

Subject Review

Antithrombotic and Thrombolytic Agents

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Antithrombotic agents

Clinical sequelae of arterial or venous thrombosis are an important cause of patient morbidity and mortality. In the past year there have been significant advances in the prevention and treatment of thrombotic disease with anticoagulant and antithrombotic agents as well as fibrinolytic agents. The growing recognition of the importance of thromboembolism in the pathogenesis of a variety of diseases has strongly stimulated the search for more effective and safer antithrombotic drugs. The search for new antithrombotic drugs is also due to limitations of presently available anticoagulants.

Unfractionated heparin is composed of a mixture of glycosaminoglycans with molecular weights of 3,000 to 30,000, which greatly enhance the activity of antithrombin (AT). Randomly distributed pentasaccharide sequence within these molecules bind to and induce conformational changes in the AT molecule resulting in an increase of approximately 1000-fold in its affinity for factor Xa and thrombin. Despite its proven efficacy, unfractionated heparin has a narrow therapeutic window and wide variation in its anticoagulant effects. Therefore there is the need for frequent laboratory monitoring

and adjustment of the dose because avid binding of unfractionated heparin to a number of plasma proteins, macrophages, and vascular endothelium produces unpredictable pharmacodynamics. Unfractionated heparin is also neutralized by platelet factor 4, which is released from activated platelets. Binding to platelet factor 4 not only renders the heparin ineffective as an anticoagulant but may also lead to the formation of antibodies that recognize platelet factor 4-heparin complexes. These antibodies bind to and activate platelets and produce thrombocytopenia, as well as potentially life-threatening arterial and venous thrombi in a small subgroup of patients.¹⁻³ Possibly the most relevant limitation of heparin is its inability to inhibit clot-bound thrombin.⁴ These biophysical limitations are responsible for the clinical resistance of heparin observed in conditions such as cardiopulmonary bypass surgery,⁵ high-risk coronary angioplasty⁶ and coronary thrombolysis.^{7,8} They are also responsible for reactivation of thrombogenesis after heparin is stopped in conditions such as unstable angina and non Q-wave myocardial infarction,^{9,10} coronary thrombolysis,⁸ and acute deep venous thrombosis.¹¹

Low-molecular-weight-heparins (LMWHs),

which range in molecular weight from 4,000 to 6,500, is produced by chemical or enzymatic depolymerization of unfractionated heparin. Its anticoagulant effects also result from the activation of AT. Complexes of AT and the smaller heparin chains (less than 18 saccharide units) are fully capable of neutralizing factor Xa but not thrombin, which may still be available to activate factors V, VIII, and XIII, as well as platelets. LMWHs have many advantages over unfractionated heparin but still do not inhibit clot-bound thrombin and can induce thrombocytopenia although less frequently than unfractionated heparin.^{12,13} However, LMWHs exhibit far less binding to plasma or platelet- and endothelial-derived proteins. Therefore, they have a more predictable anticoagulant response to weight-adjusted doses than heparin, a property that obviates the need for laboratory monitoring of LMWH preparations.¹⁴⁻¹⁷ These properties of LMWHs represent a major advance because these anticoagulants are at least as effective and safe as heparin for the treatment of venous thrombosis when administered subcutaneously without laboratory monitoring in an out-of-hospital setting.^{15,16}

LMWHs have been evaluated and compared with heparin in randomized clinical trials for the prevention and treatment of venous thromboembolism.^{17,18} LMWH preparations are now being evaluated in patients with arterial disease. Promising results have been obtained in patients with ischemic stroke.¹⁹ LMWH is effective in patients with unstable angina.²⁰⁻²² LMWH

have not been effective in reducing restenosis after coronary angioplasty.^{23,24}

In comparison, a number of the newly developed AT-independent thrombin inhibitors do not share the same biophysical limitations of heparin and LMWHs (Table 1). Numerous direct thrombin inhibitors have been synthesized. Those studied extensively in animal models of thrombosis are listed in Table 2.²⁵

