REVIEW

Antithrombotic treatment in stable coronary syndromes: long-term intermittent urokinase therapy in end-stage coronary artery disease and refractory angina pectoris

Frank-Chris Schoebel, Thomas W Jax, Yuriko Fischer, Bodo-Eckehard Strauer, Matthias Leschke

Abstract

Interventions that modify lipid metabolism and blood coagulation have been shown to favourably influence the natural course of coronary artery disease in terms of the primary prevention and treatment of acute cardiovascular events. Various findings suggest that such interventions may also preserve and enhance myocardial perfusion in the chronic stage of the disease. Long-term intermittent urokinase therapy was developed for patients with end-stage coronary artery disease and refractory angina pectoris. A dose of 500 000 IU of urokinase given intravenously as a bolus three times a week for of 12 weeks reduced symptoms by 70% and was accompanied by objective improvements in myocardial perfusion and an increase of ergometric exercise capacity. The possible therapeutic mechanisms of long-term intermittent urokinase therapy—improvement of rheological blood properties mediated by fibrinogen reduction, thrombolysis of non-occlusive subclinical thrombi, and regression of atherosclerotic plaques—are discussed in the context of other antithrombotic approaches.

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Keywords: coronary artery disease; angina; antithrombotic treatment; urokinase

Conventional treatment of myocardial ischaemia in clinically stable coronary artery disease is predominantly designed to reduce cardiac workload and enhance blood flow in the epicardial conductance vessels. The major anti-ischaemic approaches of medical treatment relate to reducing systemic vascular vasomotor tone (decrease in preload and afterload) as well as to relaxation of epicardial conductance vessels, a reduction in heart rate, and in some cases direct modification of the cellular metabolism of the myocytes.¹ Even though such approaches reduce myocardial ischaemia and hence increase the quality of life in

patients with angina pectoris they only marginally influence the pathogenesis of coronary atherosclerosis.

Like reducing LDL-cholesterol, which has been shown to reduce major cardiovascular events and morphological disease progression² and improve LDL-cholesterol dependent disturbances of coronary vasomotion,³⁻⁷ use of antithrombotic substances is another approach to favourably influence the pathogenesis of the underlying disease process and hence reduce chronic myocardial ischaemia. Substances from all three major classes—antiplatelet agents, anticoagulants, thrombolytics—have a beneficial effect on the clinical course of the acute coronary syndromes, especially in acute myocardial infarction, which is dominated by occlusive coronary thrombus formation. Aspirin has also been shown to be of benefit in the primary and secondary prevention of acute coronary syndromes in clinically stable patients.⁸ In addition to its importance in the acute coronary syndromes, coronary thrombosis is of relevance to morphological disease progression in clinically stable patients, because plaque rupture may lead to an asymptomatic, non-occlusive thrombus, which in the event of incomplete endogenous lysis is incorporated by the arterial wall as solidified plaque material.^{9,10} It is therefore likely that long term treatment with antithrombotic substances may slow the progression of morphological disease or even cause regression of vascular obstructions with subsequent preservation or enhancement of coronary blood flow. One therapeutic approach which is aimed at these mechanisms is long-term intermittent urokinase therapy, a low-dose thrombolytic regimen for the treatment of patients with end-stage coronary artery disease and refractory angina pectoris.

Long-term intermittent urokinase therapy

APPLICATION

Long-term intermittent urokinase therapy was developed for patients with refractory angina pectoris, defined as a persistence of angina pec-

Medizinische Klinik und Poliklinik B, Klinik für Kardiologie, Pneumologie und Angiologie, Heinrich-Heine Universität Düsseldorf, Germany
F-C Schoebel
T W Jax
Y Fischer
B E Strauer
M Leschke

Correspondence to:
Dr F-C Schoebel,
Medizinische Klinik und
Poliklinik B, Klinik für
Kardiologie, Pneumologie
und Angiologie, Heinrich-
Heine Universität
Düsseldorf, Moorenstraße 5,
40225 Düsseldorf, Germany.

