Nimodipine Plasma Concentration and Retinal Blood Flow in Healthy Subjects

Georg Michelson,¹ Simone Wärntges,¹ Steffen Leidig,¹ Jörn Lötsch,² and Gerd Geisslinger²

PURPOSE. Calcium antagonists are strong vasodilators, and nimodipine is known to improve cerebral blood flow. The purpose of this study was to measure retinal blood flow and nimodipine plasma concentrations during repeated oral dosing.

METHODS. In a double-blind, two-way, crossover study, 20 healthy subjects (mean age, 22.8 ± 3.7 years) underwent examination of retinal perfusion and nimodipine plasma concentrations. In a placebo-controlled fashion, nimodipine was orally administered at a dosage of 30 mg three times a day for two periods of 5 days including a 9-day washout interval. At days 1, 5, 15, and 19, plasma concentrations of nimodipine and retinal perfusion were measured 11 times within 3 hours. Stereoselective analysis of nimodipine plasma concentrations was performed with the use of liquid chromatography-tandem mass spectrometry. Scanning laser Doppler flowmetry was used to measure the microcirculation of the juxtapapillary retina. Perfusion images were evaluated with the automatic full-field evaluation procedure (AFFPIA).

RESULTS. Areas under the plasma concentration versus time curves were similar at day 1 and day 5 of nimodipine administration (t test: P = 0.64). Values of Cmax displayed a large interindividual variance and ranged from 0 ng/mL to 57.5 ng/mL. On average, maximum nimodipine plasma concentrations (Cmax) were 16.6 ± 14.9 ng/mL and 12.0 ± 10.3 ng/mL at day 1 and day 5, respectively (P = 0.068). They were observed at 81 ± 50 and at 95 ± 40 minutes (tmax) after the administration of nimodipine at day 1 and day 5, respectively (P = 0.43). Retinal microcirculation was greater after nimodipine than after placebo, as reflected in significantly larger areas under the curves of percentage change in blood flow from baseline versus time (P < 0.01). The maximum increase of retinal blood flow from baseline was significantly more pronounced after nimodipine (28.5% ± 14.4% and 39.6% ± 21.4% at day 1 and day 5, respectively) than after placebo (20.5% ± 16.8% and 31.9% ± 14.6% at day 1 and day 5, respectively; P = 0.032).

CONCLUSIONS. Oral nimodipine significantly increases retinal perfusion in healthy subjects. (Invest Ophthalmol Vis Sci. 2006;47:3479–3486) DOI:10.1167/iovs.05-1350

Although the major focus of recent neuroprotection research has been aimed at developing receptor-specific drugs, this effort has resulted in few improvements in patient outcome. Therefore, traditional techniques to increase ocular blood flow must be used to prevent and to treat retinal and optic nerve ischemic events. These involve interventions to alter systemic and local physiology to decrease the duration and severity of hypoxic insults. Therapy should include interventions to improve ocular perfusion and the oxygen-carrying capacity of the blood. In patients at risk for retinal vasospasm, treatment with calcium antagonists should be considered.

The potent vasodilating effects of calcium antagonists on cerebral vessels have been demonstrated recently in in vivo and in vitro studies, implying that the maintenance of vascular tone relies almost exclusively on extracellular calcium. The effect of the calcium antagonist nimodipine in anesthetized primates was reported by Harper et al., who found that continuous intravenous infusion caused modest decreases in mean arterial blood pressure and increases in cerebral blood flow. In fentanyl/N₂O-anesthetized pigs, an intravenous bolus dose (10 μg/kg) of nimodipine was tested for influencing the cerebral autoregulatory responses if the mean arterial pressure (MAP) was gradually increased by infusion of angiotensin or decreased by caval block. The result was a transient increase in regional cerebral blood flow (rCBF) for 5 minutes, together with a reduction of MAP. After 1 hour of nimodipine infusion (0.5 mg/kg per minute), MAP was reduced by 19% whereas rCBF, regional cerebral vascular resistance (rCVR), and cerebral metabolism were unaffected. The slope of the relationship between rCVR and MAP, defining the autoregulatory capacity, was not attenuated by nimodipine infusion if MAP was gradually increased or decreased. Oral nimodipine showed an enhanced acute reperfusion if applied within 12 hours of onset of acute stroke.

