Defibrotide Versus Heparin in the Prevention of Coronary Reocclusion After Thrombolysis in Acute Myocardial Infarction

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Summary. A multicenter controlled study versus heparin was conducted to explore the activity of defibrotide, a polydesoxyribonucleotide drug, in preventing reocclusion after urokinase thrombolysis in patients with acute myocardial infarction (AMI). The study involved 137 consecutive patients with AMI and a time from the onset of symptoms ≤6 hours, treated with urokinase (1,000,000 U intravenous bolus followed by 1,000,000 U slow-drip infusion over 12 hours). Immediately after thrombolysis, patients were allocated to treatment with defibrotide (group D: day 0, 3.6 g by intravenous infusion in 12 hours; days +1 to +6, 800 mg tid intravenously; days +7 to +10/+12, 400 mg tid intramuscularly), or heparin (group H: day 0, 1000 IU/hour infused over 12 hours; days +1 to +10/+12, 5000 IU tid subcutaneously). Coronary angiography was done, whenever possible, at +10/+12 days. The following parameters were assessed: (a) non-invasive estimate of myocardial reperfusion, through the analysis of CPK time-activity curves; (b) incidence of infarct-related artery (IRA) patency (TIMI scores 2-3) at coronary angiography. A total of 125 patients had a complete enzymatic curve (63 in group D and 62 in group H) and 106 had coronary angiography as well. IRA patency (the main end point) was observed in 63% of group D versus 43% of group H patients (p = 0.07). No statistically significant differences were found in the proportion of patients with indirect signs of early reperfusion (63% in group D versus 52% in group H patients). Combining the findings of CPK curve analysis and coronary angiographic data, the D group showed a trend towards a minor proportion of patients with reocclusion of a possibly patent IRA (28% vs. 47%) and a greater proportion of patients with “late reperfusion” of a possibly occluded IRA (44% vs. 37%), in comparison to the H group. These preliminary data suggest that defibrotide is equal, if not more effective than heparin, in combination with urokinase, in achieving IRA patency in patients with AMI.

Key Words. defibrotide, thrombolysis, reocclusion, acute myocardial infarction, heparin

The recanalization of thrombosed coronary arteries obtained with thrombolytic drugs in patients with acute myocardial infarction (AMI) is followed in a sizeable proportion of cases by a recurrence of thrombosis in the previously affected artery (infarct-related artery, IRA); this phenomenon has been variously labeled rethrombosis, restenosis, or reocclusion [1-3]. Such events recur within 10–15 days in an estimated 10–30% of patients treated successfully by thrombolysis [2-6]; the event may lead to reinfarction or other forms of acute myocardial ischemia, but it is often completely asymptomatic [3]. Reocclusion is more likely to occur in patients whose coronary stenosis is particularly severe [7]; in those not adequately treated with anticoagulants [2]; and in those with high thrombin activity, as demonstrated by increased assays of fibrinopeptide A [8] or thrombin-antithrombin complexes [9]. The main preventive measure against reocclusion of a recanalized coronary artery is heparinization [10,11], sometimes followed by treatment with oral anticoagulants [2]; and in those with high thrombin activity, as demonstrated by increased assays of fibrinopeptide A [8] or thrombin-antithrombin complexes [9]. The main preventive measure against reocclusion of a recanalized coronary artery is heparinization [10,11], sometimes followed by treatment with oral anticoagulants [2]. Two other forms of preventive treatment are currently being explored: One is the administration of platelet antiaggregants [12,13] and the other is continuous treatment with thrombolytic agents [14].

Defibrotide is an extracted polydesoxyribonucleotide derivative, characterized by the following properties: (a) enhancement of physiologic fibrinolytic activity, through the potentiation of tPA release and reduction of PAI-1 release from vascular endothelia [15-17]; (b) activation of the endothelial release of PGI2 and allied prostanoids [15,18-20] and antagonism towards the contractile activity of endothelin [21]; (c) lack of antithrombin activity or any intrinsic action on blood coagulation function [22], despite its conspicuous

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ous antithrombotic activity [15,23,24]; (d) cytoprotective activity through mechanisms at least partly mediated by PGI2 [25–28].