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Table 1 Comparison of the effects on rheological variables and clinical symptoms¹⁴ of 50 000 IU and 500 000 IU urokinase per injection given three times a week over 12 weeks

	3 × 50 000 IU/week (n = 43)		3 × 500 000 IU/week (n = 46)		P value
	Before (mean (SD))	After (mean (SD))	Before (mean (SD))	After (mean (SD))	
Rheological variables:					
Fibrinogen (mg/dl)	351 (79)	333 (63)	369 (66)	242 (40)	< 0.001
Plasma viscosity (mPa.s ⁻¹)	1.38 (0.09)	1.37 (0.09)	1.40 (0.05)	1.31 (0.05)	< 0.001
Red blood cell aggregation (U)	15.0 (3.0)	14.0 (3.2)	14.8 (2.7)	11.7 (2.3)	0.001
Clinical variables:					
Angina pectoris (events/wk)	21.9 (9.8)	15.8 (10.0)	24.2 (11.7)	7.1 (7.1)	< 0.001
Intake of nitrate capsules (capsules/wk)	13.1 (7.9)	8.9 (6.1)	14.1 (11.1)	2.3 (3.4)	< 0.001
Responders (reduction of angina pectoris > 66%) (%)		21		70	< 0.001
Patients free symptoms (%)		7		17	0.005

toris class 3 and 4 (defined according to the criteria of the Canadian Cardiovascular Society¹¹) despite maximally tolerated conventional medical treatment (nitrates, β blockers, calcium antagonists). To avoid withholding an established form of treatment, an experienced team of cardiologists and cardiac surgeons must, on the basis of a recent coronary angiogram, rule out the use of conventional invasive revascularisation procedures such as coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA).

Long-term intermittent urokinase therapy is clinically effective at a dose of 500 000 IU given as an intravenous bolus injection three times a week for 12 weeks in patients whose fibrinogen concentrations are more than 300 mg/dl at baseline.¹²⁻¹⁴ Treatment may be initiated in hospital or begun as an outpatient regimen immediately with target fibrinogen concentrations of 200–250 mg/dl. Clinical symptoms, fibrinogen concentrations, and activated partial thromboplastin time are monitored every two weeks.

Several studies in patients with refractory angina pectoris showed a reduction in the frequency of spontaneous angina pectoris accompanied by an increase in exercise capacity and an enhancement of scintigraphically and electrocardiographically measured myocardial perfusion.¹²⁻¹⁴ The improvement in clinical symptoms lasted at least three months after the end of therapy.¹³ A randomised dose-response study further validated this therapeutic approach¹⁴: it compared a rheologically effective weekly dosage of 3 × 500 000 IU with a weekly dosage of 3 × 50 000 IU and found that the therapeutic effects were significantly dose-dependent (table 1). Side effects such as an increased rate of cardiovascular ischaemic events and gastrointestinal bleeding complications were not seen (table 2).^{14,15}

MECHANISMS OF ANTI-ISCHAEMIC EFFECTIVENESS

Improvement of rheological blood properties

Long-term intermittent urokinase therapy was

originally developed under the assumption that an improvement in rheological blood properties—for example, the reduction of fibrinogen mediated by the fibrinolytic action of urokinase—may enhance blood flow at the microcirculatory level.^{12,16} Pathological alterations of rheological blood properties, including large increases in fibrinogen concentrations and increases in plasma viscosity and red blood cell aggregation are characteristic features of patients with refractory angina pectoris.¹⁴ These rheological variables are higher in patients with refractory angina not only when compared with values in subjects who have no angiographic evidence of atherosclerotic disease but also compared with patients who have coronary artery disease and non-refractory angina pectoris (fig 1).^{14,17}

