Effect of Perindopril on Cerebral and Renal Perfusion in Stroke Patients With Carotid Disease

M.R. Walters, MD; A. Bolster, PhD; A.G. Dyker, MD; K.R. Lees, MD

Background and Purpose—The purpose of this study was to investigate the effect of the angiotensin-converting enzyme inhibitor perindopril on mean arterial blood pressure (MABP), cerebral blood flow (CBF), and glomerular filtration rate in hypertensive stroke patients with moderate to severe internal carotid artery (ICA) disease or ICA occlusion.

Methods—Twenty-four nonacute ischemic stroke patients who had MABP readings >100 mm Hg and moderate to severe ICA stenosis or occlusion were randomized to receive perindopril 4 mg daily or placebo for 14 days. MABP, ICA flow, and both middle cerebral artery (MCA) velocity and resistance index were measured before dose, at 5 time points over the subsequent 24 hours, and finally at 2 weeks. Brain hexamethyl propylene amine oxide single photon emission computed tomography scans were performed before drug administration and at time of peak drug effect (6 to 8 hours) after the first dose. Glomerular filtration rate was measured with $^{51}$Cr EDTA before medication and at 14 days.

Results—A placebo-corrected BP fall of 17/10 mm Hg was seen ($P=0.017$), which was maximal at 5.5 hours. No significant change in ICA flow or MCA velocity was seen between groups. No significant change in hemispheric CBF was seen. The mean change from baseline in the treated group was $-0.79 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ (95% confidence interval [CI], 1.65 to $-3.23$); mean change in the placebo group was $-1.9 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ (95% CI, 3.02 to $-6.92$). Peri-infarct CBF was similarly unaffected. One of the treated patients developed transient acute renal impairment and was withdrawn from the study on day 4.

Conclusions—Perindopril lowers BP without lowering CBF in hypertensive stroke patients with moderate to severe ICA stenosis or occlusion; monitoring of this patient population for the complications of renal artery stenosis should be considered. (Stroke, 2001;32:473-478.)

Key Words: angiotensin-converting enzyme inhibitors • carotid artery stenosis • cerebral blood flow

Control of high blood pressure is the cornerstone of primary stroke prevention; however, the effect of blood pressure control on secondary prevention of stroke is less well defined. A large, multicenter, randomized, placebo-controlled study (Perindopril Protects Against Recurrent Stroke Study [PROGRESS]) designed to clarify the relationship is underway and is due to report in 2001. The PROGRESS study, which has enrolled 6105 patients with cerebrovascular disease and normotension or mild to moderate hypertension, is examining the effect of the angiotensin converting enzyme (ACE) inhibitor perindopril alone or in combination with a thiazide diuretic on secondary incidence of stroke. Perindopril is an ACE inhibitor with a gradual onset of action and a relatively long half-life, allowing once-daily dosing. It is less likely to cause first-dose hypotension than captopril or enalapril.

Little evidence exists to guide the choice of antihypertensive agent or the timing of its introduction after the cerebrovascular event. In the first few days after stroke, cerebral autoregulatory mechanisms are deranged; hence, blood pressure fluctuations may lead to significant changes in cerebral perfusion. Some conventional antihypertensive medications may lower cerebral blood flow and worsen outcome after acute ischemic stroke, probably as a result of reduced cerebral perfusion within and adjacent to the affected area. In acute ischemic stroke patients, clinical trials involving early administration of agents that may lower blood pressure such as nimodipine and lifarizine have shown a correlation between blood pressure reduction and poor clinical outcome. Conversely, more recent studies have suggested that no clinically significant change in cerebral perfusion occurs after administration of ACE inhibitors to patients early after ischemic stroke. This is thought to be due to increased vessel wall compliance and dilatation of the extracranial vessels.

Poor cerebral perfusion is associated with a greater risk of stroke in patients with carotid disease. Because patients with recent stroke who may have unrecognized carotid disease are already treated with antihypertensive drugs and because they will form an unidentified subgroup of the PROGRESS trial, it is desirable to discover the effects of such treatment on cerebral perfusion. Because ACE inhibitors are also known to impair renal function in patients with critical renal artery

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stenosis and because the prevalence of clinically significant renal artery disease in patients with cerebrovascular disease is unknown, we sought to investigate effect of ACE inhibitors on cerebral perfusion and glomerular filtration rate (GFR) in the subgroup of hypertensive stroke patients with moderate to severe carotid stenosis or carotid occlusion.

