European Journal of Ophthalmology / Vol. 4 / no. 1, 1994 / pp. 24-28

Influence of nifedipine on the visual fields of patients with optic-nerve-head diseases

A.Z. GASPAR, J. FLAMMER, PH. HENDRICKSON

University Eye Clinic, Basel - Switzerland

ABSTRACT: Calcium-channel blockers have long been employed in coronary disease, and recent investigations have indicated their efficacy in improving the visual field in low-tension glaucoma or presumed vasospasm, possibly by enhancing ocular circulation. We evaluated the short-term influence of a typical calcium-channel blocker, nifedipine, on 59 patients with visual-field defects, some with optic-nerve-head pathology (n = 38) and some with normal-appearing optic nerve heads (n = 21). On the average, a statistically significant improvement of 1.2 dB was observed. Different types of patients, however, behaved quite differently. The younger the patient, the greater the improvement. Patients with normal optic nerve heads improved by 1.54 dB, whereas patients with optic-nerve-head excavation improved by only 0.66 dB. No response was observed in patients with anterior ischemic neuropathy. Marked deterioration was noted in one glaucoma patient with low systemic blood pressure. The visual-field changes were observed in the scotomatous and non-scotomatous areas. Thus, the calcium-channel blocker nifedipine can be effective in some selected diseases whose pathogenesis probably involves vascular dysregulation though it may even be contraindicated in others (Eur J Ophthalmol 1994; 4: 24-8)

KEY WORDS: Calcium-channel blockers, Nifedipine, Visual fields, Optic-nerve-head disease, Ocular circulation

INTRODUCTION

Circulation disturbances are involved in the pathogenesis of many diseases in most organs, and deficiencies may be due to vascular or rheological disorders. Functional dysregulation of the ocular circulation might be involved in ocular diseases, especially in the pathogenesis of normal-tension glaucoma (1-6). It is therefore of great interest to know how local regulation can be pharmacologically influenced and whether any such pharmacological effect is of clinical relevance.

Calcium-channel blockers (CCB) are often used to influence vascular dysregulation, such as for the treatment of Raynaud's phenomenon, variant angina, and for prophylaxis against migraine. Therefore, such drugs may also be of interest in treating dysregulation of the ocular circulation (7-11).

CCB are an extremely varied group of drugs which differ markedly in their structures, receptor-binding characteristics, accessory properties, hemodynamic effects, and pharmacogenetics. An intrinsic characteristic is their tissue-selectivity. Some (e.g. nisoldipine) act preferentially on the coronary vessels, whereas others (e.g. nimodipine) act selectively on the cerebral vessels.

Little is known about the ocular-tissue selectivity of CCB. Nifedipine increases choroidal blood flow in healthy rabbits (10) and in vasospastic patients (9, 11). Diltiazem blocks KCl-induced constriction of the canine posterior ciliary arteries (12) and of the ophthalmic arteries in cats and dogs (13, 14). Endothelin-l-induced constriction of bovine retinal small arteries is abolished by nitrendipine (15). Endothelin-induced constriction of ciliary arteries, however, is not blocked by nifedipine (16). Nicardipine increases optic nerve

1120-6721/024-05 $02.50/0

head (ONH) circulation, but not retinal circulation, in cats despite a decrease in blood pressure (17).

A beneficial influence of nifedipine on the visual field of vasospastic patients, most of them without glaucomatous ONH damage, and others with normal-tension glaucoma, has been reported (18). Patients who responded favorably to nifedipine were generally younger and had a better average response in the peripheral circulation (3, 8). The effect of CCB on normal-tension glaucoma is controversial (19, 20). Because such different types of patients were treated in the various studies, it is conceivable that CCB treatment is of benefit to some but of no value — or even has an adverse effect — in others (18, 21).

The purpose of the present study was to analyze the short-term effect of nifedipine in patients with different types of ONH damage or with unexplained visual-field defects.