Blood viscosity is mainly determined by plasma viscosity, red blood cell aggregation, red blood cell deformability, and haematocrit. In non-obstructed coronary arteries, the flow-limiting resistance caused by blood viscosity can be ignored.¹⁸⁻²⁰ However, in the post-stenotic microcirculation when there have been severe and successive multiple stenoses, in occluded vessels, and in collateral vessels,²¹ blood viscosity (especially plasma viscosity and red blood cell aggregation) may limit blood flow and is therefore critical for oxygen delivery to the ischaemic myocardium.²² At the extremely low shear rates and almost zero flow in this area²³ macromolecules, particularly fibrinogen, increase red blood cell aggregation and plasma viscosity; these in turn lead to an exponential increase in blood viscosity.^{18,19,24} High linear correlations between fibrinogen and plasma viscosity as well as between fibrinogen and red blood cell aggregation have been demonstrated.¹⁴

Long-term intermittent urokinase therapy improves blood rheology in a dose-dependent manner (table 1). In a rheologically effective dose of 500 000 IU per injection fibrinogen is reduced by about 33%, while plasma viscosity and red blood cell aggregation are decreased by 6.4% and 19.9% respectively.¹⁴ Significant changes from baseline measurements are usually achieved after two to four weeks of treatment paralleled by clinical improvement and this effect levels off between the 6th and 8th week of treatment (fig 2). Reductions in fibrinogen are therefore higher than those of about 10–30% achieved with fibrate therapy²⁵ and those of 19–24% achieved when long-

Table 2 Comparison of side effects¹⁴ when 50 000 IU and 500 000 IU urokinase per injection were given three times a week over 12 weeks

Side effects	3 × 50 000 IU/wk (n = 49)	3 × 500 000 IU/wk (n = 49)
Unstable angina pectoris	3	1
Myocardial infarction	2	1
Upper gastrointestinal tract bleeding	0	1
Dropped out for no specific reason	1	0

Figure 1 Fibrinogen and rheological variables in patients with stable, refractory, and unstable angina pectoris.^{14,17}

term low molecular weight heparin treatment or extracorporeal LDL-cholesterol precipitation (HELP) was used.²⁶ HELP treatment in the secondary prevention of coronary artery disease in patients with familial hypercholesterolemia refractory to conventional lipid lowering therapy reduces angina in patients with stable coronary artery disease; this effect is in part attributed to a marked improvement in rheological blood properties.²⁷

Thrombolytic potential

In a postmortem study plaque fissures or thrombi were found in 22% of the patients with atheroma related diseases who were clinically stable and had died of non-cardiac

causes.²⁸ This figure has recently been confirmed by an angiographic study in patients with stable coronary artery disease who underwent coronary angioplasty. Angiography showed coronary thrombus at the site of the target stenosis in 19% of the cases before intervention.²⁹ Thrombi therefore may limit flow in the epicardial conductance vessels^{9,10} and in the coronary microcirculation^{30,31} not only in the acute coronary syndromes but also in clinically stable coronary artery disease. In patients with refractory angina pectoris in end-stage coronary artery disease, multiple, severe, and often successive coronary stenoses lead to regions of poststenotic recirculation and relative stasis of blood flow. The reduction in blood fluidity resulting from increases in plasma viscosity and red blood cell aggregation and the fluid-dynamic aspects of coronary stenoses favours intracoronary thrombus formation.³²

Fibrinogen has been positively related to major thrombotic cardiovascular events,³³ which is explained by its impact on blood rheology and its contribution as the major linkage molecule in platelet aggregation³⁴ and therefore it must per se be regarded as a major promotor of intracoronary thrombus formation.^{9,10,35} These aspects are further substantiated by positive interrelations between fibrinogen and thrombin generation³⁶ and by increases in plasmin- α -antiplasmin³⁷ and D-dimers³⁶ which are indicators of increased, probably secondary, endogenous thrombolytic activity in patients with raised fibrinogen concentrations. Therefore increases in fibrinogen indicate a procoagulant disease state in patients with coronary artery disease.

