A Double-Blind, Randomized Trial of PY108-068 in Acute Ischemic Cerebral Infarction

Wieslaw J. Oczkowski, MD, Vladimir C. Hachinski, MD, Julien Bogousslavsky, MD, H.J.M. Barnett, MD, and S.G. Carruthers, MD

A double-blind, randomized, pilot trial of the calcium channel antagonist PY108-068 was completed in patients with acute ischemic cerebral infarction. Nine treated patients received PY108-068 orally (150 mg/day in divided doses) and 10 control patients received placebo within 48 hours of stroke onset for 21 days. The mean age of the treated patients (four men, five women) was 63.7 years and of the control patients (seven men, three women) 64.4 years. Most infarctions were in the territory of the middle cerebral artery. One treated patient died of sudden cardiac death on Day 12; one control patient died of cerebral herniation. Two treated patients had episodes of clinically insignificant hypotension during Day 1 of treatment. Two control patients had myocardial infarctions during the trial. The mean Toronto Stroke Scale scores at stroke onset were 67 and 90 and at Week 12 were 22.5 and 34.7 in the treated and control groups, respectively. There was parallel improvement in the two groups, with no significant difference between groups (p=0.12). The mean Barthel Index functional scores at stroke onset were 32.8 and 33 and at Week 12 were 90 and 78.8 in the treated and control groups, respectively. There was a trend in favor of the treated group, but differences between groups did not reach significance. In this pilot trial, PY108-068 was found to be safe but not effective in patients with acute ischemic cerebral infarction. (Stroke 1989;20:604–608)

Neurons in the "ischemic penumbra" may remain viable for hours after the initial ischemic insult. The "final common pathway" to neuronal death involves calcium ion homeostasis. It is speculated that an influx of calcium into ischemic cells diverts respiratory energy from production of adenosine 5'-triphosphate. Through cerebral vessel spasm and erythrocyte deformation, the "no-reflow phenomenon" further impairs tissue perfusion.

PY108-068 (diethyl 4-[2,1,3-benzoxadiazol-4-yl]-1,4-dihydro-2,6-dimethyl-pyridine-3,5-dicarboxylate) is a dihydropyridine-type calcium channel antagonist. Single-dose and steady-state pharmacokinetics in healthy volunteers and in patients with angina pectoris indicate a biphasic elimination of PY108-068, with a short elimination half-life of 2 hours and a longer one of 12 hours. After oral administration there is a bioavailability of approximately 25% because of a marked first-pass effect. PY108-068 has been found to be effective in treating hypertension and effort-induced angina (unpublished).

PY108-068 in animal models of ischemic stroke has had a favorable effect on oxygen delivery, neurologic recovery, and mortality. PY108-068 in small doses increases cerebral blood flow in humans with acute stroke, but higher doses may worsen blood flow in the peri-infarct area, implying a "steal" phenomenon. Our pilot trial was undertaken to assess the potential benefits and safety of PY108-068 in patients with acute focal cerebral ischemia.

Subjects and Methods

A double-blind, randomized, pilot trial of 20 consecutive eligible patients with acute ischemic infarction in the territory of the middle cerebral...
artery was planned. Ten patients were to receive standard treatment and PY108-068 administered orally beginning within 48 hours of stroke onset (100 mg on Day 1, 112.5 mg on Day 2, 125 mg on Day 3, and 150 mg on Days 4–21). The medication was divided into four doses daily. A control group of 10 patients was to receive standard treatment and placebo medication for 21 days.

We included men and women aged 45–80 years whose main neurologic diagnosis was acute ischemic cerebral infarction in the territory of the middle cerebral artery and whose chief neurologic symptom was hemiparesis. We excluded patients with previous stroke, brain hemorrhage, brainstem infarction, severe generalized cerebral symptoms such as coma and recurrent seizures, any evidence of organ (heart, lungs, kidneys, etc.) failure, systolic blood pressure continuously >165 mm Hg or <110 mm Hg, or lacunar infarction. Vasodilators, other calcium antagonists, barbiturates, prophylactic anticoagulants, platelet antiaggregating drugs, neuroleptics, and antidepressants were not administered during the 21-day treatment period.

All patients were admitted to the Stroke Investigative Unit at University Hospital for the first 7 days of treatment. Standard medical treatment was continued after discharge from this unit for the remainder of the trial.