Subjects and Methods

We performed a randomized, double-blind, placebo-controlled study of oral perindopril (4 mg daily for 14 days) in patients with a computed tomography (CT)—or magnetic resonance imaging (MRI)—confirmed diagnosis of ischemic stroke, mild to moderate hypertension (mean arterial blood pressure >100 mm Hg), and carotid disease ranging from moderate stenosis to occlusion as assessed by Doppler ultrasonography in accordance with standard criteria. Patients whose estimated time of peak drug effect (m) was calculated in (π×diameter)2/4. A single value for total ICA flow was calculated by adding left and right ICA flow values for each individual. Doppler studies were undertaken by a single observer who was not involved in drug administration. All neck measurements were taken anterolaterally with an Acuson 128 with a 5-MHz linear transducer. Subjects were examined reclining after having rested in a reclining position for 5 minutes before insonation. The Doppler sample width was set to encompass the arterial-vessel incident angle. Velocity of blood flow through the common, internal, and external carotid arteries was measured, and the rate of decline of plasma activity was used to calculate the GFR.

Measurement of GFR was achieved with the standard single injection method. A solution of 11Cr-EDTA with a total activity of 1.6 MBq was administered as a bolus injection. Blood samples were drawn at baseline (immediately before injection) and at 2, 3, and 4 hours after injection. The plasma activity of each of these samples was measured, and the rate of decline of plasma activity was used to estimate the GFR.

Results were analyzed by repeated-measures ANOVA and ANCOVA with the use of Statistics for Windows version 5.1 (Statsoft Inc) and Arcus Quickstat Biomedical version 1.2 (Research Solutions). The power calculation was based on variability data acquired during earlier carotid Doppler studies of patients with normal carotid arteries and suggested that, with a sample size of 24 patients (12 per group), a 16% difference in ICA flow (as assessed by ICA Doppler insonation) between groups assessed by a standard t test could be detected with 80% power.

Results

Tolerance and Safety

A total of 24 patients were recruited into the study. Patients were well matched with regard to age, sex, baseline blood pressure, and stroke severity as assessed by NIH score. The clinical details, brain imaging, and carotid Doppler findings of patients at entry into the study are shown in Table 1.

Patient 1 in the treated group was withdrawn on day 3 of the study after an episode of acute renal failure. Serum creatinine at baseline had been 170 μmol/L; serum potassium, 4.9 mmol/L. Routine safety blood checks performed on day 3 revealed rises in both of these parameters to 240 μmol/L and 9.0 mmol/L, respectively. Temporary hemodialysis was required to reverse the hyperkalemia, and biochemical parameters returned to premorbid levels within 2 days.

The patient was well at the conclusion of the study; he was normokalemic with serum creatinine levels consistently between 160 and 175 μmol/L without renal replacement therapy. No other adverse events were encountered. With the exception of this patient, no significant change in safety blood readings was seen. Mean NIH scores improved in both groups over the duration of the study. No difference in improvement between the groups was observed.

Blood Pressure

A significant fall in systolic (P=0.028), mean arterial (P=0.017), and diastolic (P=0.04) blood pressures was observed in perindopril-treated patients compared with the placebo group. Figure 1 shows the absolute values of mean arterial blood pressure at each time point. At baseline, blood pressure was 161±17.6/86±7 mm Hg in the perindopril group and 164±17.5/85±8.6 mm Hg in the placebo group. After 2 weeks of treatment, blood pressure was 143±22/77±13.4 mm Hg in the perindopril group and 163±16.1/86±8 mm Hg in the placebo group, ie, a placebo-corrected
fall of 17/10 mm Hg. No associated change in heart rate was seen in either group.

