NCX 470, a nitric oxide (NO)-donating prostaglanding analog, elicits sustained IOP-lowering and modifies aqueous humor dynamic in non-human primates

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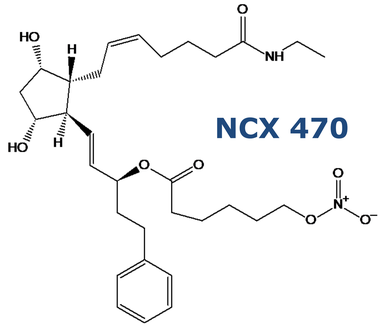
INTRODUCTION

NCX 470 is a nitric oxide (NO)-donating bimatoprost in clinical phase 3 development for the lowering of intraocular pressure (IOP) in patients with ocular hypertension or open-angle glaucoma. In preclinical models of ocular hypertension and glaucoma, NCX 470 demonstrated up to 3.5 mmHg greater IOP-lowering than equimolar bimatoprost (0.03%).[1] Moreover, the administration of NCX 470 in rabbits (known to respond poorly to bimatoprost) resulted in up to 8 mmHg IOP-lowering compared to vehicle.[1] Here we report the effects of NCX 470 on aqueous humor dynamics (AHD) in ocular normotensive non-human primates; specifically on aqueous flow, outflow facility and uveoscleral flow.

MATERIALS AND TEST SYSTEM

Nitric oxide (NO)-donating bimatoprost



Hexanoic acid, 6-(nitrooxy)-, (1S,2E)-3-[(1R,2R,3S,5R)-2-[(2Z)-7-(ethylamino)-7-oxo-2-hepten-1-yl]-3,5 dihydroxycyclopent-yl]-1-(2-phenylethyl)-2-propen-1-yl ester

Animal model

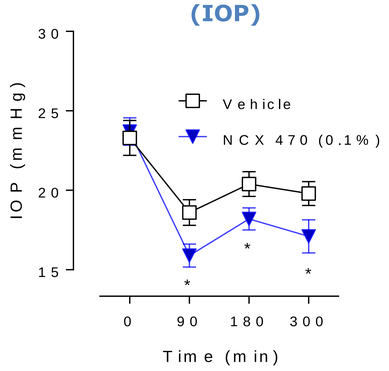
Adult female ocular normotensive Cynomolgus macaques (n=12) between 13 and 22 years of age, weighing 3-6 kg were used. Eyes were topically dosed with 30µL of NCX 470 (0.1%) or its vehicle using a randomized, masked crossover design. The crossover test was performed 34-35 days after the initial test. All animal experiments were performed in accordance with the statement for use of animals and vision research approved by the Association for Research in Vision and Ophthalmology and the Institutional Animal Care & Use Committee of the University of Nebraska Medical Center.

PURPOSE

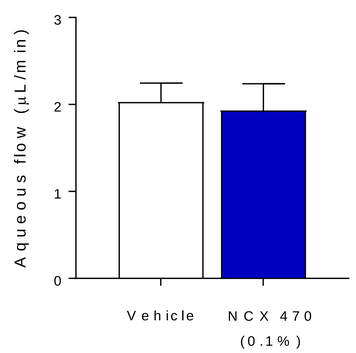
Explore the effects of NCX 470, a nitric oxide (NO)-donating bimatoprost, on aqueous humor dynamics in ocular normotensive non-human primates

RESULTS

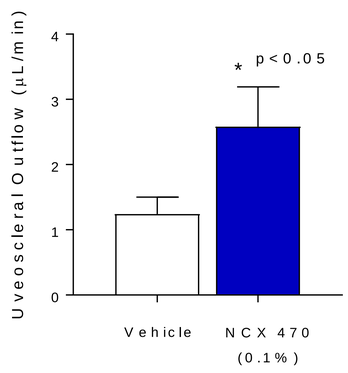
Intraocular pressure (IOP)



