Effects of brinzolamide on ocular haemodynamics in healthy volunteers

M Kaup, N Plange, M Niegel, A Remky, O Arend

Aim: A prospective, randomised study to evaluate effects of brinzolamide on ocular haemodynamics in healthy volunteers.

Methods: 30 volunteers (12 men, 18 women; 28.3 (SD 7.8) years) were prospectively randomised to either brinzolamide or placebo during a 2 week double masked treatment trial. Examinations were performed at baseline and after 2 weeks of treatment. Intraocular pressure was measured and automatic static perimetry (Humphrey field analyser, 24-2) and contrast sensitivity (CSV 1000, Vector Vision) were performed. Retrobulbar blood flow velocities (peak systolic and end diastolic velocity) and resistive indices (RI) of ophthalmic artery, central retinal artery and of temporal and nasal short posterior ciliary arteries were measured by colour Doppler imaging (Sonoline Sienna Siemens). In video fluorescein angiograms (scanning laser ophthalmoscope, Rodenstock) arteriovenous passage time (AVP, dilution curves) and peripapillary diameters of retinal arterioles and venules were measured by means of digital image analysis.

Results: Intraocular pressure was significantly decreased by brinzolamide (p<0.0001). Neither brinzolamide nor placebo changed visual field global indices after treatment. Contrast sensitivity at 3 cycles per degree was significantly higher in the placebo group (p<0.05). Apart from an increase of RI in ophthalmic artery under placebo treatment (p<0.05) there was no effect in retrobulbar haemodynamics in both groups. Brinzolamide therapy alone resulted in a significant reduction of AVP compared to baseline (p<0.05), while peripapillary retinal vessels diameters remained unaffected.

Conclusions: Apart from the expected decrease of intraocular pressure brinzolamide showed no significant change in retrobulbar haemodynamics, but a significant shortening of AVP. Since in glaucoma AVP is prolonged indicating vascular dysfunction this effect might be beneficial in glaucoma therapy.

PATIENTS AND METHODS
Thirty healthy volunteers (12 men, 18 women; age 28 (SD 8) years) participated in this prospective randomised double masked study. All volunteers underwent a complete ophthalmological and general examination. The volunteers were instructed to avoid caffeine, tobacco, and exercise for at least 3 hours before the study visits. Informed consent was obtained from each volunteer including detailed explanation of all procedures before participation in this study. The protocol for the study was reviewed and approved by the institutional review board of University Aachen, Germany.

Abbreviations: AVP, arteriovenous passage time; BP, blood pressure; CAI, carbonic anhydrase inhibitors; CDI, colour Doppler imaging; cpd, cycles per degree; CPSD, corrected pattern standard deviation; CRA, central retinal artery; CS, contrast sensitivity; EDV, end diastolic velocity; HR, heart rate; MD, mean defect; OA, ophthalmic artery; OPP, ocular perfusion pressure; PCA, posterior ciliary artery; PSD, pattern standard deviation; PSV, peak systolic velocity; RI, resistive index; SF, short term fluctuation; SLO, scanning laser ophthalmoscope.
The tenets of the Helsinki declaration were followed throughout the study.

During baseline examination visual acuity, contrast sensitivity (CS), automatic static perimetry (Humphrey field analyser), intraocular pressure (IOP), blood pressure, heart rate, colour Doppler imaging (CDI) and video fluorescein angiograms (scanning laser ophthalmoscope, SLO) were performed. The volunteers randomly received mask brinzolamide (Azopt, Alcon) or placebo (Lacrisic, Alcon) twice daily in the right eye. After 2 weeks of treatment all measurements were performed at the same time of day (plus or minus 30 minutes).

