

A dose escalation study of ORG 10172 (low molecular weight heparinoid) in stroke

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Article abstract—An intravenous infusion of a low molecular weight heparinoid, with a reduced risk of hemorrhage, may be an alternative to heparin in the management of acute ischemic stroke. To evaluate this hypothesis, we studied the safety of the heparinoid, ORG 10172, in a dose-escalation study in 26 patients. The drug was administered as a loading bolus followed by a 7-day infusion in five rates with target anti-factor Xa levels from 0.2 to 1.0 U/ml. The drug was well tolerated; no major bleeding complications or thrombocytopenia occurred. There were no deaths or hemorrhagic transformation of cerebral infarctions. The results indicate that ORG 10172 at doses to achieve a level of 1.0 U/ml or less may be used safely in management of acute cerebral infarction.

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Many therapies for acute ischemic stroke have been attempted, but none are proven effective. Despite its widespread use, heparin has not been found to be useful, in part because of the risk of bleeding complications.¹ Low molecular weight (LMW) heparinoids are an attractive alternative therapy since, despite a major antithrombotic effect, there is decreased bleeding tendency when compared with heparin. Heparinoids do not markedly affect either the activated partial thromboplastin time (PTT) or thrombin time (TT).²

We report the preliminary results of treatment of acute ischemic stroke with the heparinoid ORG 10172 (Organon, Int.).³ The goal of this study was to determine a potentially optimal and safe dose, a critical prerequisite for any large trial to establish efficacy.

Methods. Patients between the ages of 18 and 85 years, admitted to either the University of Iowa or Duke University Medical Center, with acute or progressing ischemic stroke were screened. Patients with thrombotic or embolic occlusions of large arteries, cardiogenic cerebral embolism, small artery occlusion, or cerebral ischemia of an uncertain etiology were included. Symptoms were present for at least 30 minutes but less than 24 hours. Patients or family members gave informed consent before entry into the study. The protocol was approved by the institutional review boards of both institutions.

The following were reasons for exclusion: transient symptoms, CT evidence of cerebral hemorrhage or hemorrhagic infarction, known vasculitis, coma, major confounding neurologic illnesses, recent major cardiovascular operation, active bleeding (eg, gross hematuria, active gastrointestinal bleeding, or heme-positive stools), or sustained, calculated mean arterial blood pressure (MABP) greater than 140 mm Hg. Also excluded were patients whose baseline laboratory evaluation included one or more of the following abnormalities: elevated PTT, elevated prothrombin time (PT), platelet count <125,000 mm³, bleeding time >10 minutes, or severe unexplained anemia (HCT <21%), renal failure (BUN >50 mg/100 ml, creatinine >3 mg/100 ml), active hepatic disease (PT >15 seconds), respiratory failure (Pco₂ >50 mm Hg, Po₂ <60 mm Hg), and those with a known hypersensitivity or other adverse reactions to heparin, sodium sulfite, or bisulfites.

Cranial CT, chest roentgenogram, ECG, and the following laboratory tests were performed: complete blood count with differential and platelet count, PT (rabbit brain thromboplastin, Ortho Diagnostics—University of Iowa; General Diagnostics—Duke University), PTT (Thromboscreen Kontakt, Pacific Hemostasis—University of Iowa; Partial Thromboplastin, General Diagnostic—Duke University), fibrinogen (Dade Division, Baxter Healthcare), TT (Dade Division, Baxter Healthcare), bleeding time (Simplate II Device, General Diagnostics), fibrin degradation products (Dade Division, Baxter Healthcare—University of Iowa) or euglobulin clot

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Table. Dose escalation schedule of ORG 10172 in patients with acute cerebral ischemia

Level	No. pts	ORG 10172 loading dose		ORG 10172 maintenance dose		Target level pl a-Xa-U/ml
		a-XA-U	ml	a-Xa-U/hr	ml/24 hrs	
I	5	625	0.5	62.5	1.2	0.2
II	6	1,250	1.0	125	2.4	0.4
III	5	1,875	1.5	187.5	3.6	0.6
IV	5	2,500	2.0	250	4.8	0.8
V	5	3,125	2.5	312.5	6.0	1.0

lysis⁴ (Duke University), plasma anti-factor Xa⁵ activity, blood glucose, serum electrolytes, blood chemistries, urinalysis, and stool guaiac.

