New anticoagulants and the management of their bleeding complications

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SUMMARY

Limitations of the currently available anticoagulants have fanned the continuing search for new anticoagulants with improved pharmacological and biosafety profile, and equal, if not superior efficacy. Targets of inhibition include the factor VIIa/tissue factor pathway (recombinant nematode anticoagulant peptide c2, tissue factor pathway inhibitor), factor Xa (fondaparinux, idraparinux, razaxaban), factor Va and VIIIa pathway (recombinant activated protein C, soluble thrombomodulin) and thrombin (hirudin, bivalirudin, argatroban, ximelagatran, dabigatran). Irrespective of their mode of action, bleeding complications are invariable with all anticoagulants. Conventional assessment and measures should remain as first-line responses to bleeding complicating the use of these anticoagulants. Antidotes do not exist for the overwhelming majority of these agents. The role of recombinant activated factor VIIa in controlling bleeding is still investigational. Definitive haemostatic strategies for bleeding complications can only evolve with accumulating experience with these new agents.

INTRODUCTION

Pathological thrombus formation and its embolization in the arterial system is responsible for ischemia or potentially fatal infarcts in major end organs; in the venous system, this process can lead to structural damage to the vessels and embolization that causes impairment of pulmonary gas exchange, with potentially fatal consequences. The primary and secondary prevention of venous, and some forms of arterial thromboembolism, is anticoagulation.[1–4] Heparin and warfarin are highly effective for these purposes and, as a result, have been used for more than 50 years.[5,6] However, despite their proven efficacy, these drugs have significant limitations that have prompted the research and development of newer agents with either superior efficacy or a better biosafety profile.[7]

Many new agents are currently in various stages of development and target different phases and enzymes in the coagulation cascade.[7,8] Broadly, they may be classified as:

1 Inhibitors of the factor VIIa/tissue factor pathway.
2 Inhibitors of factor Xa.
3 Inhibitors of factor Va and VIIIa.
4 Inhibitors of thrombin.

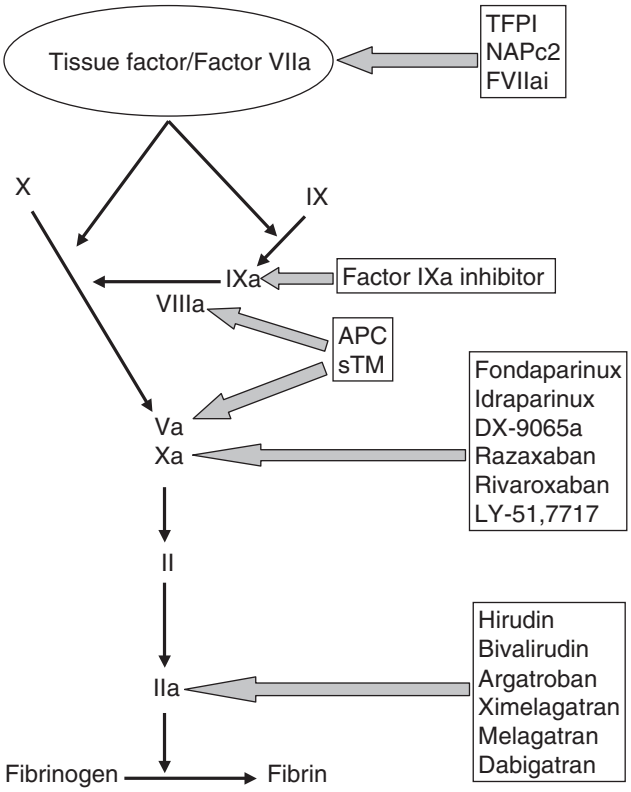

Figure 1. The coagulation pathway and sites of action of new anticoagulants. APC, activated protein C; FVIIai, active-site blocked factor VIIa; NAPc2, nematode anticoagulant peptide c2; sTM, soluble thrombomodulin; TFPI, tissue factor pathway inhibitor.

