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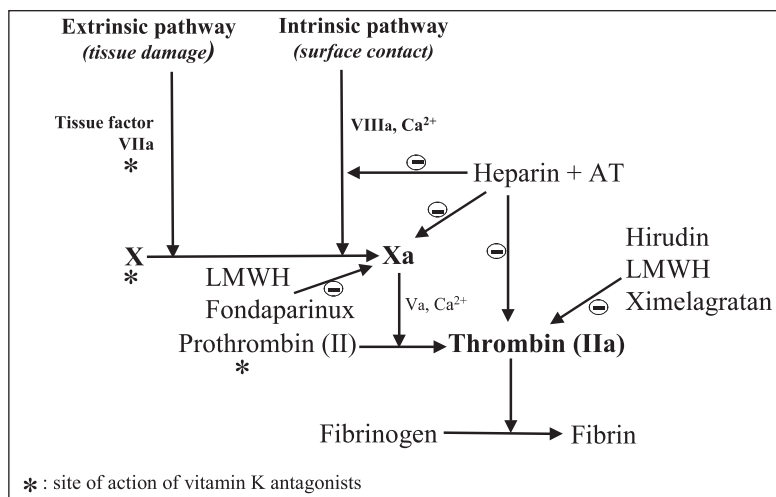
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Haemostasis is the physiological response to vascular injury designed to minimise blood loss following injury. It is regulated under physiological circumstances by a complex interplay between the processes that promote clotting (the coagulation system) and those that inhibit it. While this system is essential for the survival of the organism, it can also be triggered by a variety of pathological conditions. Venous thrombi that form under low flow conditions are predominantly composed of fibrin and red cells. They can arise anywhere within the venous system, but are more common in the deep veins of the legs. The most common cause of arterial thrombosis is spontaneous or mechanical rupture of an atherosclerotic plaque. Thrombi formed under these high shear conditions are composed primarily of platelets and fibrin strands. They are the major causes of strokes and myocardial infarction. Pharmacological interventions in haemostasis are primarily aimed at preventing the formation of these pathological thrombi, or inhibiting their propagation.

THE CLOTTING CASCADE

The trigger for initiating the coagulation system is the formation of a tissue factor/factor VIIa complex at the sites of vascular injury. The primary element in the arrest of bleeding after blood vessel injury is the aggregation and deposition of platelets. The second key element is the blood coagulation cascade. This consists of a complex sequence of biochemical events involving various factors that circulate in an inactive form until the *milieu intérieur* is disturbed. The end-point of the coagulation sequence is the cleavage of prothrombin into two fragments, one of which is the enzyme thrombin. Thrombin acts on fibrinogen to produce fibrin which then polymerises to form insoluble fibrin (Figure 1).

FIGURE 1. THE COAGULATION CASCADE



Clotting activity is balanced by the fibrinolytic system, which is activated by the deposition of fibrin. Fibrinolysis is mediated by activation of plasminogen, which is converted to plasmin by tissue plasminogen activator released from damaged endothelial cells. Plasmin degrades fibrin into soluble fibrin degradation products. Like coagulation, fibrinolysis can be pharmacologically manipulated.

HEPARIN

Heparin is a negatively charged mixture of polysaccharide molecules of different chain lengths. It acts as an anticoagulant by binding to antithrombin, via a specific pentasaccharide sequence. The heparin- antithrombin complex inhibits several clotting factors, including thrombin, IXa and Xa. Patients who are deficient in antithrombin are resistant to the anticoagulant effects of heparin. This form of heparin resistance can be treated by the administration of human plasma antithrombin, which is approved for clinical use in Europe.

FIGURE 2. MECHANISM OF ACTION OF HEPARIN

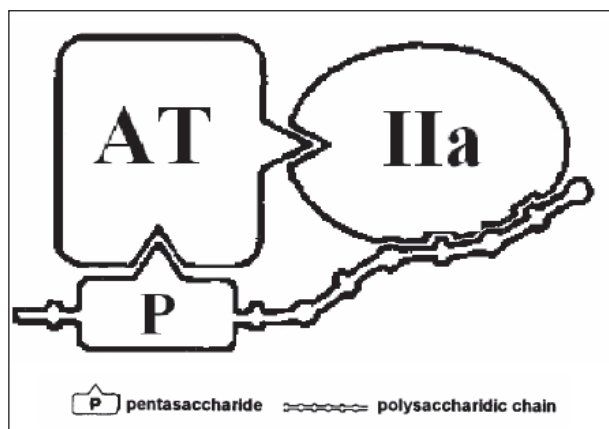


Figure 2. Schematic representation of the interaction between heparin, antithrombin, thrombin and factor Xa, showing the role of the polysaccharide chain of heparin and the pentasaccharide sequence.