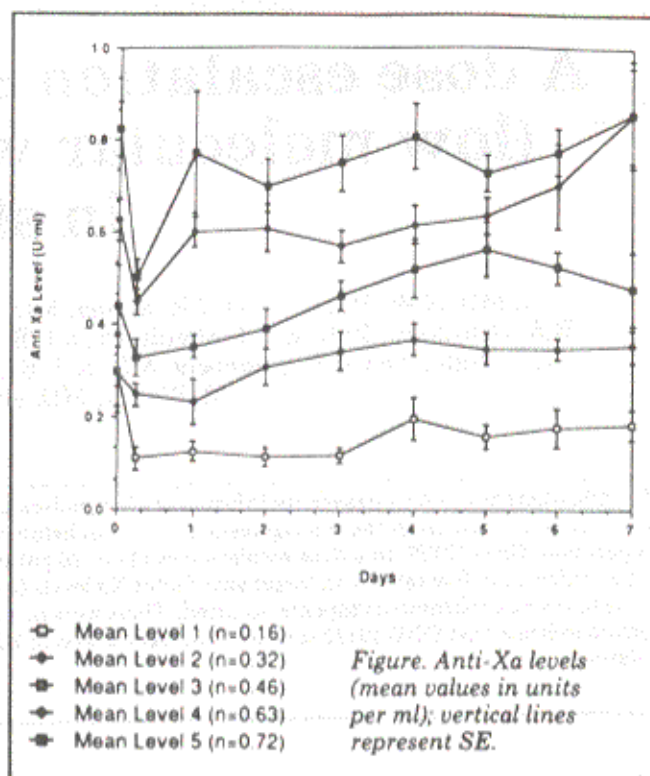
ORG 10172, from a single lot (Number PD 0028) and in a concentration of 1,250 anti-factor Xa U/ml, was given as an intravenous bolus dose followed by a continuous 7-day infusion at an hourly rate of 10% of the bolus. Five or six patients were studied at each of five dose levels, with aimed target levels of anti-factor Xa activity being 0.2 U/ml to 1.0 U/ml (table). Dosages were increased or decreased by 10% among patients weighing >80 or <60 kg, respectively. If plasma levels of anti-factor Xa activity exceeded 1.0 U/ml the infusion rate was reduced by 50%. The activity of ORG 10172 was determined from the inhibition of chromogenic substrate hydrolysis by factor X in the presence of antithrombin III (AT-III).⁵ Standard curves were prepared by using control plasma and dilutions of ORG 10172 from the same lot that was used in treatment, assuming the heparinoid concentration in anti-factor Xa units as stated by the manufacturer. Reagents for these assays were from the Coatest Heparin Kit, a product of Kabi, obtained from Helena Laboratories (Beaumont, TX).

Other treatment included bed rest, supplemental oxygen (2 l/min) during the first 24 hours, and intravenous solutions with 1/2 normal saline or normal saline to maintain adequate urinary output. No glucose-containing solutions were given during the treatment period. No food was given during the first 24 hours of treatment. Pretreatment drugs were continued except for antiplatelet or nonsteroidal anti-inflammatory drugs (NSAIDs).

Medical and neurologic assessments were done before treatment, at end of the bolus, at 6 hours, daily for 7 days, and at 3 months. We used the NIH stroke scale for assessment of the neurologic deficits.⁶ Hematologic and above-mentioned coagulation parameters were measured at selected epochs throughout the infusion. Measurements of anti-factor Xa levels were done at the time of each clinical examination during the acute treatment period. CT without and with contrast enhancement was performed at 24 to 72 hours following completion of treatment, and an unenhanced CT study was done at 3 months. All data were transmitted to Division of Stroke and Trauma, NINCDS, Bethesda, MD, for management and analysis.