Irrespective of their mode of action (Figure 1), these new anticoagulants will invariably cause bleeding. This may occur either within the usual therapeutic window or as a result of overdosing. The actual bleeding risk for many such agents will not be defined until post-marketing surveillance and experience with exposure of many patients to these drugs become available. Management of bleeding is made more complex by the fact that while heparin and warfarin both have effective antidotes for their anticoagulant effect, the same cannot be said for most of these new agents.[9]

This review will discuss the mechanism of action and utility of these new anticoagulants, with focus on their bleeding risks and the currently available strategies for their reversal.

NON-SPECIFIC MANAGEMENT OF THE BLEEDING PATIENT

Bleeding complicating anticoagulant therapy should be regarded as a serious complication with a potential for major morbidity and mortality. The seriousness with which bleeding is regarded is a function of the type and location of bleeding, co-morbidities, concomitant medications (most importantly platelet inhibitors) and the dose and type of anticoagulant.[10]

Bleeding should be classified as nuisance, minor and major. Nuisance bleeding is generally the most commonly reported bleeding. While often distressing to the patient, it usually has no medical consequences. Examples of nuisance bleeding include self-limiting epistaxis, menorrhagia and bruising. Such bleeding will often be adequately treated with local measures and usually does not require specific medical interventions. It also usually does not result in changes in anticoagulant medications or their dose and frequency. Persistent nuisance bleeding may be a marker, however, for imminent and more serious bleeding. Minor bleeding precipitates some form of medical intervention and may result in changes in medication type, dose or frequency. It is often significantly inconvenient for the patient. Examples of minor bleeding include epistaxis requiring nasal packing, hematochezia without hemodynamic compromise and most forms of post-surgical bleeding in patients receiving anticoagulants. Major bleeding, by definition, requires a significant medical intervention (such as transfusion, endoscopy or surgery), will routinely result in withholding or discontinuing of anticoagulants, and may cause long-term morbidity or death.[11]

The bleeding patient should undergo a careful clinical assessment and should receive interventions titrated to the seriousness of his or her bleeding.[12] A fine balance is required to provide appropriate, but not overly aggressive intervention for the bleeding patient. The intensity of intervention may be difficult to judge initially. It is not uncommon for patients and healthcare practitioners to overestimate the severity of active bleeding. The first priority should be to attentively monitor the patient and to provide hemodynamic stability with crystalloid resuscitation as specific measures are introduced. Mechanical causes of bleeding should be identified and addressed; this may require surgical or endoscopic evaluation. The anticoagulant should be stopped. In critically ill patients the anticoagulant

should be removed from the patient's bedside to avoid inadvertent bolus dosing. The activity of the coagulation cascade should be immediately and frequently assessed; this measurement should include global parameters [activated partial thromboplastin time (aPTT), prothrombin time/international normalized ratio (INR) and fibrinogen] and specific parameters (such as drug levels or echarin clotting times, where appropriate). 'Reflexive transfusion', the empiric use of blood products in response to bleeding, should be avoided. Thus, transfusion of fresh frozen plasma or cryoprecipitate should only be provided if there is convincing evidence attributing the bleeding to clotting factor deficiencies.[13,14] Prophylactic transfusion exposes patients to risks of transmission of infection and allergic, anaphylactic or immunological reactions, without clear benefit.[13] Inappropriate administration of blood products may falsely reassure healthcare providers and may delay the use of more effective and specific measures to secure hemostasis. Red blood cell transfusion should only be provided to patients with clear and imminent risk of fatal bleeding, or patients with documented symptomatic anemia.

Non-specific prohemostatic agents should be considered. Desmopressin (DDAVP) is efficacious for bleeding in patients other than von Willebrand disease and hemophilia,[15] and it results in the release of von Willebrand factor and factor VIII from the endothelium, as well as other cellular effects that remains unclear.[16] Tachyphylaxis will be seen if doses are given more often than every 6–8 hours.[17] Fibrinolytic inhibitors, such as tranexamic acid and ε-aminocaproic acid, are highly effective at controlling some forms of bleeding, and may be particularly useful in selected clinical settings (such as when used as a mouth wash in patients with dental or gingival bleeding).[18] Intravenous estrogen appears to have benefit in selected patients, including patients with significant vaginal bleeding, and patients with bleeding in the setting of uremia.[18] If bleeding is very significant, administration of specific antidotes should be considered. Thus, protamine will reverse all of the anticoagulant effect of heparin and part of the effect of low-molecular-weight heparins.[19] Plasma or coagulation factor concentrates (if given at the correct dose) will reverse the anticoagulant effect of warfarin.

