Effect of niacin on the choroidal circulation of patients with age related macular degeneration

T I Metelitsina, J E Grunwald, J C DuPont, G-S Ying

Aim: To investigate the effects of niacin on choroidal blood flow in age related macular degeneration (AMD).
Methods: 12 AMD patients with bilateral drusen and visual acuity of 20/40 or better in the study eye received a single oral dose of niacin (six subjects received 500 mg and six received 250 mg) or matching placebo on two separate occasions. Laser Doppler flowmetry was used to assess relative choroidal blood velocity (ChBVel), volume (ChBVol), and flow (ChBFlow) in the foveola of the study eye at baseline, 30, and 90 minutes after dosing.
Results: In comparison with placebo, a statistically significant 24% increase in ChBVol was observed 30 minutes after niacin administration (ANOVA, p = 0.01). In comparison with placebo, a significant decrease in ChBVol of 23% was observed in the 500 mg group (p = 0.04) and no significant change in ChBVol was seen in the 250 mg group at 30 minutes. No significant changes in ChBFlow were detected at 30 or 90 minutes. Also, there were no statistically significant changes in ChBVol or ChBFlow at 90 minutes. In comparison with placebo, a significant 24% increase in ChBVol was observed 30 minutes after niacin administration. Owing to simultaneous decrease in ChBVol, however, no significant change in ChBFlow was detected.

METHODS
This was a double blinded, randomised, placebo controlled, crossover study, which was carried out in a group of 12 white patients (nine women and three men) ranging in age from 62 to 84 years (mean 72 (SD 7) years). All patients had AMD features similar to those of AMD category 3 or worse of the AREDS study. In each patient, the eye with better visual acuity was considered as the study eye. All study eyes had large drusen and no evidence of choroidal neovascularisation (CNV). Retinal pigment epithelium hypertrophic changes were present in seven eyes and two eyes had a small area of extrafoveal geographic atrophy. Two patients had exudative AMD with disciform scar in the fellow eye.

Immediate release niacin (crystalline nicotinic acid) is a widely used lipid lowering agent which was first introduced in 1954 and was the first monotherapy shown to significantly reduce cardiovascular all-cause mortality. Niacin inhibits the production of very low density lipoprotein (VLDL) particles by the liver and consequently reduces the levels of circulating VLDL available for conversion to low density lipoproteins (LDL). The oral administration of a standard therapeutic dose of 500 mg of immediate release niacin induces intense flushing reactions in humans. The cutaneous capillary vasodilatation observed after niacin administration is the result of a massive release of prostaglandin PGD2 from niacin responsive skin cells.

Potentially, this vasodilatory quality of niacin could be of use in the treatment of age related macular degeneration (AMD) and other ocular diseases characterised by a decreased choroidal perfusion. Several recent reports have suggested that choroidal blood flow is reduced in AMD. Results obtained in our laboratory have shown a significant 37% decrease in choroidal blood flow in subjects with the non-exudative form of macular degeneration. The purpose of this study was to perform a preliminary assessment of the effects of niacin on the choroidal circulation of patients with AMD. Evidence of an effect of niacin on the choroidal circulation could open the way for further studies looking at the efficacy of niacin in the treatment of AMD.

Abbreviations: AMD, age related macular degeneration; CS, contrast sensitivity; CV, coefficient of variability; LDL, low density lipoproteins; VA, visual acuity; VLDL, very low density lipoprotein
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Placebo pills were designed to be identical to the niacin ones, but they did not contain the active component. To reduce the measurement bias, both the investigators and the patients were blinded to the treatment.

All circulatory measurements were performed in one eye of each patient (study eye). Measurements were obtained in the right eye in eight patients and in the left in four patients. Before administration of the drug, visual acuity (VA) was measured using ETDRS charts at 3.2 metres and contrast sensitivity (CS) testing was performed at 1 metre using Pelli-Robson contrast sensitivity charts.

All subjects received either 250 mg of immediate release niacin or placebo. Placebo pills were designed to be identical to the niacin ones, but they did not contain the active component. To reduce the measurement bias, both the investigators and the patients were blinded to the treatment.

