivitis was the second most common side effect, but was the most common reason for discontinuation of the drug. This side effect is thought to be caused by a toxic effect or a hypersensitivity reaction.¹² A similar follicular conjunctivitis associated with topical sympathomimetic compounds has been described.¹³ In the first long term investigation of primary therapy with apraclonidine, 0.5% and 0.25% concentrations were compared with 0.5% timolol in a double masked randomised parallel group study. An allergic reaction was present in eight of 22 patients taking 0.5% apraclonidine and in two of 23 patients using the 0.25% concentration.¹⁴ In this present study, allergic response was observed in 19% of patients; it was characterised by a follicular conjunctivitis with or without contact dermatitis. The severity of the follicular conjunctivitis varied from tearing, discomfort, foreign body sensation, and hyperaemia, sometimes accompanied by itching, to a more severe reaction with lid oedema and contact dermatitis. This reaction resolved within 5 days on discontinuation of apraclonidine in all patients. Although lid retraction has been described in normals¹⁵ and in eyes with ocular hypertension,¹⁶ we had no patients in whom this was observed. Dry mouth has been a common side effect in other reports,¹⁷ but was present in only one patient in our study. There was one patient who may have developed a related systemic side effect. He was a 77 year old man who developed nausea with chilled extremities and refused further apraclonidine.

Posterior segment blood flow to the optic nerve, choroid, or retina was not affected by single dose topical or intravenous administration of apraclonidine in monkeys or cats.^{18,19} Preliminary studies in humans using colour Doppler imaging have showed a small reduction in mean pulsatility difference induced by apraclonidine, mainly in the short posterior ciliary arteries.²⁰ Another study found no significant change in colour Doppler variables in the posterior ciliary arteries after the acute use of apraclonidine.²¹ In two of our patients with low tension glaucoma colour Doppler examination suggested a decreased perfusion in the short posterior ciliary artery system. Apraclonidine was stopped in these patients and calcium channel blockers started. A follow up colour Doppler examination showed further changes consistent with an improvement in the haemodynamics of the ciliary arteries in one patient and a return to baseline values in the other. Although we observed changes in the haemodynamics of the short posterior ciliary arteries in two patients, this finding should be taken with caution; the

Table 5 Hypotensive effect of chronic apraclonidine on treated eyes compared with baseline

Follow up (weeks)	IOP (mean (SD))*
3-6	2.7 (6.1)
7-8	2.2 (4.6)
9-12	2.8 (6.0)
13-16	2.6 (5.8)
17-20	3.6 (5.6)
21-24	0.7 (5.8)
≥25	4.8 (5.9)

*IOP=IOP treated eye-IOP baseline.

validity of colour Doppler as an estimate of optic nerve blood flow has not been established with certainty.²² Further studies need to be carried out to determine the role of apraclonidine, if any, in periocular blood flow.

With regard to the IOP lowering effect of apraclonidine, we obtained a variable result throughout the length of follow up. The mean difference in IOP varied depending on the number of patients who were evaluated at a particular follow up period in whom the drug was having a good effect in lowering IOP.

At the 3–6 week interval of follow up, 24% of patients examined during that period had no lowering of IOP after use of apraclonidine. This number increased to 57% at 7–8 weeks of follow up. At 9–12 weeks of follow up, the percentage of patients showing no effect on IOP decreased, but this probably reflects earlier discontinuation of the drug owing to lack of effect. Considering all patients who did not experience any IOP lowering effect from the use of apraclonidine, 73% at each follow up interval, we had at least 24% of patients examined who showed no IOP lowering effect from the drug. The reason for the high rate of tachyphylaxis with apraclonidine in many patients is unclear.

There are previous reports of a small IOP lowering effect with apraclonidine use in the contralateral, non-treated eye.¹⁵ This has also been noted in patients treated with topical clonidine^{23,24} and timolol maleate.²⁵ The present study showed no difference in IOP response when comparing the IOP effect on treated eyes only related with baseline IOP versus the difference in IOP between treated and control eyes.

In the present study, some physicians have preferred to use apraclonidine three times a day; one report suggested that the duration of action of apraclonidine is such that more than twice daily dosing is required.¹⁶ A recent report suggested that the effect on IOP could be increased if apraclonidine was given three times daily.²⁶ The present study found no difference in IOP response or side effects between patients using apraclonidine three times a day versus twice a day.

In summary, long term treatment with apraclonidine is associated with side effects requiring discontinuation of the drug in 23%, and may not have a significant further lowering of pressure in patients who are already on glaucoma medications in 31%. Patients in this study were often already on medications and many had already had laser or surgical treatment. In this patient population it should be no surprise that the drug had no significant effect in many of the patients. Apraclonidine should not be considered as first line of treatment because of its high rate of tachyphylaxis and significant incidence of allergic reactions. In 46% of patients with an uncontrolled IOP on medication, apraclonidine resulted in a clinically significant decrease in IOP that persisted up to 35 weeks. Further studies will

be required to give us a complete understanding of the effects of apraclonidine with prolonged use.

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