If bleeding is considered immediately life-threatening, other non-specific prohemostatic agents such as recombinant activated factor VII (rFVIIa) should be considered. The strength of the recommendations for the use of these agents is poor. The widespread use of rFVIIa to treat anticoagulant-associated bleeding is based on a combination of case reports and the absence of alternate therapies that might be effective.

INHIBITORS OF FACTOR VIIa/TISSUE FACTOR PATHWAYS

Nematode anticoagulant peptide c2 (NAPc2), tissue factor pathway inhibitor (TFPI) and active-site blocked factor VIIa (factor VIIai) are three inhibitors of this pathway.

NAPc2 and rNAPc2

NAPc2 was originally isolated from the canine hookworm, *Ancylostoma caninum*,[20] but its recombinant form, rNAPc2, is now available. It essentially prevents the initiation of coagulation by binding to factor X and Xa, and then inhibiting factor VIIa within the factor VIIa/tissue factor complex.[21] rNAPc2 has a half-life of 50 hours after subcutaneous injections. At clinically effective plasma levels, it is associated with minimal prolongation of prothrombin time and has no effect on aPTT.[22] A dose of 3 μg/kg given 1 hour after surgery and every second day thereafter for four doses has been considered most effective in thromboprophylaxis for knee arthroplasty. Doses beyond 7.5 μg/kg were associated with significant bleeding in patients undergoing elective coronary angioplasty.[23]

In view of its long half-life, reversal following excessive or uncontrolled bleeding is a concern. Apart from supportive measures, rFVIIa may be effective in reversing its anticoagulant activity. This has been demonstrated in healthy volunteers where the effect of rNAPc2 was effectively reversed through the induction of a transient procoagulant state.[24] The clinical use of rFVIIa in a bleeding patient treated with this medication has not been reported.

Tissue factor pathway inhibitor

TFPI is a naturally occurring inhibitor of the factor VIIa/tissue factor complex, and prevents the initiation of coagulation. In animal models, it was shown that TFPI attenuates the coagulopathy and improves survival in sepsis. Its recombinant form, tifacogin, has been com-

pared against placebo in phase II[25] and phase III[26] studies in patients with severe sepsis. In the phase III study tifacogin did not prolong survival compared with placebo but did cause more bleeding (6.5% *vs*. 4.8%). Reversal strategies for bleeding have not been defined but the product has a short half-life after the infusion is discontinued. A phase III study on tifacogin for severe community-acquired pneumonia is currently being conducted.[27]

INHIBITORS OF FACTOR Xa

Fondaparinux

This is a synthetic analog of the pentasaccharide sequence found in heparin and low-molecular-weight heparin. Fondaparinux binds to antithrombin and enhances its activity against factor Xa but not thrombin.[28] It is administered subcutaneously and has a half-life of 17 hours, which allows for once daily dosing. In some jurisdictions fondaparinux has been approved for use as thromboprophylaxis in high-risk orthopedic surgery and for the treatment of both acute deep vein thrombosis and acute pulmonary thromboembolism. In comparison with enoxaparin for hip and knee surgeries, four large trials have demonstrated fondaparinux to be superior.[29] For the initial treatment of venous thromboembolism, it is at least as effective and safe as low-molecular-weight heparin or unfractionated heparin.[30,31]

There is currently no specific antidote for fondaparinux. If uncontrolled bleeding does occur, and it cannot be controlled using non-specific therapy, rFVIIa has been demonstrated to reduce some markers of impaired hemostasis in healthy volunteers treated with fondaparinux.[32] Successful control of postoperative bleeding by rFVIIa in a patient given fondaparinux was recently reported.[33] Fondaparinux has also been shown to be degraded and inactivated by heparinase I *in vitro*; this may be a potential reversal agent.[34] Protamine, however, does not reverse this agent. Fondaparinux will bioaccumulate in patients with renal insufficiency.