MATERIALS AND METHODS

This study included patients with visual-field defects, due either to ONH pathology or to indeterminate causes (with normal-appearing discs, n = 21). Among the 38 patients with ONH changes there were:

— 12 patients with glaucomatous cupping, including 9 open-angle glaucomas and 3 normal-tension glaucomas,
— 8 patients with pale optic discs of unknown origin, 4 patients with acute, and 1 with chronic anterior ischemic neuropathy, and
— 13 patients with both glaucomatous cupping and pale optic discs, including 5 with open-angle glaucoma and 8 with normal-tension glaucoma.

The 21 patients with normal-appearing OHN and unexplained visual-field defects had other ocular conditions such as mild myopia, or status after ocular trauma. These changes, however, did not fully explain their visual-field defects.

To rule out, or at least to minimize learning effects (22), only patients with experience in Octopus automated perimetry were included. For the purpose of this study, we included the visual fields measured one or two days before nifedipine, and those measured between 1 and 24 hours. Only one eye was randomly selected for each patient. The dosage of nifedipine varied between 10 and 20 mg/day.

The visual fields were tested with the Octopus Program G1 (23). We analyzed the influence on total visual-field damage (MD) and on the Bebie curve (cumulative defect curve) (24). We chose Point 19 of the Bebie curve to analyze the influence on the non-scotomatous areas (25). MD before treatment minus MD after treatment is referred to as Delta MD and, likewise, Point 19 before treatment minus Point 19 after treatment as Delta Point 19. The Pearson correlation and paired T-test were employed for statistical analysis.

RESULTS

Average influence of nifedipine

The mean MD (± SEM) improved from 10.3 ± 0.8 dB to 9.1 ± 0.8 dB; this was significant ($p < 0.01$). Point 19 on the cumulative defect curve improved on the average from 6.5 ± 0.7 dB to 5.2 ± 0.6 dB, which was also significant ($p < 0.001$). The average improvement, therefore, was 1.09 dB for MD and 1.22 dB for Point 19. The changes in MD (Delta MD) were highly significantly correlated to the changes in Delta Point 19, $R = 0.79$ ($p < 0.001$). This indicates that if the visual fields changed in the scotomatous areas they also changed in the non-scotomatous ones. The changes in visual fields are only weakly related to the patients' ages. For Delta MD, R was −0.29 ($p < 0.05$), and for Delta Point 19, $R = -0.32$ ($p < 0.05$). In other words, the younger the patient, the greater the chance of improvement of the visual field.

Influence in different types of disease

Although the whole group improved on the average, some individual patients either did not respond or even deteriorated. This might be partially due to spontaneous fluctuation of the visual field (26), and partially, however, to different pathomechanisms involved in the disease. The influence was best in the group with normal-appearing ONH, where the average improvement was 1.54 dB. In patients with pale but not excavated ONH the improvement was 1.33 dB. The average improvement in patients with excavated ONH was only 0.66 dB. The group with the combination of excavated ONH and pale neuroretinal rims

was somehow in-between, with a mean improvement of 1.07 dB. When glaucoma patients (with excavated ONH) were grouped as having either open-angle glaucomas (untreated IOP 24 mmHg or higher) or normal-tension glaucomas (untreated IOP less than 24 mmHg) the nifedipine had a clearly different effect; the mean improvement in the first group was 0.68 dB and in the latter 1.20 dB.

One of the patients with open-angle glaucoma and systemic hypotension showed a reversible deterioration of several dB. The four patients with acute and the one with chronic anterior optic neuropathy showed no change. In the group with normal ONH, one patient with depression and two patients with a history of ocular trauma deteriorated. However, two patients having presumed trauma or the optic nerve of chiasma improved.

DISCUSSION

CCB have been applied in coronary disease, angina pectoris, cardiac arrhythmias, systemic hypertension, and Raynaud's phenomenon, and recent investigations have indicated their efficacy in improving visual fields, probably through an increase in ocular circulation. The present study found some generally beneficial effect of nifedipine and, to view these findings in their proper context we want to summarize some concepts about ocular circulation.