The plasma half-life of unfractionated heparin is about 90 min (range 30-360 min). Endothelial and reticuloendothelial uptake is the most important process for termination of the anticoagulant effect with renal clearance being a much slower process. Heparin-induced anticoagulation is monitored by the activated partial thromboplastin time (aPTT) or the activated clotting time (ACT). The anticoagulant effects of standard heparin are rapidly neutralised by equimolar doses of protamine.

The main use of unfractionated heparin is the treatment of thromboembolic diseases, e.g. pulmonary embolism, myocardial infarction or established deep venous thrombosis, or the prevention of coagulation during cardiac and vascular surgery. Low-dose subcutaneous unfractionated heparin as prophylaxis against deep venous thrombosis has been replaced by low molecular weight heparins.

LOW MOLECULAR WEIGHT HEPARIN

Low molecular weight heparins (LMWH) are fractions of unfractionated heparin with mean molecular weights of 4000-6000. They also bind to antithrombin, but this results in much less antithrombin activity. LMWH exhibit higher anti-Xa activity than unfractionated heparin. Activated clotting time (ACT) and activated partial thromboplastin time (aPTT) are relatively unaffected by LMWH. Although protamine has some effect on LMWH about 60-80% of the anti-thrombotic activity will persist. This is because of the reduced protamine binding to these drugs and because only the anti-IIa activity is completely reversed whereas anti-Xa activity is only partially neutralised. In contrast to unfractionated heparin, LMWHs bind weakly to endothelial cells and are cleared mainly by renal excretion. As a consequence there is a risk of accumulation in patients with reduced renal function. In this group of patients it may be advisable to monitor the anti-Xa activity.

SIDE EFFECTS OF HEPARIN

Bleeding is uncommon with prophylactic doses of unfractionated or LMWH but more likely in patients receiving therapeutic doses. Unlike warfarin, heparin does not cross the placenta and has not been associated with foetal malformations and heparin is therefore used for anticoagulation during pregnancy. Heparin-induced thrombocytopenia (HIT) occurs in 1-3% of patients receiving therapeutic doses of intravenous heparin. There are two types of HIT [1]. In Type I the thrombocytopenia is mild and the platelet count seldom falls below $100 \times 10^9 \text{ L}^{-1}$, and may return to normal even if the heparin is continued. In contrast, in Type II the platelet count is often below $60 \times 10^9 \text{ L}^{-1}$. The onset usually appears 4-14 days after starting treatment, and will not recover unless the heparin is stopped. Type I is probably related to the platelet aggregating effect of heparin itself. The mechanism of Type II is thought to be immune. The risk of thrombocytopenia is less with the LMWHs.

PENTASACCHARIDES

Fondaparinux sodium is a synthetic analogue of the critical pentasaccharide sequence of the heparin molecule. The anticoagulant activity of heparin depends on the binding of antithrombin to this sequence. It increases the rate of factor Xa inactivation by antithrombin, thereby blocking thrombin generation [2]. Fondaparinux produces a predictable anticoagulation so that routine coagulation monitoring is not needed. Unlike heparin, it does not bind to platelets and has no effect on platelet function. The half-life is 17 hours, allowing once-daily subcutaneous dosing. Fondaparinux is as effective as heparin in patients with deep vein thrombosis and pulmonary embolism [3]. It is almost completely excreted by the kidneys as the unchanged compound, and clearance may be delayed in patients with renal insufficiency. A potential problem with this drug is that there is no

antagonist to its anticoagulant effect, should severe bleeding occur. It does not interact with protamine, but recombinant factor VIIa is effective in this situation. However, this is not available in all hospitals, is very expensive, and can cause thrombotic complications.

A related drug is idraparinux, a methylated derivative of fondaparinux. Because it binds antithrombin with very high affinity, the half life for its anticoagulant activity is 80 hours, which is similar to that of antithrombin. Consequently, it is administered subcutaneously once weekly. As with fondaparinux, dose adjustments are needed in patients with renal impairment, and it should not be used in patients with renal failure.