Calcium antagonists have also been shown to improve ocular circulation in patients who have vascular diseases in which considerable vascular tone is present. As well, contrast sensitivity in patients with normal tension glaucoma (NTG) was found ameliorated by calcium channel inhibition. A single dose of 30 mg nimodipine normalizes the significantly reduced retinal blood flow in NTG patients with clinical signs of vasoconstrictive hyperreactivity.

NTG is a disease accompanied by an increased prevalence of “vascular problems,” including hemodynamic crises, hypercoagulability, arterial hypertension, arterial hypotension, increased blood viscosity, elevated cholesterol levels, carotid artery disease, coronary artery disease, migraine, vasospasm, decreased blood velocity, and increased resistance index in the orbital vessels. The role of a systemic or local therapy against a vasoconstrictive mechanism has been investigated. Calcium channel antagonists may aid in retarding the retinal artery to improve the retinal circulation in vascular diseases in which considerable vascular tone is present.

To date no double-masked study had been conducted on the effect of nimodipine in retinal blood flow or on its plasma concentrations. The purpose of the present study was to mea-

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sure simultaneously the retinal blood flow and the plasma concentration of nimodipine.

**METHODS**

**Study Design**

This study was conducted in accordance with the Declaration of Helsinki on Biomedical Research Involving Human Subjects. The Clinical Investigation Ethics Committee of the University of Erlangen-Nürnberg approved the study protocol, and written informed consent was obtained from all subjects after explanation of the nature and possible consequences of the study.

Twenty healthy participants (10 men, 10 women; mean age, 22.8 ± 3.7 years; mean body weight, 64.4 ± 10.4 kg) were examined in a double-blind, two-way, crossover study. Only subjects without eye disease or systemic disease, including arterial hypertension and diabetes, and without concomitant systemic or topical drug administration were included in the study. Exclusion criteria were pregnancy, wearing of contact lenses, myopia greater than 4 D, and intraocular pressure lower than 10 mm Hg or higher than 21 mm Hg.

**Administration of Nimodipine.** Nimodipine (Nimotop; Bay e 9756; Bayer AG, Leverkusen, Germany) or placebo (lactose) was orally administered at a dosage of 30 mg three times a day for two periods of 5 days (days 1–5 and days 15–19) and including a 9-day washout phase (days 6–14). Ten subjects started with nimodipine, and the other 10 started with placebo. Medication was administered at 8:00 AM, 12:00 PM, and 4:00 PM. The order of administration was randomized, and the medication was masked and coded by the manufacturer.

Nimodipine is chemically characterized by the formula (±)-isopropyl-2-methoxyethyl-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate.

**Measurement of the Nimodipine Plasma Concentrations.** At days 1, 5, 15, and 19, blood was drawn 11 times within 3 hours by puncture of the cubital vein with a vein catheter. A blood sample of 6 mL was withdrawn on oral administration of the study medication and 15, 30, 45, 60, 75, 90, 105, 120, 150, and 180 minutes after it. Within 30 minutes of collection, blood samples were centrifuged, and plasma was separated and frozen at −20°C. To protect the blood samples from light-induced damage, the experiments were performed in a room without daylight. All materials were free of polyvinylchloride (PVC) to avoid adhesion of nimodipine at the surfaces. Samples of frozen plasma were sent to Bayer AG. Stereoselective determination of nimodipine plasma concentrations was performed by liquid chromatography-tandem mass spectrometry (LC-MS-MS) according to regulations (Verfahrensvorschrift [process regulation] 1 D, Bay e9736 enantiomers; LC-MS method for the determination of Bay e9736 enantiomers in human plasma). Concentrations of both R (+) and S (−) enantiomers were analyzed separately. Variations in accuracy and in intraday and interday precision (n = 6 for each concentration) were less than 10% over the range of calibration. The reliable lower limit of quantification was 0.2 μg/L for each enantiomer.

