A double masked placebo controlled study on the effect of nifedipine on optic nerve blood flow and visual field function in patients with open angle glaucoma

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Aims To investigate whether nifedipine affects ocular perfusion or visual fields in open angle glaucoma patients.

Methods In a parallel group study nifedipine or placebo was administered for 3 months ($n=30$). Ocular fundus pulsation amplitude (FPA), cup blood flow ($Flow_{cup}$) and visual field mean deviation (MD) were measured.

Results Five patients receiving nifedipine discontinued due to adverse events. Nifedipine did not affect FPA [difference: 0.3 μm (95% CI −0.3,0.9); $P=0.70$], $Flow_{cup}$: [difference: −9 rel.units (95% CI −133,114); $P=0.99$], or MD [difference: 0.2dB (95% CI −2.2,2.7); $P=0.51$] *vs* placebo.

Conclusions Systemic nifedipine is not well tolerated in glaucoma patients and exerts no effect on visual fields or ocular perfusion.

Keywords: calcium channel blockers, glaucoma, ocular blood flow, visual field

Introduction

Glaucoma is one of the most common causes of blindness in the industrialized nations. Recent investigations show that the most widely used indicator for glaucoma, the intraocular pressure (IOP), is not necessarily an adequate predictor of clinical severity [1]. Hence, factors other than IOP are probably involved in the pathogenesis of glaucoma. There is evidence from several studies that vascular factors play a role in this context [2]. Nevertheless the current treatment of glaucoma aims to decrease IOP without attention to ocular perfusion.

There is increasing evidence that calcium channel blockers may be useful in the treatment of glaucoma patients [2, 3]. However, results from placebo controlled-randomised clinical trials are lacking. We therefore performed a study investigating the effect of nifedipine treatment on ocular blood flow and visual fields in patients with open angle glaucoma.

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Methods

Subjects

Based on the variability of the haemodynamic measurements, an *a priori* sample size calculation was performed. Accordingly 40 subjects with primary open angle glaucoma were scheduled. Approval from the local Ethics Committee was obtained and all subjects gave written informed consent.

Primary open angle glaucoma was defined as pathologic optic disc appearance and pathologic visual field. All patients had their intraocular pressure controlled with an IOP <21 mmHg during the previous 3 months with a history of increased IOP values ≥ 22 mmHg measured on at least three independent time points. Visual acuity was $>20/30$ in all patients. During the study period all patients took their usual topical antiglaucoma medication.

Exclusion criteria were: ametropia >4 diopters, evidence of any other eye disease which may influence ocular perfusion, limited view of the fundus because of cataract, inability to fixate, history of trabeculectomy or laser trabeculoplasty, diabetes mellitus and uncontrolled hypertension (defined as SBP >170 mmHg and DBP >100 mmHg). Patients were allowed to take their

usual antihypertensive medication except calcium channel blockers. Only one eye of each patient was studied.

Some of the patients took concomitant vasoactive medication, because of diseases other than glaucoma, including oral β-adrenoceptor blockers, ACE inhibitors, diuretics, aspirin, digitalis, ginkgo biloba, and codergocrine.

Study design

The study was performed in a double masked, placebo-controlled, randomized, parallel group design. Subjects were randomized (1 : 1) to nifedipine or placebo treatment. Nifedipine (Adalat retard®, Bayer, Vienna, Austria) was administered in its sustained release form as an oral dose of 20 mg twice daily Placebo tablets were identical in appearance and taste. Subjects were instructed to take the medication at breakfast and dinner, respectively.

Baseline measurements were performed on the first study day. In the morning of the next day subjects started their treatment. Subjects were re-admitted for measurements after 1 week, 1 and 3 months. A difference of $\pm$ 2 days was allowed for follow-up investigations. The measurements were performed in the morning before drug intake. Patient compliance was assessed by tablet count.

Study methods

Blood pressure and pulse rate were recorded automatically (HP-CMS patient monitor, HP, Palo Alto, CA, USA).

Synchronous pulsations of the ocular fundus were assessed by laser interferometry. The method is described in detail by Schmetterer *et al.* [4]. Briefly, the eye is illuminated by a laser beam, which is reflected at both the front side of the cornea and the retina. The resulting interferences allow detection of small changes in the corneo-retinal distance during the cardiac cycle. The maximum distance change is called fundus pulsation amplitude (FPA) and estimates pulsatile choroidal blood flow [5].

Optic disc microcirculation was assessed with a commercially available scanning laser Doppler flowmeter (Heidelberg Retina Flowmeter, HRF, Heidelberg Engineering, Heidelberg, Germany) [6]. In the present study two 200×200 μm areas were chosen for calculation of retinal haemodynamic parameters. One area was located at the cup ($Flow_{cup}$), the second area was located at the temporal neureoretinal rim ($Flow_{rim}$). At least two recordings were taken and the mean of the two values from the best images obtained was calculated. Only flow readings with a coefficient of variation of less than 20% were included for analysis.

Mean deviaton was determined with automated visual field testing using the Humphrey Field Analyser (program 30–2). Peripheral colour contrast sensitivity along the tritan axis was measured with a computer graphics device in 20° off-axis [7]. A Goldmann applanation tonometer was used to measure intraocular pressure (IOP).