ICA Flow
No significant difference in total ICA flow was seen in the treated group compared with the placebo group ($P = 0.37$). Figure 2 shows the percentage change in total ICA flow at each time point for the treated and placebo groups. A nonsignificant trend toward an increase in total ICA flow was observed on the first dosing day. In the treated group, the 95% confidence interval for percentage change in ICA flow from baseline at 5.5 hours after dose ranged from 23.8% to 41.4%. The equivalent confidence interval in the placebo group ranged from 14.6% to 21.0%. In treated patients with asymmetrical hemodynamically significant carotid artery lesions or unilateral carotid disease, no significant difference in relative flow through each artery was observed after perindopril administration.

MCA Velocity and Resistance Index
Successful insonation of both MCAs was achieved in 7 treated patients and 8 placebo patients. No significant difference in change in MCA velocity over time was seen in the treated group compared with the placebo group. The MCA resistance index is a measure of arterial tone and distensibility. No significant difference ($P = 0.07$) in the change in this parameter was observed between the 2 groups (Figure 3).

Glomerular Filtration Rate
No significant change in GFR was seen within or between groups. In the active group, baseline and 14-day GFR values were 89.3 ± 19.4 and 89.0 ± 20 mL/min, respectively. Repeated GFR estimation was not performed on the patient who developed acute renal failure. In the placebo group, baseline and 14-day values were 73.0 ± 12.1 and 74.1 ± 10.5. Mean within-group change in GFR was $-0.36 ± 2.8$ in the treated group and $1.17 ± 3.1$ in the placebo group ($P = 0.49$).

SPECT Measurements
Twenty-two of 24 patients completed the SPECT protocol. One patient in the treated group (patient 11) failed to
complete the SPECT protocol because of claustrophobia; in 1 placebo recipient (patient 12), the SPECT data images were unsuitable for analysis. Analysis of both whole hemisphere and focal brain perfusion differences was undertaken. Figure 4 shows the mean change in flow in whole hemisphere brain perfusion values from baseline for both the affected and unaffected hemispheres in both the treated and untreated groups. No significant deviation from baseline was observed in either the treated or untreated group ($P < 0.43$). No significant difference between placebo and active groups was observed. Figure 5 shows the change in perfusion values within the template zones that contained or were immediately adjacent to the ischemic lesion. The template zones containing the cerebral infarct were identified either by direct examination of the SPECT images or by extrapolation from the initial x-ray CT or MRI. Data from these zones and from all directly adjacent zones within the same hemisphere were used to assess peri-infarct perfusion. No significant difference in percentage change in peri-infarct perfusion was seen either between or within groups after perindopril administration ($P = 0.27$).

**Discussion**

Perindopril lowered blood pressure by $\approx 8\%$ without adversely affecting global or regional cerebral perfusion in hypertensive stroke patients with moderately stenosed to occluded carotid arteries. Of 12 patients treated with perindopril, 1 patient developed acute renal failure that required temporary hemodialysis. The study was not designed to demonstrate any long-term effect on neurological outcome; however, no drug-associated neurological deterioration was seen. Although the numbers of patients studies in each group were relatively small, the study was adequately powered to detect a clinically significant difference in cerebral blood flow between groups. Although wide, the confidence intervals presented suggest that a clinically significant reduction in ICA flow or hemispheric perfusion is unlikely after administration of perindopril.

We acknowledge a number of limitations of the methodology used in the execution of this study. The technique used to assess ICA blood flow assumes that the lumen of the vessel being studied is cylindrical, ie, that the cross-sectional area of the vessel can be calculated from its diameter. If the atherosclerotic lesions in the arteries of the patients studied cause a nonconcentric reduction in the cross-sectional area of the vessel, errors may be introduced in the calculation of ICA flow. Although this may lead to inaccuracies in the quantitative ICA blood flow measurement, no significant change over time in arterial diameter was seen within ($P < 0.7$) or between ($P = 0.31$) groups; hence, the comparison of the magnitude of change in flow between groups remains valid. There is a degree of heterogeneity in the severity of carotid arterial disease. Although all patients had hemodynamically significant carotid lesions and the severity of carotid disease did not differ between groups, a larger study would enable more detailed analysis of differing drug effects as the degree of hemodynamically significant carotid disease increased.

