Large-Dose Infusions of Heparinoid ORG 10172 in Ischemic Stroke

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We evaluated the safety and possible efficacy of large doses of the heparinoid ORG 10172 in 57 patients with acute or progressing ischemic stroke. Patients received a loading bolus of the drug followed by a maintenance intravenous infusion for 7 days. The plasma level of ORG 10172 was monitored by the degree of inhibition of coagulation factor Xa. In general, the drug was well tolerated and few hemorrhagic complications occurred. Two patients with large cardioembolic hemispheric strokes had intracranial hemorrhagic complications. Most patients improved during treatment. By 3 months after the stroke, 37 patients (65%) had a favorable outcome (minimal or no residual disability). This study suggests that high-dose intravenous infusions of ORG 10172 can be safely given to patients with acute ischemic stroke. (Stroke 1990;21:1289–1292)

Because the treatment of stroke patients with heparin is associated with hazardous hemorrhagic complications,1,2 there has been an ongoing search for safer antithrombotic preparations.3–7 Recently developed preparations have allowed a dissociation of the antithrombotic activity of heparin from its anticoagulant and platelet-aggregating effects. Low-molecular-weight heparinoids have strong selective anti-factor Xa activity but weak antithrombin activity and a negligible anticoagulant effect. These preparations offer an alternative therapy with a decreased bleeding tendency.5–9

A low-molecular-weight heparinoid, ORG 1017210 is a mixture of natural sulfated glycosaminoglycans obtained from animal intestinal mucosa. ORG 10172 contains approximately 80% low-molecular-weight heparan sulfate with low affinity for antithrombin-III, approximately 8–10% dermatan sulfate, approximately 5% chondroitin sulfate, and 4% heparan with a high affinity for antithrombin III. Both heparan sulfate and dermatan sulfate have minor anticoagulant effects mediated through heparin cofactor II, a plasma protein inhibitor that reacts only with thrombin. With a specific activity of approximately 15 anti-factor Xa units/mg, ORG 10172 has a molecular weight distribution between 4,000 and 10,000 daltons and is an effective antithrombotic agent with a higher antithrombotic/bleeding ratio than heparin.5,8 Because it has no appreciable effect on the activated partial thromboplastin time (aPTT), the activity of ORG 10172 is monitored by assaying plasma anti-factor Xa activity. On the basis of early clinical studies in patients with deep vein thrombosis, plasma anti-factor Xa activity between 0.4 and 0.8 unit/ml is considered therapeutic.11–13

We undertook a pilot study to determine the potential safety and the best method of administering ORG 10172 intravenously in patients with acute ischemic stroke. The results of our preliminary dose-escalation study have been reported.14 We conducted the current study to evaluate the potential safety of high-dose ORG 10172 in patients with acute ischemic stroke and to evaluate (before efficacy studies) a method of delivering a dose of ORG 10172 designed to maintain steady-state plasma anti-factor Xa activity from the onset of the infusion.

Subjects and Methods

We screened patients aged 18–85 years admitted to either the University of Iowa Hospitals or to Duke University Medical Center with acute or progressing ischemic stroke. We included patients with thrombotic or embolic occlusions of the large arteries, cardiogenic cerebral embolism, small-artery occlusion, or cerebral ischemia of uncertain etiology as determined clinically and by cranial computed
tomography (CT). Symptoms were present for at least 30 minutes but less than 24 hours. The patients or family members gave informed consent before entry into the study, and the protocol was approved by the institutional review boards of the participating institutions.

Reasons for exclusion included transient neurologic symptoms, CT evidence of cerebral hemorrhage or hemorrhagic infarction, known vasculitis, coma, confounding neurologic illnesses, recent major cardiovascular surgery, active bleeding (e.g., gross hematuria, active gastrointestinal bleeding, or positive stool guaiac), or a sustained calculated mean arterial blood pressure (MABP) of >140 torr. Also excluded were patients whose baseline laboratory evaluations indicated one or more of the following abnormalities: elevated aPTT, elevated prothrombin time (PT), platelet count of >125,000 mm$^3$, bleeding time of >10 minutes, severe unexplained anemia (hematocrit of <21%), renal failure (blood urea nitrogen concentration of >50 mg/100 ml, creatinine content of >3 mg/100 ml), active hepatic disease (PT of >15 seconds), respiratory failure (PCO$_2$ of >50 mm Hg, PO$_2$ of <60 mm Hg), and those with known hypersensitivity or other adverse reactions to heparin, sodium sulfite, or bisulfites. Later in the study, two deaths secondary to hemorrhagic transformation of large hemispheric cardioembolic infarcts led us to add two additional exclusions: 1) cerebral edema and midline shift on the initial cranial CT scan, and 2) MABP of >130 torr.

Baseline studies included complete blood count with differential, platelet count, fibrinogen content, PT, aPTT, thrombin time, bleeding time, fibrin degradation products, euglobulin clot lysis time, plasma anti-factor Xa activity (measured by chromogenic assay), blood glucose concentration, serum electrolytes, blood chemistries, urinalysis, stool guaiac, cranial CT, chest roentgenography, and 12-lead electrocardiography. All blood was drawn from peripheral veins, and no anticoagulants were used.

