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Current Options in the Prevention of Thromboembolic Disease

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Abstract

Significant advances in the pharmacological prophylaxis of venous thromboembolism have occurred since warfarin and unfractionated heparin were introduced for this indication nearly 60 years ago. Despite these advances, coumarin derivatives such as warfarin remain the only orally active anticoagulants available for prophylaxis in venous thromboembolism. Although administered orally, coumarin derivatives are not convenient to use, because they have narrow therapeutic indexes and require routine coagulation monitoring and dose adjustment. This is inconvenient for patients and physicians and costly for the healthcare system. Low-molecular-weight heparins, which are administered in fixed or weight-adjusted doses and do not require monitoring, are widely used for the prevention of venous thromboembolism in patients in both the hospital and the outpatient setting. However, these drugs must be given subcutaneously, which can be difficult for outpatients and resource-intensive for in-hospital use. Likewise, fondaparinux, the synthetic pentasaccharide, must be administered subcutaneously. Consequently, there remains a need for new orally active anticoagulants that can be given in fixed doses and do not have a narrow therapeutic index, so that coagulation monitoring is unnecessary. Because such agents would be more convenient for patients and physicians, they would probably expand the use of prophylaxis in venous thromboembolism in those at risk, and would simplify treatment of patients with established venous thromboembolism.

1. Introduction

Thromboembolism is a major cause of morbidity and mortality in the Western world. In the USA alone, more than 2 million people die each year from the consequences of arterial or venous thrombosis.[1] Venous thromboembolism is a general term that encompasses two conditions – deep vein thrombosis (DVT) and pulmonary embolism. Asymptomatic DVT often precedes acute pulmonary embolism,[2] which can be fatal.[3-5]

The goal of venous thromboembolism prophylaxis is to prevent DVT, thereby eliminating its complications, which include potentially fatal pulmonary embolism and postphlebitic syndrome, a disorder that reduces quality of life, is expensive for society and can lead to venous ulcers.[6] This review provides a background to the strengths and limitations of currently available agents for management of venous thromboembolism.

2. Epidemiology of Venous Thromboembolism

Deep vein thrombosis can be a consequence of vascular endothelial damage, venous stasis, hypercoagulability of the blood, or combinations thereof.[7] Together, these three pathological states constitute Virchow's triad. When any one of these processes occurs, a procoagulant state arises. There

Table I. Examples of risk factors for development of venous thromboembolism. (Adapted from Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. Circulation 2003; 107 (23 Suppl. 1): I9-16.[7])

Strong risk factors	Hip or knee replacement
	Hip or leg fracture
	Major general surgery
	Major trauma
	Spinal cord injury
Moderate risk factors	Central venous lines
	Chemotherapy
	Congestive heart or respiratory failure
	Oestrogen use
	Malignancy/chemotherapy
	Paralytic stroke
	Pregnancy/postpartum period
	Previous venous thromboembolism
	Thrombophilia
Weak risk factors	Increasing age
	Obesity
	Pregnancy/antepartum period
	Prolonged immobility
	Varicose veins

are many risk factors for venous thromboembolism (table I). Factors that, by themselves, are sufficient to prompt physicians to consider prophylaxis in venous thromboembolism include major general or orthopaedic surgery, major trauma, fractures of the pelvis, hip or leg and spinal cord injury.[7] Other risk factors include previous venous thromboembolism, malignancy, older age, obesity and prolonged immobility. Congenital or acquired thrombophilic conditions also are risk factors for venous thromboembolism. These include the Factor V Leiden or prothrombin gene mutation, deficiencies of antithrombin, protein C or protein S, the antiphospholipid antibody syndrome and heparin-induced thrombocytopenia.[7]

Major orthopaedic surgery of the lower extremities imposes a particularly high risk of venous thromboembolism. Although the majority of cases are asymptomatic, contrast venography indicates that the prevalence of DVT 7–14 days after total hip replacement, total knee replacement or hip fracture surgery is about 50–60% in the absence of thromboprophylaxis.[8] For surgical patients, the incidence of DVT is affected by factors related to the procedure itself, patient-related factors and the extent of postoperative immobilisation.[8]