Best corrected visual acuity was tested using objective refractometry. Static contrast sensitivity (CSV 1000, Vector Vision, Dayton, OH, USA) was performed on all subjects at four spatial frequencies: 3, 6, 12, and 18 cycles per degree (cpd). 23

The automatic static perimetry (program 24-2, conventional full threshold white on white) was performed with a Humphrey field analyser (Humphrey Inc, San Leandro, CA, USA) was performed on all subjects at four spatial frequencies: 3, 6, 12, and 18 cycles per degree (cpd). 23

The conventional full threshold perimetry parameters (mean (SD) showed a significant difference of CPSD between brinzolamide and placebo after treatment (ANOVA for repeated measures), but neither brinzolamide nor placebo significantly changed CPSD in the subgroup analysis (Bonferroni-Dunn).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical data of blood pressure, heart rate, intraocular pressure, and calculated ocular perfusion pressure at baseline and after 2 weeks of treatment (mean (SD))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Brinzolamide</strong></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>120 (17)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>73 (11)</td>
</tr>
<tr>
<td>Heart rate (beats/ min)</td>
<td>66 (9)</td>
</tr>
<tr>
<td>Intraocular pressure (mm Hg)</td>
<td>12.3 (2.0)</td>
</tr>
<tr>
<td>Ocular perfusion pressure (mm Hg)</td>
<td>46.2 (8.2)</td>
</tr>
</tbody>
</table>

Apart from a significant decrease of intraocular pressure after brinzolamide no significant differences between visits were detected in both groups (ANOVA for repeated measures).

*p<0.0001 (Bonferroni-Dunn).
density profile was performed perpendicular to the vessel and by identifying the half height from the maximum height of the ascending and the descending slope diameter measurements. To reach subpixel accuracy, the results represent the average of five separate diameter measurements. Results of AVP and vessel diameters from the temporal superior and inferior vessels were averaged to characterise posterior pole circulation.

Mean value and standard deviation were analysed for all samples using normal distributions (Kolmogorov-Smirnov test). For multiple comparisons ANOVA for repeated measures was used and p values were obtained using Bonferroni-Dunn test. Results of p<0.05 were considered to be statistically significant.

**RESULTS**

Brinzolamide significantly reduced IOP after 2 weeks of treatment (p<0.0001), while the control group showed no change in IOP (table 1). Neither brinzolamide nor placebo changed visual field global indices, but there was a significant difference in CPSD between brinzolamide and placebo after treatment (table 2). Contrast sensitivity at 3 cpd was significantly higher in placebo group after treatment (table 2). Contrast sensitivity at 3, 6, 12, and 18 cycles per degree (cpd) at baseline and after treatment showed only after brinzolamide treatment (p<0.05), while brinzolamide left RI unchanged in any vessel (table 4). The analysis of the video fluorescein angiograms at baseline and after treatment showed only after brinzolamide significant changes of retinal AVP. Brinzolamide therapy resulted in a significant reduction of AVP compared to baseline (p<0.05), while placebo had no significant effect on retinal passage time. In both groups peripapillary arterial and venous diameters remained unaffected during treatment. The results of the retinal parameters are presented in table 5.

**DISCUSSION**

In this study we found that topical brinzolamide treatment in healthy volunteers lowers IOP and accelerates the retinal AVP, while the retinal vessel diameters and the retrobulbar haemodynamics remain unaltered.

Our results of shortened AVP during brinzolamide treatment agree with previous studies of the haemodynamic effects of dorzolamide. Decreased AVP coupled with unaltered retinal vessel diameter was associated with more rapid capillary transit in the macula and in superficial capillaries of the optic nerve head after dorzolamide treatment in normal subjects. These findings suggested that topical applied CAI

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### Table 3  Means of static contrast sensitivity at 3, 6, 12, and 18 cycles per degree (cpd) at baseline and after treatment

<table>
<thead>
<tr>
<th></th>
<th>Brinzolamide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Drug</td>
</tr>
<tr>
<td>3 cpd</td>
<td>1.85 (0.10)</td>
<td>1.81 (0.13)</td>
</tr>
<tr>
<td>6 cpd</td>
<td>1.93 (0.47)</td>
<td>2.04 (0.18)</td>
</tr>
<tr>
<td>12 cpd</td>
<td>1.76 (0.18)</td>
<td>1.82 (0.17)</td>
</tr>
<tr>
<td>18 cpd</td>
<td>1.34 (0.20)</td>
<td>1.35 (0.12)</td>
</tr>
</tbody>
</table>

Brinzolamide treatment showed no change in contrast sensitivity (ANOVA for repeated measures), in placebo group contrast sensitivity at 3 cpd was significantly higher after treatment. *p<0.05 (Bonferroni-Dunn).