Neurologic recovery was graded using the Toronto Stroke Scale (a graded neurologic score, no deficit = 0, maximal deficit = 155) before the start of treatment, on Days 1, 7, 14, and 21, and at Week 12. Functional recovery and activities of daily living were assessed using the Barthel Index (a graded functional status score, no deficit = 100, maximal deficit = 0) at the same times. Computed tomography (CT) of the head was obtained before the start of treatment, on Day 7, and at Week 12. Electrocardiography (ECG) was performed before the start of treatment and on each subsequent day until a stable dose of PY108-068 or placebo was reached. Continuous cardiac monitoring was undertaken for 7 days. Laboratory investigations before the start of treatment, on Days 1, 7, 14, and 21, and at Week 12 included serum electrolytes, liver and kidney function, serum hemoglobin, hematocrit, leukocyte count, and urinalysis. Chest x-ray was obtained before the start of treatment. Concentrations of cardiac CK isoenzymes were measured before and 6 hours after treatment was started and on Days 2, 3, and 4.

The trial was approved by the Health Sciences Standing Committee on Human Research of the University of Western Ontario. Both the purpose and the risks of the trial were explained to all patients and/or their families. Written consent was obtained in all cases.

Clinical scores for the groups were compared using the computer statistical package MINITAB. 16

<table>
<thead>
<tr>
<th>Category</th>
<th>Treated (n=9)</th>
<th>Control (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal level of consciousness; face, arm paresis</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Normal level of consciousness; hemiplegia/hemiparesis</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Altered level of consciousness; hemiplegia/hemiparesis</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

Data are number of patients.
TABLE 3. Clinical Events During Trial of PY108-068 in Acute Cerebral Infarction

<table>
<thead>
<tr>
<th>Event</th>
<th>Treated (n=9)</th>
<th>Control (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Transient hypotension</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Painful shoulder</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Data are number of patients.

isoenzyme concentrations were elevated at 25 (normal range <10) units. This patient tolerated PY108-068 well. His functional status improved.

and 34.7, respectively. Nonparametric analysis using the Mann-Whitney rank sum test indicated greatest significance at Day 14 (p=0.12) in favor of the treated group. The control group had an initially poorer mean neurologic score, but the groups showed a parallel improvement in scores, suggesting no benefit or adverse effect from PY108-068 (Figure 1).

At randomization, mean Barthel Index scores for the treated and control groups were 32.8 and 33, respectively; at Week 12 they were 90 and 78.9, respectively. Nonparametric analysis using the Mann-Whitney rank sum test indicated greatest significance for mean Barthel Index scores also at Week 12 (p=0.19) in favor of the treated group. Barthel Index scores of the groups were similar initially, with divergence after Day 7 in favor of the treated group (Figure 2), which suggests better functional recovery in the treated group.

Other clinical events are shown in Table 3. One patient within each group died during the trial. Initially, one 69-year-old man in the treatment group had a Toronto Stroke Scale score of 102.5. On Day 7, his CT head scan showed a right frontal-parietal infarct. On Day 2, his ECG showed mild anteroseptal ST segment elevation and cardiac CK

isoenzyme concentrations were elevated at 25 (normal range <10) units. This patient tolerated PY108-068 well. His functional status improved. On Day 12, 3 hours after the noon-time dosage of PY108-068 (37.5 mg), he developed the sudden onset of chest pain, collapsed, and died. Nursing records from just before the onset of chest pain showed his blood pressure to be normal and his pulse to be regular. In the control group, a 61-year-old man presented with severe hemiplegia and altered consciousness. His clinical status deteriorated, and he died on Day 4. A repeat CT scan prior to death was consistent with either extension of infarction or severe cerebral edema.

Two other patients in the control group had documented myocardial infarctions during Week 8 of the trial. At entry, cardiac CK isoenzyme concentrations were normal in both patients. Two patients in the treatment group had clinically insignificant episodes of transient hypotension on Day 1. Their lowest recorded blood pressures were 105/70 and 100/50 mm Hg.

An area of low density was visible on 16 of the 19 initial CT scans. All infarcts were visualized by Day 7.

Four patients (two in each group) had ECG changes consistent with ischemia and/or acute myocardial infarction, but only one (treatment patient) of these four had elevated concentrations of cardiac CK isoenzymes. Two patients in the control group had demonstrated intracardiac thrombus. Neither had previously documented cardiac disease or evidence of cardiac disease on clinical examination. Both patients had normal concentrations of cardiac CK isoenzymes at entry into the trial. One patient had ECG changes compatible with anterior myocardial infarction.