To assess the reproducibility of our blood flow data, we calculated for each of the 12 subjects a coefficient of variability (CV) derived from three subsequent measurements in time (baseline, 30 minutes, and 90 minutes) on the day of placebo administration. CV was calculated using the following formula: CV = (standard deviation/mean) × 100. The mean brachial artery pressure (BPm) was calculated from the systolic blood pressure (BPs) and diastolic blood pressure (BPD) according to the following formula: BPm = BPs/2 + BPD. Perfusion pressure (PP) for the study eye was estimated according to the following formula: PP = 3/2BPm − IOP.

A diode laser beam (670 nm) with a 20 mW intensity and diameter of 200 μm was delivered to the eye through a fundus camera (model TFC; Topcon, Tokyo, Japan). Subjects were asked to fixate on the probing laser beam. Proper fixation was monitored by observation through the fundus camera. The light scattered back was electronically analysed. A detailed description of the technique has been previously reported.

Three measurements of choroidal circulation of approximately 30 seconds were obtained while patients were seated in the darkened room. Following ocular circulatory measurements, heart rate (HR) and brachial artery systemic blood pressure were assessed by automated sphygmomanometry (Accutorr 1A, Datascope, Paramus, NJ, USA). IOP was measured by Tonopen in both eyes.

RESULTS

When all 12 subjects were analysed together, mean ChBVol at baseline, 30 minutes, and 90 minutes was 0.21 (SD 0.05) AU, 0.21 (0.05) AU, and 0.21 (0.06) AU following placebo, and 0.19 (0.06) AU, 0.23 (0.06) AU, and 0.19 (0.06) AU following administration of niacin, respectively (fig 1). In comparison with placebo, a statistically significant 24% increase in mean ChBVol was observed 30 minutes after niacin administration (ANOVA; p = 0.01).

Most of the circulatory effect of niacin on ChBVol was dose related and derived from the six subjects who received the 500 mg dose. Further analysis carried out in this group of six patients, showed a 39% increase in mean ChBVol at 30 minutes after niacin administration (ANOVA, p = 0.03,
In contrast with a 10% increase in mean ChBVol in the group of six subjects who received 250 mg of niacin (ANOVA, $p = 0.36$), Figure 3 shows the individual values for percentage change in ChBVol for the subjects who received 250 mg and 500 mg of niacin. There were no statistically significant changes in mean ChBVol at 90 minutes.

In comparison with placebo, there was no statistically significant change in mean ChBVel after niacin administration at 30 minutes or 90 minutes for the group of 12 patients (ANOVA; $p = 0.17$; fig 4). Mean ChBVel at baseline, 30 minutes, and 90 minutes were 0.43 (0.09) AU, 0.42 (0.08) AU, and 0.41 (0.08) AU following administration of placebo, and 0.43 (0.07) AU, 0.38 (0.1) AU, and 0.42 (0.1) AU after niacin, respectively. When the analysis of ChBVel was conducted separately for the six subjects who received 500 mg of niacin, however, we found a significant 23% decrease in mean ChBVel at 30 minutes (ANOVA; $p = 0.04$; fig 5). No significant effect on mean ChBVel was observed in the niacin 250 mg group. Figure 6 shows the individual values for percentage change in ChBVel for the subjects who received 250 mg and 500 mg of niacin. There were no statistically significant changes in mean ChBVel at 90 minutes.

In comparison with placebo, there was no statistically significant change in mean ChBFlow after niacin administration at any of the time points (ANOVA; $p = 0.64$; fig 7). Mean ChBFlow at baseline, 30 minutes, and 90 minutes was 8.1 (2.2) AU, 8.0 (2.5) AU, and 7.8 (2.5) AU following administration of placebo and 7.5 (2.4) AU, 7.9 (2.7) AU, and 7.2 (2.9) AU after niacin, respectively. No changes in ChBFlow were detected in the group of six subjects, who received 500 mg of niacin (ANOVA; $p = 0.93$; fig 8).