INHIBITORS OF FIBRIN FORMATION

The conversion of fibrinogen to fibrin by thrombin can be blocked either by inactivating the enzyme itself, or by preventing its generation. Indirect thrombin inhibitors like unfractionated heparin and LMWH act by catalyzing the naturally occurring thrombin inhibitors, antithrombin and/or heparin cofactor II. In contrast, direct thrombin inhibitors bind directly to thrombin and block its interaction with substrates, thus preventing fibrin formation and thrombin-induced platelet aggregation.

DIRECT THROMBIN INHIBITORS

Direct thrombin inhibitors bind directly to thrombin's active site without interaction with the cofactor, antithrombin III. They produce a more predictable anticoagulant effect than heparin because they do not bind to plasma proteins [4]. Four parenteral direct thrombin inhibitors are available, hirudin, argatroban, lepirudin and bivalirudin. They are an important advance in the treatment of patients with heparin-induced thrombocytopenia [5].

Hirudin, originally isolated from the saliva of the medicinal leech, *Hirudo medicinalis*, is now produced through recombinant DNA technology. It is a potent and specific inhibitor of thrombin. It has been used during cardiac surgery in patients with heparin-induced thrombocytopenia [6]. The main disadvantages of hirudin, and the other direct thrombin inhibitors, are the lack of an antidote or readily available clinical monitoring [7].

Lepirudin and argatroban are effective in treatment of heparin-induced thrombocytopenia resulting in rapid normalization of platelet counts and a reduction in thrombotic events [8,9]. Because of differences in clearance mechanisms, argatroban is preferable in patients with renal insufficiency and lepirudin if there is hepatic impairment. Bivalirudin, a parenteral direct thrombin inhibitor, has been used in place of heparin in percutaneous coronary interventions. It is also licensed in the USA as an alternative to heparin in patients undergoing cardiac surgery. Since only 20% of the drug is eliminated by the kidneys, it is a safe alternative to hirudin in patients with renal failure.

Ximelagatran is an oral direct thrombin inhibitor. It is a prodrug, with little intrinsic activity, but is rapidly metabolised in the liver to the active agent, melagatran. Melagatran is available for subcutaneous administration. Oral ximelagatran and subcutaneous melagatran are licensed in Europe for venous thrombosis prevention in patients undergoing hip or knee replacement surgery. Ximelagatran does not inhibit cytochrome P450 enzymes and therefore has a low potential for drug-drug interactions [10]. It produces a predictable anticoagulant response after oral administration and no coagulation monitoring appears to be necessary. Because melagatran, the active agent, is eliminated by the kidneys, dose adjustments may be needed in patients with severe renal insufficiency. Elevation of liver transaminases occurs in about 8 % of patients receiving long-term therapy. Typically, changes in liver enzymes occur after 6 weeks to 4 months of therapy and are asymptomatic and reversible, even if the medication is continued. As with other direct thrombin inhibitors, there is no antidote for ximelagatran. However, this drug's short half-life makes it unlikely that this will be a real problem. Dabigatran etexilate, another oral direct thrombin inhibitor in clinical development is, like ximelagatran, a prodrug that is converted to its active metabolite, dabigatran [11]. While early clinical studies are promising, further work is needed to establish the safety and efficacy of this drug [12].

ORAL ANTICOAGULANTS

Warfarin is the prototypical coumarin oral anticoagulant, but the anticoagulant action of all the drugs in this class is similar, differing mainly in potency and duration of action. Coumarins are competitive inhibitors of vitamin K, which is required for the formation in the liver of the amino acid, gamma carboxyglutamic acid. This is necessary for the synthesis of prothrombin and factors VII, IX and X (Figure 1). After starting treatment the anticoagulant effect is delayed until the concentration of normal coagulation factors falls (36-72 hr). The effects can be reversed by vitamin K (slow; maximum effect only after 3-6 hr) or by whole blood or plasma (fast).

The prothrombin time (PT) is used to monitor anticoagulation. This is now almost universally reported as the INR (International Normalized Ratio), the ratio of the patient PT to a control PT obtained using a primary standard (human) thromboplastin. Therapeutic anticoagulation requires an INR in the range 2.5-3.5, although higher values (3.5-5.0) are indicated in patients with artificial heart valves.