The potential source of inaccuracy may influence the power calculation of the study. As stated above, the calculation was based on variability data acquired during earlier studies of patients with normal carotid arteries and suggested that a 16% difference in ICA flow between groups determined with a standard $t$ test could be detected with 80% power with a sample size of 24 patients. Examination of the variability of the SPECT data acquired during this study allows a further power calculation for future studies. From the variability data from the SPECT scans performed during this study, it has been calculated that a sample size of 24 patients will allow detection of a $6 - m L \cdot 100 g^{-1} \cdot min^{-1}$ difference in hemispheric cerebral perfusion (as assessed by SPECT) with 80% power. As anticipated, the technical failure rate of transcranial Doppler ultrasound was higher than reported in previous studies of patients without significant carotid arterial
disease\(^7\); for this reason, the transcranial Doppler parameters were not used in the power calculation.

This study has used SPECT techniques to examine the effect of perindopril on peri-infarct cerebral perfusion. The cerebral infarction was localized with CT or MRI; however, these images were not coregistered with the SPECT data, and we acknowledge that this may introduce a degree of error in the precise localization of the cerebral infarct on the SPECT image. Because of the variability in infarct size between patients and the size of each individual region within the template, it was not possible to fully exclude the infarcted zone and analyze only the noninfarcted tissue adjacent to the lesion.

Although a previous study has examined the effect of perindopril on global cerebral perfusion early after ischemic stroke in patients with normal carotid arteries,\(^7\) this study is the first to investigate the effects of perindopril in stroke patients with carotid arterial disease. Control of hypertension in this group of patients is associated with the theoretical risk of reduction in cerebral perfusion distal to the site of a stenotic lesion. Patients with severe carotid arterial disease are likely to have atheromatous disease elsewhere. The use of ACE inhibitors in patients with renal artery stenosis may lead to adverse consequences, and renal function should be closely monitored after introduction of ACE inhibitor therapy. Our data suggest that perindopril will reduce blood pressure without reduction in global or focal cerebral perfusion as assessed by Doppler and SPECT, respectively; however, the mechanistic basis of this observation remains unclear.

In rats, angiotensin II receptors within large cerebral arteries are involved in cerebral autoregulation after a rise in blood pressure, and inhibition of ACE resets cerebral autoregulation at a lower level.\(^15\) ACE inhibition in healthy volunteers does not change; however, the resistance index increased, suggesting cerebral arteriolar vasconstriction.\(^16\) In hypertensive patients without a history of stroke, the ACE inhibitor captopril has been shown to increase cerebral perfusion (measured with Xe\(^{133}\) SPECT) while lowering blood pressure. An inverse correlation between magnitude of blood pressure fall and mean cerebral blood flow was observed.\(^17\)

The deleterious effect of ACE inhibition on GFR in patients with bilateral renal artery stenosis is well recognized;\(^18\) however, detrimental effects in unilateral artery stenosis remain controversial.\(^19\) Atherosclerosis is a generalized disease, and the coexistence of hemodynamically significant atheroma in the renal, carotid, and lower limb vessels has been documented.\(^20\) In a large case-control study of hypertensive patients, carotid artery ultrasound revealed the prevalence of significant atheroma in 83% of patients with known renovascular hypertension and in 43% of patients with essential hypertension.\(^21\) An overall trend for patients with increasingly severe renal artery disease to have increasingly severe degrees of carotid disease has also been reported.\(^22\) The prevalence of severe renal artery stenosis among stroke patients with carotid arterial disease is as yet undefined.

### Conclusions

We conclude that the ACE inhibitor perindopril reduces blood pressure without adversely affecting global or focal cerebral perfusion in patients with carotid artery stenosis. Because renal artery stenosis is known to be associated with hemodynamically significant carotid disease, monitoring of this patient population for the complications of renal artery stenosis should be considered.

### Acknowledgments

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### Table 2. Placebo Group Demographics

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<th>Clinical</th>
<th>Doppler</th>
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Mean (SD) 70.3 (10) 26 (13) 4.7 (2.8) 3.4 (3) 112 (8)

Abbreviations as in Table 1.
ciah or editorial involvement. We are grateful to Professor John L. Reid, Dr Peter F. Semple, and Dr Gordon T. Mclnnes for permission to study their patients. We also are grateful to Karen Shields for assistance in performing the Doppler studies.

References


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