Because we found no significant change in ChBFlow it is important to provide information on the magnitude of the changes that we would be able to detect with our methodology. We have estimated that we have 96% power to detect 20% changes in ChBFlow at type I error of 0.05. The coefficients of variability for ChBVel, ChBVol and ChBFlow were 6% (4%), 10% (7%) 10% (6%) respectively.

There were no statistically significant changes in mean contrast sensitivity or mean visual acuity at any of the time points (table 1). In comparison with placebo, there was a 9% decrease in BPm at 30 minutes after niacin administration ($t$ test, $p = 0.02$), a 7% increase in heart rate at 30 minutes ($p = 0.01$), and a decrease of 9% at 90 minutes ($p = 0.05$). A significant decrease in IOP of 23% was also seen at 30 minutes after niacin administration ($p = 0.01$).

There was no significant correlation between the percentage changes in BPm, PP, or IOP and the percentage changes in ChBVel, ChBVol and ChBFlow after administration of placebo or niacin. We observed a direct correlation of borderline significance between age and the % change in ChBVol at 30 minutes after administration of niacin ($R = +0.565$, $p = 0.055$; fig 9); in other words, after niacin administration older individuals tended to show larger increases in ChBVol than younger ones. No such significant correlation was seen after placebo treatment.

From the 12 subjects who participated in the study six experienced side effects related to niacin treatment. Two people experienced intense flushing with nausea, dizziness,
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That received 500 mg dose of niacin. In comparison with placebo, no significant effect on ChBflow was detected following niacin administration (ANOVA; \( p = 0.93 \)). Error bars correspond to ± 1 SE.

and loss of balance. These two subjects were not taking aspirin before the study. The other four subjects experienced mild hyperaemia of face and neck. Two of them were taking aspirin before the study and two of them were not. There was no association between flushing reactions and changes in circulatory parameters.

DISCUSSION

The peak plasma concentration of niacin occurs about 30 minutes after oral administration.\(^2\) Our results suggest at this time there is a statistically significant increase in ChBvol of 24% when all 12 subjects are analysed together. Concurrently, however, there is also a decrease in ChBvel that is statistically significant in the group of six subjects that received the 500 mg dose. Because the increase in ChBvol is accompanied by a simultaneous decrease in ChBvel there is no significant change in ChBFlow. Possibly, this could be due to an autoregulatory attempt to maintain a constant choroidal blood flow.

Interestingly, 30 minutes after niacin we observed a direct correlation of borderline significance (\( p = 0.055 \)) between age and the percentage change in ChBvol. In other words, older individuals tended to show larger increases in ChBvol, suggesting that perhaps older individuals may have less robust autoregulatory responses (fig 9).

This increase in ChBvol seen in our study is similar to the results of Chandra and Friedman,\(^3\) who used the krypton desaturation technique in anaesthetised cats and found decreased choroidal vascular resistance after niacin administration.

Our results show that a larger increase in ChBvol is present in the six patients who received the higher dose of 500 mg (39% increase, \( p = 0.03 \)) than in the group with a lower dose of 250 mg (10% increase, \( p = 0.36 \)). This suggests that the lower concentration of systemically administered niacin may not be sufficient to saturate the receptor sites in the choroidal vasculature to cause a large increase in ChBvol. This finding is in agreement with the results of Chandra and Friedman,\(^3\) who did not detect choroidal circulatory changes with systemic doses but observed decrease in vascular resistance following direct niacin administration through the posterior ciliary artery. This last route of administration most probably achieved a higher concentration in the choroid.

An increase in the ChBvol parameter measured by the LDF technique most probably represents an increase in the number of red blood cells present within the tissue measured by the laser Doppler flowmetry technique. Such an increase may be caused by vasodilatation, capillary recruitment, or increase in the haematocrit.