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### Table 4  Peak systolic velocity (PSV), end diastolic velocity (EDV) and resistive index (RI) in four retrobulbar vessels after double masked treatment with brinzolamide or placebo (mean (SD))

<table>
<thead>
<tr>
<th></th>
<th>Ophthalmic artery</th>
<th>Central retinal artery</th>
<th>Temporal posterior ciliary artery</th>
<th>Nasal posterior ciliary artery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Drug</td>
<td>Baseline Placebo</td>
<td>Baseline Drug Placebo</td>
<td>Baseline Drug Placebo</td>
</tr>
<tr>
<td><strong>PSV (cm/s)</strong></td>
<td>29.8 (5.9)</td>
<td>28.4 (6.2)</td>
<td>32.1 (7.0)</td>
<td>31.6 (8.0)</td>
</tr>
<tr>
<td><strong>EDV (cm/s)</strong></td>
<td>5.8 (1.9)</td>
<td>5.6 (1.4)</td>
<td>6.0 (2.3)</td>
<td>5.1 (2.1)</td>
</tr>
<tr>
<td><strong>RI</strong></td>
<td>0.81 (0.06)</td>
<td>0.80 (0.05)</td>
<td>0.81 (0.07)</td>
<td>0.83 (0.05)*</td>
</tr>
<tr>
<td><strong>PSV (cm/s)</strong></td>
<td>9.6 (2.1)</td>
<td>10.0 (2.1)</td>
<td>9.8 (1.2)</td>
<td>10.3 (1.4)</td>
</tr>
<tr>
<td><strong>EDV (cm/s)</strong></td>
<td>2.9 (1.2)</td>
<td>3.2 (0.9)</td>
<td>2.9 (0.6)</td>
<td>2.9 (0.7)</td>
</tr>
<tr>
<td><strong>RI</strong></td>
<td>0.70 (0.09)</td>
<td>0.68 (0.07)</td>
<td>0.70 (0.06)</td>
<td>0.72 (0.08)</td>
</tr>
<tr>
<td><strong>PSV (cm/s)</strong></td>
<td>9.1 (2.1)</td>
<td>9.5 (1.8)</td>
<td>8.3 (2.0)</td>
<td>8.4 (2.1)</td>
</tr>
<tr>
<td><strong>EDV (cm/s)</strong></td>
<td>3.6 (1.3)</td>
<td>3.7 (1.2)</td>
<td>3.0 (0.8)</td>
<td>2.9 (0.7)</td>
</tr>
<tr>
<td><strong>RI</strong></td>
<td>0.60 (0.07)</td>
<td>0.62 (0.08)</td>
<td>0.63 (0.07)</td>
<td>0.64 (0.08)</td>
</tr>
<tr>
<td><strong>PSV (cm/s)</strong></td>
<td>8.2 (2.5)</td>
<td>8.1 (2.1)</td>
<td>7.6 (1.1)</td>
<td>7.8 (1.2)</td>
</tr>
<tr>
<td><strong>EDV (cm/s)</strong></td>
<td>3.2 (1.2)</td>
<td>3.0 (1.0)</td>
<td>2.6 (0.5)</td>
<td>2.6 (0.5)</td>
</tr>
<tr>
<td><strong>RI</strong></td>
<td>0.62 (0.06)</td>
<td>0.63 (0.08)</td>
<td>0.66 (0.06)</td>
<td>0.67 (0.04)</td>
</tr>
</tbody>
</table>

Apart from an increase of RI in ophthalmic artery under placebo treatment there was no therapy effect in retrobulbar haemodynamics in both groups (ANOVA for repeated measures).

*p<0.05 (Bonferroni-Dunn).
Table 5  The results of the analysis of fluorescein angiograms at baseline and after treatment

<table>
<thead>
<tr>
<th></th>
<th>Brinzolamide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Drug</td>
</tr>
<tr>
<td>AVP (s)</td>
<td>1.64 (0.43)</td>
<td>1.46 (0.39)</td>
</tr>
<tr>
<td>Retinal arterial diameter (μm)</td>
<td>103.2 (13.8)</td>
<td>102.6 (12.7)</td>
</tr>
<tr>
<td>Retinal vein diameter (μm)</td>
<td>139.3 (15.2)</td>
<td>138.3 (16.3)</td>
</tr>
</tbody>
</table>

Brinzolamide therapy alone resulted in a significant shortening of AVP, while peripapillary retinal vessels diameters remained unaffected. *p<0.05 (Bonferroni-Dunn).