We chose an ORG 10172 dosage regimen designed to achieve a plasma anti-factor Xa activity of 0.8 unit/ml based on data from our earlier study as well as from other studies using ORG 10172.$^5,6$ In our previous dose-escalation study, a bolus of ORG 10172 was followed by a constant infusion. Plasma anti-factor Xa activity did not plateau until 4 days after the bolus injection, and a striking postbolus decrease in activity was noted, suggesting that ORG 10172 has a multicompartmental kinetic profile.$^4$ Therefore, to achieve a stable plasma anti-factor Xa activity of 0.8 unit/ml at the onset of treatment in the present study, we used a three-stage dosage regimen (Table 1). A bolus was administered, followed by a rapid infusion for 4 hours, a slower infusion for the next 12 hours, and then a maintenance infusion for the remainder of the 7 days. Maintenance infusion doses were adjusted by 10% increments or decrements based on the degree of inhibition of factor Xa. No adjustments for body weight were made.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>ORG 10172 (units)</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bolus</td>
<td>2,500</td>
<td>10 min</td>
</tr>
<tr>
<td>2</td>
<td>Rapid infusion</td>
<td>2,400</td>
<td>4 hr</td>
</tr>
<tr>
<td>3</td>
<td>Slower infusion</td>
<td>4,800</td>
<td>12 hr</td>
</tr>
<tr>
<td>4</td>
<td>Maintenance infusion</td>
<td>7,200</td>
<td>24 hr</td>
</tr>
</tbody>
</table>

Treatment included bed rest and supplemental oxygen (2 l/min) during the first 24 hours and intravenous half-normal or normal saline to maintain adequate urinary output. Glucose-containing solutions were not given during the 7 days of treatment. No food was given during the first 24 hours of treatment. Pretreatment drugs were continued with the exception of platelet antiaggregating drugs or antithrombotic medications.

Medical assessments were made before the initiation of treatment, at the end of the bolus, at 4 and 16 hours, daily for 7 days, and at 3 months. The National Institutes of Health stroke scale was used to assess neurologic deficits and determine improvement.$^{15,16}$ Favorable outcome was indicated by improvement. Hematologic and coagulation parameters were measured at selected times during treatment. Plasma anti-factor Xa activity was measured at the time of each clinical examination. Cranial CT without contrast enhancement was performed ≤24 hours after the initiation of treatment, ≤72 hours after the completion of treatment, and at 3 months. All data were transmitted to the Division of Stroke and Trauma, National Institute of Neurological and Communicative Disorders and Stroke for management and analysis.

**Results**

Of the 57 patients who fulfilled inclusion and exclusion criteria, 30 were men and 27 were women; 50 were white and seven were black; 55 were right-handed, one was left-handed, and in one handedness was unknown. The patients' ages ranged from 33 to 83 (mean 63) years. Determined from clinical and radiologic examinations, the left hemisphere was involved in 25 patients and the right in 25, two patients had bilateral involvement, and five had involvement of other locations. Based on clinical criteria developed for the Harvard Cooperative Study Registry,$^{16}$ 19 strokes were large-artery thrombotic occlusions, 17 were small-artery occlusions (lacunes), 11 were large-artery embolic occlusions, eight were cerebral emboli of cardiac origin, and two were of unknown type.

The mean and range of plasma anti-factor Xa activity during treatment is shown in Figure 1. After 24 hours of treatment, 27 patients (47%) were improved, 21 (37%) were unchanged, and nine (16%) were worse (Table 2). By 7 days, 41 patients (72%) had improved, nine (16%) were unchanged, five (9%) were worse, and two (3%) had died. No
cases of recurrent stroke, myocardial infarction, or pulmonary embolism occurred during treatment. By 3 months, 17 patients (30%) had recovered completely, 23 (40%) had recovered partially, eight (14%) were unchanged, two (4%) were worse, and six (11%) had died; one patient (1%) was lost to follow-up. At 3 months, 37 patients (65%) had favorable outcomes (with no or minimal disability). The causes of death were intracranial hemorrhage in two patients, recurrent ischemic stroke in two, pulmonary embolism in one, and pneumonia and renal failure in one.

No nonhemorrhagic side effects occurred during treatment. Minor hemorrhagic side effects occurred in four patients; two developed epistaxis and two had guaiac-positive stools. These side effects did not necessitate discontinuation of ORG 10172.

