

Effects of 0.5% apraclonidine on optic nerve head and peripapillary retinal blood flow

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Abstract

Aims—To examine the effects of 0.5% apraclonidine on optic nerve head (ONH) and peripapillary retinal blood flow by scanning laser Doppler flowmetry (SLDF).

Methods—ONH and peripapillary retinal blood flow of 17 healthy subjects were measured by SLDF before and 1 hour and 3 hours after unilateral administration of 0.5% apraclonidine. The fellow eyes were treated with balanced salt solution and the examiners were masked as to which eye was treated with apraclonidine. On each occasion, three scans were obtained and haemodynamic variables (volume, flow, and velocity) were analysed at eight locations, four in the neural rim and four in the peripapillary retina, avoiding ophthalmoscopically visible vessels. The statistical significance of changes from the baseline value of variables and the differences in the measured quantities between apraclonidine treated eyes and fellow eyes at each time point were evaluated using Wilcoxon signed rank test.

Results—The intraocular pressure was reduced significantly in apraclonidine treated eyes by 15.0% ($p=0.001$) at 1 hour and 30.0% ($p=0.000$) at 3 hours after administration. In the volume, flow, or velocity of ONH and peripapillary retinal blood flow, there were no significant changes from the baseline values at 1 hour and 3 hours after apraclonidine administration in either apraclonidine treated eyes ($p>0.4$) or fellow eyes ($p>0.2$). Also, no significant differences were found in the measured quantities between apraclonidine treated eyes and fellow eyes at each time point ($p>0.1$).

Conclusion—A single dose of topical apraclonidine 0.5% in healthy subjects does not have adverse effects on the ONH and peripapillary retinal blood flow.

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Apraclonidine hydrochloride, an α_2 adrenergic agonist, is an efficient ocular hypotensive agent in subjects with normal or increased intraocular pressure (IOP).¹⁻⁵ The reduction in IOP is associated with an increase in fluorophotometric outflow facility and a decrease in aqueous flow and in episcleral venous pressure.⁶ Apraclonidine has also been shown to produce constriction of the precapillary sphincters in the vessels supplying the ciliary body.⁷ Several side

effects have been noted with apraclonidine administration, including lid retraction, mydriasis, conjunctival blanching, and allergic reaction. Clinically apparent conjunctival blanching is associated with conjunctival hypoxia, with a reduction of conjunctival oxygen tension to 76% of baseline values at 1 hour, which lasts up to 5 hours after administration of apraclonidine.⁸

Studies have been made to examine whether apraclonidine administration also exerts a vasoconstrictive action on the optic nerve head (ONH) or retina. Colour Doppler ultrasound measurements of ophthalmic and central retinal arteries suggested that apraclonidine does not have adverse vasomotor effect on retinal arterial blood flow.^{9,10} Evaluation of vasoconstriction of arterioles supplying the anterior optic nerve using intraluminal corrosion casting technique showed no significant differences between the apraclonidine treated and untreated eyes.^{11,12} We measured the effects of apraclonidine on capillary blood flow in ONH and peripapillary retina using scanning laser Doppler flowmetry (SLDF).

Subjects and methods

Seventeen healthy subjects were recruited. They included 12 men and five women with a mean age of 27.5 years (range 25 to 35 years). Subjects were excluded if they had undergone previous intraocular or laser surgery, worn contact lenses within 2 days before the study, had evidence of a current eye infection, or had taken any medications within 2 weeks of the study. After informed consent was obtained,

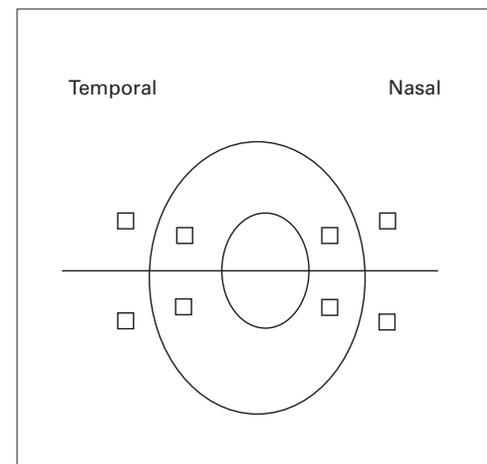


Figure 1 Schematic diagram showing eight locations where haemodynamic variables were measured. The four retinal points were located approximately 100 μ m from the edge of the optic disc.