Idraparinux

Idraparinux is a derivative of fondaparinux that binds antithrombin with very high affinity producing a complex that has a half-life similar to that of antithrombin.[35] Its exceptionally long half-life allows once weekly dosing and phase III clinical trials are currently underway examining its use in the treatment of acute venous thromboembolism. Reversal of its anticoagulant effect is a concern, considering its long half-life. As with fondaparinux, studies in healthy volunteers suggest that rFVIIa may be use for its reversal.[36] In contrast to fondaparinux, heparinase I does not neutralize idraparinux.[34] Protamine would not be expected to reverse its anticoagulant effect.

DX-9065a

DX-9065a is a direct, selective, reversible factor Xa inhibitor that inhibits both free factor Xa and factor Xa within the prothrombinase complex.[37] Initial experience with this drug given as continuous infusion for percutaneous angiogram and acute coronary syndromes suggests very low bleeding rates.[38,39] Reversal strategies are not established.

Razaxaban and other oral direct factor Xa inhibitors

Razaxaban is a small-molecule, oral, direct factor Xa inhibitor with demonstrated efficacy for thromboprophylaxis in orthopedic surgery when compared with enoxaparin and similar low rates of bleeding at the lowest effective dose tested. There is no known antidote. Other oral direct factor Xa inhibitors that are currently in development include rivaroxaban (BAY 59-7939) and LY-51,7717.

INHIBITORS OF FACTOR Va AND VIIIa

Activated protein C

Activated protein C (APC) proteolytically inactivates factors Va and VIIa and thus modulates thrombin generation.[40] Its recombinant form, drotrecogin alfa (rAPC), was compared against placebo in a phase III study involving 1690 patients with severe sepsis and found to reduce mortality at 28 days by 6%.[41] In this study rAPC increased the risk of major bleeding from 2% to 3.5%. It is currently licensed for use in patients with severe sepsis. Management of bleeding in patients treated with rAPC is simplified by its very short half-life after the

infusion is discontinued. When considering the use of this product, nuisance or minor bleeding (such as bleeding from arterial puncture sites and in nasogastric drainage) is common and, given the life-saving potential of this medication in qualifying patients, should not be considered to preclude its use. There is no known antidote for drotrecogin.

Soluble thrombomodulin

Soluble thrombomodulin exerts its anticoagulant effect by binding to thrombin and converting it into a potent activator of protein C. Its recombinant form (ART-123) has a half-life of 2–3 days after subcutaneous injections and has been evaluated in a phase II study of patients undergoing hip surgery.[42] Major bleeding occurred in 1.4% and 6.3% of patients receiving the low or high dose of thrombomodulin. There is currently no known antidote for this agent.

INHIBITORS OF THROMBIN

Hirudin

Hirudin and its variants are direct thrombin inhibitors originally isolated from medicinal leech and currently manufactured using recombinant technology. Lepirudin (the most commonly available variant) has a half-life of 60 minutes when given in the intravenous form and 120 minutes after subcutaneous injection.[8] It is monitored using the aPTT or ecarin clotting time. Hirudin and its derivatives have been evaluated for acute coronary syndromes and treatment and prevention of venous thromboembolism but it is currently only indicated for the treatment of patients with suspected heparin-induced thrombocytopenia.[43,44] Rapid renal clearance accounts for its short half-life, which precludes the need for urgent reversal in patients with normal renal function; in patients with impaired renal function hirudin (and its derivatives) may bioaccumulate.[45,46] There is no known antidote for the anticoagulant effect of lepirudin. However, if bioaccumulation has occurred it may be removed by dialysis with a hirudin-permeable hemodialyzer membrane.[47] There is limited experience with the use of rFVIIa in the treatment of hirudin-associated bleeding, although experimental models suggest that it might be partially effective in the case of bleeding in the setting of high hirudin levels.[48]

Bivalirudin

An analog of hirudin, bivalirudin, is also a direct thrombin inhibitor but with a shorter half-life of 25 minutes and rapid clearance via a combination of renal and proteolytic mechanism.[49] It is approved as an alternative to heparin in patients undergoing percutaneous coronary angioplasty[50] and has been studied as an adjunct to thrombolytic therapy.[51] It has been used as an alternative to heparin in patients with heparin-induced thrombocytopenia undergoing cardiopulmonary bypass surgery.[52] While no antidote exists, its short half-life means that the likelihood of need for urgent reversal is limited.