We have previously reported that ChBflow is reduced by 37% in patients with age related macular degeneration (AMD) in comparison with age matched normal controls. This phenomenon is mainly due to a 33% reduction in ChBvol. Studies showing obliteration of choriocapillaries in the macular area,\(^4\) narrowing of the lumen and loss of the cellularity of choriocapillaries,\(^5\) and thinning of the choroid, especially the choriocapillaris layer\(^6\) provide evidence of AMD related morphological changes that could explain a decrease in choroidal blood volume and flow observed in AMD.

Because of this decrease in ChBflow in AMD it is possible that therapies that increase the circulation of the choroid may be of benefit in the treatment of AMD. Further studies are needed to investigate whether niacin may have a potential role in the treatment of AMD.

Our current study suggests increases in ChBvol in AMD patients after treatment with niacin. Whether this may be of benefit to patients with AMD is beyond the scope of this article. Theoretically, however, it is possible that an increase in ChBvol may facilitate the diffusion of gases and substances across the RPE-Bruch’s membrane. This may improve removal of the waste products and metabolic debris from the outer retina, a process that is probably impaired in AMD leading to the accumulation of drusen material.

The circulatory changes observed after niacin ingestion may have a role in the development of reversible nicotinic acid maculopathy, which has been observed in patients taking high doses of niacin as a lipid lowering agent. Gass\(^7\) was the first one to report three cases of nicotinic acid maculopathy. Similar cases were reported by Millay\(^8\) and Callanan\(^9\) in patients who took 1–6 g of niacin daily and recovered upon discontinuation of niacin. A recent study by

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**Table 1** Mean number of letters correctly identified during contrast sensitivity and visual acuity testing

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>30 minutes</th>
<th>90 minutes</th>
<th>( p ) Value (ANOVA)</th>
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<td><strong>Contrast sensitivity</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>31.8 (6.6)</td>
<td>31.6 (7.5)</td>
<td>31.4 (7.3)</td>
<td>0.83</td>
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<tr>
<td>Niacin</td>
<td>32.4 (5.9)</td>
<td>31.8 (5.3)</td>
<td>31.8 (6.0)</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>Visual acuity</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>50.6 (10.4)</td>
<td>49.4 (10.3)</td>
<td>49.0 (12.6)</td>
<td>0.89</td>
</tr>
<tr>
<td>Niacin</td>
<td>51.5 (10.8)</td>
<td>49.8 (11.8)</td>
<td>49.3 (13.3)</td>
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Spiri\textsuperscript{39} showed the presence of cystoid spaces mainly in the outer plexiform layer. Although the mechanism responsible for this type of reversible maculopathy is not well known, impairment of the blood-retinal barrier does not seem to play a large part, since there is no evidence of increased leakage on fluorescein angiography.\textsuperscript{27} Possibly, changes in the choroidal circulation such as the increased ChBV\textsubscript{ol} and decreased ChBV\textsubscript{cr}, observed in our study with the higher doses of nicotinic acid may facilitate extravasation of fluid from the blood vessels leading to a disturbed metabolism of the outer retina with intracellular fluid accumulation.\textsuperscript{27}

Our results show a significant increase in heart rate at 30 minutes after nacin, similar to those reported by Gadegbeku et al\textsuperscript{8} and decrease in heart rate at 90 minutes. These effects represent a compensatory response to a decrease in peripheral vascular resistance and as a result decreased BPm, which we observed 30 minutes after treatment with nacin. They are aimed to maintain constant cardiac output.

Our results do not show any effect of nacin on visual acuity or contrast sensitivity suggesting that the changes in ChBV\textsubscript{ol} and ChBV\textsubscript{cr} do not result in a large effect on visual function.

In summary, our results suggest that therapeutic doses of nacin produce changes in choroidal circulation in AMD patients. Additional studies are needed in order to find out whether this type of therapy may be of benefit in patients with this condition.

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Grant/financial support: NIH grant EY 12769, the Vivian S Lasko Grant/financial support: NIH grant EY 12769, the Vivian S Lasko Research Fund and Research to Prevent Blindness.

Disclosure statement: None of the authors have any conflict of interest regarding the contents of the article.

Commercial relationship: None.

\textbf{REFERENCES}

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