



New Trends in Anticoagulant Therapy

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Abstract

Classic anticoagulant drugs, such as heparin and warfarin, are very effective. However, although in use for more than 50 years, they do have some clinical drawbacks. Heparin, now better termed unfractionated heparin, can only be used intravenously and its laboratory control is complicated. Warfarin is orally administered, but its therapeutic window is very narrow and patients need repeated laboratory tests. Moreover, both drugs are non-specific, as they inhibit the coagulation cascade at several steps. Pharmaceutical research has developed new drugs, some of which are already on the market, such as fondaparinux, a pentasaccharide that can interact with antithrombin, thus inhibiting factor Xa. This pentasaccharide is part of the parent heparin molecule and can be chemically synthesized, with the advantage of avoiding extractive compounds. Fondaparinux has a half-life compatible with once-a-day administration; modification of its structure (idraparinux) has led to more stable binding with antithrombin and to an increase in its half-life to allow once-a-week administration. Alternatives to oral anticoagulants have been developed following the study of some compounds like hirudin, which directly binds thrombin and blocks its catalytic site. One of these molecules, ximelagatran, is in advanced clinical development. Ximelagatran is converted into its active form, melagatran, in the circulation, and thrombin activity can be blocked by oral administration twice daily. There is no need for laboratory control and phase II and phase III studies are encouraging. The next few years should bring great changes to the treatment of patients with thromboembolic disorders.

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Antithrombotic drugs are essential for fighting cardiovascular disorders. They comprise compounds aimed at inhibiting platelet function (antiplatelet drugs) and those limiting the coagulation process (anticoagulant drugs). A great deal of research has recently been devoted to the search for new more effective and safe antithrombotic agents. In this review, we discuss the role and clinical development of some of these new drugs.

Classic anticoagulants

Heparin was discovered in 1916 by McLean, and its first clinical use dates back to 1937. Heparin is extracted from various organs and is a mixture of mucopolysaccharide chains of differing molecular weight (average 15,000 D). Some chains specifically interact with antithrombin, which undergoes a conformational change and blocks several coagulation enzymes, particularly factor IIa and, to a lesser extent, factor Xa.

Warfarin was discovered by Link in 1939 and the first clinical report appeared in 1953. Like other currently used oral anticoagulants, warfarin can block the synthesis of functionally active vitamin K-dependent coagulation factors (II, VII, IX, X), thus slowing down the coagulation process. Both heparin and warfarin are non-specific drugs that have several drawbacks.

Heparin must be given parenterally, is not effective in clot-bound thrombin, and may induce immunologically mediated thrombocytopenia. Moreover, its marked binding to plasma proteins gives rise to unpredictable pharmacokinetic behavior, with consequent problems in monitoring. Similarly, warfarin has a small therapeutic window and requires careful laboratory monitoring, clinical surveillance, and continuous patient education. In addition, there is always the burden of drug and food interactions.

New anticoagulants

Two main approaches have been taken to develop new anticoagulants. The first exploits the digestion of unfractionated heparin to develop low molecular weight heparins (average molecular weight 4,500 D). After research on the length of mucopolysaccharide chains, it was finally discovered that the minimal antithrombin-binding unit of heparin is a pentasaccharide, which has been synthesized. The second approach derives from study of the direct interaction between hirudin and thrombin, which led to the discovery of other direct thrombin inhibitors – argatroban and melagatran.

Pentasaccharide

Pentasaccharide is produced by chemical synthesis and acts by means of selective and reversible binding to antithrombin [1]. At the end of the reaction, fondaparinux is released without any conformational or chemical changes and can be used again to bind to another antithrombin molecule [2] [Figure 1].

This molecule does not bind to plasma proteins and therefore has a predictive pharmacologic effect. Its half-life in plasma is 17 hours and is dose-independent. It can be administered subcutaneously once a day without the need for laboratory control. It is not metabolized and is eliminated as it is by the kidney. There are no reported drug or food interactions.

