Pentoxifylline Increases Cerebral Blood Flow in Patients With Cerebrovascular Disease

David L. Bowton, MD, David A. Stump, PhD, Donald S. Prough, MD, James F. Toole, MD, David S. Lefkowitz, MD, and Laura Coker, BSN

We determined the immediate effects of pentoxifylline on cerebral blood flow in 10 patients with cerebrovascular disease; four received 400 mg and six received 800 mg pentoxifylline orally. Regional cerebral blood flow was measured before (baseline) and 2, 4, and 6 hours after pentoxifylline administration using the xenon-133 clearance technique with 16 detectors (eight per hemisphere). Global cerebral blood flow as a percentage of the baseline value increased significantly after 800 mg but not 400 mg pentoxifylline (p=0.017 and p=0.29, respectively). Regional cerebral blood flow as a percentage of the baseline value at the detector with the lowest baseline value increased significantly 2 hours after both 400 mg and 800 mg pentoxifylline (p=0.038 and p=0.010, respectively). Cerebrovascular reactivity to carbon dioxide was preserved despite the increases in cerebral blood flow. Pentoxifylline increases cerebral blood flow and is not associated with "intracerebral steal" in patients with cerebrovascular disease. (Stroke 1989;20:1662-1666)

Pentoxifylline (Hoechst-Roussel, Somerville, New Jersey) is a methylxanthine recently approved by the Food and Drug Administration for the symptomatic relief of intermittent claudication due to peripheral vascular disease. Although its mechanisms of action have been incompletely elucidated, it is known that pentoxifylline decreases blood viscosity and inhibits platelet aggregation by inhibiting membrane-bound phosphodiesterase.1-2 Pentoxifylline also appears to increase the synthesis of prostacyclin, a vasodilatory eicosanoid that inhibits platelet aggregation.3

Previous studies have demonstrated that pentoxifylline increases cerebral blood flow (CBF) after 2-4 weeks of therapy.4-6 Only one study has reported on the acute effects of pentoxifylline on CBF.7 That study reported a 17% increase in CBF immediately following a large intravenous bolus dose of pentoxifylline in three subjects; CBF was measured with only two detectors (one over each hemisphere) and therefore the effects of pentoxifylline on regional cerebral blood flow (rCBF) and the development of "intracerebral steal" could not be assessed. The effect of pentoxifylline on cerebrovascular reactivity to CO2 (CRCO2) was also not assessed.

Our study was undertaken to ascertain the acute effects of orally administered pentoxifylline on global CBF, rCBF, and CRCO2 in patients with cerebrovascular disease.

**Subjects and Methods**

We studied 10 patients (two women, eight men; mean age 68.8 [range 57-88] years) in a project approved by the institutional clinical review board. All patients provided informed consent. They had had an acute vascular neurologic insult (nonhemorrhagic focal cerebral infarction in eight and reversible ischemic neurologic deficit lasting >24 but <72 hours in two) at least 3 months previously. The diagnoses were corroborated by an appropriate clinical history and physical examination and confirmed by computed tomography. The patients were instructed not to ingest methylxanthines (e.g., tea, coffee, cocoa, and cola drinks) for at least 12 hours before the start of the study. The patients were randomized to one of two groups; Group I patients (n=4) received 400 mg and Group II patients (n=6) received 800 mg pentoxifylline administered as a single oral dose of a sustained-release preparation, the standard marketed form of this drug.

All 10 patients underwent four paired determinations of rCBF. Because the time required to perform the determinations was considerable, schedul-
ing requirements necessitated that the study be performed over 2 days; baseline rCBF was determined the day before pentoxifylline administration. After acclimation to the laboratory and the apparatus, baseline rCBF was determined in each patient breathing room air (normocarbia), followed 30 minutes later by a similar rCBF determination in each patient during inhalation of 5% CO₂ (hypercarbia). The next day, again after acclimation, pentoxifylline was administered and rCBF was determined 2, 4, and 6 hours later, first under normocarbia then under hypercarbic conditions. All rCBF determinations, under normocarbic and hypercarbic conditions, were conducted identically. The electrocardiogram was monitored continuously, and end-tidal CO₂ (Petco₂) was recorded during each determination. Blood pressure was obtained by auscultation before each rCBF determination.

rCBF was measured using the xenon-133 clearance method and the technique originally described by Obrist et al. For 1 minute the patient inhaled a gas mixture containing 25 mCi of xenon-133. For 10 minutes thereafter, the clearance of xenon-133 from multiple cranial areas was measured using 16 sodium iodide scintillation detectors (eight per hemisphere) connected to a modified NOVO Cerebrograph (NOVO Laboratories, Inc., Wilton, Connecticut). Simultaneous scintillation detection of xenon-133 in the exhaled gas permitted deconvolution of the clearance curves for recirculation of the xenon-133. We employed the "flow gray" method of calculation, which estimates CBF in the fast-clearing, or gray-matter, compartment. Data were analyzed using a Vax 730 computer.