**Retinal Blood Flow Measurement.** Examinations of blood flow were performed on days 1, 5, 15, and 19, on oral administration of the study medication, and at 15, 30, 45, 60, 75, 90, 105, 120, 150, and 180 minutes after oral administration of the study medication. Retinal blood flow was measured with scanning laser Doppler flowmetry (SLDF; 670 nm, Heidelberg Flowmeter [HRF]; Heidelberg Engineering, Heidelberg, Germany). Acquired perfusion images were analyzed with automatic full-field evaluation of the perfusion images (SLDF-AFFPIA). Principles of the measuring technique have been described elsewhere in detail.Briefly, the laser Doppler frequency shift was measured by SLDF in each of 16,384 points in a retinal area of 2.7 mm × 0.7 mm within 2 seconds. Confocal optics of this device registered only the capillary blood flow of the superficial retinal layer of 300 μm. Detection of laser Doppler signals from deeper layers (choroid) was excluded because of confocal characteristics of the optics. Signals from vitreous or choroid were not detected because they were out of focus. A map of the retinal blood flow was generated, encoded by the laser Doppler shift. Spatial resolution of the device was 10 μm × 10 μm. In the retina, the coefficient of reliability of blood flow measurements was calculated to 0.7 to 0.8 with the use of a flowmeter (HRF; Heidelberg Engineering). — Capacillary retinal blood flow was recorded in a juxtapapillary area localized 2 to 3 mm temporally beside the optic nerve head. These regions were chosen because subjects did not show relevant fixation problems during measurement. The HRF scanned an intensity matrix of 256 points × 64 lines × 128 times using a repetition rate of 4000 Hz. Backscattered intensities of each scanned point were obtained as a function of time, resulting in 16,384 intensity time curves. Collected intensity data of each retinal point of measurement were analyzed by discrete fast Fourier transformation calculating the frequency laser Doppler shift for each point of measurement. SLDF-AFFPIA was used to analyze the perfusion images offline after the experiments. It calculated the laser Doppler frequency shift and the hemodynamic parameter flow of each pixel according to the theory of Bonner and Nossal. For valid estimation of retinal blood flow by HRF, some assumptions must be fulfilled: adequate brightness, no artificial movement, and a Doppler shift lower than 2000 Hz. To meet these requirements, the resultant perfusion image was processed by the SLDF-AFFPIA with respect to underexposed and overexposed pixels, saccades, and retinal vessel tree. In the first step of the statistical analysis, the operator marked saccades and the location of the rim area. In the second step, capillaries and vessels of the retinal vessel tree were identified automatically by a vessel detection algorithm, based on the intensity and the perfusion image. After these procedures, retinal vessels with a diameter larger than 30 μm, underexposed or overexposed pixels, and saccades were excluded automatically from the perfusion image. These processes led to a perfusion map with vessels smaller than 30 μm in diameter, without lines caused by saccades, and without pixels of inadequate reflectivity. Based on this processed perfusion map and all flow values, SLDF-AFFPIA automatically calculated the mean flow, SD, and cumulative frequency distribution curve in the scanned retinal area. Figure 1 depicts the retinal area of one eye with the cumulative frequency distribution curve and the histogram of all flow values within this area.

The mean of five measurements per subject defined basal retinal blood flow. The effect of nimodipine on the retinal blood flow was determined as percentage change from baseline (measurement on day 1 at 0 minute).

The order of measurements was equal for all subjects at the related time points: (1) measurement of retinal perfusion, (2) drawing of blood samples, (3) control of blood pressure and heart rate. All examinations were performed at the sitting subject.

**Measurement of Intraocular Pressure.** Intraocular pressure was determined with the Goldmann tonometer on days 1, 5, 15, and 19, and at 0 and 180 minutes after administration of the medication.

**Measurement of Arterial Blood Pressure and Heart Rate.** Arterial blood pressure was measured by the method of Riva-Rocci at the brachial artery on days 1, 5, 15, and 19 and at 0 and 180 minutes after administration of nimodipine. Pulse rate was determined at the radial artery.

All examinations were performed with the subject in the sitting position.