Pentasaccharide was first used in patients undergoing major orthopedic surgery. It is well known that these patients have a high incidence of venous thromboembolism despite the best available

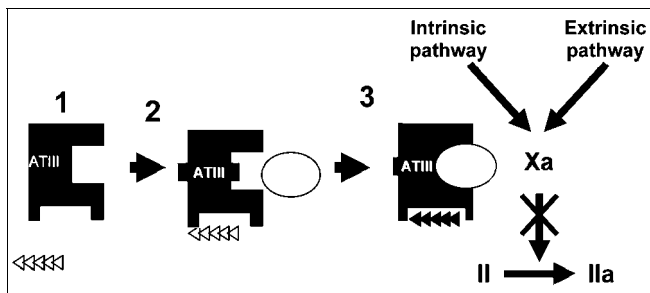


Figure 1. Mechanism of action of pentasaccharide.

antithrombotic prophylaxis. Studies with pentasaccharide in this clinical setting were reviewed by Turpie and colleagues [3] in a meta-analysis. Three of the four studies reviewed showed significant benefits when pentasaccharide was compared with a low molecular weight heparin (enoxaparin). Overall, the relative risk reduction of venous thromboembolism was 55.2% ($P < 0.001$). The risk of major bleeding was increased in the pentasaccharide group but did not reach statistical significance ($P < 0.08$). In one of these studies [4], a regimen of prolonged prevention in hip fracture surgery was tested. Pentasaccharide (fondaparinux 2.5 mg s.c. q.d.) resulted in a significant reduction of all venous thromboembolic events from 35% to 1.4% (RRR 96%). A significant reduction of symptomatic venous thromboembolism from 2.7% to 0.3% (RRR 89%) without any significant increase in clinically relevant bleeding was also achieved. With regard to treatment of pulmonary embolism or deep vein thrombosis, fondaparinux at fixed dosages (5, 7.5 or 10 mg subcutaneously once a day according to body weight) is at least as effective and safe as unfractionated heparin for the initial treatment of pulmonary embolism [5] and as a low molecular weight heparin for the initial treatment of deep vein thrombosis. Pentasaccharide has also been used in the setting of acute coronary syndromes. The Pentalyse study (alteplase plus pentasaccharide vs. unfractionated heparin) measured the re-occlusion rates of the infarct-related artery on days 5–7 in patients with TIMI grade 3 flow or TIMI 2–3 flow at 90 minutes who did not undergo coronary operation. Re-occlusion rates were 7% and 8% using unfractionated heparin and 0.9% and 2.3% with pentasaccharide [6]. In the event of life-threatening bleeding, no antidote for fondaparinux is available, and plasma infusion, administration of prothrombin complex concentrates or recombinant factor VIIa must be considered [7].

A chemical modification of the fondaparinux molecule by replacement of N-sulphated groups and methylation of hydroxylated groups generate O-methyl, O-sulphate pentasaccharide (idraparinux). This compound has a high affinity for antithrombin and a prolonged half-life (80 hours), with possible administration once weekly. A dose-finding study [8] was designed to ascertain whether 2.5–5.0–7.5 mg idraparinux once a week for 3 months was as effective as adjusted-dose warfarin after DVT [8]. The primary

RRR = relative risk reduction
DVT = deep vein thrombosis

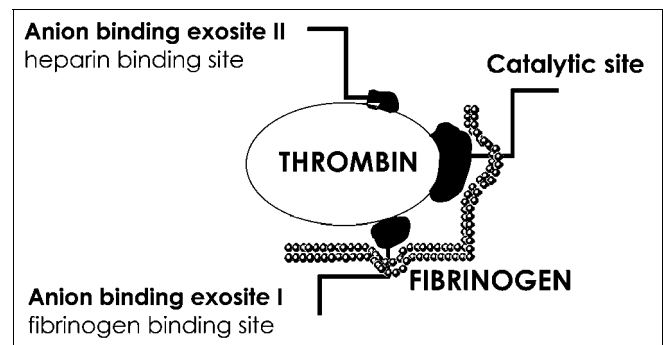


Figure 2. Melagatran and oral prodrug ximelagatran block the catalytic site of thrombin.

efficacy outcome (symptomatic proven DVT or thrombotic burden) did not differ among various dosages and was comparable to that in the warfarin group. A dose relationship for major bleeding was also observed, but the 2.5 mg group had less bleeding than the warfarin group. A phase III study has now been organized to compare idraparinux (2.5 mg once weekly) with adjusted-dose warfarin in stroke prevention in atrial fibrillation (Amadeus study).

