Optic nerve vasomotor effects of topical apraclonidine hydrochloride

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Abstract

Aims—To examine, in vivo, the anterior optic nerve vasomotor effects of chronic apraclonidine hydrochloride in rabbits.

Methods—After local treatment in one randomly chosen eye with apraclonidine hydrochloride 0.5% over 21 days, the microvasculature of the optic nerve was examined in five rabbits using an intraluminal microvascular corrosion casting technique. The investigators were masked as to which eye was treated. The vasoconstriction near the branching point of arterioles supplying the optic nerve was calculated as a percentage of the downstream vessel calibre. An average constriction was calculated and compared between the treated and the contralateral, untreated, eyes by means of a two tailed *t* test for paired variables. Constriction values of a total of 72 arterioles supplying the optic nerve were obtained for the five rabbits.

Results—The average constriction in the treated and the control eyes was comparable ($p=0.96$).

Conclusion—Chronic administration of apraclonidine hydrochloride 0.5% produces no observable optic nerve vasomotor effects in the rabbit eye.

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Apraclonidine hydrochloride is an α_2 adrenergic agonist which is a very efficient ocular hypotensive agent in subjects with normal or increased intraocular pressure.¹⁻⁵ Prevailing studies suggest that apraclonidine hydrochloride may be a reasonable choice for use in conjunction with β blocker therapy.⁶ However, many clinical observations lend credence to the potential role of microcirculatory changes in glaucoma,⁷ and there is concern whether some topical antiglaucomatous drugs, although effective in lowering intraocular pressure, could have adverse vascular effects.⁸ Apraclonidine hydrochloride manifests potent vasoconstrictive activity in anterior segment tissues of the eye.⁹⁻¹⁰ However, optic nerve blood flow seems not to be affected by single dose topical or intravenous administration of apraclonidine hydrochloride in monkeys, rabbits, or cats.¹¹⁻¹³

The present study was designed to evaluate, in vivo, whether chronic topical administration of apraclonidine hydrochloride may induce vascular constrictions in the anterior optic nerve vascular bed in an animal model.

Materials and methods

Five adult New Zealand white rabbits of both sexes, weighing ≥ 2.5 kg, were assigned to 21 days of topical ocular treatment with apraclonidine hydrochloride 0.5%. The eyedrops were administered once a day in one randomly chosen eye. All experiments conformed to the Association for Research in Vision and Ophthalmology resolution on the use of animals in research.

The microvasculature of the optic nerve was examined with the intraluminal microvascular corrosion casting technique described in detail elsewhere.¹⁴ In brief, the castings of the ocular vasculature were obtained under controlled physiological conditions. The rabbits were anaesthetised with intravenous sodium pentobarbitone. Mechanical ventilation was provided by a Harvard small animal respirator. Systemic blood pressure, blood gases, and rectal body temperature were maintained stable. Arterial blood gases were drawn from an indwelling aortic catheter immediately before injection. Batson's no 17 methylmethacrylate injection media, modified to reduce the viscosity to approximately 11 centipoise, was injected into the superior circulation through ascending branches of the aorta. The injection pressure was maintained at approximately 100 mm Hg for 15 minutes, until the plastic began to polymerise and arrest flow in the vascular system. Two hours after injection, the eyes were enucleated, stored overnight in warm formalin to complete the polymerisation, and corroded in 6 mol/l potassium hydroxide. The resulting plastic vascular castings were rinsed in running water and air dried. Whole globe vascular castings were hemisected at the equator and the posterior segments were mounted on aluminium stubs, sputter coated with gold palladium, and examined with a scanning electron microscope (Etec Autoscan).

The optic nerve microvasculature in rabbits is primarily supplied by the short posterior ciliary arteries via an arterial loop encircling the optic nerve.¹⁵ Direct arteriolar branches from the short posterior ciliary arteries or branches from the arterial circle which penetrate and supply the optic nerve normally display focal zones of relative constriction near their branching point from the proximal arterial supply, compared with downstream vessel calibre.¹⁶ The primary and secondary arteriolar branches from the arterial circle were measured at these constriction zones near the branching point and 50 μ m distal to the end of the constriction zone (Fig 1). Because of the large variation in vascular diameter as well as the statistical

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Figure 1 Example of an arterial vessel which supplies the optic nerve and displays a focal zone of relative constriction near the branching point (arrowhead), compared with downstream vessel calibre (arrow).

variability of individual vascular responses, earlier studies did not show significant differences in actual vessel diameter after pharmacological manipulations.^{10 14 17} For this reason, the present analysis was confined to the assessment of the relative branch point constrictions. The relative amount of branch point constriction at the focal zones near the branching point was expressed as a percentage constriction relative to the distal diameter ($100 \times (\text{distal diameter} - \text{constricted diameter} / \text{distal diameter})$). Analysing specific vessels alone with corrosion casting technique provides very limited functional information for the optic nerve microvasculature. Only vessels providing distinct measurement sites at their branching point and 50 μm distal from this point can be included in the analysis. Owing to the complex anatomy of the anterior optic nerve microvasculature, this restriction limits significantly the number of the vessels which can be included in the analysis. For the present analysis, arteriolar branches from the arterial circle around the optic nerve, just adjacent to the posterior portion of the choroidal vasculature, which penetrate and supply the optic nerve were included.¹⁵ Because often the short length of primary branches from the arterial circle precludes a measurement 50 μm distal from the branching point, secondary branches were included as well. During the measurements, the investigators were masked to the rabbit and to the treatment. The measurements of arteriolar constriction as a percentage of the downstream vessel calibre were pooled for each eye and an average constriction value was calculated for each eye. The average constriction was compared in the treated eyes and the contralateral, untreated eyes by means of a two tailed *t* test for paired variables. Moreover, because the varying number of vessels assessed in the eyes causes a differential contribution of the animals to the data, a common maximum number of vessels per eye (selected randomly for the eyes providing more vessels) was used to analyse the difference between the treated and untreated eyes as described above.