Because of the properties listed above, defibrotide constitutes a drug agent of potential therapeutic interest for the prevention of coronary rethrombosis after successful thrombolysis. Indeed

- Subthrombotic doses of exogenous tPA are effective in preventing coronary reocclusion [29].
- Even at high dosage levels, defibrotide does not cause fibrinogen depletion nor create a hemorrhagic risk [30,31].
- Postinfarct patients with high PAI1 levels are at particularly high risk of cardiovascular mortality [32–34].
- Abnormalities of PGI2 generation and/or activity have been detected in patients with acute myocardial infarction [35,36].

Overall, therefore, defibrotide possesses actions that seem ideal for correcting several important alterations of hemostasis that characterize the early postinfarct period and are possibly contributory to reocclusion. Seeking preliminary verification of the potential therapeutic value of defibrotide in this indication, we conducted a multicenter randomized controlled study of the drug versus heparin in patients with acute myocardial infarction recovering from systemic thrombolysis with urokinase.

**Materials and Methods**

This was a multicenter, randomized, controlled study of defibrotide versus heparin. Study candidates were informed and consenting patients diagnosed with AMI by GISSI criteria [37] (including non-Q AMI cases), presenting no contraindication to thrombolytic treatment, and with a time from the onset of symptoms ≤6 hours were included. All patients received thrombolytic therapy with urokinase: 1.0 M unit immediately by intravenous (i.v.) push injection, followed by 1.0 M unit administered by slow i.v. drip injection over the next 12 hours. Next, each participating center allocated its cases by a suitable random distribution list to treatment with either defibrotide or heparin. We did not adopt a double-blind, double-dummy experimental design (involving simultaneous administration of medications by intravenous and subcutaneous (s.c.) routes), because the different pharmacologic effects of heparin and defibrotide would at any rate reveal the drug being used; particularly, the frequent appearance of subcutaneous hematomas at the sites of calcium heparin injection would defeat blinding the study.

Defibrotide and calcium heparin were administered as follows:

1. On day 0, next to the 12 hours of urokinase infusion:
   - Defibrotide: 0.3 g/hr for 12 hours by i.v. drip infusion of 500 ml of physiological salt solution (total dose 3.6 g)
   - Heparin: 1000 U/hr for 12 hours by i.v. drip infusion (total dose 12,000 IU)
2. On days +1 to +6:
   - Defibrotide: 800 mg tid as slow i.v. injections (5 minutes each; total dose 2.4 g)
   - Heparin: 5000 IU tid by s.c. injection (total dose 15,000 IU)
3. On days +7 until coronary angiography:
   - Defibrotide: 400 mg tid by i.m. injection (total dose 1.2 g)
   - Heparin: same dosage as in period 2

Coronary angiography was contemplated by protocol at 10–12 days of the trial. The heparin dosage schedule was that used in a number of published studies [1,2,8,10]. The dosage of defibrotide, as can be noted, was reduced stepwise after thrombolysis, consistent with the recognized fact that the thrombophilic status of these patients is particularly marked in the first few days after recanalization [8,9,12]. Defibrotide in parenteral doses of 0.8 g daily was found effective in preventing the onset of deep venous thrombosis in postoperative patients [22]; at higher dosages (5.6 g daily by the i.v. route, starting with 2.8 g infused within the first hour of treatment), defibrotide produced measurable thrombolytic effects in humans [30,31]. Accordingly, in view of the high thrombotic attendant risk to these patients, a dosage intermediate between the two mentioned above was chosen for the trial.

Patients of both groups were treated with various combinations of nitrates, beta-blockers, or calcium antagonists; platelet antiaggregants were allowed only after coronary angiography. Parameters examined were as follows:

1. Site of AMI and time from the onset of symptoms
2. Incidence of complications during patients’ stay in coronary care unit:
   a. Postinfarction angina
   b. Pericardial effusion
   c. Arrhythmias: ventricular tachycardia (VT), ventricular fibrillation (VF), atrial fibrillation (AF), paroxysmal supraventricular tachycardia (PSVT), 2nd-3rd degree atrioventricular block (AVB)
   d. Heart failure
   e. Intracardiac thrombosis
   f. Death
3. Periodic blood sampling for plasma CPK and CPK-MB assays at time 0 and at 3, 6, 9, 12, 15, 18, 21, 24, and 48 hours
4. Cardiac echograms on admission day (after thrombolysis), on day +7, and if possible on day +60