Ximelagatran

Ximelagatran, an oral direct thrombin inhibitor, is a prodrug with an estimated bioavailability of 20%. After oral administration it is rapidly metabolized to its active form, melagatran, which is mainly excreted through the kidneys [9]. Melagatran is a dipeptide with a molecular weight of 490 D, derived from the site of the fibrinogen molecule ($A\alpha$ chain), which binds to the active form of thrombin [Figure 2]. It has a short half-life of 1.7 hours and a predictable anticoagulant effect. As a thrombin inhibitor, it prolongs tests exploring thrombin formation (prothrombin time, activated partial prothrombin time, etc). Notably, no or low food and drug interactions are described. It is important to emphasize the ability of ximelagatran to inactivate fibrin-bound thrombin and the fact that it may be administered without laboratory control. Many studies are now being completed on venous thromboembolism prevention and treatment, and ximelagatran appears to be as safe and effective as warfarin. Ximelagatran has also been compared with warfarin in patients with non-rheumatic atrial fibrillation. This common arrhythmia is the most frequent reason for warfarin treatment. Results from the SPORTIF trials [10] demonstrated the efficacy of ximelagatran, the only adverse event being a transient rise in hepatic enzymes. In the SPORTIF III trial [11], an open-label study, high risk patients with atrial fibrillation were randomized to warfarin (adjusted dose to reach an INR of 2.0–3.0) or ximelagatran (36 mg, b.i.d). Systemic thromboembolism of 2.1% per year was recorded in the ximelagatran group and 2.9% per year in the warfarin group (absolute risk reduction 0.8% per year). Combined major and minor bleeding was less frequent in the ximelagatran group. SPORTIF V had a similar design but was a double-blind study in which systemic thromboembolism was found to occur in 1.6% per year in patients treated with ximelagatran and 1.2% per year in those treated with warfarin, without any differences in major

bleeding. Overall, these two studies demonstrated that, in high risk patients with non-valvular atrial fibrillation, fixed doses of ximelagatran are at least as effective and safe as well-monitored warfarin treatment in preventing stroke and systemic embolism.

Although no antidote is available, the action of ximelagatran is promptly reversible. Needless to say, although this drug will cost much more than warfarin, direct and indirect costs related to laboratory controls will be avoided.

Future trends in anticoagulant drugs

Many new specific anticoagulant drugs are currently being developed. Of special interest among these is a potent inhibitor of coagulation, recombinant nematode anticoagulant protein c2 (rNAPc2) [12]. This compound binds with high affinity to zymogen FX in solution, and the resulting stable bimolecular complex of rNAPc2/FX serves as an inhibitory scaffold that facilitates docking to the membrane-bound FVIIa/TF complex. The clinical development of this compound is in progress. The first clinical evidence that inhibition of the factor VIIa/TF complex is effective in reducing the development of postoperative venous thromboembolism was obtained using 3.0 µg/kg rNAPc2, administered within the first hour of surgery [13]. The overall DVT rate was 12.2% – far lower than that expected in such high risk patients. Other interesting results in patients undergoing elective coronary angioplasty were recently presented [14]. Additional selective inhibitors of coagulation like oral anti-Xa compounds are being studied in clinical trials.