Results. Patients. From May 3, 1986, through September 14, 1986, 96 consecutively admitted patients were screened; 70 patients met one or more of the exclusion criteria.

Sixteen patients were treated in Iowa City, IA, and 10 in Durham, NC. Their ages ranged from 38 to 82 years (mean, 63.6); 14 were men and 12 women; 21 were white and five black. Sixteen patients had a history of hypertension, 16 were cigarette smokers, five had a history of



alcohol abuse, four were diabetics, four had prior myocardial infarction, three had atrial fibrillation, two had cardiomegaly, two had a history of congestive heart failure, and one had leg claudication. Six patients had prior TIAs dating 1 to 120 days (mean, 47.3 days) prior to cerebral infarction; two had prior strokes, and only two had carotid bruits. Ten patients had used either antiplatelet or NSAIDs within 1 week prior to stroke.

Stroke was attributed to large artery atherothrombotic or atheroembolic occlusions in 13 patients, small artery occlusion in 10, and cardiogenic cerebral embolism in three. Diagnoses were based on the clinical criteria developed for the Harvard Cooperative Study Registry.⁷ The right hemisphere was involved in 13 patients, the left hemisphere in 10, and brainstem-cerebellum in three. Sixteen CT examinations done on days 7 to 10 showed new ischemic lesions, but no areas of hemorrhage were detected.

Outcomes. After 24 hours of treatment, 14 patients had improved, eight were unchanged, and four were worse. By 1 week, 20 patients had improved, four were worse than admission, and two were unchanged. At 3 months, no patients had died, 11 patients had completely recovered, 14 had partially improved, and one was worse. Patient performances at 3 months were independent—14, mild impairment—four, moderate impairment—six, and severe impairment—two.

Eight patients had the doses for the bolus injection and the 24-hour infusion volume increased by 10%. Four patients had the doses decreased by 10%. Three Level V patients had anti-factor Xa levels greater than 1.0 U/ml during the course of therapy. There was a general trend for the anti-factor Xa levels to decrease immediately after bolus injection and after 6 hours to

increase steadily throughout the course of therapy. The figure demonstrates the correlation between mean values of anti-factor Xa activity and the dose of ORG 10172.

Mild bleeding complications occurred during treatment in three patients. Epistaxis occurred in one patient treated at the lowest dosage. A second patient in Level IV had heme-positive stools that occurred 24 hours following the completion of ORG 10172 infusion. After completion of the heparinoid infusion, he had received indomethacin for gout. Endoscopy revealed esophageal ulcerations. A third patient in Level V who had had previous surgery for a duodenal carcinoma also developed heme-positive stools for 1 day. Endoscopy revealed a small ulcer at the site of surgical anastomosis. No patient required treatment for an adverse event or had ORG 10172 discontinued. There were no deaths. There was a decrease in the mean hemoglobin concentration at day 7 from baseline ($p = 0.032$). No significant changes per group in platelet count or PT occurred nor was there any obvious dose-related trend. There was a tendency for the PTT to increase, in most instances within the normal range. No changes on liver or renal function tests were encountered.

Discussion. Because of the potentially hazardous complications of heparin, including thrombocytopenia and bleeding, a search has been undertaken for safer preparations of heparin or heparin-like substances.⁸⁻¹² A dissociation between antithrombotic activity and anticoagulant capacity of heparin is now possible. Recently developed preparations of low molecular weight (2,500 to 10,000 daltons) possess significant anti-factor Xa activity in plasma, weak antithrombin activity, and exhibit a negligible net anticoagulant effect.¹⁰⁻¹²