**Statistical Analysis**

Plasma concentrations of nimodipine and of its active enantiomer were plotted against time, and the areas under the curves (AUCs) were calculated separately for the 3-hour observation periods on days 1 and 5 according to the log-linear trapezoidal rule. In addition, maximum concentrations at day 1 and day 5 and at time from the last nimodipine administration were directly read from the observed data. These values were compared between days by means of paired t tests. Retinal flows were transferred into percentage changes from baseline—that is, from the values obtained at the beginning of the two 5-day study periods (placebo or nimodipine; time 0 in Fig. 2 and Fig. 3) before administr
FIGURE 1. Retinal blood flow of one examined eye measured by SLDF-AFFPIA of perfusion maps gained by HRF.

FIGURE 2. Time course of the nimodipine plasma concentrations (racemic and enantio-selective: mean ± SD). At day 1, measurements started with oral nimodipine administration (30 mg/d). At day 5, data recording started with nimodipine administration (last dose) after 30 mg three times a day for 5 days.
Figure 3. Time course of the changes in retinal blood flow from baseline, expressed as percentage changes from baseline—i.e., from the flow measured before the first administration of either nimodipine or placebo at both study periods. At day 1, measurement started with oral nimodipine administration (30 mg/d). At day 5, data recording started with nimodipine administration (last dose) after 30 mg three times a day for 5 days.

Table 1. Absolute Values and Difference from Baseline ($\Delta_{\text{base}}$) of Temporal Retinal Flow

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Day 1</th>
<th></th>
<th>Day 5</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Nimodipine</td>
<td>Placebo</td>
<td>Nimodipine</td>
</tr>
<tr>
<td></td>
<td>Absolute Values</td>
<td>$\Delta_{\text{base}}$</td>
<td>Absolute Values</td>
<td>$\Delta_{\text{base}}$</td>
</tr>
<tr>
<td>0</td>
<td>267.9 (56.4)</td>
<td>0</td>
<td>246.0 (49.7)</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>277.9 (67.1)</td>
<td>9.9 (50.0)</td>
<td>269.7 (66.6)</td>
<td>25.7 (44.7)</td>
</tr>
<tr>
<td>30</td>
<td>262.0 (50.0)</td>
<td>-5.9 (38.6)</td>
<td>255.1 (46.7)</td>
<td>9.1 (24.7)</td>
</tr>
<tr>
<td>45</td>
<td>259.7 (68.6)</td>
<td>-8.3 (37.8)</td>
<td>271.5 (58.5)</td>
<td>20.5 (38.0)</td>
</tr>
<tr>
<td>60</td>
<td>266.3 (61.4)</td>
<td>-1.7 (24.5)</td>
<td>261.0 (68.6)</td>
<td>15.0 (42.6)</td>
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<tr>
<td>75</td>
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<td>266.5 (68.3)</td>
<td>20.5 (46.1)</td>
</tr>
<tr>
<td>90</td>
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<td>-2.1 (36.3)</td>
<td>266.4 (68.3)</td>
<td>20.4 (39.6)</td>
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<tr>
<td>105</td>
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<td>-9.9 (39.9)</td>
<td>257.7 (75.0)</td>
<td>11.7 (44.9)</td>
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<tr>
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<td>-3.5 (24.5)</td>
<td>262.6 (59.4)</td>
<td>16.6 (24.5)</td>
</tr>
<tr>
<td>150</td>
<td>272.6 (84.4)</td>
<td>3.9 (56.3)</td>
<td>267.5 (76.0)</td>
<td>21.3 (38.6)</td>
</tr>
<tr>
<td>180</td>
<td>270.2 (78.4)</td>
<td>1.5 (37.0)</td>
<td>267.9 (79.3)</td>
<td>23.7 (51.6)</td>
</tr>
<tr>
<td>Total</td>
<td>267.1 (65.9)</td>
<td>-1.0 (36.9)</td>
<td>262.8 (64.5)</td>
<td>16.5 (38.1)</td>
</tr>
</tbody>
</table>

Values are mean (SD) expressed in arbitrary units.
tion of the medications. Percentage changes in flow were plotted against time, and AUCs were calculated separately for day 1 and day 5 according to the trapezoidal rule. Values of AUC and the maximum flow percentage change from baseline were submitted to repeated-measures analysis of variance (rm-ANOVA) with within-subject factors medication (nimodipine or placebo) and day (day 1 or day 5). Post-hoc *t* tests with *α*-correction for multiple testing were performed if ANOVA findings were significant. Systolic and diastolic blood pressure and heart rate were analyzed analogously. Analyses were performed (SPSS release 12 software; SPSS Inc., Chicago, IL). The *α*-level was set at 0.05. All values are expressed as mean ± SD.