There are two main classes of direct (AT-independent) thrombin inhibitors: the low molecular weight active site inhibitors and the multivalent inhibitors, hirudin and hirulog. These direct thrombin inhibitors form a tight stoichiometric complex with thrombin, abrogating all its known biologic activities. They are able to access fibrin-bound thrombin and therefore have a number of theoretical advantages over heparin and LMWH in heparin-resistant conditions.⁴ Hirudin and hirulog have the additional advantage that they have a more predictable dose response than heparin,²⁶ because they do not bind to acute phase reactant proteins or to platelet-derived or endothelial-derived proteins, and do not cause immunologically mediated thrombocytopenia. Conversely, they effectively inhibit fibrin-bound thrombin and thrombin-induced platelet activation.

The direct thrombin inhibitors have been shown to be more effective than heparin in experimental animal models, particularly in experimental arterial thrombosis.²⁷ Hirudin and hirulog have also been evaluated for the prevention and treatment of venous thrombosis and

Table 1 Properties of heparins and direct thrombin inhibitors

Unfractionated heparin	LMW-heparins	Direct thrombin inhibitors
Inhibits to the same extent thrombin and factor Xa, much less IXa and XIa	Inhibits mainly factor Xa, Thrombin to some extent	Specific and potent inhibitor of thrombin
Antithrombin III-dependent	Antithrombin III-dependent	Antithrombin III-independent
Neutralized by heparinase, several plasma proteins, platelet factor 4 and endothelium	Neutralized by heparinase, Weak endothelium binding	Not neutralized by heparinase, endothelium, macrophages, fibrin monomer and plasma proteins
Does not inactivate clot-bound thrombin and factor VII	Does not inactivate clot-bound thrombin and factor VII	Inactivates clot-bound thrombin
Inhibits platelet function	Inhibits platelet function	Prevents thrombin induced aggregation but not other platelet agonists
Induced thrombocytopenia is not rare	Can induce thrombocytopenia	Does not induce thrombocytopenia
Bioavailability after s.c. injection 30%	Bioavailability after s.c. Injection > 90%	Good bioavailability after s.c. injection, about 85%
Poor dose-effect response	Fair dose-effect response	Fair dose-effect response
Not immunogenic	Not immunogenic	Not or barely immunogenic
Transient increase of liver enzymes is common	Transient increase of liver enzymes possible	No liver toxicity
Increases vascular Permeability	No increase in vascular Permeability	No increase in vascular permeability

Table 2 Direct thrombin inhibitors

Hirudin (recombinant : Desirudin)	Inogatran
Hirugen	PPACK and related compounds
Bivalirudin (HirulogTM)	Aptamers
Hirunorms	Thrombin receptor antagonists
Argatroban (Argidipin)	Lysyl-a-ketocarbonyl derivatives
Efegatran	Hirudisins
Napsagatran	

in patients with myocardial ischemia.²⁷ The initial results of studies in the prevention and treatment of venous thrombosis are promising.^{28,30} In contrast, the results of large phase III studies in coronary thrombolysis^{31,32} and non-Q-wave myocardial infarction³¹ have not borne out the promise of studies in experimental animals and phase II human trials.

A number of new anticoagulants are under development but are yet to be studied in humans. The most advanced of these new anticoagulants are activated protein C (APC), tissue factor pathway inhibitor (TFPI), the direct (AT-independent) factor Xa inhibitors, the tick anticoagulant protein (TAP) and the leech antiprotease, antistasin.

APC exerts its anticoagulant effect by inactivating factor Va and factor VIIIa, thereby modulating thrombin-mediated amplification of coagulation.³³ Human APC has been prepared by plasma fractionation and by recombinant techniques. It is an effective anti-thrombotic agent in a variety of experimental animal models at concentrations that do not prolong the skin bleeding time.³⁴ It has also been shown to be effective in a primate model of septicemic shock and is being studied clinically for this indication.

