Study Synopsis

Title	An open study comparing the effects of moxaverine on ocular blood flow in patients with age related macular degeneration, primary open angle glaucoma and healthy control subjects
Development phase	Phase II a
Principle investigator	Department of Clinical Pharmacology Währinger Gürtel 18-20 1090 Wien, Austria
Co-investigators	Department of Clinical Pharmacology and Centre of Biomedical Engineering and Physics Währinger Gürtel 18-20 1090 Wien, Austria
Background	A number of common eye diseases such as age-related macular degeneration and glaucoma are associated with ocular perfusion abnormalities. Although this is well recognized there is not much possibility to improve blood flow to the posterior pole of the eye in these diseases. For many years, moxaverine has been used in the therapy of perfusion abnormalities in the brain, the heart and the extremities. This is based on a direct vasodilatory effect of the drug, but also on the rheological properties of red blood cells. In a recent study we have shown that intravenous moxaverine increases choroidal blood flow in healthy young subjects. The present study aims to investigate, whether moxaverine also improves blood flow in the diseased eye after systemic administration.
Study objectives	To compare the effect of moxaverine on ocular blood flow in patients with age related macular degeneration, primary open angle glaucoma and healthy control subjects
Study design	Open Study with three groups of subjects
Study population	20 patients with age related macular degeneration; Main inclusion criteria: stage AREDS II, III or IV, visual acuity > 20/60, Main exclusion criteria: Diabetes, Glaucoma, other ocular vascular disease, intraocular surgery within the last 3 months 20 patients with primary open angle glaucoma: Main inclusion criteria: treated intraocular pressure< 21 mmHg, visual field MD <10; Main exclusion criteria: other ocular vascular disease, uncontrolled IOP intraocular surgery within the last 3 months 20 age and sex matched control subjects, control subjects will be matched to fit as close as possible to each of the two groups of patients.

Study medication	Medication: Moxaverine (Ursapharm. Saarbrücken, Germany) i. v. infusion of 150 mg in 250 ml NaCl, applied over 30 minutes.
Methods	Laser Doppler flowmetry (choroidal and optic nerve head blood flow) Laser Doppler velocimetry (blood velocities in retinal veins) Retinal Vessel Analyzer (diameter of retinal arteries and veins) Colour Doppler imaging (retrobulbar vessels) Non-invasive measurement of systemic blood pressure Applanation tonometry (intraocular pressure)
Study endpoints	Primary endpoint: Choroidal and optic nerve head blood flow (Laser Doppler Flowmetry) Secondary endpoint: Retrobulbar flow velocities (Colour Doppler imaging) Retinal blood flow velocity (Laser Doppler velocimetry) Retinal venous and arterial diameters (Zeiss retinal vessel analyzer) Intraocular pressure (Applanation tonometry) Systolic and diastolic blood pressure (non- invasive)
Statistical methods	Statistical significance will be assessed by an ANOVA model for measurements. Post hoc comparisons will be done using planned comparisons. A $p < 0.05$ will be considered the level of significance.
First volunteer enrolled	15.05.2008
Study completion date	Last patient last visit: 11.03.2009
Summary of Results	Administration of moxaverine increased choroidal blood flow from 11.9 ± 1.8 a.u. to .12.9 ± 2.2 a.u. 90 minutes after start of infusion. This effect was statistically significant compared to baseline ($p = 0.012$). However, no difference was detected between the 3 included study groups ($p = 0.65$). Administration of moxaverine also increased optic nerve head blood flow from 14.7 ± 2.2 a.u. to .16.2 ± 2.7 a.u. 60 minutes after start of infusion ($p = 0.021$). Again, no difference was detected between the 3 included groups ($p = 0.52$). In response to moxaverine red blood cell velocity showed a non-significant tendency to increase from 2.08 ± 0.36 mm/s to a maximum of 2.21 ± 0.36 mm/s 60 minutes after the start of infusion. A significant increase was also seen in mean flow velocity of the posterior ciliary arteries over time ($p < 0.001$). In the ophthalmic artery mean flow velocity also increased, but this effect was only seen 30 minutes after the start of infusion ($p < 0.001$). The response in mean flow velocities in the ophthalmic artery and the posterior ciliary arteries was comparable between groups. No significant change was observed after administration of moxaverine on retinal vessel diameters. At a dose of 150 mg moxaverine was well tolerated. 7 subjects experienced mild adverse events such as a slight feeling of dizziness or heat.

Conclusions

In conclusion the present study indicates an increase in ocular blood flow after systemic infusion of a single dose of moxaverine in elderly patients with eye diseases associated with hypoperfusion and also in age-matched controls. Further studies in patients are needed to investigate whether long-term treatment with moxaverine is clinically beneficial for patients with ocular vascular disease.