These aspects of thrombogenic (and therefore dynamic) impairment of blood flow indicate that the thrombolytic efficacy of long-term intermittent urokinase therapy is a major factor in improving myocardial perfusion in patients with refractory angina pectoris and raised concentrations of fibrinogen. Different therapeutic regimens of low-dose urokinase have thrombolytic potential^{12,38,39} and indirect evidence of pharmacodynamic effectiveness is indicated by a reduction of about 8% in the activity of plasminogen, which is the substrate of urokinase, in patients with refractory angina pectoris after the long-term intermittent administration of 500 000 IU of urokinase (fig 3).¹²

Figure 2 Time course of fibrinogen (A) and clinical symptoms (B) during treatment with long-term intermittent urokinase therapy at a dose of 50 000 IU (n = 43; open circles) or 500 000 IU urokinase per injection (n = 46; closed circles).¹⁴

Figure 3 Significant decrease of fibrinogen (closed circles, $P < 0.001$) and plasminogen (open circles, $P < 0.05$) during treatment with 500 000 IU per injection (n = 21).¹²

It has been pointed out previously that the prolonged administration of other antithrombotic substances, namely the anticoagulants heparin and warfarin reduces residual thrombus and therefore enhances coronary blood flow after the acute treatment of patients with acute coronary syndromes.⁴⁰⁻⁴¹ Furthermore, two recent studies of the anti-ischaemic efficacy of low molecular weight heparin⁴²⁻⁴³ support the use of antithrombotic therapy to improve myocardial perfusion in clinically stable patients. As well as the induction of collateral angiogenesis and functional improvement of collaterals suggested by one group⁴³ the antithrombotic efficacy of low molecular weight heparin³⁶⁻⁴² was particularly useful in patients with high fibrinogen concentrations. Interestingly one study showed a 15% reduction in fibrinogen after low-molecular weight heparin was given for three months.⁴²

Plaque regression

Fibrinogen and fibrin are major constituents of atherosclerotic plaques,⁴⁴⁻⁴⁶ and high concentrations of fibrinogen are positively correlated with the extent of atheroma in the coronary and carotid arteries.⁴⁷⁻⁴⁸ This correlation is probably the result of repetitive plaque fissuring and the secondary formation of coronary thrombus, which because of incomplete endogenous lysis becomes incorporated into the plaque. Subsequently there is rapid, non-linear morphological plaque progression.⁹⁻¹⁰ In addition, high plasma concentrations of fibrinogen increase the fibrin content of the plaque by direct permeation.⁴⁴⁻⁴⁹

It is therefore probable that long-term thrombolytic therapy can lead to morphological plaque regression, which is important for blood flow in critically stenosed arteries. This effect of thrombolytic therapy on plaque regression may explain the persistence of clinical long-term results of a weekly dose of $3 \times 500\,000$ IU urokinase beyond the treatment period.¹³⁻¹⁵

In this context it is noteworthy that the administration of another antithrombotic regimen, high dose aspirin (975 mg/d) in combination with dipyridamole (225 mg/d), even though it did not retard angiographic progression of pre-existing coronary lesions, reduced the formation of new lesions compared with placebo (23% v 35%) over a five year period).⁵⁰ Investigations of disease progression in coronary and carotid atherosclerosis indicated that the effects on morphological progression may be dose-dependent.⁵¹⁻⁵² Even though major effects on the morphological regression of coronary artery disease during heparin-induced extracorporeal LDL-cholesterol apheresis and bezafibrate relate to reductions in lipids they may be partially mediated by the decrease of fibrinogen which in a practical sense makes these interventions "anti-thrombotic".²⁷⁻⁵³

Conclusion

Based on the current concepts of the pathogenesis of coronary atherosclerosis, antithrom-

botic agents offer ways to favourably influence morphological disease progression as well as functional aspects of coronary blood flow. These effects are mainly but not exclusively mediated by antithrombotic mechanisms as for example in the case of rheological effectiveness of long-term urokinase or the probable angiogenic impact of low-molecular weight heparin. Even though these various approaches may be limited in their practical usefulness in the general population of patients with coronary artery disease—for example, by dose or mode of application—they point to the clinical relevance of an important therapeutic principle, which may be addressed in more practical ways by future developments. In this context long-term intermittent urokinase therapy represents a therapeutically effective and safe approach to the treatment of patients with end-stage coronary artery disease and refractory angina pectoris.

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