Emerging concepts in thromboprophylaxis

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Introduction

Venous thromboembolism (VTE), comprising pulmonary embolism (PE) and deep vein thrombosis (DVT), is a common and potentially fatal disease. Since it is frequently asymptomatic, prevention is the most effective means to reduce morbidity and mortality. Although thromboprophylaxis is recommended in patients undergoing general and orthopaedic surgery and those with trauma, acute myocardial infarction, and ischemic stroke, it is still significantly underused [1–3]. Reasons for not using prophylaxis include lack of awareness among clinicians, difficulties in determining when and how prophylaxis should be administered, identification of high-risk patients and insufficient data on the comparative efficacy of prophylactic regimens [2,3]. The objectives of this presentation are to examine the issues and challenges in the use of thromboprophylaxis, and to discuss the role of low molecular heparins (LMWHs) in the prevention of VTE.

Benefits of thromboprophylaxis with low molecular weight heparins

The efficacy of unfractionated heparin (UFH) as an antithrombotic agent was first established over 60 years ago [4]. Subsequently, LMWHs were developed and clinical trials demonstrated their distinct advantages in terms of subcutaneous administration, tolerability and the lack of need for laboratory monitoring. Both UFH and LMWHs exert their anticoagulation activity in part through activation of antithrombin. However, because UFH contains heterogeneous polysaccharide chains (molecular weight 3000–30 000 daltons), as well as accelerating the interaction between antithrombin and activated factor Xa, it also inactivates thrombin with an anti-Xa:anti-IIa ratio of 1:1 [5]. Moreover, UFH binds to other cell components making anticoagulation difficult to predict [6]. In contrast, the small size of LMWHs (molecular weight 1000–10 000 daltons), means that inhibition of thrombin activity is negligible with little non-specific binding to endothelial cells [7]. The antithrombotic effect of LMWH is mediated by the release of tissue factor pathway inhibitor (TFPI), as well as the anti-Xa and anti-IIa activity [8]. Following administration of UFH or LMWHs, TFPI is released at high concentrations at the sites of tissue damage and ongoing thrombosis. Released TFPI, but not plasma TFPI, contains the basic carboxy-terminal, which is important for the anticoagulant effect. Experimental studies demonstrate that UFH and LMWH exert differential effects on intravascular TFPI [9]. UFH, but not LMWH, given in therapeutic doses, is coupled with a progressive depletion of TFPI,
which is in turn associated with a strong rebound activation of coagulation after cessation of treatment. Such depletion may explain the apparent superior efficacy of LMWHs observed in clinical trials. In summary it now seems that the antithrombotic activity of heparins is not dependent solely on molecular weight but also on their TFPI releasing effects.

Bemiparin, a new second generation LMWH, with a molecular weight of 3600 daltons and an anti-Xa/anti-IIa ratio greater than 8, has been demonstrated in experimental studies to have a pharmacological profile distinct from UFH and other LMWHs [10,11]. In endothelial cells subjected to shear stress in vitro, bemiparin was more efficient than UFH or dalteparin in modulating the expression, release and activity of TFPI. Although all three preparations increased the expression of TFPI by 60–120% in endothelial cells under minimal flow, only bemiparin enhanced TFPI mRNA in endothelial cells under arterial flow. These properties may explain the superiority of bemiparin over older LMWHs in maintaining the anticoagulation properties of the endothelium [10,11].

Thromboprophylaxis with low molecular weight heparins in high-risk patients

Multiple clinical trials support the use of thromboprophylaxis with LMWHs postoperatively in surgical/medical patients at risk for VTE [12–16]. However, the different pharmacological profiles and dosing methods of LMWHs suggest that efficacy and safety may not be equivalent [4]. As part of the extensive clinical trial development programme the use of bemiparin in the prevention of VTE has been extensively studied. A meta-analysis of 21 studies involving 4605 patients undergoing orthopaedic surgery, confirmed its efficacy and tolerability in the prevention of VTE with a significantly reduced rate of DVT and no increase in postoperative bleeding [17].

Dosage regimens of thromboprophylaxis

One of the main outstanding issues in the use of LMWHs in surgical and medical patients is the determination of the optimal timing of administration and most appropriate dosage regimens to provide therapeutic efficacy but to prevent adverse events. In general, the recommended dosage of LMWHs is 2–4000 IU or 100–150 IU/kg once or twice daily. In a large-scale, comparative trial in 300 patients scheduled to undergo elective hip arthroplasty, 149 patients received 3500 anti-Xa IU of bemiparin and 149 received 5000 IU UFH twice a day. In the postoperative period significantly more patients treated with UFH developed VTE complications than those treated with bemiparin (18.7 versus 7.2%, p=0.01). There were no significant differences in the frequency of bleeding complications between the two groups. Interestingly, anti-Xa activity and TFPI levels were significantly increased following bemiparin administration providing confirmation of its unique pharmacological activity. This study demonstrates that a single administration of bemiparin (3500 anti-Xa IU in high-risk patients undergoing hip replacement surgery is more effective than UFH (5000 IU, twice daily), in the prevention of post-operative VTE [18]. The effects of administration of bemiparin postoperatively were investigated in 57 patients undergoing total hip replacement surgery [19]. The incidence of DVT following bemiparin (3500 IU anti-Xa) administered 6 hours after surgery was consistent with those reported by Kakkar when bemiparin was given preoperatively (7.0 versus 7.2%). No episodes of major bleeding were observed with this new protocol for postoperative administration and the rates of postoperative bleeding were similar to those previously reported with LMWHs.

References