The heparinoid, ORG 10172, is a mixture of natural sulfated glycosaminoglycans obtained from animal intestinal mucosa. It contains a low molecular weight heparin-like component (4%) with a high affinity for AT-III, approximately 80% low molecular weight heparan sulfate, approximately 8 to 10% dermatan sulfate, and about 6 to 8% of chondroitin sulfate. Both heparan sulfate and dermatan sulfate have some anticoagulant effects mediated through heparin cofactor II, a plasma protein inhibitor that reacts only with thrombin.¹³ ORG 10172 has a specific activity of about 15 U/mg and a molecular weight distribution between 4,000 and 10,000 daltons. It is an effective antithrombotic agent with a higher antithrombotic/bleeding ratio than heparin. Because ORG 10172 has no appreciable effect on PTT, its activity is monitored by assay of plasma anti-factor Xa activity.⁵ Direct measurement of these heparinoids in plasma might also be possible.¹⁴ On the basis of early clinical studies, plasma anti-factor Xa levels between 0.4 and 0.8 U/ml have been considered therapeutic.¹⁵ The anti-factor Xa activity of ORG 10172 is possibly associated with only a minor component of the drug mixture; thus, pharmacokinetic factors may reflect only a part of the behavior of the compound.

ORG 10172 has been used with success to prevent thrombosis in patients undergoing maintenance renal dialysis; anti-factor Xa plasma levels were maintained

at 0.4 to 0.8 U/ml.¹⁶ Harenberg et al¹⁷ and Kiers et al¹⁸ have successfully used ORG 10172 in patients with documented thrombosis secondary to heparin-induced thrombocytopenia. Treatment with ORG 10172 kept the plasma anti-factor Xa levels at 0.4 to 0.5 U/ml. Ten Cate et al¹⁵ used ORG 10172 in four patients with deep venous thrombosis complicating a hemorrhagic stroke and in one patient with a right parietal hematoma and a left ventricular thrombus discovered by echocardiography; no major side effects were reported. Plasma anti-factor Xa levels were maintained between 0.6 and 0.9 U/ml in most patients. ORG 10172 has also been used without complications in a 14-year-old patient on chronic hemodialysis who required a craniotomy for removal of an intracerebral hemorrhage.^{15,19}

Turpie et al²⁰ tested the ability of ORG 10172 to prevent deep vein thrombosis in 75 patients with atherothrombotic cerebral infarction. Fifty patients received ORG 10172 and 25 were given placebo within 7 days of stroke. The mean anti-factor Xa level was 0.061 U/ml after 1 day of therapy and reached a level of 0.179 U/ml by day 11. Venous thrombosis occurred in 4% of the actively treated group and in 28% of those receiving placebo. One major hemorrhage occurred among the patients receiving ORG 10172. The study concluded that ORG 10172 was safe and effective in preventing deep vein thrombosis in patients with acute atherothrombotic cerebral infarction.

Our results suggest that large intravenous doses of ORG 10172 can be given safely to patients with acute ischemic stroke. The highest dose of ORG 10172 leads to levels of inhibition of factor Xa that is greater than 1.0 U/ml; this level is higher than is considered desirable. Although we were primarily interested in the safety of ORG 10172 in patients with acute ischemic stroke, we were impressed by the very favorable outcomes noted in our patients. Further study of the possible efficacy of ORG 10172 in a dosage to achieve an anti-factor Xa level of 0.8 U/ml is warranted. The 3-month mortality was 0, and almost half of the patients had complete recovery from the stroke.

Using a bolus followed by a maintenance infusion at a 10% maintenance dosage rate, there is a postbolus drop in the anti-factor Xa levels. This finding is consistent with a multicompartmental kinetic profile. The level of anti-factor Xa activity does not reach a plateau until 4 days after initiating therapy if the previously described regimen is used. To avoid a postbolus nadir and to achieve a steady state more quickly, more rapid administration of the maintenance infusion of ORG 10172 should be given.

Addendum. As of February 1, 1988, 57 additional patients have been studied on the phase II protocol. There were two fatal hemorrhagic transformations of cerebral infarction. Both patients had history of atrial fibrillation and large hemispheric cardioembolic infarctions. One patient had a baseline MABP of 138 mm Hg, and MABP >140 mm Hg at the time of bleeding. The other patient had severe hemispheric cerebral edema noted on baseline CT. Protocol adjustments now include the