The ocular circulation is anatomically and functionally complex on account of the different embryogenic origins of the individual parts of the eye. The retinal circulation is totally separate from that of the choroid (27). The retina has a blood-retinal barrier similar to the blood-brain barrier (28). The capillaries of the choroidal vessels, however, are fenestrated (27, 29). The blood supply to the ONH is special in two ways: a) while the arterial blood supply is provided by the ciliary vessels, venous drainage is achieved by the central retinal vein; b) whereas the capillaries of the ONH have tight junctions, like the retinal capillaries, molecules can diffuse freely from the adjacent choroid in the prelaminar region (30-32).

Blood flow in the different parts of the eye is regulated by many different mechanisms. The retinal vessels, only rarely innervated by the autonomic nerve system, exert autoregulation for a wide range of IOP and blood pressure, similar to the brain (28). The choroid is highly innervated (33). The ocular circulation is further influenced by the regulation of the extraocular feeding vessels, such as the posterior ciliary arteries (16, 34-37).

Less is known about the local regulation of blood flow. Stimulation of alpha-1 receptors constricts the small arteries branching from the ciliary circle (38). Alpha- and beta-adrenergic and cholinergic receptors (39), as well as angiotensin-II receptors, are present (40, 41). Their exact role remains to be elucidated. Alpha-adrenergic stimulation reduces the blood flow of the choroid and the ONH, despite an increase in blood pressure (38, 42). The retinal circulation thus remains unchanged. Endothelin I and III, angiotensin II, and some prostaglandins reduce circulation in the choroid and the retina (15, 36, 41, 43). Reduced nitric-oxide production reduces ocular circulation drastically (16,34). On the other hand, histamine, acetylcholine, angiotensin-II blockers, endothelin-blockers, and alpha-1-receptor blockers all dilate ocular vessels (15, 44).

In experimental studies some CCB increased ocular circulation, especially in the ONH, even when the blood pressure decreased. However, under pathological conditions, the beneficial effect might depend on the type of disease. The influence on visual fields of glaucoma patients remains controversial (18, 20).

All patients studied here had experience with automated perimetry. Thus, even if a learning effect could not be totally excluded, it was at least minimized.

The present study indicates that CCB generally do have a beneficial effect. In some cases, however, no influence or even deterioration of the visual field was observed. Although the number of patients was too small for any definite statement, there are some indications that different groups of patients behave differently. Whereas no effects whatsoever were seen in the patients with non-artheritic anterior ischemic neuropathy, a significant improvement was observed in others. In other words, the statistical significance of the drug's influence in the whole sample does not necessarily apply to its effect on functional damage due to individual ONH diseases. Its influence was significantly correlated to age, younger patients responding better than older patients. Patients with normal or slightly pale ONH clearly responded more than patients with glaucomatous cupping. When glau-

comatous patients were compared, those with normal IOP improved more than those with high IOP. The observation that one glaucoma patient with low blood pressure showed reversible deterioration of the visual field indicates that nifedipine might be carefully used in patients with very low blood pressure.

As a conclusion, CCB are potentially helpful in selected patients in whom vascular dysregulation is probably involved in the pathogenesis of an ONH disease (18). Much more research is needed to define more exactly in which patients treatment might be beneficial and in which it might even be contra-indicated. Although short-term studies give some interesting pharmacological information, only long-term studies will establish the clinical relevance.

Reprint requests to:
Josef Flammer, M.D.
University Eye Clinic
Mittlere Strasse 91
CH-4056 Basel, Switzerland