Patients with a prior history of venous thromboembolism have a risk of recurrence, particularly when other high-risk conditions are present.[7] It has been estimated that about 10–15% of patients with idiopathic venous thromboembolism and those with continuing risk factors, such as underlying cancer, will suffer a recurrent venous thromboembolism within 1 year of discontinuing anticoagulant treatment.[9] In contrast, the risk of recurrence after 3 months of anticoagulant treatment is less than 4% in patients in whom venous thromboembolism developed after a transient risk factor such as trauma or surgery.[9] Consequently, it is recommended that patients whose venous thromboembolism arose after a reversible or time-limited risk factor be treated for 3–6 months, whereas those with a first episode of idiopathic DVT should be treated for at least 6 months and possibly longer. Patients with recurrent DVT or continuing risk factors should be treated for a minimum of 12 months up to a lifetime.[10]

3. Prevention Options

Venous thromboembolism is often clinically silent. Consequently, the first manifestation of the disease may be fatal pulmonary embolism. To prevent this, routine thromboprophylaxis should be given to all high-risk patients. The intensity and duration of prophylaxis depends on the risk profile of the patient.

3.1 Anticoagulation Strategies

Thrombin has a pivotal role in haemostasis and thrombosis, and anticoagulant strategies to inhibit thrombogenesis focus on inhibiting thrombin or its generation, either by targeting coagulation factors higher in the cascade or by directly blocking thrombin. Unfractionated heparin, low-molecular-weight heparins (LMWHs) and coumarin derivatives prevent the generation of thrombin, and are the drugs most frequently used for the prevention of venous thromboembolism.[8]

3.1.1 Coumarin Derivatives

Coumarin derivatives produce their anticoagulant effect by interfering with the cyclic conversion of vitamin K, which is a co-factor for γ-glutamyl carboxylation of the vitamin K-dependent proteins, which include coagulation factors II, VII, IX and X. Vitamin K-dependent γ-carboxylation of these clotting factors endows them with the capacity to bind to negatively charged phospholipid surfaces in a calcium-dependent fashion. By blocking this process, coumarin derivatives result in the production of coagulation factors with little or no biological activity.[11]

Warfarin, the most widely used vitamin K antagonist, is rapidly absorbed from the gastrointestinal tract. However, its anticoagulant effect appears only after 3–4 days of treatment, because it takes time for the fully γ-carboxylated clotting factors to be replaced by their non-carboxylated counterparts. Consequently, warfarin must be supported with rapidly acting parenteral anticoagulants when treatment is initiated in patients with established thrombosis or at high risk for thrombosis.[12] In addition, warfarin produces an unpredictable anticoagulant response, because several drugs affect its absorption or metabolism. Dietary intake of vitamin K and genetic polymorphisms in the cytochrome P450 enzyme system also influence warfarin metabolism.[11,12] This is problematic, because warfarin has a narrow therapeutic index: inadequate anticoagulation provides incomplete protection against thrombosis, whereas excessive anticoagulation increases the risk of bleeding.[13]

Consequently, routine coagulation monitoring is essential to ensure that a therapeutic anticoagulant response is obtained.[11,12] The prothrombin time is used to monitor the anticoagulant activity of warfarin, and the international normalised ratio (INR) is calculated to account for the variability in prothrombin times that can occur as a result of different sensitivities of thromboplastin agents to reductions in the vitamin K-dependent clotting factors.[14] Optimal warfarin therapy depends on regular and reliable monitoring, and maintenance of the INR within the therapeutic range (2–3) for the duration of treatment.[11]

3.1.2 Heparin-Based Drugs

Unfractionated heparin was the first parenteral drug to show efficacy in the management of venous thromboembolism. It is administered intravenously or subcutaneously, and exerts its anticoagulant activity by activating antithrombin, which then inhibits thrombin and factor Xa.[15]

The anticoagulant response to unfractionated heparin is variable, because the drug binds to a number of plasma proteins, the concentrations of which differ between patients.[16] Because of this between-patient variability in the anticoagulant response to unfractionated heparin, it is standard practice to monitor the anticoagulant activity of the drug when it is given in treatment doses. Typically, this is done using the activated partial thromboplastin time.[17] Unfractionated heparin also carries a risk of heparin-induced thrombocytopenia, which is a heparin-dependent IgG-antibody-mediated event.

