NOTE *Internal Medicine*

The Effect of 0.12% Unoprostone Isopropyl (Rescula) on Intraocular Pressure in Normotensive Dogs

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(Received 9 March 2000/Accepted 12 August 2000)

ABSTRACT. Rescula (0.12% unoprostone isopropyl) is the first docosanoid compound approved for treatment of glaucoma in humans. It is commercially available in Japan, and is undergoing clinical testing elsewhere. The aim of this study was to evaluate the effect of Rescula on intraocular pressure (IOP) in normotensive dogs. After establishing a baseline diurnal IOP curve, six dogs were unilaterally treated with Rescula while the contralateral eye was treated with a placebo. Applanation tonometry was performed in both eyes, and pupil size was evaluated, 30 min after treatment, and at 1-hr intervals for the next 9 hr. Rescula caused a significant ($p=0.014$) and long-lasting decrease in IOP, from 20.49 ± 2.02 mm Hg in control eyes to 15.49 ± 0.69 mm Hg in treated eyes. These results suggest that Rescula is potentially efficacious in treatment of canine glaucoma.

KEY WORDS: canine, glaucoma, unoprostone isopropyl.

J. Vet. Med. Sci. 62(12): 1313–1315, 2000

Glaucoma is a disease characterized by retinal ganglion cell death and optic neuropathy usually associated with elevated intraocular pressure (IOP). In animals, the disease is most common in the dog [1]. More than 45 dog breeds, including popular breeds such as the cocker spaniel, German shepherd and poodle are predisposed to primary glaucoma, with spontaneous disease affecting 0.5% of the general canine population [1]. Numerous other dogs (and other animals) are afflicted by secondary glaucomas, caused by lens luxation, uveitis and other ocular diseases.

Glaucoma is a painful disease. It is also characterized by progressive loss of vision that could result in blindness. Therefore, the goal of glaucoma therapy is to lower IOP, thereby preserving ocular function and reducing pain. While some supplemental surgical procedures are available in specialist referral clinics, this goal is usually achieved through long-term (or even life-long) drug therapy. Categories of drugs currently available for glaucoma treatment include hyperosmotic agents, carbonic anhydrase inhibitors, miotics and adrenergic drugs (α agonists and β blockers). Rescula (0.12% unoprostone isopropyl) is the first docosanoid compound approved as topical treatment for glaucoma and ocular hypertension in humans. It is commercially available in Japan, and is undergoing clinical testing elsewhere. The aim of this study was to evaluate the effect of this drug on IOP in normotensive dogs.

Use of experimental animals in this study was approved by the Institutional Animal Care and Use Committee. Six healthy, adult, laboratory-quality Beagle dogs were used in the study. Dogs were defined as normotensive following a complete physical and ophthalmic examination, including gonioscopy and tonometry, that did not reveal any abnormalities. A 12-hr baseline IOP curve was established using an applanation tonometer (Tono-Pen™ XL, Mentor Ophthalmics Inc., Norwell, MA, U.S.A.) which had recently been calibrated by the manufacturer. Two sequential readings with a variance ≤ 10% (as determined by the Tono-Pen) were taken in each eye; the order of the eyes tested was randomly determined.

The following day, after measurement of pre-treatment IOP values, the right eye of each dog was treated with a single installation of Rescula (Ueno Fine Chemicals Industry, Ltd., Osaka, Japan). The left eye was treated with an artificial tear solution, and served as a control. The dog's head was held upright, and the dog was prevented from blinking for 1 min after application of the ophthalmic solutions. IOP was measured in both eyes 30 min after treatment, and at 1-hr intervals for the next 9 hr, in the manner described above. The initial protocol also called for the tonometrist to be masked regarding the treated eye; however, due to the extreme miosis induced by the treatment, this goal could not be achieved.

Repeated measures analysis of variance (ANOVA) was used to evaluate the potential effects of treatment, time, and replicate (and their two and three-way interactions) on IOP. At each measurement time the IOP from the contralateral (untreated) eye was considered as a time-dependent covariate to control for any diurnal baseline fluctuations that could potentially confound treatment effects. Post-hoc bivariate comparisons were employed when the global ANOVA was significant ($p<0.05$).

Significant IOP differences were observed as a result of treatment ($p=0.006$), and across time ($p=0.005$). Figure 1 shows the effect of a single Rescula treatment on the IOP in normotensive dogs. Mean (± standard deviation) baseline IOP in the placebo-treated contralateral eyes was 20.49 ± 2.02 mm Hg, with a range of 17.84–23.67 mm Hg (a range that could be the result of diurnal variations). Mean IOP in the Rescula-treated eyes was 15.49 ± 0.69 mm Hg, with a range of 14.33–16.50 mm Hg. Mean IOP in Rescula-treated

