Intraocular pressure lowering activity of NCX 470, a novel nitric oxide-donating bimatoprost in preclinical models of ocular hypertension and glaucoma

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The prostaglandin F2alpha (PGF2alpha) analog, bimatoprost, lowers IOP by increasing aqueous humor (AH) uveoscleral outflow. However, this drug has been shown to induce itching and redness of the eye at clinically effective doses. Therefore, strategies aiming at increasing the therapeutic index of bimatoprost are of potential interest. Nitric oxide (NO)-donating latanoprost (Vesneo^{TM}) has been shown to have enhanced intraocular pressure (IOP)-lowering effects compared to the PGF2alpha analog, latanoprost, in both animal models and ocular hypertensive glaucomatous patients.
Here we report on NCX 470, a novel dual acting compound combining bimatoprost with NO, known to lower IOP with a mechanism independent from that of PGF2alpha analogs.
We used three animal models of either ocular hypertensive or normotensive glaucoma to compare the IOP-lowering effects of NCX470 with that of equimolar bimatoprost doses. Specifically, the hypertonic (5%) saline-induced transient IOP raise rabbit model, the laser-induced ocular hypertension non-human primate model and the ocular normotensive dog model were used. In addition, the levels of bimatoprost acid and cGMP as surrogate markers respectively of bimatoprost- and NO-mediated activities over time following topical dosing of either bimatoprost or NCX 470 in rabbits were monitored.
NCX 470 (0.14%) lowered IOP in ocular hypertensive rabbits with an Emax of -7.2±2.8 mmHg at 90 min. Bimatoprost was not effective in this model. NCX 470 (0.042%) was more effective than equimolar (0.03%) bimatoprost in normotensive dogs (change from baseline, -5.4±0.7 and -3.4±0.7 mmHg, respectively, $p<0.05$) and in ocular hypertensive non-human primates (change from baseline, -7.7±1.4 and -4.8±1.7 mmHg, respectively, $p<0.05$) at 18 hours post-dosing. The IOP-lowering effect of NCX 470 in dogs was dose-dependent between 0.014% and 0.065%. NCX 470 or bimatoprost treatment resulted in similar bimatoprost acid exposure while cGMP accumulation was evident after NCX 470.
NCX 470 lowers IOP more than equimolar bimatoprost in three animal species. These results suggest that NCX 470 warrants clinical evaluation for the treatment of ocular hypertension in glaucoma.