ANTIPLATELET DRUGS

ASPIRIN

All NSAIDs interfere with platelet function by mechanisms involving inhibition of cyclo-oxygenase. This blocks the formation not only of platelet-activating eicosanoids, such as PGG₂, PGH₂ and thromboxane A₂, but also of the platelet inhibitors PGD₂ and PGI₂. For all NSAIDs, except aspirin, the inhibition of cyclo-oxygenase is reversible and the anti-platelet effect is present only while the drug is present in sufficient concentration. For aspirin the effect lasts for the 5-11 days of the life of the platelet because of the irreversible acetylation of platelet cyclo-oxygenase, coupled with the inability of platelets to synthesise new enzyme. Aspirin in low doses is widely used in patients with cardiovascular disease to reduce the incidence of myocardial infarction and strokes. Doses as low as 40 mg per day can produce maximal inhibition of thromboxane and prostacyclin synthesis.

CLOPIDOGREL

Clopidogrel, a thienopyridine derivative, is an antiplatelet drug that acts by inhibition of ADP-dependent activation of the GPIIb/IIIa receptor. It is a prodrug, working through an active metabolite, and the onset of action is slow; peak platelet inhibition taking 4-7 days. It is widely prescribed in combination with low-dose aspirin to patients with coronary artery and cerebrovascular disease. Recovery is also slow after drug withdrawal, because of irreversible platelet inhibition, and the return of normal coagulation relies on the formation of new platelets, similar to aspirin. Clopidogrel should, therefore, be stopped at least 7 days before major surgery to prevent excessive intra- and postoperative bleeding. However, the plasma half-life of clopidogrel is relatively short (2-4 hours), so that concentrations fall quickly below those that will inhibit platelets. In an emergency situation, e.g. severe bleeding or acute surgery, coagulation can be restored by administration of fresh platelets within a few hours of stopping the drug.

PLATELET GLYCOPROTEIN IIb/IIIa RECEPTOR ANTAGONISTS

The glycoprotein IIb/IIIa receptor on the platelet surface is important for platelet aggregation, and has been called the "final common pathway" of platelet activation.

The adhesion and aggregation of platelets is mediated by these receptors, which interact with the distal ends of fibrinogen, forming a bridge between adjacent platelets. Glycoprotein IIb/IIIa receptor antagonists represent an important new class of drugs with increasing use in acute ischemic coronary syndromes and cerebral ischemia [13].

Abciximab, the first drug of this class to be used extensively in man, is the Fab fragment of a murine monoclonal antibody to GPIIb/IIIa. The binding the glycoprotein IIb/IIIa receptor is a rapid high-affinity interaction, and the inhibitory effects are immediate (within minutes). All receptors are blocked within 15 min with a bolus dose of abciximab. The half-life of abciximab is 10-26 min, but resolution of glycoprotein IIb/IIIa block is related primarily to the turnover of platelets. Twenty-four hours after administration, 50 - 60% of receptors are still blocked, and abciximab can be detected on circulating platelets for more than 15 days. Abciximab prolongs the activated clotting time and the activated partial thromboplastin time.

Eptifibatide binds to the glycoprotein IIb/IIIa receptor between the IIb and IIIa arms of the extracellular parts of the receptor and prevents binding of fibrinogen. It has a rapid onset of action and a rapid reversibility of platelet inhibition. Four hours after termination of an eptifibatide infusion, platelet aggregation recovers to approximately 70% of normal with the return of normal haemostasis. Doses should be reduced in patients with renal impairment as majority of the drug is eliminated renally.

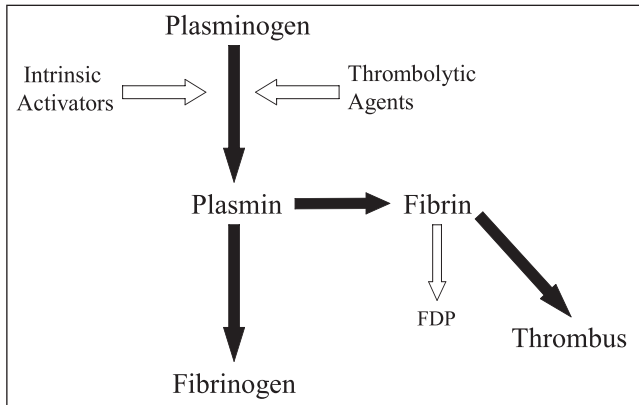
Tirofiban is a nonpeptide with a high affinity for the glycoprotein IIb/IIIa receptor. The plasma clearance of tirofiban is significantly decreased in patients with impaired renal function. Lamifiban is another nonpeptide glycoprotein IIb/IIIa receptor antagonist that is intravenously administered and reversible. Sibrafiban is an orally active prodrug that is converted to the active amidine compound in the liver.