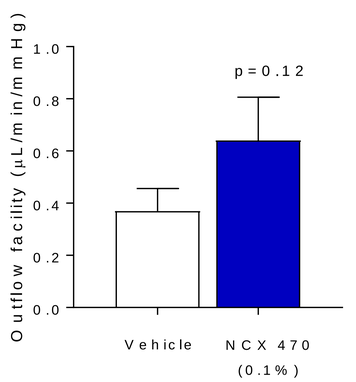
Inflow (AH production)



Uveoscleral outflow (non-conventional pathway)



Outflow facility (conventional pathway)



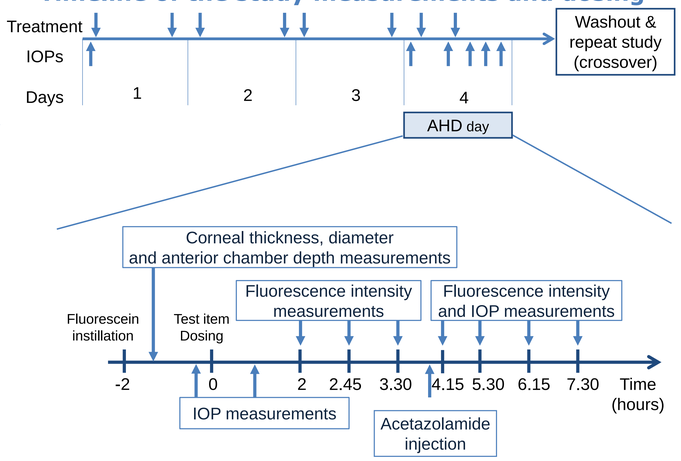
Data are reported as mean ± SD of n=6-12 eyes. *p<0.05 vs vehicle using a multiple t-test (GraphPad Prism 7.05).

CONCLUSIONS

NCX 470 increased the non-conventional uveoscleral outflow and albeit not significantly, enhanced the conventional outflow. No effects was observed on aqueous humor production. Repeated administration of NCX 470 was well tolerated with no signs of ocular discomfort.

METHODS

Timeline of the study measurements and dosing



Intraocular pressure (IOP) & Aqueous humor dynamics (AHD) evaluation

Baseline IOP was measured (pneumatonometer Classic 30, Reichert) on day 1. Dosing started immediately after baseline IOP for 3 consecutive days, bid. On day 4 IOPs were taken at 90, 180 and 300 min after AM dose. One topical drop of proparacaine HCl (0.5%) was instilled before measuring IOPs.

On day 4, animals were dosed with fluorescein (10%) and fluorophotometric scans (Fluorotron Master, OcuMetrics) of the cornea and anterior chamber were taken at 45min intervals to address changes in AH inflow, outflow facility and uveoscleral outflow. Central corneal thickness and anterior chamber depth were measured by ultrasound pachymetry (Sonomed). Cornea diameter was measured with calipers (Fine Science Tools). Cornea and anterior chamber volumes as well as aqueous inflow (Fa) were calculated according to formulas reported in details elsewhere.[2,3] Outflow facility (Cfl) was calculated as the ratio of the change in aqueous flow to the change in mean IOP using equation (1). Uveoscleral outflow (Fus) was calculated using equation (2).

$$Cfl = \Delta Fa / \Delta IOP \quad (1)$$

$$Fus = Fa - Cfl\ (IOP - Pev) \text{ where } Pev = 17mmHg \quad (2)$$

REFERENCES

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2. Brubaker RF, *Trans Am Ophthalmol Soc*. 1982; 80:391–474.
3. Yablonski ME, et al., *Am J Ophthalmol*. 1985; 99:579–582.

Commercial Relationships Disclosure:
E. Bastia, Nicox Research Institute (E), F. Impagnatiello, Nicox Research Institute (E), S. Brambilla, Nicox Research Institute (E), C. Galli, Nicox Research Institute (E), C. Toris, Nicox Research Institute (F), S. Fan, Nicox Research Institute (N), J. Boyer, Nicox Ophthalmic Inc. (E)

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