**RESULTS**

Nineteen subjects successfully completed the study. One woman was excluded from the study because the optic quality of the perfusion images was below the quality standard. A few nimodipine concentrations and flow data were missing because of technical problems, but this was never more than an occasional one or two per sampling point.

**Side Effects**

**Headache.** There was no significant difference in the subjects’ reports of headache between the nimodipine and the placebo periods. Five of 20 subjects experienced headache for 6 days overall during the administration of nimodipine (6% of all subjects × days). During the placebo period, 3 of 20 subjects reported headache for 4 days overall (4% of all subjects × days).

**Platelet Count.** Platelet count did not change after the administration of nimodipine or placebo.

**Arterial Blood Pressure.** Systolic blood pressure (SBP) did not change after the administration of nimodipine compared with placebo (medication effect: *P* = 0.46), whereas diastolic blood pressure (DBP) was significantly lower after the administration of nimodipine than after administration of placebo (rm-ANOVA medication effect: *df* = 1,18, *F* = 5.76, *P* = 0.027). Heart rate was not altered significantly by nimodipine compared with placebo (medication effect: *F* = 0.86).

**Intraocular Pressure.** Intraocular pressure was not altered by the administration of nimodipine or placebo.

**Nimodipine Plasma Concentrations**

Concentrations of racemic nimodipine were approximately 1.2 times higher than concentrations of the R(+)-enantiomer and approximately 8.2 times higher than concentrations of the S(–)-enantiomer, judged by AUC. In this article, only the concentrations of the racemate are presented.

At the first and fifth days, similar concentration-time courses of nimodipine were observed (Fig. 2). AUCs were similar on both days (*t* test: *P* = 0.64). Values of *C*<sub>max</sub> displayed a large interindividual variance and ranged from 0 ng/mL to 57.5 ng/mL. On average, maximum nimodipine plasma concentrations (*C*<sub>max</sub>) were 16.6 ± 14.9 ng/mL and 12.0 ± 10.3 ng/mL on day 1 and day 5, respectively (*P* = 0.068). They were observed at 81 ± 50 and at 95 ± 40 minutes (*t*<sub>max</sub>) after the administration of nimodipine on day 1 and day 5, respectively (*P* = 0.45).

**Retinal Blood Flow**

Absolute values of retinal perfusion are shown in Table 1, and relative changes in blood flow from baseline are represented in Figure 3.

AUCs of the percentage change in flow versus time (Fig. 4, left) were significantly larger after nimodipine than after placebo administration (rm-ANOVA medication effect: *df* = 1,18, *F* = 9.94, *P* < 0.01). With both nimodipine and placebo administration, the respective AUCs were larger on day 5 than on day 1 (rm-ANOVA effect day: *df* = 1,18, *F* = 5.9, *P* = 0.026). However, this difference between days was similar for nimodipine and placebo (rm-ANOVA interaction medication by day: *df* = 1,18, *F* = 2.0, *P* = 0.174).

