Catheter thrombosis during primary percutaneous coronary intervention for acute ST elevation myocardial infarction despite subcutaneous low-molecular-weight heparin, acetylsalicylic acid, clopidogrel and abciximab pretreatment

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CE Buller, GE Pate, PW Armstrong, et al. Catheter thrombosis during primary percutaneous coronary intervention for acute ST elevation myocardial infarction despite subcutaneous low-molecular-weight heparin, acetylsalicylic acid, clopidogrel and abciximab pretreatment. Can J Cardiol 2006;22(6):511-515.

BACKGROUND: Subcutaneous enoxaparin is increasingly employed as the antithrombin of choice in non-ST elevation myocardial infarction and in conjunction with various fibrinolytic regimens in acute ST elevation myocardial infarction (STEMI). Few data exist describing the use of subcutaneous or intravenous enoxaparin as an anticoagulant in the highly thrombotic setting of primary percutaneous coronary intervention (PCI) for STEMI.

METHODS: The Which Early ST Elevation Therapy (WEST) study compared fibrinolysis (with and without early cardiac catheterization) with primary PCI in a setting that expedited both strategies on first medical contact. Patients assigned primary PCI are administered acetylsalicylic acid 325 mg, clopidogrel 300 mg and subcutaneous enoxaparin 1 mg/kg before transport to a PCI centre. Of 36 initial patients treated with primary PCI, three patients had procedures that were complicated by extensive thrombosis within coronary catheters and on PCI equipment.

RESULTS: Index cases were men aged 43 to 68 years who presented with confirmed STEMI and angiographically proven acute total or subtotal occlusion of a major epicardial coronary segment. During PCI, performed 76 min to 102 min following enoxaparin administration, a clot developed within the guide catheter or on the coronary guidewires and balloon catheter shafts, thus necessitating the replacement of all PCI equipment. In one case, there was evidence of continued intracoronary clot propagation and embolization.

CONCLUSION: A single, conventional, weight-adjusted dose of subcutaneous enoxaparin before expedited primary PCI for STEMI may not provide a reliable antithrombotic effect. Supplementary intravenous enoxaparin is now strongly recommended within the WEST study, and a substudy evaluating pre- and postprocedural antifactor Xa activity has been initiated.

Key Words: *Acute myocardial infarction; Angioplasty; Enoxaparin*

Thrombose sur cathéter en cours d'intervention coronarienne percutanée pratiquée d'emblée pour un infarctus aigu du myocarde avec sus-décalage du segment ST malgré l'administration préalable d'héparine de faible masse moléculaire par voie sous-cutanée, d'acide acétylsalicylique, de clopidogrel ou d'abciximab

CONTEXTE : L'énoxaparine est administrée de plus en plus souvent par voie sous-cutanée comme antithrombotique de première intention dans les cas d'infarctus du myocarde (IM) sans sus-décalage du segment ST et administrée en association avec des fibrinolytiques dans les cas d'IM avec sus-décalage du segment ST. Il existe toutefois peu de données sur l'utilisation de l'énoxaparine par voie sous-cutanée (s.c.) ou par voie intraveineuse (i.v.) comme anticoagulant dans le contexte fortement thrombogène des interventions coronariennes percutanées (ICP) pratiquées d'emblée pour un IM avec sus-décalage du segment ST.

MÉTHODE : L'étude *Which Early ST Elevation Therapy* (WEST) en cours vise à comparer le traitement fibrinolytique (avec ou sans cathétérisme cardiaque précoce) associé aux ICP pratiquées d'emblée dans un contexte qui appelle les deux stratégies dès la première consultation médicale. Les patients qui doivent subir une ICP d'emblée reçoivent 325 mg d'acide acétylsalicylique, 300 mg de clopidogrel et une dose d'énoxaparine administrée par voie s.c. à raison de 1 mg/kg avant le transport au centre d'ICP. Sur les 36 premiers patients qui ont été soumis à une ICP d'emblée, trois ont connu une intervention qui s'est compliquée d'une thrombose étendue dans les cathéters coronariens et sur le matériel d'ICP.

RÉSULTATS : Les cas de référence se composaient d'hommes âgés de 43 à 68 ans chez qui un IM avec sus-décalage du segment ST avait été diagnostiqué et qui présentaient à l'angiographie une occlusion totale ou subtotale d'un segment coronarien épicardique important. Au cours des ICP pratiquées de 76 à 102 min après l'administration d'énoxaparine, il y a eu formation d'un caillot dans le cathéter-guide ou sur les fils-guides et la tige des cathéters à ballonnet, nécessitant le remplacement de tout le matériel d'ICP. Dans un cas, il y avait même des signes de migration intracoronarienne continue du caillot et d'embolie.