In the treatment group, carotid Doppler ultrasonography demonstrated carotid disease in two patients and findings were entirely normal in two. In neither patient with normal findings was angiography performed, nor was a cardiac source of stroke found. In the control group, all six patients who underwent carotid Doppler ultrasonography showed evidence of carotid artery disease.

In the control group, a 51-year-old man who presented with left hemiparesis and right neck pain was found subsequently by angiography to have a right carotid artery dissection.

Five patients in the treatment group and three patients in the control group had mildly elevated
A subsequent prospective, double-blind, random-

gen availability in the same regions. 27 A descriptive

that were normal by Week 12.

during the first week were due to transtentorial

from the final analysis, was found to have a pontine

goography was a cardiac thrombus found. A third

this nature of their stroke, and only by echocardi-

believed to have infarction on the basis of athero-

tially designed to randomize patients who were

channel antagonist PY108-068. Our trial was ini-

Calcium channel blocker nicardipine dilates human

cerebral vessels intraoperatively and increases oxy-

In primates, membrane permeability increases with

influx of calcium ions during ischemia. 24 In baboons, nimodipine improves cera-

blood flow but increases peri-ischemic edema. 25

In humans, oxygen extraction in the ischemic

region may increase, compensating for reduced

blood flow, thus retaining viability of the ischemic

tissue with potential for early intervention. 26 The

calcium channel blocker nicardipine dilates human cerebral vessels intraoperatively and increases oxy-

gen availability in the same regions. 27 A descriptive study of patients with cerebrovascular ischemia

treated with either verapamil or nifedipine and heparin was believed to show promising results. 28 A

single blinded study of acute stroke patients treated with nimodipine was believed to show improved

neurologic recovery 28 days after stroke onset. 29,30 A subsequent prospective, double-blind, random-

ized trial of nimodipine in patients with acute ischemic stroke showed decreased mortality and improved neurologic functional recovery after 4 weeks of treatment. 31

Much information can be gained from closely studying a few patients with relatively uniform
disease. Our trial was designed in such a manner to try to assess the efficacy and safety of the calcium channel antagonist PY108-068. Our trial was initially designed to randomize patients who were believed to have infarction on the basis of atherosclerotic disease of the cranial vessels. It is remarkable that even in this small group of closely followed and extensively investigated patients, we identified multiple causes of stroke. Two patients had cardioembolic strokes; neither had a medical history or physical examination that gave clues to this nature of their stroke, and only by echocardiography was a cardiac thrombus found. A third patient was found to have carotid artery dissection on angiography. A fourth patient, who was excluded from the final analysis, was found to have a pontine lacunar infarct. The cause of stroke was not obvious in two patients with normal findings on Doppler ultrasonography and cardiac investigations.

In a prospective study of more than 1,000 consecutive stroke patients, the majority of deaths during the first week were due to transfuntorial herniation. 32 Cardiac deaths occurred throughout the first month. One patient in our trial died of cerebral herniation, while a second patient had sudden cardiac death.

Patients with acute stroke may be predisposed to the development of cardiac arrhythmias. 33 The recent trial of nimodipine showed a reduction in cardiac deaths in treated patients. 31 The large proportion of hypertensive patients in the treatment group in our trial may have benefited from the antihypertensive effects of PY108-068.

All 19 patients in our trial underwent sequential CT scanning; 16 had visualization of the ischemic infarct within 48 hours of stroke onset. Our results support the high frequency of visualization of ischemic infarct within the first 24-48 hours after stroke onset. 34,35 Given the small size of our pilot trial, it was not surprising that nonidentical patients according to hypertension, initial neurologic score, and evidence of atherosclerosis on carotid ultrasonography were randomized to treatment and control groups.

Even though neurologic recovery (using the Toronto Stroke Scale) showed parallel improvement in both groups, the Barthel Index of functional recovery showed a trend to improved outcome in the treated group. The number of patients required to be confident (one-tailed a=0.05) that a clinically important (25%) risk reduction in the treatment group was not missed, given the observed event rates in our trial, is estimated to be 254 patients per group. 36

Our pilot trial has shown that the calcium channel antagonist PY108-068 can be safely given to patients with acute ischemic cerebral infarction. A larger trial is required to demonstrate whether in fact this calcium channel antagonist is also effective in improving neurologic recovery.

Acknowledgments

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