Brinzolamide treatment resulted in a shortening of AVP. This reduction associated with unchanged retinal arterial and venous diameters suggests that the drug enhances retinal perfusion. Even AVP itself is only an indirect marker of total retinal perfusion. The analysis of AVP, however, allows us to detect haemodynamic alterations closely related to clinical abnormalities in glaucoma. Patients with open angle glaucoma showed prolonged retinal passage time compared with healthy subjects. These circulatory deficits of the retinal tissue are linked together with visual field loss. In hemispheres with more severe glaucomatous field loss the AVP was significantly prolonged compared with the less affected hemisphere. Since prolonged AVP has been associated with disease progression in glaucoma the visual function may benefit from increased retinal perfusion by brinzolamide seen in shortened AVP. Studies of long term application of brinzolamide are needed to evaluate the effects on ocular blood flow and visual function in glaucoma patients.

To date, a comparative study of different topical applied CAI on ocular blood flow has been presented in rabbits, but not in humans. The IOP reduction, as well as the improvement of optic nerve head blood flow in rabbits, was statistically equivalent after treatment with either brinzolamide or dorzolamide.

Both CAI were found in the retina after topical administration to rabbits, but in different concentrations, though further studies are needed to confirm these results because of methodological differences. In humans, no differences were found in the IOP effects of the two CAI, whereas brinzolamide appeared to be slightly more effective in reducing aqueous humour flow than dorzolamide. A comparative study between brinzolamide and dorzolamide is necessary to detect possible different effects on ocular blood flow in humans.

Brinzolamide lowers IOP by locally inhibiting the CA II and CA IV in ciliary processes and suppressing aqueous humour secretion. The mechanism by which brinzolamide may increase retinal perfusion is unclear. Ocular isoenzymes that could be inhibited would be membrane bound CA IV in the retinal pigment epithelium and vascular endothelium of the choriocapillaris and the soluble CA II in the Mueller cells of the retina. The inhibition of CA II in the Mueller cells by topical applied CAI is uncertain because the diffusion across the blood-retinal barrier would depend on the lipophilicity and an adequate concentration of free drug. Since brinzolamide is more lipophilic than dorzolamide at physiological pH, this higher lipophilicity may favour the ability to move across lipid membrane barriers. Brinzolamide has its highest affinity and inhibitory potency for CA II. The potency for inhibiting CA IV is comparable to dorzolamide. It is unclear, if different properties of CA inhibition may influence the effects on ocular blood flow.

Systemic CAI induced a significant increase in retinal blood flow measured by laser Doppler velocimetry in healthy volunteers combined with a vasodilatation of retinal vessels.
determined from monochromatic fundus photographs.\textsuperscript{9} Rassam et al concluded that the mechanisms responsible for the increase in retinal blood flow acted via significant increases in perfusion pressure, red cell velocity, and retinal vessel dilatation. An increase in tissue pCO\textsubscript{2} and a reduction in pH were thought to be responsible for the vascular dilatation as it was postulated for the effects of acetazolamide on cerebral circulation.\textsuperscript{44} The animal study in tranquilised Dutch belted rabbits revealed that brinzolamide and dorzolamide significantly increased optic nerve head blood flow measured by fundus camera based laser Doppler flowmeter.\textsuperscript{12} The authors suggested that the enhanced optic nerve head blood flow might be the result of a possible increase in ocular tissue carbon dioxide tension. The carbon dioxide and pH mediated mechanism may account for the shortening of AVP in humans by brinzolamide. In a study of hypercapnia in healthy volunteers AVP fell and mean arterial dye velocity and capillary blood velocity rose as pCO\textsubscript{2} increased.\textsuperscript{45} Anderson and Davis found that an increase of local pCO\textsubscript{2} in cell cultured bovine pericyte monolayer caused a relaxation of AVP with unaltered peripapillary retinal vessel diameters on these findings the brinzolamide induced acceleration of retinal organ culture.\textsuperscript{45} They suggested that CAI could relax perfusion seen in shortened retinal AVP. Further testing of benefit optic nerve head blood flow. Graves Arch Clin Exp Ophthalmol 1999;237:495–500.

**REFERENCES**


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