Table 1 Average relative arteriolar branch point constrictions (%)

Rabbit	Treated eye (number of vessels)	Control eye (number of vessels)
1	18.20 (9)	22.93 (7)
2	23.98 (11)	25.61 (14)
3	28.19 (4)	17.21 (8)
4	21.35 (5)	24.88 (5)
5	22.68 (5)	24.48 (4)

The intraocular pressure was measured three times with a pneumotonometer in both eyes after general anaesthesia before intraluminal microvascular corrosion casting. The pneumotonometer was calibrated before intraocular pressure measurements. An average value of intraocular pressure was calculated for each eye. The intraocular pressure in the treated eyes and the contralateral, untreated eyes was compared by means of a two tailed *t* test for paired variables.

Results

Constriction values of a total of 72 arterioles supplying the optic nerve ranged from 0% to 42.86% (Fig 1). The average (SD) number of vessels analysed per eye was 7 (3) vessels (range 4–14 vessels per eye). The average arteriolar constriction values are shown in Table 1. The mean (SD) average constriction for the treated eyes was 22.88% (3.66%). The mean (SD) average constriction for the contralateral, untreated eyes was 23.02% (3.31%). No statistically significant differences were found between the treated eyes and the contralateral, untreated eyes (mean difference 0.14%; 95% confidence interval (CI) of the difference -7.74 to 8.02 ; $p=0.96$). After selecting four vessels (maximum common number of vessels per eye), the mean (SD) average constriction was 21.90% (4.15%) and 21.85% (3.85%) for the treated and untreated eyes, respectively. These values were comparable as well (mean difference 0.05%; 95% CI of the difference -6.57 to 6.67 ; $p=0.98$).

The intraocular pressure was comparable in the treated (11.47 (1.17) mm Hg) and untreated (12.23 (3.07) mm Hg) eyes ($p=0.60$).

Discussion

The current study suggests that topical apraclonidine hydrochloride 0.5% does not produce vasomotor effects in the optic nerve of the rabbit eye. No statistically significant differences between treated and untreated eyes were found.

Preservation of the visual field is the main goal of the antiglaucomatous therapy. It is theoretically possible that adverse vascular effects of some topical drugs might tend to neutralise the beneficial effect of a reduced intraocular pressure on the preservation of the visual field. Apraclonidine hydrochloride manifests a potent vasoconstrictive activity in anterior segment tissues.^{9–12} In view of the potential role of microcirculatory changes in glaucoma,⁷ such a mighty vasoconstrictive

drug may have a deleterious effect on visual field survival in glaucoma patients on long term therapy.

Topical ocular treatment with apraclonidine hydrochloride has been shown to cause substantial constriction in arterioles that supply the ciliary processes of albino rabbits.¹⁰ This study may have raised concerns about impaired vascular perfusion in glaucoma patients undergoing a long term therapy with apraclonidine hydrochloride. Optic nerve blood flow, however, seems not to be affected by single dose topical or intravenous administration of apraclonidine hydrochloride in monkeys, cats, or rabbits.¹¹⁻¹³ The present data suggest, furthermore, that a chronic topical administration of apraclonidine hydrochloride 0.5% does not provoke arteriolar vasoconstriction in the anterior optic nerve vascular bed.

While corrosion casting seems to be an excellent method for studying the anatomy of a microvascular system, the application of this technique to study vasoreactivity is more controversial. Reasonable concerns have arisen about vascular alterations induced by the plastic itself during the injection process. Earlier studies, however, could show that the methacrylate itself has little or no vasoreactivity on microvessels.¹⁴ Furthermore, it has been demonstrated that drug related vasomotor effects can be induced by α adrenergic agonists in the anterior vascular bed of the optic nerve in albino rabbits after chronic topical ocular treatment and that these effects can be shown by means of intravascular casting technique.¹⁶ In contrast with the ciliary vessels, the filling of the optic nerve microvasculature is more inconsistent.¹⁶ For this reason, maintaining the physiological variables constant throughout the surgical procedure is of primary importance. Improving the monitoring of the physiological variables has shown a tremendous improvement in the filling of the optic nerve microvasculature, but also an increase of the arteriolar constrictions. In a consequent study, the robustness of the corrosion casting technique to overcome potential methodological artefacts to demonstrate the known physiological effect of variations of blood gases was analysed.¹⁸ The latter study demonstrated a high correlation between arteriolar branch point constriction of the vessels supplying the optic nerve and arterial blood gases. In the latter investigation, the average constriction in the optic nerve microvasculature was of approximately 22% with physiological blood gases. Further studies

confirmed similar constriction values in placebo treated eyes.¹⁹ Therefore, a contralateral effect in the untreated eye with a consequent increase of arteriolar constriction on both sides in the present study is improbable.

In conclusion, chronic topical administration of apraclonidine hydrochloride 0.5% does not seem to have major adverse effects on the microvasculature of the anterior optic nerve. None the less, the long term safety of this medication with regard to optic nerve perfusion remains to be confirmed in glaucoma patients.

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