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Table 1 Cardiovascular responses to 0.5% apraclonidine instilled after baseline measurement (mean (SEM), n=17)

	Baseline	1 hour	3 hours
Heart rate (beats/min)	73 (1)	73 (1)	74 (2)
Blood pressure (mm Hg)			
systolic	117 (4)	116 (4)	117 (4)
diastolic	78 (2)	77 (2)	79 (2)
mean arterial	91 (2)	90 (2)	91 (2)

Table 2 Intraocular pressure and calculated perfusion pressure responses to 0.5% apraclonidine instilled after baseline measurement (mean (SEM), n=17)

	Baseline	1 hour	3 hours
Intraocular pressure (mm Hg)			
apraclonidine treated eyes	15.4 (0.7)	13.0 (0.6) (p = 0.001)	10.8 (0.4) (p = 0.000)
fellow eyes	15.2 (0.6)	14.9 (0.6) (NS)	14.9 (0.6) (NS)
Calculated ocular perfusion pressure (mm Hg)			
apraclonidine treated eyes	45 (2)	47 (2) (p = 0.001)	50 (2) (p = 0.000)
fellow eyes	45 (2)	45 (2) (NS)	46 (2) (NS)

NS = not significant.

heart rate (by radial artery pulsation), blood pressure (by sphygmomanometry), and IOP (by non-contact applanation tonometry) were measured three times. ONH and peripapillary retinal blood flow of each eye was measured by SLDF. Subjects then received two drops of 0.5% apraclonidine in a randomly selected eye and two drops of balanced salt solution in the fellow eye as a placebo. The drug and placebo drops were provided with coded labels so that neither the investigators nor the subjects had any knowledge of which eye was receiving the drug. Measuring IOP, heart rate, blood pressure, and blood flow in the ONH and peripapillary retina were repeated 1 hour and 3 hours after instillation. On each occasion of SLDF, three scans centred on the ONH using a 10×2.5 degrees scan angle were obtained.

The principle, validity, and reliability of SLDF have been described previously.¹³ The scanning laser Doppler flowmeter (Heidelberg retina flowmeter, Heidelberg Engineering GmbH, Heidelberg, Germany) used in this study combines a laser Doppler flowmeter with a scanning laser system by which the retinal perfusion is simultaneously quantified in an area of 2.7×0.7 mm composed of 64 horizontal lines of 256 points and provides a two dimensional map showing the microvascular perfusion of the retina and ONH.¹⁴ Each line is scanned sequentially a total of 128 times with a diode laser for approximately 2 seconds. Blood

volume, flow, and velocity can be quantified in any location of the perfusion map by placing a square of variable size (1×1 , 4×4 , or 10×10 pixels, or larger) in the area of interest. The values of each pixel within this square are averaged and the final results are given for blood volume, flow, and velocity.

All images were reviewed by the same observer. Haemodynamic variables (volume, flow, and velocity) were analysed at eight locations, two each in the temporal and nasal neural rim and two each in the temporal and nasal peripapillary retina, avoiding ophthalmoscopically visible vessels (Fig 1). The analysis window was 10×10 pixels ($100 \times 100 \mu\text{m}$) and each window was located at the same area as closely as possible in each subject. In eyes with peripapillary atrophy, windows were located outside of that to measure peripapillary retinal blood flow. The observer who chose the area to be measured was unaware of the results of the measurements because the part of the monitor where the values appeared was masked.

Three scans of each occasion were all analysed and the averages of the measurements on three scans were used for statistical analysis. Wilcoxon signed rank test was applied to evaluate the statistical significance of changes from the baseline value of blood flow variables and the differences in the measured quantities between apraclonidine treated eyes and fellow eyes.

Results

The heart rate and blood pressure at each time point are summarised in Table 1. Compared with the baseline values, there were no statistically significant differences in the heart rate and blood pressure at 1 hour or 3 hours after instillation of apraclonidine ($p > 0.2$).

The IOP was reduced in apraclonidine treated eyes by 15.0% ($p=0.001$) at 1 hour and 30.0% ($p=0.000$) at 3 hours after administration when compared with baseline values (Table 2). Calculated ocular perfusion pressure (COPP, $2/3$ mean arterial pressure – IOP) was increased by 4.4% ($p=0.002$) at 1 hour and 11.0% ($p=0.000$) at 3 hours after administration. In the fellow eyes, the IOP and COPP did not vary significantly compared with baseline values.