Conclusions

In the last few years new anticoagulant drugs have been tested in several clinical trials. Results are encouraging, and the classic anticoagulants may be completely replaced by the new compounds. This is the case of unfractionated heparin, whose use is declining in favor of low molecular weight heparins and pentasaccharide. New oral thrombin inhibitors may also replace warfarin and other classic oral anticoagulants, provided that the raised liver enzyme problem can be solved. In any case, phase IV studies are necessary to convince physicians and patients to opt for the new agents.

References

1. Koopman MM, Buller HR. Short- and long-acting synthetic pentasaccharides. *J Intern Med* 2003;254(4):335–42.
2. Olson ST, Biork I, Sheffer R, Craig PA, Shore JD, Choay J. Role of the antithrombin-binding pentasaccharide in heparin acceleration of antithrombin-proteinase reactions. Resolution of the antithrombin conformational change contribution to heparin rate enhancement. *J Biol Chem* 1992;267(18):12528–38.

3. Turpie AG, Bauer KA, Eriksson BI, Lassen MR. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. *Arch Intern Med* 2002;162(16):1833–40.
4. Eriksson BI, Lassen MR. Pentasaccharide in hip-fracture surgery plus investigators. Duration of prophylaxis against venous thromboembolism with fondaparinux after hip-fracture surgery: a multicenter randomised placebo-controlled study, double-blind study. *Arch Intern Med* 2003; 163:1337–42.
5. Buller HR, Davidson BL, Decousus H, et al., for the Matisse Investigators. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med* 2003;349:1695–702.
6. Coussement PK, Bassand JP, Convens C, et al., for the PENTALYSE investigators. A synthetic factor-Xa inhibitor (ORG31540/SR9017A) as an adjunct to fibrinolysis in acute myocardial infarction. The PENTALYSE study. *Eur Heart J* 2001;22(18):1716–24.
7. Bijsterveld NR, Vink R, Van Aken BE, et al. Recombinant factor VIIa reverses the anticoagulant effect of the long-acting pentasaccharide idraparinux in healthy volunteers. *Br J Haematol* 2004;124(5):653–8.
8. PERSIST investigators. A novel long-acting synthetic factor Xa inhibitor (idraparinux sodium) to replace warfarin for secondary prevention in deep vein thrombosis, a phase II evaluation. *Blood* 2002;100:115.
9. Eriksson UG, Bredberg U, Hoffman K-J, et al. Absorption, distribution, metabolism and excretion of ximelagatran, an oral direct thrombin inhibitor, in rats, dogs and humans. *Drug Metab Dispos* 2003;31:294–305.
10. Halperin JL, Executive Steering Committee, SPORTIF III and V Study Investigators. Ximelagatran compared with warfarin for prevention of thromboembolism in patients with nonvalvular atrial fibrillation: rationale, objectives, and design of a pair of clinical studies and baseline patient characteristics (SPORTIF III and V). *Am Heart J* 2003;146(3):431–8.
11. Olsson SB. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. *Lancet* 2003; 362:1691–8.
12. Brendan M, Duggan H, Dyson J, Wright PE. Inherent flexibility in a potent inhibitor of blood coagulation, recombinant nematode anticoagulant protein c2. *Eur J Biochem* 1999;265:539–48.
13. Lee A, Agnelli G, Buller H, et al. Dose-response study of recombinant factor VIIa/tissue factor inhibitor recombinant nematode anticoagulant protein c2 in prevention of postoperative venous thromboembolism in patients undergoing total knee replacement. *Circulation* 2001;104(1):74–8.
14. Moons AH, Peters RJ, Bijsterveld NR, et al. Recombinant nematode recombinant protein c2, an inhibitor of the tissue factor/VIIa complex, in patients undergoing elective coronary angioplasty. *J Am Coll Cardiol* 2003;41:2147–53.

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Every formula which expresses a law of nature is a hymn of praise to God

Maria Mitchell (1818-89), American astronomer who discovered the comet of 1846, known as Comet Mitchell 1847VI. She was the first female professor of astronomy in the U.S., the first woman to be appointed to the Academy of Arts and Sciences, to the faculty of Vassar and to be awarded the first advanced degree.