The gene for human TFPI has been cloned and the recombinant protein has been synthesized.³⁵ Limited animal studies indicate that it is an effective antithrombotic agent.

The direct antifactor Xa inhibitors, TAP and anti-stasin, are able to access and inactivate

factor Xa bound to phospholipid in the prothrombinase complex. Results of studies in experimental animal models of thrombosis have been very promising,³⁵⁻³⁸ but to date there are no data available on efficacy or safety in humans.

Thrombolytic agents

Thrombolytic therapy provides an added dimension in the treatment of thrombosis, namely, a more rapid return to the physiologic state and prevention of immediate and late sequelae of disease by decreasing the ischemic damage produced by thrombotic events.³⁹ Currently available therapeutic agents all essentially impart proteolytic activity to the inactive plasma zymogen plasminogen. The agents either induce a conformational change in plasminogen or proteolytically cleave plasminogen to plasmin, its active form, which in turn digests fibrin to soluble degradation products.

The major problem for the physician is to identify reliably the patient who will benefit from thrombolytic therapy but who is unlikely to suffer a serious hemorrhagic complication. Thus, the anticipated clinical benefit of thrombolytics in treating the five major categories of thrombotic disease, namely, deep vein thrombosis, pulmonary embolism, acute peripheral arterial occlusion, acute cerebrovascular ischemia, and acute myocardial infarction, must be balanced individually against the constant risk of bleeding, especially intracranial hemorrhage.⁴⁰

In the past decade, there has been an enormous expansion of interest and application of this approach to thrombotic disease, due pri-

marily to the impressive evidence of survival benefit in patients with acute myocardial infarction. Thrombolytic agents that are either approved for clinical use or under clinical investigation in some patients with acute myocardial infarction include streptokinase (SK), recombinant tissue-type plasminogen activator (rt-PA, prepared either as alteplase or as duteplase), rt-PA derivatives such as reteplase and TNK-rt-PA, anisoylated plasminogen streptokinase activator complex (APSAC), two-chain urokinase-type plasminogen activator (tcu-PA), recombinant single-chain urokinase-type plasminogen activator (rscu-PA, prourokinase), and more recently, recombinant staphylokinase (Sak) and derivatives.⁴¹

SK, APSAC and tcu-PA induce extensive systemic activation of the fibrinolytic system, deplete α_2 -anti-plasmin and degrade circulating fibrinogen. In contrast, the physiologic plasminogen activators, t-PA and rscu-PA, activate plasminogen preferentially at the fibrin surface. Plasmin, associated with the fibrin surface, is protected from rapid inhibition by α_2 -antiplasmin and may thus efficiently degrade the fibrin of a thrombus.⁴² Sak, a protein obtained from *Staphylococcus aureus* resembles the physiologic plasminogen activators in that it was also found to induce fibrin-specific clot lysis in human plasma in vitro. Larger clinical studies to determine its safety and clinical value for thrombolytic therapy in patients with acute myocardial infarction would appear to be warranted.⁴³

Despite their widespread use in patients with acute myocardial infarction, all currently avail-

able thrombolytic agents suffer from a number of significant limitations, including resistance to reperfusion, the occurrence of acute coronary reocclusion and bleeding complications. Therefore, the quest for thrombolytic agents with a higher thrombolytic potency, specific thrombolytic activity and/or a better fibrin-selectivity continues. Several lines of research towards improvement of thrombolytic agents are being explored, including the construction of mutants and variants of plasminogen activators, chimeric plasminogen activators, or plasminogen activators from animal or bacterial origin. Several of these new thrombolytic agents have been evaluated in animal models of venous or arterial thrombosis, some in pilot studies in patients with acute myocardial infarction and a few in large clinical trials with mortality end points. Definition of their relative therapeutic benefit, against presently available "classical" thrombolytic agents will require further dose-finding studies and randomized clinical trials.

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มองแต่ แง่ดี เถิด.

เขามีส่วน เผลอบ้าง ช่างหัวเขา
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