In the volume, flow, or velocity of ONH and peripapillary retinal blood flow, there were no significant changes from the baseline values at

Table 3 Volume, flow, and velocity of the optic nerve head and peripapillary retinal blood flow measured by scanning laser Doppler flowmetry (mean (SEM), n=17)

	Volume		Flow		Velocity	
	AE	FE†	AE	FE†	AE	FE†
Neural rim						
baseline	19.45 (0.94)	18.48 (0.85)	454.26 (20.69)	443.15 (30.33)	1.55 (0.07)	1.55 (0.11)
1 hour*	19.27 (1.02)	20.84 (0.93)	459.81 (32.40)	481.95 (31.18)	1.59 (0.10)	1.81 (0.12)
3 hours*	18.99 (0.78)	19.31 (0.67)	462.28 (32.01)	468.42 (22.81)	1.61 (0.10)	1.73 (0.08)
Peripapillary retina						
baseline	19.59 (0.72)	19.08 (0.88)	354.28 (21.01)	340.78 (19.38)	1.22 (0.07)	1.18 (0.06)
1 hour*	19.75 (1.71)	19.15 (0.95)	359.88 (18.29)	346.68 (22.14)	1.23 (0.06)	1.19 (0.07)
3 hours*	19.48 (0.07)	19.79 (0.97)	355.23 (28.99)	377.80 (18.00)	1.27 (0.09)	1.25 (0.09)

*No significant changes from the baseline values in either AE ($p > 0.4$) or FE ($p > 0.2$).† No significant differences between AE and FE at each time point ($p > 0.1$).

AE = apraclonidine treated eyes; FE = fellow eyes.

1 hour and 3 hours after apraclonidine administration in either apraclonidine treated eyes ($p > 0.4$) or fellow eyes ($p > 0.2$). Also, no significant differences were found in the measured quantities between apraclonidine treated eyes and fellow eyes at each time point ($p > 0.1$) (Table 3).

Discussion

Apraclonidine demonstrated ocular hypotensive, but not systemic hypotensive, actions which is in accord with previous studies.¹⁵

Apraclonidine penetrates the eye via the conjunctival/scleral pathway because of its relatively low lipophilicity.¹⁶ The drug serves as an agonist at α_2 adrenoceptors in the ciliary epithelium¹⁷ and at vasoconstrictive α_2 adrenoceptors in all regions of the eye to which it has access. In the present study, topical administration of 0.5% apraclonidine did not significantly change the ONH and peripapillary retinal blood flow, while lowering the IOP. These results suggest three possibilities.

Firstly, apraclonidine may not penetrate posterior to the ONH and peripapillary retina to influence the haemodynamics of that area. Secondly, vasoconstrictive α_1 and α_2 adrenoceptors may be absent in ONH and peripapillary retinal vessels. Thirdly, the change in the blood flow is within the variability of measurement by SLDF.

The independence of the ocular haemodynamics from the short term or chronic application of topical apraclonidine has been reported in rabbits,¹¹ cats,¹⁸ and human subjects⁹ with the use of corrosion casting technique, laser Doppler flowmeter imaging, or colour Doppler imaging (CDI). However, these measurements were accomplished at arterioles supplying the anterior optic nerve or ophthalmic and central retinal arteries. Using the Heidelberg retinal flowmeter, which provides physiological picture of the ONH and retinal perfusion with visualisation of capillaries, we measured the haemodynamic variables in the capillary bed. This assessment reflects the actual tissue perfusion more accurately than corrosion casting technique or CDI.

While the ONH and peripapillary retinal blood flow remain unchanged, the COPP was increased significantly as the IOP lowered after apraclonidine administration. This apparently incompatible result may be explained by the autoregulatory mechanisms of the ONH and peripapillary microcirculations that control the blood flow to be unchanged against the

elevated ocular perfusion pressure. Otherwise, the possibility that vasoconstrictive activity of apraclonidine prevents blood flow from increasing in response to the increased perfusion pressure cannot be ruled out.

In conclusion, our results confirm that a single dose of topical apraclonidine 0.5% in healthy subjects does not have adverse effects on the ONH and peripapillary retinal blood flow. None the less, further studies are needed to confirm the safety of this medication in glaucomatous eyes with regard to optic nerve perfusion.

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