Coronary Thrombolysis: Single-Chain Urokinase-Type Plasminogen Activator

Cerebral Thrombolysis with Intravenously Administered Recombinant Low-Molecular-Weight Urokinase and Recombinant Pro-Urokinase in a Dog Model

H. Hirschberg, A. Manoutcheh, B. Clemens, B. Hofferberth,
Department of Neurology, University of Munster, Munster, FRG.

There is increasing evidence that recombinant pro-urokinase (rec-pro-UK) is a proenzyme which, in vivo systems may induce activation of the fibrinolytic system with a better thrombus selectivity than that obtained with active urokinase. In order to study the effects of rec-pro-UK and low-molecular-weight-urokinase (LMW-UK) on acute stroke, a thrombus was induced in the middle cerebral artery (MCA) of anesthetized mongrel dogs (n=12). Occlusion of the vessel was confirmed by angiography. Following a 1 hour period of MCA occlusion, in six animals LMW-UK was administered intravenously at a dose of 600 IU/kg/min. Angiographically confirmed thrombolysis occurred after 30 minutes. Thrombolysis by LMW-UK was accompanied by bleeding from all surgical wounds and consumption of plasminogen, alpha-2-antiplasmin and fibrinogen. Rec-pro-UK was administered to six other dogs in a LMW-UK-equivalent dose. Thrombolysis was achieved after 30 minutes in all six cases without inducing a systemic lytic state. Neither in the LMW-UK group nor in the group treated with rec-pro-UK intracerebral bleeding complications were observed on post mortem examination.

Our findings indicate that intravenous administration of rec-pro-UK - because of the lack of systemic side-effects - may be the therapy of occluded cerebral arteries in acute stroke.

The Efficacy and Relative Fibrin Selectivity of Prourokinase in Patients with Acute Myocardial Infarction

J. Loscalzo for the Prourokinase in Myocardial Infarction Study Group, Boston, MA, U.S.A.

The use of thrombolytic agents in acute myocardial infarction has gained widespread acceptance as an important early therapeutic option. Acute coronary thrombosis has been found in approximately 80% of patients with acute infarction and the use of standard thrombolytic agents has been effective in most cases. Unfortunately, in many individuals standard agents also produce a systemic lytic state with its attendant hemorrhagic complications. Prourokinase (PUK) has been shown to be a relatively fibrin selective thrombolytic agent in vitro owing to its localized conversion to urokinase at the clot surface. Because of this desirable property, we studied the efficacy and selectivity of PUK in vivo in 19 patients with acute myocardial infarction. Each of these patients was documented by angiography to have a totally occluded infarct-related artery. Each patient was treated within six hours (range: 2 to 5.8 hours) of the onset of symptoms with 62.5 mg of PUK derived from the human kidney, B2-chymotrypsin, and Prourokinase. Prourokinase (150000 IU over 1 hour) administered intravenously in 19 patients was successful in the reperfusion of occluded coronary arteries in 17 patients.

Influence of Recombinant Pro-Urokinase on the Hemostatic System in Patients with Acute Myocardial Infarction

U. Schmitz-Huebner (1), H. Dietmann (2), D. G. Mathey (2), J. Schofer (2), Ch. Diefenbach (3) and R. Erbel (3), Dept. of Internal Medicine, Univ. of Hamburg, FRG (2) and 2. Dept. of Internal Medicine, Univ. of Mainz, FRG (3).

Recombinant urocoagulated prourokinase (recombiant single chain urokinase-type plasminogen activator, USP90) was studied in twelve patients (n=12) with acute myocardial infarction as a 20 mg bolus followed by a 60 mg intravenous infusion (iv.inf.) over 1 hour and in twelve patients a 30 mg bolus followed by a 3 mg iv.inf. over 1 hour. Reperfusion was angiographically confirmed in 9/12 pts. with the higher dose and in 6/12 pts. who obtained the lower dose. Different parameters of hemostasis were determined before admission, 30 minutes after the beginning of inf., at the end of inf., 60 min thereafter and 6-12 hours afterwards.

The most significant systemic changes were observed 60 min after the end of inf. when the following mean values ± SEM were determined (pre-inf. values in brackets):

Fibrinogen (mg/dl): 80 mg: 207.9 ± 14.1 (333.1 ± 39.1)
Plasminogen (%): 80 mg: 179.8 ± 33.0 (291.7 ± 21.5)
Antiplasmin (%): 80 mg: 40.4 ± 9.8 (116.7 ± 4.0)
Fibrinogen Split Products (µg/ml): 80 mg: 13.9 ± 4.9 (85.9 ± 5.2)

Fibrinolytic activity in plasma determined on fibrin plates was highest in both groups 30 min after the beginning of inf. and hardly measurable 60 min after the end of inf. No bleeding complications were observed. Based on these results, a randomized double-blind multicenter trial was started to study the effects of 80 mg USP90 versus 1.5 million U streptokinase iv.

Intravenous Thrombolysis with Single-Chain Urokinase-Type Plasminogen Activator in Patients with Acute Myocardial Infarction

C. Bode, F. Fiedler, H. H. Schuster, B. Zingg, and M. Schwarz, Department of Internal Medicine III (Cardiology), University of Heidelberg, 6900 Heidelberg, West Germany.

Seventeen patients with acute myocardial infarction were treated with heparin combined with intravenous single-chain urokinase-type plasminogen activator (scu-PA), obtained from transformed human kidney cells in 2 cases. Thrombolysis was achieved in no patient of group I during intravenous infusion of scu-PA. However, upon subsequent intracoronary infusion of 250000 IU streptokinase, reperfusion could be established in two out of three patients. In group II seven patients were successfully treated with intravenous infusion of scu-PA. In 2 of the 6 patients unsuccessfully treated with intravenous scu-PA, intracoronary streptokinase was subsequently administered. In both cases recanalization could not be achieved. The effects on the hemostatic system are summarized below. In all patients a severe residual stenosis persisted after thrombolytic treatment and 13 patients under- went PTCA.

Group Reperfusion Fibrinogen Plasminogen Antiplasmin rate (at end of therapy in % of baseline)
I 1/4 95±5 95±7 84±19
II 7/13 96±15 93±30 66±36

There was no difference between successful and unsuccessfully treated patients in group II with respect to the effect of treatment on serum parameters.

It is concluded that intravenous infusion of scu-PA at a dose of 15 mg over 60 minutes is ineffective treatment for patients with acute myocardial infarction. However, at a dose of 45 mg over 60 minutes this form therapy is effective, safe and specific.

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