After the administration of nimodipine, maximum increases in retinal blood flow from baseline were 28.5% ± 14.4% and 39.6% ± 21.4% on day 1 and day 5, respectively (Fig. 4, right). Related time points were calculated to 96.3 ± 62.5 minutes and 71.1 ± 63.2 minutes on day 1 and day 5, respectively. After placebo administration, maximum increases in retinal blood flow were 20.5% ± 16.8% and 31.9% ± 14.6% at the time points 87.6 ± 61.1 minutes and 82.1 ± 58.2 minutes on day 1 and day 5, respectively. The more pronounced maximum increase in blood flow was statistically significant (rm-ANOVA medication effect: *df* = 1,18, *F* = 5.38, *P* = 0.032) after nimodipine administration than after placebo administration. In addition, the more pronounced increase was also statistically significant (rm-ANOVA effect day: *df* = 1,18, *F* = 14.12, *P* = 0.001) at day 5 than at day 1, whereas the increase from day 1 to day 5 did not differ between nimodipine and placebo (rm-ANOVA interaction medication by day: *df* = 1,18, *F* = 0.002, *P* = 0.964). However, *α*-corrected post hoc *t* tests did not reveal significant differences in maximum increases from baseline in retinal blood flow between nimodipine and placebo at day 1 or at day 5. The difference between day 5 and day 1 was significant for placebo (*P* < 0.05) but not for the nimodipine condition. Finally, the time points at which the maximum increases were observed did not differ between medications or days (rm-ANOVA, *P* > 0.29 for main effects and the interaction).

**DISCUSSION**

We have examined the effect of orally administered nimodipine on retinal blood flow in a double-blind, two-way, crossover study compared with plasma concentration. We found that the percentage change in flow versus time was significantly larger after oral administration of nimodipine at a dosage of 30 mg three times a day than after placebo. In addition, it was larger on day 5 than on day 1. Similarly, the maximum increase in retinal blood flow was significantly larger after nimodipine than after placebo administration and again was larger on day 5 than on day 1. However, the differences of maximum increases between days 1 and 5 were similar for both, nimodipine and placebo.

**Calcium Antagonists and Brain Circulation**

Our results, which reveal increased retinal blood flow of approximately 29% on 96 minutes at day 1 and near 40% at 71 minutes on day 5 and decreased diastolic blood pressure after oral administration of nimodipine, are in agreement with many reports of the impact of nimodipine on the brain. The effect of nimodipine in anesthetized primates was reported by Harper et al., who found that continuous intravenous infusion of 2 μg/kg per minute nimodipine increased cerebral blood flow and gradually increased to 27% above control after 50 minutes of infusion, causing a modest decline in mean arterial blood pressure. Cerebral blood flow was also measured in rabbits by Haws et al., who reported an approximately twofold increase in cerebral blood flow associated with a small decrease in arterial pressure after an infusion of 0.1 μg/kg per minute nimodipine. In addition, intracarotid infusion of nimodipine produced dose-dependent increases in cerebral blood flow with no change in cerebral oxygen consumption.

As summarized from the literature, nimodipine (1) significantly increases cerebral blood flow depending on the dose...
applied, (2) does not change oxygen use, (3) does not interfere with autoregulation capacity, and (4) does not alter the rate of glucose use.\textsuperscript{2,24–26}

The beneficial effect of nimodipine on ischemia in the brain was demonstrated by Kawagushi et al.\textsuperscript{27} In a rat model of 2-hour transient focal ischemia, nimodipine (50\textsuperscript{g}/kg) was shown to reduce ischemic damage by 33\% if administered intravenously 5 minutes before the induction of ischemia.\textsuperscript{27} Nimodipine influences endothelin (ET)–mediated vasoconstriction. Pierre et al.\textsuperscript{28} have demonstrated that 0.3 to 3\textsuperscript{M} nimodipine significantly attenuates the vasoconstrictive response to ET-1.

