Pravastatin Improves Cerebral Vasomotor Reactivity in Patients With Subcortical Small-Vessel Disease

Philipp Sterzer, MD; Frank Meintzschel; Alexander Rösler, MD; Heinrich Lanfermann, MD; Helmuth Steinmetz, MD; Matthias Sitzer, MD

Background and Purpose—Recent investigations have suggested an important role of statins in the prevention of stroke and dementia independent of their lipid-lowering properties. Using transcranial Doppler sonography (TCD), we examined acetazolamide reactivity as a marker of cerebral vasoreactivity in patients with subcortical small-vessel disease before and after pravastatin treatment.

Methods—In 16 patients (mean age 68±10 years) with subcortical small-vessel disease, cerebral vasomotor reactivity was tested using TCD insonating the middle cerebral artery. Cerebral blood flow velocity (CBFV) increase after bolus injection of 1 g acetazolamide was determined before and after 2-month treatment with pravastatin sodium 20 mg daily.

Results—Relative CBFV increase was significantly greater after pravastatin treatment (41.9±23.7% versus 55.7±18.3%, P=0.004). Comparison of CBFV at rest before and after treatment with pravastatin did not show significant differences.

Conclusions—This pilot study provides the first evidence for a significant improvement of cerebral vasomotor reactivity by statin therapy in patients with cerebral small-vessel disease. The results may help to elucidate the preventive effect of statins and provide insights into the pathophysiology of cerebral small-vessel disease. (Stroke. 2001;32:2817-2820.)

Key Words: endothelium • HMG-CoA reductase inhibitors • small-vessel disease • ultrasonography • vasomotor reactivity

Recent studies have demonstrated a significant reduction of risk for ischemic stroke in patients with coronary heart disease treated with β-hydroxy-β-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins). In addition, these agents may also prevent vascular dementia. Current evidence suggests that the beneficial effects of statins on the vascular system seem to be mediated not only by their lipid-lowering properties but also by improving vascular endothelial function. They are known to activate endothelial nitric oxide synthase (eNOS) and thereby propagate NO-dependent vasodilation. In patients with cerebral small-vessel disease, impaired vasoregulation of the subcortical microvasculature may be an important pathogenetic mechanism, leading to white matter hypoperfusion, recurrent lacunar infarctions, and vascular dementia. Accordingly, reduced vasomotor reactivity as measured by transcranial Doppler (TCD) has been shown to correlate with the severity of leukoencephalopathy seen on MRI. The purpose of the present pilot study was to investigate the effects of statin treatment on vasomotor reactivity in patients with cerebral small-vessel disease.

Subjects and Methods

We prospectively studied 16 patients (9 men, 7 women; mean age 68±10 years) with subcortical small-vessel disease, defined by periventricular or subcortical white matter lesions on fluid-attenuated inversion recovery (FLAIR)-weighted MRI in addition to one or more of the following criteria: ≥1 ischemic events consistent with transient ischemic attack or lacunar infarction, history of cognitive decline, gait instability, and symptomatic epileptic seizure with no evident cause other than cerebral small-vessel disease. Exclusion criteria were previous statin treatment, severely impaired cognitive function (Mini-Mental State Examination <20 points), internal carotid or middle cerebral artery (MCA) stenosis of >40% luminal narrowing as evidenced by duplex sonography, and territorial infarction on MRI. All patients gave written informed consent for the study. Prevalences of vascular risk factors were as follows: smokers (2/16), arterial hypertension (11/16), diabetes mellitus (4/16), and fasting LDL cholesterol >3.9 mmol/L (150 mg/dL) (10/16).

Cerebral vasomotor reactivity was tested using TCD (2-MHz pulsed-wave, TC 4040, EME, Pioneer) insonating the MCA unilaterally (50- to 60-mm depth) with the patient in a supine position. The mean cerebral blood flow velocity (CBFVmean) was calculated from the envelope curve of the velocity spectrum during rest and 5 minutes after bolus injection of 1 g acetazolamide over an averaging period of 5 minutes each. Relative CBFVmean changes were calcu-
pravastatin effect on vasomotor reactivity ($\beta = -0.033, P = 0.911$).

LDL cholesterol was decreased by pravastatin treatment from $4.40 \pm 1.31$ mmol/L (169.3 ± 50.5 mg/dL) to $3.30 \pm 1.24$ mmol/L (126 ± 47.8 mg/dL), a reduction of 25% ($P = 0.001$). No significant associations were found between pravastatin-induced vasomotor reactivity changes and pretreatment LDL cholesterol ($\beta = -0.096, P = 0.745$) or LDL cholesterol changes ($\beta = 0.193, P = 0.497$). Pretreatment vasomotor reactivity tended to be positively correlated with LDL cholesterol levels ($\beta = 0.498, P = 0.050$).