Data analysis

All subjects who received at least one tablet were included for analysis. Data analysis was done by intention to treat with last observation carry forward. The effect of nifedipine on haemodynamic parameters was assessed with repeated measure ANOVA *vs* placebo. Data are presented as means $\pm$ 95% CI. $P<0.05$ was considered the level of significance.

Results

Because of the high rate of adverse events the study was stopped after 30 patients (15 patients in the nifedipine group and 15 in the placebo group). In the placebo group one subject reported dizziness and therefore decided to discontinue, whereas another patient did not appear at the 1 week visit without specifying any reason. In the nifedipine group five out of the 15 patients discontinued prematurely because of headache, flushing, dizziness, oedema and/or systemic hypotension.

The other 23 patients completed the clinical trial as scheduled. Whereas the patients in the placebo group did not report any side-effects, 6 out of the 10 remaining patients in the nifedipine group reported side-effects including headache, dizziness and nausea. In the 23 patients who finished the trial compliance was high, the tablet count was within 10% of the expected value.

Three patient's results in the rim and four patient's results at the cup did not fulfil the study criteria and therefore were not included in the analysis. In the nifedipine group two patients' results were not included for analysis at both fundus locations.

Baseline ocular and systemic haemodynamic parameters were similar in the two study groups (Table 1; FPA: $P=0.70$, $Flow_{rim}$: $P=0.41$, $Flow_{cup}$: $P=0.99$). Nifedipine had no significant effect on FPA ($P=0.31$ *vs* placebo), $Flow_{rim}$ ($P=0.32$ *vs* placebo), or $Flow_{cup}$ ($P=0.21$ *vs* placebo; Tables 1 and 2). Nifedipine caused a small decrease in systolic blood pressure (data not shown; $P=0.04$ *vs* placebo), whereas diastolic blood pressure and pulse rate were unchanged. There were no differences in baseline colour contrast sensitivity or visual fields between groups (threshold: $P=0.87$, mean deviation: $P=0.55$). Nifedipine exerted no effects on the threshold along the tritan axis ($P=0.83$) or on mean deviation ($P=0.51$) *vs* placebo (Table 2).

Table 1 The effect of 3 months nifedipine ($n=15$) or placebo ($n=15$) on fundus pulsation amplitude (FPA), flow on the neuroretinal rim ($Flow_{rim}$) and flow at the cup ($Flow_{cup}$). The data are presented as mean (95% CI).

	Baseline	*1 week*	*1 month*	*3 months*
Nifedipine				
FPA (μm)	3.1 (2.5, 3.7)	3.1 (2.6, 3.6)	3.2 (2.7, 3.7)	3.3 (2.8, 3.8)
$Flow_{rim}$ (rel.units)	533 (436, 630)	525 (443, 608)	540 (453, 627)	550 (459, 641)
$Flow_{cup}$ (rel.units)	264 (210, 318)	266 (224, 308)	290 (240, 340)	281 (229, 333)
Placebo				
FPA (μm)	3.0 (2.5, 3.5)	2.9 (2.6, 3.2)	2.9 (2.5, 3.3)	2.9 (2.6, 3.2)
$Flow_{rim}$ (rel.units)	481 (407, 555)	460 (391, 529)	438 (372, 504)	500 (428, 572)
$Flow_{cup}$ (rel.units)	265 (212, 318)	271 (207, 335)	259 (197, 322)	260 (207, 313)

Table 2 Mean and 95% confidence intervals (CI) for differences of main comparisons of treatment with nifedipine *vs* placebo (FPA = fundus pulsation amplitude, $Flow_{rim}$ = flow on the neuroretinal rim, $Flow_{cup}$ = flow at the cup, threshold = threshold along the tritan axis).

	Nifedipine vs *placebo* *mean of difference (CI)*
FPA (μm)	0.3 (−0.3, 0.9)
$Flow_{rim}$ (rel.units)	44 (−118, 266)
$Flow_{cup}$ (rel.units)	−9 (−133, 114)
Threshold (%)	0.7 (−6.0, 7.4)
Mean deviation (dB)	0.2 (−2.2, 2.7)

Discussion

The present trial was discontinued prematurely because of the high incidence of adverse events, which has previously been reported in patients receiving systemic calcium channel blockers [8]. Our results clearly demonstrate that a considerable number of patients with open angle glaucoma are not willing or able to take nifedipine.

Moreover, the results of the present study do not indicate that nifedipine exerts beneficial effects on ocular perfusion, visual fields, or colour vision. With regard to blood flow assessment in the optic disc using scanning laser Doppler flowmetry, the final number of patients may have been insufficient to detect small changes, because only 75% of the originally calculated sample size was achieved, but no tendency of a blood flow change with nifedipine was seen. Premature discontinuation is less critical for fundus pulsation measurement, because of the high reproducibility of this technique [5]. Hence, the negative result from the present study shows that nifedipine is unlikely to increase ocular blood flow in glaucoma patients.

Randomized clinical trials on the effect of calcium channel blockers on visual fields in open angle glaucoma have not yet been performed. Our results are in keeping with retrospective studies, which did not show any beneficial effect of calcium channel blockers on the course of open angle glaucoma [3, 9] and indicate that 3 months nifedipine administration does not exert beneficial effects in open angle glaucoma patients.

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