Calcium Antagonists and Eye Circulation

Increasing evidence indicates that impaired ocular blood flow participates in the development of glaucoma.\textsuperscript{29,30} Through the use of different techniques, it has been shown that retinal blood flow is reduced in patients with glaucoma.\textsuperscript{31} Calcium antagonists such as nimodipine may be helpful in NTG therapy because they are known for their suggested vasodilatory effects given that they reduce calcium influx through the cell membrane.\textsuperscript{52,53} Luksch et al.\textsuperscript{54} have examined the impact of 60 mg nimodipine in NTG patients 2 hours after oral administration. Results disclosed that nimodipine increased the blood flow of the optic nerve head by 18\% and improved color-contrast sensitivity. The beneficial effect of calcium antagonists for visual field loss in NTG was also examined in a cohort of 110 patients with NTG who were followed up for more than 2 years. An association was observed between change in visual field and treatment with calcium channel blockers. Additionally, change in visual field was found to be correlated with recovery rate from a cold recovery test, with systolic blood pressure, and with disk hemorrhage.\textsuperscript{55} Other authors have also described a performance-corrected improvement in visual field deviation and contrast sensitivity in patients with NTG and in control subjects after oral administration of nimodipine (30 mg twice a day).\textsuperscript{36,55} In contrast, Wilson et al.\textsuperscript{58} did not find a change in blood flow velocity of the central retinal artery and the ciliary circulation after 6-week administration of 30 mg/d sustained-release nifedipine in patients with primary open-angle glaucoma or NTG. However, the authors concede that the variability in response to nifedipine, attributed to heterogeneous risk factors for the development of glaucoma, may be responsible for the insignificant results. Nifedipine from a non-sustained release formulation (30 mg/d) administered over 6 months failed to provide uniform improvement of visual function and ocular hemodynamic responses in NTG patients.\textsuperscript{39} Other calcium antagonists were also examined for their potential beneficial impact on ocular circulation. Yamamoto et al.\textsuperscript{40} have reported that the calcium channel blocker nilvadipine reduces vascular resistance in distal retrobulbar arteries and significantly increases velocity in the central retinal artery in patients with NTG. The calcium channel blocker brovimecamine fumarate was shown to improve the visual field in NTG patients and to increase initial systolic blood pressure.\textsuperscript{41}

Studies examining NTG patients arrived at different conclusions about the efficacy of calcium antagonists with regard to ocular perfusion. Lower doses were administered in these trials than in our study (maximum 60 mg conventional nimodipine or 30 mg sustained-release nimodipine versus 90 mg/d conventional nimodipine).

The effect of calcium channel inhibitors requires preexisting vascular tone.\textsuperscript{42} In patients with advanced NTG, this vascular tone may be reduced markedly, detaining nimodipine to...
exert its effect on the vessels. Thus, the lack of efficacy of this medication in some studies may be also explained. 

Topical administration of a calcium inhibitor was shown to decrease the vascular resistance index in the central retinal artery because of increased end-diastolic velocity. This study included healthy human volunteers, lending credence to the assumption that in patients with normal vascular tone, as in our trial, the cross-sectional area of the vessel is less important than end-diastolic velocity for increased perfusion.

Nimodipine Plasma Concentrations

It was reported that the mean maximum plasma concentrations ($C_{max}$) of nimodipine after administration of 30 mg three times a day were 12.5 to 17.5 ng/mL in young subjects and 26 ± 10 ng/mL in elderly subjects.22–25 Our results confirm a large interindividual variance in maximum nimodipine concentration in plasma and average concentrations of 17 ng/mL and 12 ng/mL at day 1 and day 5, respectively.

Limitations of the Study

The difference in the increase of maximum flow from baseline between the nimodipine and placebo groups was not significant between day 1 and day 5. However, visual inspection of the data (Fig. 3) suggested an increase in retinal blood flow from day 1 to day 5 that was not observed for the nimodipine plasma concentrations. It remains to be examined whether, under chronic treatment with the same dose of nimodipine (30 mg three times a day) for a longer period, retinal perfusion maintains this trend to increase.

In a recently published study, it has been shown that HRF flow maps of the rat eye reflect blood flow in the larger elements of the microvasculature (i.e., retinal arteries, retinal arterioles, retinal veins, and choroidal vessels) rather than the capillary network. The present study does not allow for an appraisal of the influence of nimodipine on the circulation in retinal capillaries or for estimation of the total volumetric blood flow. However, if the perfusion in larger vessels is increased, it may be that the capillaries must absorb the increased blood volume. On the other hand, we did not examine whether, at day 5, all counterregulatory responses were equilibrated. Extension of the treatment period could yield information about this as well. In addition, studies in patients with glaucoma examining the effects of nimodipine at higher doses (e.g., 30 mg three times daily, as in the present study) could clarify whether the differences between the present positive results with respect to an effect of nimodipine and the previously reported negative results are due to the lower doses used in previous trials.

References