REFERENCES

1. Gasser P, Flammer J. Influence of vasospasm on visual function. Doc Ophthalmol 1987; 66: 3-18.
2. Flammer J, Guthauser U, Mahler M. Do ocular vasospasms help cause low-tension glaucoma? Doc Ophthalmol 1987; 49: 397-9.
3. Guthauser U, Flammer J, Mahler F. The relationship between digital and ocular vasospasm. Graefe's Arch Clin Exp Opthalmol 1988; 226: 224-6.
4. Gasser P, Flammer J, Guthauser U, Mahler F. Do vasospasms provoke ocular diseases? Angiology 1990; 41: 213-9.
5. Gasser P, Flammer J. Blood cell velocity in the nailfold capillaries of patients with normal-tension or high-tension glaucoma and of healthy controls. Am J Ophthalmol 1991; 111: 585-8.
6. Flammer J, Gasser P, Prünte Ch, Yao K. The probable involvement of factors other than intraocular pressure in the pathogenesis of glaucoma. In: Drance SM, Van Buskirk EM, Neufeld A, eds. Pharmacology of glaucoma. Baltimore: Williams and Wilkins, 1992; 273-83.
7. Gasser P, Flammer J, Guthauser U, Niesel P, Mahler F, Linder HR. Bedeutung des Vasospastischen Syndroms in der Augenheilkunde. Klin Mbl Augenheilk 1986; 188: 409-11.
8. Kitazawa Y, Shirai H, Go FJ. The effect of calcium antagonists on visual field in low-tension glaucoma. Graefe's Arch Clin Exp Ophthalmol 1989; 227: 408-12.
9. Gasser P, Flammer J. Short- and long-term effect of nifedipine on the visual field in patients with presumed vasospasm. J Int Med Res 1990; 18: 334-9.
10. Miyoshi T. Effect of nifedipine on choroidal circulation 1. Change of choroidal blood flow in rabbits. Trans Jpn Soc Ophthalmol 1984; 35: 664-70.
11. Prünte Ch, Flammer J. Choroidal angiography findings in patients with glaucoma-like visual field defects. In: Heijl A, ed. Perimetry update. Amstelveen: Kugler & Ghedini, 1989; 325-7.
12. Okudo H, Chiba S. Regional differences of vascular sensitivities in canine long posterior ciliary arteries. Curr Eye Res 1988; 7: 457-63.
13. Okubo H, Chiba S. Vascular responses of ophthalmic arteries to exogenous norepinephrine. Exp Eye Res 1989; 48: 539-47.
14. Yi Yu D, Alder V, Su EN, Cringle S. Relaxation effects of Diltiazem, Verapamil and Tolazoline on isolated cat opthalmociliary artery. Exp Eye Res 1992; 55: 757-66.
15. Nyborg NCB, Prieto D, Benedito S, Nielsen PJ. Endothelin I-induced contraction of bovine retinal arteries is reversible and abolished by nitrendipine. Invest Ophthalmol Vis Sci 1991; 32: 27-31.
16. Haefliger IO, Flammer J, Lüscher TF. Nitric oxide and Endothelin-1 are important regulators of human ophthalmic artery. Invest Opthalmol Vis Sci 1992; 33: 2340-3.
17. Harino S, Riva C, Petrig B. Intravenous nicardipine in cats increases optic nerve head but not retinal blood flow. Invest Ophthalmol Vis Sci 1992; 33: 2885-90.
18. Flammer J. Therapeutic aspects of normal-tension glaucoma. Curr Opin Ophthalmol 1993; 4:11: 58-64.
19. Lumme P, Tuulonen A, Airaksinen PJ, Alanko HI. Neuroretinal rim area in low-tension glaucoma: effect of nifedipine and acetazolamide compared to no treatment. Acta Ophthalmol 1991; 69: 293-8.
20. Netland PA, Chatuverdi N, Dreyer EB. Calcium channel blockers In the management of low-tension and open-angle glaucoma. Am J Ophthalmol 1993; 115: 608-13.