If the patient's clinical condition permits, a delay of surgery for at least 12 h after administration of abciximab and 4 - 6 h after administration of eptifibatide or tirofiban would appear prudent. Prophylactic platelet transfusion may be useful to reduce bleeding after abciximab but is not efficacious in patients who have received eptifibatide or tirofiban. Literature concerning the safety of central neuraxial regional block in these patients is not available. Avoiding spinal or epidural anaesthesia in patients recently treated with glycoprotein IIb/IIIa inhibitors would appear wise.

THROMBOLYTIC (FIBRINOLYTIC) DRUGS

Thrombolytic agents accelerate and amplify the conversion of plasminogen to plasmin (Figure 3). They are used to restore vascular patency when given within 12 hours after a myocardial infarction. Their use in the immediate management of strokes is still controversial. Streptokinase and urokinase are first-generation thrombolytic drugs. Urokinase is less effective than streptokinase and its clinical usefulness is limited. Streptokinase, a nonenzymatic protein produced by β -haemolytic streptococci, is cleared rapidly from the circulation, with a half-life of 15 minutes.

FIGURE 3. SCHEMATIC REPRESENTATION OF THE FIBRINOLYTIC SYSTEM.



Anistreplase is a complex of human plasminogen and streptokinase that can be given as an intravenous bolus, whereas streptokinase must be given as an infusion. Newer thrombolytic agents, such as alteplase, duplase, reteplase and lanotreplase, are recombinant versions of the naturally occurring tissue plasminogen activator (tPA). Like tPA, their activity is markedly enhanced in the presence of fibrin. Because they are more active on fibrin-bound plasminogen than on free plasminogen in the plasma, they are referred to as 'clot-selective'. The main adverse effect of all these agents is bleeding.

ANTIFIBRINOLYTIC AGENTS

TRANEXAMIC ACID

Tranexamic acid is a lysine analogue that inhibits the breakdown of cross-linked fibrin by plasmin (Figure 4). It improves haemostasis by a combination of inhibition of fibrinolysis, reduced release of tPA and preservation of platelet function. Concern about its adverse effects have centred upon the potential to produce or potentiate abnormal thrombus formation. However, there is no clear evidence of increased thrombosis with short-term administration.

FIGURE 4. MECHANISM OF ACTION OF TRANEXAMIC ACID

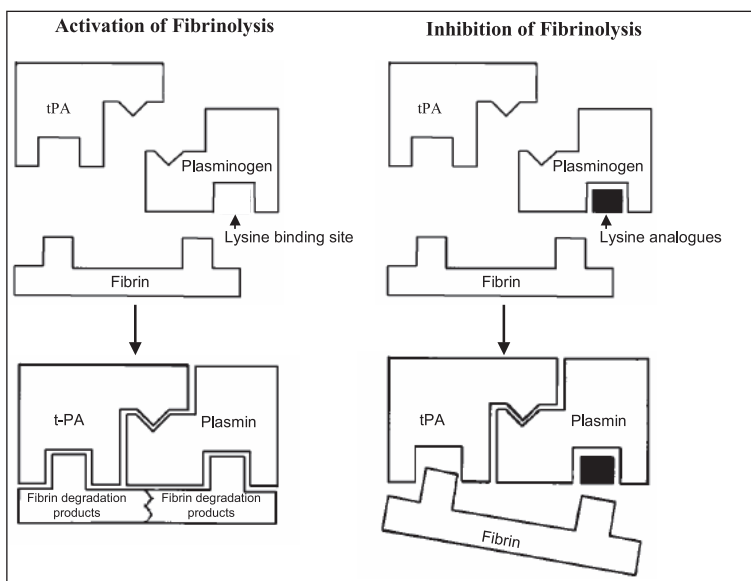


Figure 4. Antifibrinolytic action of the lysine analogues. Normally plasminogen binds to fibrin at a lysine binding site and is converted in the presence of tissue plasminogen activator (t-PA) to plasmin. The lysine analogues block the lysine binding site and prevent access of plasminogen to the fibrin molecule.