CONCLUSION : L'injection d'une seule dose d'énoxoparine ordinaire, calculée en fonction du poids par voie s.c. en vue d'une ICP pratiquée d'emblée pour un IM avec sus-décalage du segment ST peut ne pas produire un effet antithrombotique fiable. Il est fortement recommandé maintenant, dans l'étude WEST, d'administrer des doses complémentaires d'énoxoparine par voie i.v., et les chercheurs ont entrepris une étude secondaire sur l'activité de l'antifacteur Xa avant et après l'intervention.

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Received for publication June 8, 2005. Accepted August 3, 2005.

Low-molecular-weight heparins, principally enoxaparin, are widely employed in the treatment of acute coronary syndromes (ACS) and are increasingly used during nonemergent percutaneous coronary intervention (PCI). Enoxaparin for primary PCI performed during evolving ST elevation myocardial infarction (STEMI) has not been systematically evaluated.

The Which Early ST Elevation Therapy (WEST) study is a randomized clinical trial comparing contemporary fibrinolysis (either with or without early catheter-based cointervention) with contemporary primary PCI. A key design feature is the expedited delivery of all reperfusion strategies through prehospital diagnosis and drug administration, and advance notification of PCI centres. In the WEST study, subcutaneous enoxaparin 1 mg/kg administered at first medical contact serves as the antithrombotic agent for both the fibrinolysis and primary PCI treatment arms.

An unexpected cluster of bulky, catheter-associated thrombi was observed in three patients assigned to primary PCI. These observations led to a recommendation to administer intravenous enoxaparin (0.3 mg/kg to 0.5 mg/kg) at the time of PCI and to a dedicated antifactor Xa activity substudy.

METHODS

The WEST study was a prospective, randomized, 300-patient study of regional STEMI care in four Canadian urban centres that compared contemporary fibrinolytic therapy with primary PCI reperfusion therapy (please see appendix). Patients with high-risk STEMI (4 mm or greater total ST deviation) were eligible if their first medical contact occured within 6 h of symptom onset in a prehospital setting, or at hospitals where primary PCI could not be performed within 60 min. Three strategies were tested: fibrinolysis with tenecteplase followed by usual care; tenecteplase followed by protocol-defined rescue PCI or routine early invasive management (within 24 h of presentation); and primary PCI. Reperfusion in each arm was expedited by diagnosis and initiation of therapy wherever first medical contact occurred.

Patients were administered acetylsalicylic acid (ASA) 160 mg to 325 mg orally and subcutaneous enoxaparin 1.0 mg/kg (capped at 100 mg) on enrollment. Those assigned primary PCI also received clopidogrel 300 mg orally and were then transported directly to the regional PCI centre where weight-adjusted abciximab (bolus plus infusion) was administered. The protocol permitted, but did not require, supplementary intravenous enoxaparin before PCI. Administration of unfractionated heparin (UFH) is proscribed. All participating PCI centres were high-volume provincial referral facilities with extensive experience performing PCI in various STEMI settings. The study was approved by the research ethics board at each participating institution, and all patients provided written informed consent.

Three cases of extraordinary, intraprocedural, catheter-associated thrombosis developing in patients enrolled in the WEST study and assigned to primary PCI were recognized and reported on a case-by-case basis to the Clinical Coordinating Centre by individual PCI operators or investigators. A systematic review of the first 36 patients treated in the primary PCI arm was undertaken by the Steering Committee and constitutes the basis of the present report.