LMWHs were developed to overcome the pharmacokinetic limitations of unfractionated heparin.[16] These agents produce a more predictable anticoagulant response than unfractionated heparin because they exhibit less binding to plasma proteins. Consequently, coagulation monitoring is not usually necessary.[17] LMWHs have a longer biological half-life than unfractionated heparin, permitting once-daily subcutaneous administration. However, LMWHs still require subcutaneous administration, which can limit their utility in the outpatient setting.[18]

3.1.3 Selective Factor Xa Inhibitors

A synthetic analogue of the pentasaccharide sequence in unfractionated heparins or LMWHs that mediates their interaction with antithrombin, fondaparinux, has a half-life of approximately 17h after subcutaneous injection. Consequently, this agent is given once-daily for prevention of venous thromboembolism. Like LMWHs, fondaparinux also has a predictable dose–response relationship,[19] so that coagulation monitoring is unnecessary. Fondaparinux does not bind to platelet factor 4 and does not elicit heparin-induced antibodies. Clinical studies to date support this

attribute, and fondaparinux is being studied as an alternative to unfractionated heparin in patients with a history of heparin-induced thrombocytopenia.

Fondaparinux has been studied as prophylactic therapy in patients undergoing total hip replacement or knee replacement surgery or hip fracture surgery, and has shown a 50% reduction in total occurrence of venous thromboembolism compared with enoxaparin.[20] It is currently approved as a prophylactic agent in these conditions.

3.1.4 Direct Thrombin Inhibitors

Whereas thrombin bound to fibrin is relatively protected from inactivation by heparins and selective factor Xa inhibitors, which work by binding to and activating antithrombin, direct thrombin inhibitors have the theoretical advantage of being able to inhibit both clot-bound and free thrombin.[21] Four direct thrombin inhibitors, lepirudin,[22] desirudin,[23] bivalirudin,[24] and argatroban,[25] are available for limited indications, such as in patients with heparin-induced thrombocytopenia who require anticoagulant therapy, and as an alternative to heparin in patients undergoing percutaneous coronary interventions. All are given intravenously and, as with unfractionated heparin, need to be monitored using an activated partial thromboplastin time or, in the case of bivalirudin, using the activated clotting time.[19] Ximelagatran, which is converted to its active form, melagatran, is an orally active direct thrombin inhibitor. The possibility for oral administration makes it attractive from a practical point of view, especially in situations of prolonged prophylaxis.

4. Needs Unmet by Current Options

The needs of patients who require effective and consistent anticoagulation with convenient administration are not currently being met. Although LMWHs can be used for outpatient use, patients must be willing and able to self-administer the drug subcutaneously. In addition, LMWH is expensive, particularly when given for extended treatment. Although warfarin is administered orally and is inexpensive, it requires routine coagulation monitoring, which is inconvenient for patients and physicians and costly for the healthcare system. These problems contribute, at least in part, to the underuse of warfarin for such indications as atrial fibrillation.

Prophylaxis is key to the prevention of fatal pulmonary embolism in high-risk settings. Despite guidelines advising the use of prophylaxis in certain surgical patients, appropriate means of thromboprophylaxis are underused, even in high-risk surgical patients.[26] A retrospective review of the medical charts of 1907 patients who underwent high-risk surgical procedures between 1996 and 1997 showed that appropriate venous thromboembolism prophylaxis ranged from 84.3% and 75.9% for patients undergoing total hip and knee replacement surgery, respectively, to 50.3% and 45.2% for those having abdominal surgery and hip fracture repair, respectively.[26] Underutilisation reflects a perception that the risk of complications from bleeding outweighs the benefits of routine thromboprophylaxis.[8] However, such an approach may lead to large numbers of preventable venous thromboembolisms.

Thromboprophylaxis in venous thromboembolism is most widely used in orthopaedic surgery. There are, however, geographical differences in the type, dose regimen and timing of prophylaxis in relation to surgery. In Europe, LMWHs are generally initiated 12h before operation in an attempt to optimise the efficacy of preventive therapy whereas, in North America, prophylaxis is initiated 12–24h after operation in an attempt to minimise the risk of bleeding. According to a recent review, the optimal timing for starting prophylaxis is somewhere between 2h before surgery and 8–10h after it.[27] However, the safety of this approach remains a matter of debate and is further discussed by Professor Dahl in this Supplement.

A rapidly acting oral anticoagulant without a narrow therapeutic index has the potential to streamline the prevention of venous thromboembolism. With no need for coagulation monitoring, such an agent would simplify postoperative throm-

boprophylaxis and would render long-term management easier than warfarin therapy.

5. Conclusions

Although prevention of venous thromboembolism has advanced in recent years, there remains a need for safe and effective oral anticoagulants that do not require coagulation monitoring. Anticoagulants that are predictably effective and well tolerated after oral administration have the potential to simplify the prevention of venous thromboembolism.

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