APROTININ

Aprotinin is a naturally occurring inhibitor of plasmin and kallikreins. It is only active by the intravenous route and is largely excreted by the kidney. Inhibition of plasmin and thrombin production is probably responsible for the preservation of platelet function and reduction in perioperative haemorrhage. Aprotinin is also effective in reducing transfusion requirements in patients on aspirin. High-dose aprotinin reduces bleeding by around 50% in open heart surgery, but its benefits in patients undergoing liver transplantation are less evident [14].

DESMOPRESSIN

Desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP) is a synthetic analogue of vasopressin. Its haemostatic effects are mediated via extra-renal vasopressin V₂ receptors. It has been used in the treatment of type I von Willebrand's disease, mild factor VIII deficiency (haemophilia A) and intrinsic platelet function defects for almost three decades. It increases platelet adhesiveness by mechanisms that are not fully understood, but may involve platelet von Willebrand factor and platelet GP IIb/IIIa receptors. Desmopressin shortens the bleeding time prolonged by drugs such as aspirin. It can be administered intravenously, subcutaneously or by intranasal spray. Because it does not interact with V₁ receptors desmopressin has virtually no vasoconstrictive effect. Although of minor value in reducing blood transfusion requirements in cardiac surgery, it may have some role in correcting the bleeding tendency in uraemic patients, which is in part due to acquired platelet dysfunction. Desmopressin is a potent anti-diuretic, but although water retention rarely occurs in clinical practice it should be used with caution in patients with congestive heart disease.

REFERENCES

1. Chong BH. Heparin-induced thrombocytopenia. *Br J Haematol* 1995;89:431-9.
2. Weitz JI, Bates SM. New anticoagulants. *J Thromb Haemost* 2005; 3:1843-53.
3. Nijkeuter M, Huisman MV. Pentasaccharides in the prophylaxis and treatment of venous thromboembolism: A systemic review. *Curr Op Pulmonary Med* 2004; 10:338-44.
4. Weitz JI, Hudoba M, Massel D, et al. Clot-bound thrombin is protected from inhibition by heparin-antithrombin III but is susceptible to inactivation by antithrombin III-independent inhibitors. *J Clin Invest* 1990; 86: 385-91.
5. Becker RC. Hirudin-based anticoagulant strategies for patients with suspected heparin-induced thrombocytopenia undergoing percutaneous coronary interventions and bypass grafting. *J Thromb Thrombolysis*. 2000;10 Suppl 1:59-68.
6. Latham P, Revelis AF, Joshi GP, et al. Use of recombinant hirudin in patients with heparin-induced thrombocytopenia with thrombosis requiring cardiopulmonary bypass. *Anesthesiology* 2000;92:263-6.
7. Kam PCA, Kaur N, Thong CL. Direct thrombin inhibitors: Pharmacology and clinical relevance. *Anaesthesia* 2005; 60: 565-74.
8. Francis CW. Direct thrombin inhibitors for treatment of heparin induced thrombocytopenia, deep vein thrombosis and atrial fibrillation. *Curr Pharm Des* 2005;11:3931-41.
9. Hyers TM. Heparin and other rapidly acting anticoagulants. *Semin Vasc Surg* 2005;18:130-3.
10. Bredberg E, Andersson TB, et al. Ximelagatran, an oral direct thrombin inhibitor, has a low potential for cytochrome P450-mediated drug-drug interactions. *Clin Pharmacokinet* 2003; 42: 765-77.
11. Eriksson BI, Dahl OE, Buller HR, et al. A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: the BISTRO II randomized trial. *J Thromb Haemost* 2005; 3: 103-11.
12. Eriksson BI, Dahl OE, Ahnfelt L, et al. Dose escalating safety study of a new oral direct thrombin inhibitor, dabigatran etexilate, in patients undergoing total hip replacement: BISTRO I. *J Thromb Haemost* 2004; 2: 1573-80.
13. Kam PCA, Egan MK. Platelet Glycoprotein IIb/IIIa Antagonists. *Pharmacology and Clinical Developments Anesthesiology* 2002; 96:1237-49.
14. Lentschener C, Roche K, Ozier Y. A review of aprotinin in orthotopic liver transplantation: can its harmful effects offset its beneficial effects? *Anesth Analg* 2005;100:1248-55.