CRCO₂ was calculated as (CBF Co₂-CBF air) ÷ (P a CO₂-P e CO₂), where CBF Co₂ and CBF air and P a CO₂ and P e CO₂ represent values during hypercarbia and normocarbia, respectively. CRCO₂ calculated in this manner represents the specific reactivity as defined by Ackerman. CRCO₂ was not significantly affected by pentoxifylline at either dose (Table 3). Despite the increases seen after pentoxifylline under normocarbic conditions, both global CBF and lowest rCBF increased further after CO₂ inhalation; the increases were significant after 800 mg (p=0.005 and p=0.002, respectively). The responses to hypercarbia in the 400 mg group did not quite achieve significance for either global CBF or for lowest rCBF (p=0.076 and p=0.072, respectively), though the trend was toward increased blood flow with hypercarbia. The failure to achieve significance in the 400 mg group may reflect the few patients in it and the heterogeneous physiologic response to hypercarbia.

Discussion

In our study, pentoxifylline administered orally as a single sustained-release capsule increased global CBF and rCBF in patients with cerebrovascular disease. Under conditions of normocarbia, a dose of 800 mg, but not 400 mg, increased global CBF within 2 hours, while both doses increased rCBF at the detector with the lowest baseline blood flow. Our findings demonstrating an acute effect of pentoxifylline complement those of Passero et al., who described a 17% increase in CBF immediately fol-

Results

Table 1 summarizes data for the two groups at each time. Table 2 gives global CBF for each patient at each time. Pentoxifylline produced an immediate dose-dependent increase in global CBF under normocarbic conditions, significant after 800 mg (p=0.017) but not after 400 mg (p=0.29) (Table 1). The increase in global CBF after 800 mg was long-lasting, with five of the six patients demonstrating increases in CBF at both 4 and 6 hours (Table 2). The increase in global CBF was accompanied by an increase in lowest rCBF under normocarbic conditions (Table 1). Indeed, the region with the lowest baseline rCBF appeared to be more sensitive than global CBF to the effects of pentoxifylline as both 400 mg and 800 mg doses significantly increased lowest rCBF (p=0.038 and p=0.010, respectively). No patient manifested a decrease in lowest rCBF (see Figure 1 for 800 mg group), and within patients, the increase in lowest rCBF was qualitatively similar but of greater magnitude to that in global CBF.

CRCO₂ was not significantly affected by pentoxifylline at either dose (Table 3). Despite the increases seen after pentoxifylline under normocarbic conditions, both global CBF and lowest rCBF increased further after CO₂ inhalation; the increases were significant after 800 mg (p=0.005 and p=0.002, respectively). The responses to hypercarbia in the 400 mg group did not quite achieve significance for either global CBF or for lowest rCBF (p=0.076 and p=0.072, respectively), though the trend was toward increased blood flow with hypercarbia. The failure to achieve significance in the 400 mg group may reflect the few patients in it and the heterogeneous physiologic response to hypercarbia.
lowing 400 mg i.v. pentoxifylline in three subjects with "chronic cerebrovascular" disease, and those of Hartmann,4-6 who described increases in CBF following 2-6 weeks of pentoxifylline administration.

It is unlikely that the increase in CBF following pentoxifylline is secondary to variability or "drift" in our CBF measurement technique. Repeated determination of CBF is usually associated with a slight decrease, and the change in baseline CBF over 24 hours and the CBF response to placebo are considerably smaller than the response to pentoxifylline that we observed.11 In our laboratory, the mean±SEM difference in resting "baseline" CBF (flow gray) between two determinations 24 hours apart in 15 healthy adult volunteers with a mean age of 45 years was -2.4±2.4 ml/100 g/min (95% confidence interval -7.1-2.3 ml/100 g/min)11; the mean±SEM change in CBF 2 hours after placebo administration was 1.4±1.3 ml/100 g/min (95% confidence interval -1.2-4.0 ml/100 g/min).11 Hence, our observed increases in CBF after pentoxifylline administration appear to be drug-related.