Major hemorrhagic complications occurred in three patients. None had contributing factors such as thrombocytopenia, increased bleeding time, or a prolonged aPTT. One patient had a gastrointestinal tract hemorrhage and hematuria with an associated decrease in hematocrit but did not require transfusion and recovered uneventfully. Two patients died of hemorrhagic transformation of large hemispheric infarcts. One elderly, hypertensive patient with an extensive cardioembolic hemispheric infarction had a fatal hemorrhagic transformation approximately 6 hours after the initiation of treatment. At that time, the plasma anti-factor Xa activity was 1.22 units/ml and MABP was >140 torr. Another elderly patient who suffered a large cardioembolic stroke with "mass effect" noted on the admission cranial CT scan had a fatal intraparenchymal hemorrhage on the sixth day of treatment. The plasma anti-factor Xa activity at the time of the symptomatic hemorrhage was 0.6 unit/ml. The exclusion criteria were subsequently altered to increase safety after these hemorrhagic events. We also adjusted the ORG 10172 dosage regimen to lessen the possibility of excessive antithrombotic effects.

### Table 2. Neurologic Condition Among 57 Patients With Acute or Progressing Ischemic Stroke Given Heparinoid ORG 10172

<table>
<thead>
<tr>
<th>Condition</th>
<th>24 hours</th>
<th>7 days</th>
<th>3 months*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>No. 27</td>
<td>% 47</td>
<td>41 72</td>
</tr>
<tr>
<td>Unchanged</td>
<td>No. 21</td>
<td>% 37</td>
<td>9 16</td>
</tr>
<tr>
<td>Worse</td>
<td>No. 9</td>
<td>% 16</td>
<td>5 9</td>
</tr>
<tr>
<td>Dead</td>
<td>No. 0</td>
<td>% 0</td>
<td>2 3</td>
</tr>
</tbody>
</table>

*One patient lost to follow-up.

We included acute ischemic stroke patients with the onset or progression of neurologic signs in the preceding 24 hours. For intervention to have any major benefit on the outcome of such patients, it must be given soon. For drug therapy to prevent neurologic worsening, it should be given ≤24 hours after the onset, when progression is most likely. Therefore, the possible benefit as well as the safety of a promising intervention must be tested in patients with acute stroke (<24 hours after onset).

We included patients with the entire clinical spectrum of acute ischemic stroke. Ideally, to generalize to patient management, the results of any treatment trial should be applicable to the entire stroke population and not to only a select subgroup. For this reason, we treated patients with anterior circulation hemispheric and posterior fossa ischemic events as well as those with neurologic events of all possible etiologies. However, effective therapy for a subgroup would also be of interest.

We tested the safety of ORG 10172 in patients with strokes of all clinical severities, including large lesions secondary to cardioembolism. Some physicians have advised that heparin not be given to patients with arterial hypertension, an altered level of consciousness, or large hemispheric infarcts of cardioembolic origin because such patients appear to be at high risk of hemorrhagic transformation. The incidence of hemorrhage in our study was lower than that among patients given heparin17 and should also be compared with the reportedly high incidence of spontaneous hemorrhagic transformation following ischemic stroke. However, our results suggest caution in the use of ORG 10172 in patients with major hemispheric infarcts secondary to cardioembolism, particularly if the patient has severe hypertension (MABP of >130 torr). As our study progressed, we expanded the exclusion criteria to reflect these concerns. After changing the criteria, no further hemorrhagic events occurred. Future trials of the efficacy of ORG 10172 should have similar inclusion and exclusion criteria. While a future efficacy trial could be criticized for not including seriously ill patients, it can also be argued that any patient with a major hemi-

**Discussion**
spheric infarct and midline shift on cranial CT performed ≤24 hours after onset probably will not have a satisfactory outcome regardless of treatment. Many patients required adjustment of their ORG 10172 dosage. Rapid achievement of a "therapeutic" plasma anti-factor Xa activity within minutes of initiating treatment will allow testing of possible early therapeutic benefits. The dosage regimen worked well and could be applied in a multicenter clinical trial. Adjustment of ORG 10172 dosage to avoid excessive inhibition of factor Xa may have helped reduce the number of hemorrhagic complications. A future trial of ORG 10172 efficacy should include measurements of plasma anti-factor Xa activity to assure patient safety. Patients and physicians can be blinded to avoid bias in evaluating outcome in such a trial.

Heparinoids do not markedly affect either the aPTT or the thrombin time. Therefore, study of ORG 10172 as a potential therapeutic agent for stroke began with the development of reliable measures of its presence in plasma and an evaluation of its ability to inhibit factor Xa. In our present study, ORG 10172 levels were monitored by assaying plasma anti-factor Xa activity, although direct measurement of the concentrations of heparinoids in plasma should be possible and might also prove useful.

In an earlier study, we evaluated various doses of ORG 10172 and the resultant plasma anti-factor Xa activities in 26 patients. Based on that study, a three-stage dosage regimen with bolus, rapid infusion, and maintenance infusion of ORG 10172 (Table 1) was evaluated in this study. Plasma anti-factor Xa activity could be maintained between 0.4 and 0.8 unit/ml over 7 days (Figure 1). This regimen avoided the "overshoot" seen after a single bolus followed by infusion yet allowed the rapid achievement of steady plasma levels of ORG 10172.

Our results suggest that ORG 10172 may be safely given to selected patients with acute ischemic stroke. This drug can be administered in a manner that will achieve nearly instantaneous steady anti-factor Xa activity.

Acknowledgments

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References

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