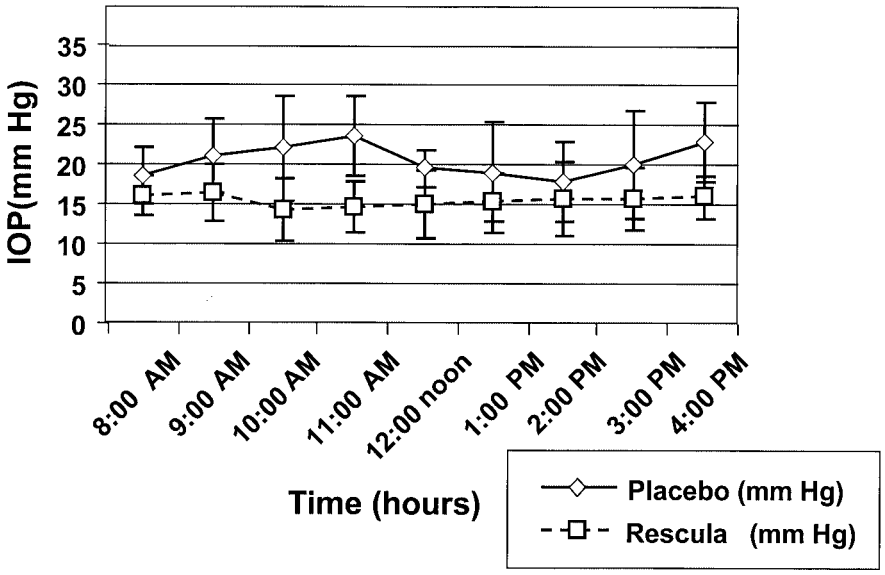

Fig. 1. Mean hourly IOP in 6 normotensive Beagles following a single application of 0.12% unoprostone isopropyl (Rescula). Treatment caused a significant (p=0.014) decrease in IOP, from 20.49 to 15.49 mm Hg. Dashed line: Rescula-treated eye. Solid line: placebo-treated contralateral eye.

eyes was consistently lower than in the placebo-treated contralateral eyes, for all readings and across time (p=0.014).

Figure 2 shows the mean difference in IOP across time between the Rescula-treated eye and the placebo-treated contralateral eye. The mean decrease in IOP as a result of Rescula treatment was 5.0 ± 2.35 mm Hg, with the largest decrease observed 3–4 hr following treatment. There were no significant differences between replicate readings (p=0.63). All 2-way and 3-way replicate interactions were also insignificant (p>0.17).

Rescula has been shown to effectively decrease IOP in several species. Taniguchi *et al.* reported a 5.2 mm Hg decrease in the IOP of rabbits following treatment with Rescula [6]. In normotensive and glaucomatous cynomologus monkeys, a single Rescula application caused a 3.8 mm Hg reduction in IOP, with the hypotensive effect enhanced by repeated applications [4]. In humans suffering from glaucoma or ocular hypertension, Rescula (twice a day) reduced the mean IOP from 23.4 to 19.3 mm Hg [5]. Yoshida *et al.* reported that after 6 months of treatment, 53% of the patients treated twice a day still evidenced a decrease in IOP greater than 20% [8]. Though the exact mode of Rescula's action remains unknown, results in rabbits [6], monkeys [4] and humans [8] suggest that the drug increases aqueous outflow, rather than reduce aqueous production.

A single application of Rescula induced miosis in the treated canine eyes. The exact mechanism of this side-effect has yet to be elucidated, but it should be noted that no other signs of ocular inflammation, or any other side effects, were observed in the experimental dogs. In humans treated with Rescula for four weeks, no increase in conjunctival hyperemia or blood-ocular barrier breakdown was noted [5]; nor are

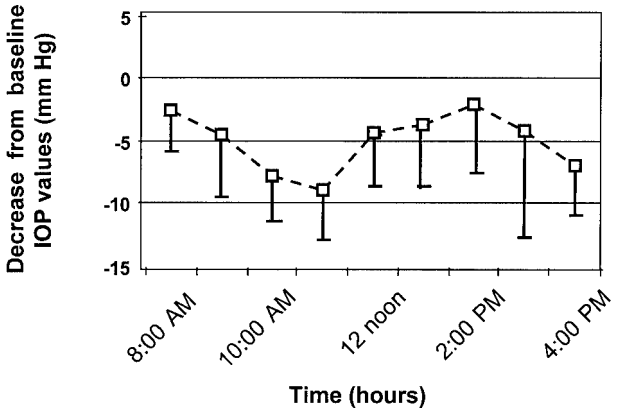

Fig. 2. Hourly decrease (relative to placebo-treated contralateal eye) of mean IOP in 6 Beagles treated with 0.12% unoprostone isopropyl (Rescula). The drug caused a significant decrease in IOP.

there any reports of Rescula-induced miosis in humans.

In the current study, conducted on normal dogs, one application of Rescula caused a 5.00 mm Hg (or 24%) decrease in IOP. This decrease is larger than the 3.8 mm Hg decrease noted in glaucomatous cynomologus monkeys [4], or the 4.1 mm Hg decrease recorded in humans suffering from glaucoma or ocular hypertension [5]. The decrease is also larger than, or equal to, the decrease noted in normotensive dogs using other topical anti-glaucoma drugs. Apraclonidine (0.5%), an α_2-adrenergic agonist, decreased canine IOP by an average of 3 mm Hg [3]. Timolol maleate (0.5%), a β adrenergic blocker, decreased canine IOP by an average of 2.5 mm Hg [7], while a 2% solution of a topical carbonic anhy-

drase inhibitor lowered IOP in normotensive dogs by an average of 5 mm Hg [2].

The 5.00 mm Hg reduction in IOP following a single administration of Rescula was significant (p=0.014) and long-lasting, with significantly-lower IOP still recorded 9 hr after a single treatment. These results suggest that Rescula may be efficacious in the treatment of canine glaucoma.

ACKNOWLEDGEMENTS. This study was supported by an unrestricted research grant from CIBA Vision (a Novartis company) to the Koret School of Veterinary Medicine, Hebrew Univesity of Jerusalem, Israel.

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