Intracerebral steal, the redistribution of blood flow away from ischemic regions, is a potential adverse effect of cerebral vasodilator drugs.12,13 Intracerebral steal was not observed with pentoxifylline as lowest

<table>
<thead>
<tr>
<th>Time</th>
<th>Inhaled gas</th>
<th>$P_{CO_2}$ (mm Hg)</th>
<th>MABP (mm Hg)</th>
<th>Global CBF ml/100 g/min</th>
<th>% baseline</th>
<th>Lowest rCBF ml/100 g/min</th>
<th>% baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Air</td>
<td>34.8±1.4</td>
<td>95±3</td>
<td>55.5±13.9</td>
<td>100</td>
<td>44.3±11.3</td>
<td>100</td>
</tr>
<tr>
<td>2 hours</td>
<td>Air</td>
<td>34.0±2.0</td>
<td>91±6</td>
<td>56.6±13.8</td>
<td>101±8</td>
<td>58.8±12.9</td>
<td>100</td>
</tr>
<tr>
<td>4 hours</td>
<td>Air</td>
<td>33.7±1.9</td>
<td>93±5</td>
<td>54.9±10.1</td>
<td>101±15</td>
<td>51.3±10.0</td>
<td>119±24</td>
</tr>
<tr>
<td>6 hours</td>
<td>Air</td>
<td>33.6±2.3</td>
<td>102±7</td>
<td>60.1±13.5</td>
<td>110±15</td>
<td>60.8±10.7*</td>
<td>144±39*</td>
</tr>
<tr>
<td>High dose (800 mg)</td>
<td>Air</td>
<td>44.0±1.2</td>
<td>106±10</td>
<td>70.6±14.2*</td>
<td>116±77</td>
<td>70.0±13.7</td>
<td>121±13</td>
</tr>
</tbody>
</table>

$P_{CO_2}$, end-tidal carbon dioxide tension; MABP, mean arterial blood pressure; CBF, cerebral blood flow; rCBF, regional cerebral blood flow. Data are mean±SD.

*tp<0.01, 0.02, respectively, different from baseline by t test.
rCBF increased at least as much as global CBF. Further, cerebrovascular responses to metabolic change, specifically Pco2, appear to be unaffected by pentoxifylline at either a global or a regional level.

Pentoxifylline has been approved for the relief of claudication in patients with peripheral vascular disease. It is likely that many of these patients also have cerebrovascular disease, and it appears unlikely that pentoxifylline would have deleterious effects on the cerebral circulation in these patients. In fact, it is possible that the CBF increase caused by pentoxifylline could be beneficial. Theoretically, cerebral vasodilators are an attractive therapeutic option in patients with symptomatic cerebrovascular disease and reduced rCBF. Studies in polycythemic patients and cigarette smokers support the hypothesis that reduced CBF is associated with impaired and increased CBF is associated with improved neuropsychologic function. To date, however, clinical improvement in neuropsychologic function produced by cerebral vasodilators has been largely anecdotal and difficult to substantiate.

Whether this is related to the magnitude of the CBF increase, to intracerebral steal and worsening dysfunction in areas already most severely compromised, to impairment of metabolic vascular reactivity, or to demonstration of the error of the underlying hypothesis is not known.

A large, placebo-controlled, international, multicenter trial of pentoxifylline in acute nonhemorrhagic stroke has been published recently. Pentoxifylline therapy was begun as a 50-mg i.v. bolus within 12 hours after the onset of symptoms; therapy continued as an intravenous infusion at 16 mg/kg/day for 72 hours and then as 400 mg orally t.i.d. for 25 days. There were no differences in mortality nor in motor strength or ataxia scores between the placebo and pentoxifylline groups at the conclusion of the study. There was a trend toward improved level of consciousness in the pentoxifylline group, though this difference did not achieve significance. However, early in the study, while subjects received intravenous infusion, the pentoxifylline group had significantly higher level of consciousness, motor strength, cranial nerve function, and total neurologic deficit scores than did the control group; CBF was not measured. It is interesting to speculate that a higher oral dose of pentoxifylline, one more likely to increase global CBF, might have resulted in sustained neurologic improvement. Further carefully designed trials are indicated to determine whether the increased CBF following pentoxifylline is associated with improved neuropsychologic function in patients with cerebrovascular disease.

References


Table 3. Cerebrovascular Reactivity at Each Time for Patients With Cerebrovascular Disease Treated With Low or High Dose of Pentoxifylline

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Baseline</th>
<th>2 hours</th>
<th>4 hours</th>
<th>6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (400 mg)</td>
<td>0.8±0.7</td>
<td>0.9±0.4</td>
<td>1.4±1.0</td>
<td>1.0±0.3</td>
</tr>
<tr>
<td>High (800 mg)</td>
<td>1.3±0.8</td>
<td>2.5±3.3</td>
<td>1.7±1.1</td>
<td>1.7±0.7</td>
</tr>
</tbody>
</table>

Data are mean±SD ml/100 g/min/mm Hg.


**KEY WORDS** • cerebral blood flow • pentoxifylline • xenon
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