**Discussion**

This pilot study provides the first evidence of a significant improvement of vasomotor reactivity by statin therapy in patients with cerebral small-vessel disease. The effect was more pronounced in patients with a more severe impairment of vasomotor reactivity. Because the baseline CBFV$_{\text{mean}}$ remained unchanged, the findings indicate a specific effect of pravastatin on the reactivity of the cerebral microvasculature. Despite a considerable interindividual variability in CBFV$_{\text{mean}}$ and vasomotor reactivity, this effect was present even when absolute increases before and after pravastatin treatment were compared. Pretreatment vasomotor reactivity and the effect of pravastatin were independent of baseline CBFV$_{\text{mean}}$, excluding that the results were confounded by different levels of baseline values. It should be mentioned that pravastatin considerably enhanced vasomotor reactivity even though we applied a relatively low dosage (20 mg daily) as compared with previous studies.$^1$

From a pathophysiologial point of view, it is tempting to speculate that the observed increase in vasomotor reactivity was the result of an improvement of endothelial function. Statin treatment has been shown to improve NO-dependent coronary vasomotor regulation and endothelial function in the forearm vasculature in patients with cerebral small-vessel disease. There was no association between pretreatment baseline CBFV$_{\text{mean}}$ and pretreatment vasoreactivity ($\beta = -0.166, P = 0.510$) or the

**Results**

Comparison of CBFV$_{\text{mean}}$ at rest before and after treatment with pravastatin did not show significant differences ($44.3 \pm 11.0$ versus $43.2 \pm 11.2$ cm/s, $P = 0.72$). Relative CBFV$_{\text{mean}}$ increase after injection of 1 g acetazolamide was significantly greater after the 2-month period of pravastatin treatment as shown in Figure 1 ($41.9 \pm 23.7\%$ versus $55.7 \pm 18.3\%, P = 0.004$). A significant enhancement of acetazolamide reactivity could be observed even when absolute values of CBFV$_{\text{mean}}$ increase before and after pravastatin treatment were compared ($17.0 \pm 10.6$ versus $22.7 \pm 7.0$ cm/s, $P = 0.041$). Pravastatin-induced relative enhancement of vasoreactivity was negatively correlated with pretreatment CBFV$_{\text{mean}}$ increase ($\beta = -0.64, P = 0.019$; see Figure 2), indicating a more pronounced effect of pravastatin in patients with an initially impaired cerebrovascular reactivity. There was no association between pretreatment baseline CBFV$_{\text{mean}}$ and pretreatment vasoreactivity ($\beta = -0.166, P = 0.510$) or the

**Figure 1.** Vasomotor reactivity, defined as the percent change in cerebral blood flow velocity (CBFV$_{\text{mean}}$) after injection of 1 g acetazolamide, was significantly greater ($P = 0.004$, Wilcoxon test) after a 2-month treatment with pravastatin. Box plots show median values, 25th and 75th percentiles, and total ranges.

**Figure 2.** The effect of pravastatin, expressed as the difference of cerebral blood flow velocity (CBFV$_{\text{mean}}$) change after and before treatment, was negatively correlated with vasomotor reactivity (CBFV$_{\text{mean}}$ change) prior to treatment ($\beta = -0.64, P = 0.019$).
hypercholesterolemia. Since these effects could be blocked by simultaneous administration of an inhibitor of NO synthesis, the statin-induced improvement of endothelial function was suggested to be mediated by an increased bioavailability of NO. Endothelial function has been shown to be impaired in hypercholesterolemia, suggesting that the statin-induced improvement of vasoregulation is mediated by its cholesterol-lowering properties. In accordance with this hypothesis, a recent study demonstrated an increased cerebral CO2 reactivity after lowering LDL cholesterol by heparin-mediated extracorporal LDL precipitation. In our study, the statin-induced improvement of vasomotor reactivity did not correlate with the decrease in serum cholesterol. It could be argued that the relatively small sample size might be responsible for this lack of correlation. However, pretreatment vasomotor reactivity even tended to be positively correlated with higher LDL cholesterol levels, which makes the effect of pravastatin treatment unlikely to be solely the result of its cholesterol-lowering properties. Of note, in other studies also it has been difficult to establish correlations between LDL cholesterol levels or the extent of its reduction and the statin-induced improvement of vasoregulation in extracranial vessels. A likely explanation for the effect of statins on vasoregulation in previous studies seems to be the well-documented enhancement of eNOS activity by statins. In fact, recent animal studies have shown an improvement of cerebral blood flow by statin treatment that was not only independent of changes in cholesterol levels but also absent in eNOS-deficient animals. Endothelial function has been elucidated the pathophysiology of cerebral small-vessel disease.

In conclusion, our study suggests that cerebral vasomotor reactivity can be improved by short-term administration of pravastatin in patients with cerebral small-vessel disease. This may stimulate further clinical studies to better understand the preventive effects of statins and may help to elucidate the pathophysiology of cerebral small-vessel disease.

Acknowledgments

This study was funded in part by the Volkswagen Foundation. Pravastatin sodium (Pravasin) was provided by Bristol-Myers Squibb Germany.

References


Pravastatin Improves Cerebral Vasomotor Reactivity in Patients With Subcortical Small-Vessel Disease
Philipp Sterzer, Frank Meintzschel, Alexander Rösler, Heinrich Lanfermann, Helmuth Steinmetz and Matthias Sitzer

Stroke. 2001;32:2817-2820
doi: 10.1161/hs1201.099663

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/32/12/2817

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/