21. Goldberg I. Calcium-channel blockers — are they an answer? In; Drance SM, ed. International symposium on Glaucoma, Ocular Blood Flow, and Drug Treatment. Baltimore: Williams and Wilkins, 1992; 11: 90-6.
22. Marra G, Flammer J. The learning and fatigue effect in automated perimetry. Graefe's Arch Clin Exp Opthalmol 1991; 229: 501-4.
23. Flammer J, Jenni H, Bebie H, Keller B. The Octopus Glaucoma G1 Program. Glaucoma 1987; 9: 67-72.
24. Bebie H, Flammer J, Bebie T. The cumulative defect curve: separation of local and diffuse components of visual field damage. Graefe's Arch Clin Exp Ophthalmol 1989; 227: 9-12.
25. Funkhouser A, Flammer J, Fankhauser F, Hirsbrunner HP. A comparison of five methods for estimating general glaucomatous visual field depression. Graefe's Arch Clin Exp Ophthalmol 1992; 230: 101-6.
26. Flammer J. Fluctuations in the visual field. In: Drance SM, ed. Automated perimetry in glaucoma. Orlando: Grune and Stratton, 1985; 161-73.
27. Bill A. Some aspects of the ocular circulation. Invest Opthalmol Vis Sci 1985; 26/4: 410-24.
28. Bill A, Nilsson SEF. Control of ocular blood flow. J Cardiovasc Pharmacol 1985; 7 (Suppl 3): S96-102.
29. Törnquist P, Alm A, Bill A. Studies on ocular blood flow and retinal capillary permeability to sodium in pigs. Acta Physiol Scand 1979; 6: 343-50.
30. Weinstein JM, Funsch D, Page RB, Brennan RW. Optic nerve blood flow and its regulation. Invest Opthalmol Vis Sci 1982; 23: 640-5.
31. Hayreh SS. Blood supply of the anterior optic nerve. In: Ritch R, Shields MB, Krupin T, eds. The glaucomas. Baltimore: CV Mosby, 1989; 133-61.
32. Robert Y, Grauwiller Th, Hendrickson Ph, Brunner HR. Die Autoregulation der Papillengefässe und ihr Verhalten unter Halothan. Klin Mbl Augenheilk 1988; 192: 117-21.
33. Ruskell GL. Facial parasympathetic innervation of the choroidal blood vessels in monkeys. Exp Eye Res 1971: 12: 166-72.
34. Yao K, Tschudi M, Flammer J, et al. Endothelium-dependent regulation of the vascular tone of the porcine ophalmic artery. Invest Ophthalmol Vis Sci 1992; 32: 1791-8.
35. Haefliger IO, Flammer J, Lüscher TF. Heterogeneity of endothelium-dependent regulation in ophthalmic and ciliary arteries. Invest Ophthalmol Vis Sci 1993; 34/5: 1722-30.
36. Meyer P, Flammer J, Lüscher T. Endothelium-dependent regulation of the ophthalmic microcirculation in the perfused porcine eye. Invest Ophthalmol Vis Sci (in press).
37. Meyer P, Flammer J, Lüscher TF. Local anesthetic drugs reduce endothelium-dependent relaxations of porcine ciliary arteries. Invest Ophthalmol Vis Sci (in press).
38. Sugiyama K, Bacon DR, Cioffi GA, et al. The effects of phenylephrine on the ciliary body and optic nerve head microvasculature on rabbits. Glaucoma 1992; 1: 156-64.
39. Okubo H, Gherezghiher T, Koss MC. Long posterior ciliary arterial blood flow and systemic blood pressure. Invest Ophthalmol Vis Sci 1990; 31: 819-25.
40. Ferrari-Dileo G, Davis EB, Anderson DR. Angiotensin II binding receptors in retinal and optic nerve head blood vessel. Invest Ophthalmol Vis Sci 1991; 32: 21-6.
41. Sossi N, Anderson DR. Blockage of axonal transport in optic nerve induced by elevation of intraocular pressure: effect of arterial hypotension induced by Angiotensin I. Arch Opthalmol 1983; 101: 94-7.
42. Gherezghiher R, Okubo H, Koss MC. Choroidal and ciliary blood flow analysis: Application of laser Doppler flowmetry in experimental animals. Exp Eye Res 1991; 53: 151-6.
43. Sugiyama T, et al. Low-tension glaucoma and endothelin (ET-1). Folia Opthalmol Jpn 1992; 43: 554-9.
44. Bucci MG, Quaranta L, Manni GL. Dapiprozole increases ocular blood flow in glaucomatous eyes. New Trends Opthalmol 1992; 7: 131-3.