Argatroban

Argatroban is a competitive inhibitor of thrombin and is licensed for the treatment of heparin-induced thrombocytopenia.[53] It has a half-life of 45 minutes and is metabolized in the liver. It will bioaccumulate if used in usual doses in patients with impaired hepatic function.[8] There is currently no antidote for argatroban although preliminary studies on whole blood suggest that rFVIIa may reverse at least part of its anticoagulant effect.

Ximelagatran and melagatran

Melagatran is a direct thrombin inhibitor that is orally available as its prodrug, ximelagatran.[54] It provides a predictable anticoagulant effect with no interactions with food or other drugs and has a half-life of 4–5 hours. Monitoring is not required but dose adjustment is required in renal impairment.[54] Ximelagatran has been evaluated for initial and long-term treatment of venous thromboembolism (VTE),[55,56] thromboprophylaxis in high-risk orthopedic patients[57–60] and prevention of embolic events in non-valvular atrial fibrillation.[61,62]

There is currently no available antidote. In a study on healthy volunteers, rFVIIa did not significantly reverse the effects of high concentrations of melagatran.[63] Its short half-life, however, will make reversal unnecessary in most instances. This drug was not commercially approved in North America because of potential liver toxicity. It has recently been withdrawn from other markets, with its development terminated.

Dabigatran

Dabigatran is another orally active direct thrombin inhibitor that is in early phase of development. It is administered as its prodrug dabigatran etixilate and has a half-life of 12 hours with mainly renal elimination. It is being evaluated in studies for the treatment of VTE and atrial fibrillation.

ANTITHROMBIN CONCENTRATES

Antithrombin is a naturally occurring anticoagulant that inhibits thrombin as well as several other factors in the coagulation cascade, such as factors Xa, XIa and XIIa. Its action is enhanced about 1000-fold by heparin.[64] Additionally, antithrombin also has anti-inflammatory properties.[65] Low antithrombin levels found in patients with sepsis have provided the rationale for the use of antithrombin concentrates for treatment of patients with severe sepsis.[66] A large phase III trial in patients with sepsis has however failed to show a survival benefit compared with placebo, and an increase in bleeding complications, especially in patients given heparin concomitantly.[67] There is, however, still an interest in its potential role in sepsis and other thrombotic disorders. Reversal strategy has not been defined, but its normal half-life of 18–27 hours is likely to be much shorter in patients with sepsis and ongoing thrombosis.[68]

rFVIIa – A UNIVERSAL ANTICOAGULANT ANTIDOTE?

rFVIIa was originally developed for use in hemophilia A and B patients with inhibitors of endogenous or exogenous coagulation factors. Factor VIIa has the capacity, as demonstrated in laboratory experiments, to initiate hemostasis at sites of bleeding because it can directly activate thrombin on the surface of platelets. Given the lack of effective alternate therapies and extensive anecdotal experience, rFVIIa has been widely used to treat life-threatening bleeding in many clinical situations. rFVIIa has been used extensively to treat warfarin-associated bleeding; in this setting, it has been shown to correct the INR in healthy volunteers, and case series suggest that it effectively stops bleeding in warfarin-anticoagulated patients.[69] Recommendations for the widespread use of rFVIIa in the setting of major or life-threatening hemorrhage due to other anticoagulants must await publication of clinical trials, as there are, at present, few reports of efficacy in the clinical setting.

CONCLUSION

Despite their recognized limitations, heparins and warfarin remain the established standards against which new anticoagulants are compared. Novel agents, although now entering late stages of clinical investigation, are confined in large part to restricted clinical settings such as the cardiac catheterization laboratory or the treatment of patients with heparin-induced thrombocytopenia. Reversal strategies, an important component of safety for these agents, are ill defined. In the absence of good-quality evidence of efficacy, interventions such as rFVIIA should be regarded as experimental and their use limited to appropriate clinical situations, including life-threatening hemorrhage, where other treatments have failed.

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