Repeated dosing of NCX 667, a new nitric oxide (NO) donor, retains IOP-lowering activity in animal models of glaucoma

2106

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INTRODUCTION

A wealth of experimental and clinical data support the role of nitric oxide (NO) in lowering intraocular pressure (IOP) by increasing aqueous humor outflow via relaxation of the trabecular meshwork and Schlemm's canal (conventional route).[1,2] NCX 667 is a novel stand alone NO-donor, proven to effectively lower IOP in rabbit and non-human primate models of glaucoma after single administration.[3]

METHODS

Treatment paradigm A - repeated topical ocular dosing over 1 day -

Ocular normotensive New Zealand white (NZW) rabbits were treated every hour for 4 consecutive hours with NCX 667 (1%, 30 µL) or vehicle (PBS with cremophor EL 5%, DMSO 0.3%, BAC 0.02%). Intraocular pressure (IOP) was recorded prior to dosing and hourly post-dosing using a pneumatonometer (Model 30™ Reichert, Depew, NY, USA). One topical drop of the local anesthetic, Novesina® 0.4% (Novartis) was applied to the eye prior to each IOP measurement.

Treatment paradigm B - repeated topical ocular dosing over 1 week -

NCX 667 (1%, 30 µL) or vehicle (PBS with cremophor EL 5%, DMSO 0.3%, BAC 0.02%) were administered twice a day (9AM and 4PM) for 5 consecutive days to ocular normotensive NZW rabbits or laser-induced ocular hypertensive non-human primates. IOP was measured hourly through 4 hours (in rabbits) and 9 hours (in non-human primates) on days 1, 3 and 5. A pneumatonometer (Model 30™ Reichert, Depew, NY, USA) was used to measure IOP. One topical drop of Novesina® 0.4% (Novartis) was applied to the rabbit eye prior to each IOP measurement. Non-human primates were topically treated with one drop of 0.5% proparacaine hydrochloride, five minutes before tonometry, and ketamine hydrochloride 2-5 mg/kg of body weight administered intramuscularly for adequate sedation.

Safety assessment

Safety assessment by slit lamp of the anterior segment of the non-human primate hypertensive eyes was conducted at baseline, day 1, 3 and 5 following the first daily administration using the Hackett-McDonald ocular scoring system[4].

Statistical analysis

Data are expressed as mean of IOP change ± SEM. IOP change was calculated as follows: (Drug IOP_{Tx}-Drug IOP_{T0}) - (Veh IOP_{Tx} - Veh IOP_{T0}) where IOP_{Tx} and IOP_{T0} are respectively the IOP at the time of interest and prior to dosing. A *P*-value <0.05 was considered significant. Two-way ANOVA followed by Bonferroni's multiple comparison test was used.

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Commercial Relationships Disclosure:
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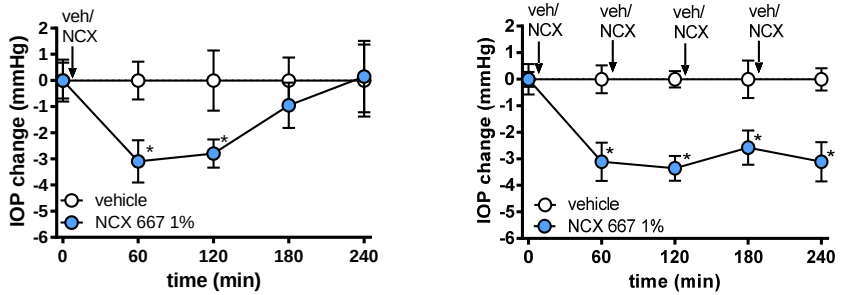
PURPOSE

To study, the IOP lowering effects of NCX 667, a novel NO-donor, following repeated dosing in ocular normotensive New Zealand white rabbits and laser-induced ocular hypertensive non-human primates

RESULTS

Repeated (4 times, 1 hour apart) topical dosing of NCX 667 elicits sustained IOP-lowering activity in ocular normotensive New Zealand white rabbits

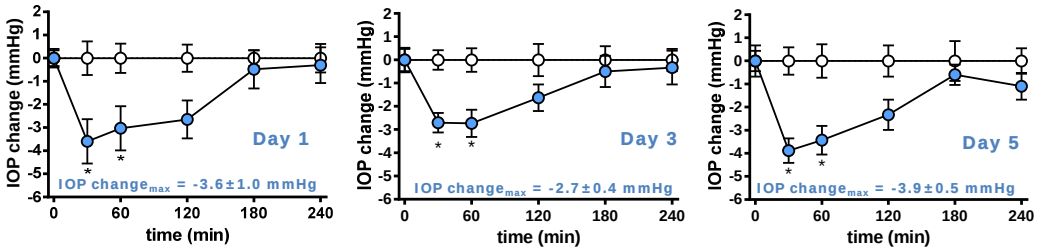
Treatment paradigm A



Data are reported as mean ± SEM of n=5-9;*p<0.05 vs vehicle at the respective time point

NCX 667 retains IOP lowering activity following twice daily topical dosing over 1 week in ocular normotensive New Zealand white rabbits

Treatment paradigm B

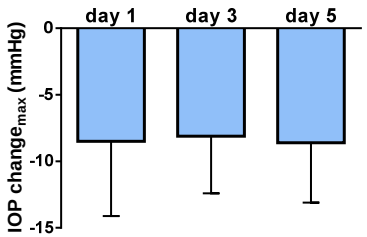


Data are reported as mean ± SEM of n=10;*p<0.05 vs vehicle at the respective time point

○ vehicle ● NCX 667 1.0%

NCX 667 retains IOP lowering activity following twice daily topical dosing over 1 week in laser-induced ocular hypertensive non-human primates

Treatment paradigm B



Data are reported as mean ± SEM of n=6. IOP change$_{max}$ was calculated versus pre-test values as follow: Drug IOP_{Tmax}-Drug IOP_{T0}.

Slit lamp of the anterior segment of the non-human primate eyes

Conjunctiva	No signs of redness, swelling, or discharge
Cornea	Normal
Iris	Normal
Lens	No signs of opacity

CONCLUSION

Repeated dosing with NCX 667 resulted in comparable IOP-lowering activity over time with no signs of tachyphylaxis, tolerance, or ocular discomfort

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