CASE PRESENTATIONS

Case 1

A 68-year-old man with hypertension and type II diabetes presented to a community hospital emergency department with acute inferior STEMI and was enrolled in the WEST study 110 min following symptom onset. ASA, enoxaparin and clopidogrel were administered according to protocol before transport for primary PCI, and abciximab weight-adjusted bolus and infusion was initiated after arrival in the catheterization laboratory. The infarct-related artery (IRA) was determined to be the right coronary artery. A subtotal stenosis was associated with a suspected lesion-related thrombus and initial thrombolysis in myocardial infarction grade 1 flow. A guide catheter (6 French [Fr]) was inserted through the right femoral artery, with first balloon inflation occurring 76 min after enoxaparin administration. PCI balloon passage across the lesion was difficult and a second PCI guidewire was introduced. Extensive thrombus was observed within the guide catheter and proximal Y-connector, thus necessitating removal and replacement of all PCI equipment (90 min after enoxaparin and 14 min after the first inflation). New PCI equipment was introduced and, following initial IRA stent deployment, the no-reflow phenomenon was accompanied by hypotension and bradycardia requiring a temporary pacemaker. Additional anticoagulation with UFH 2000 U was administered (107 min after enoxaparin administration). Ultimately, five stents were deployed and there was evidence of a residual intraluminal thrombus with distal embolization at termination of the procedure. Recovery was prolonged (total hospitalization was 10 days) but event free.

Case 2

A 53-year-old man presented to the emergency department of a community hospital with acute anterior STEMI. Two episodes of polymorphic ventricular tachycardia requiring cardioversion occurred before enrollment and assignment to primary PCI occurred 58 min following symptom onset. ASA, enoxaparin and clopidogrel were administered according to protocol before transfer to the PCI centre, where abciximab was subsequently administered. During diagnostic angiography, a limited filling defect at the inlet of the infarct-related lesion was apparent. A guide catheter (6 Fr) was inserted through a right radial sheath with first balloon inflation occurring 84 min following initial enoxaparin. A second PCI guidewire was inserted in a diagonal branch followed by predilation and stent deployment in the left anterior descending. Following three more balloon inflations in the diagonal artery, a bulky clot developed on the guidewire proximal to the infarct-related lesion, thus requiring removal of PCI equipment (113 min after enoxaparin administration). New PCI equipment was inserted and intravenous UFH 7000 U was administered 126 min after initial enoxaparin with another 2000 U administered 21 min later.

Case 3

A 49-year-old man who was an active smoker with acute inferior STEMI was enrolled in the WEST study by the prehospital ambulance crew, assigned primary PCI and transferred to the PCI centre. In-field administration of ASA, enoxaparin and clopidogrel according to protocol was achieved. On arrival, hemodynamic deterioration with hypotension, bradycardia and respiratory distress was noted and the patient was intubated. In the catheterization laboratory, a temporary pacemaker was inserted and abciximab was administered. The IRA was the right coronary artery and initial IRA flow was thrombolysis in myocardial infarction grade 1. A guide catheter

TABLE 1
Patient characteristics and treatment variables

Patient characteristics	Patients randomly assigned to primary PCI (n=36)	Case 1	Case 2	Case 3
Sex	75% (27/36) men	Male	Male	Male
Age, years	61 (mean)	68	53	49
Weight, kg	85.3 (mean)	95	97	84
Body mass index, kg/m^2	29.1 (mean)	27.8	21	27.4
Diabetes	17% (6/36)	Yes	No	No
Prior myocardial infarction	11% (4/36)	No	No	No
Smoking status	36% (13/36) smoker 36% (13/36) ex-smoker	Ex-smoker	Ex-smoker	Smoker
Myocardial infarction location	39% (14/36) anterior 56% (20/36) inferior 22% (8/36) lateral 8% (3/36) apical 14% (5/36) posterior	Inferior	Anterior	Inferior
Killip Class preangiogram	100% (36/36) Class 1	1	1	1
Prehospital randomization	36% (13/36)	No	No	Yes
Infarct-related artery	RCA: 53% (19/36) LAD: 36% (13/36) CX: 5.5% (2/36) Other: 5.5% (2/36)	RCA	LAD	RCA
Baseline TIMI flow	TIMI 0: 47% TIMI 1: 28% TIMI 2: 11% TIMI 3: 14%	1	0	3
Baseline TIMI thrombus grade	Grade 0: 17% Grade 1: 11% Grade 2: 0% Grade 3: 17% Grade 4: 22% Grade 5: 33%	3	5	5
Time from symptom onset to randomization, min	144 (mean)	110	58	68
Enoxaparin subcutaneous dose, mg	83 (mean)	90	95	80
Time from enoxaparin administration to start of procedure, min	70 (median) (range 57 to 89)	61	73	76
Time from enoxaparin administration to first balloon inflation, min	70 (median) (range 64 to 103)	76	84	102
Time from randomization to abciximab, min	83 (median) (range 70 to 110)	84	60	110

CX Circumflex artery; LAD Left anterior descending artery; PCI Percutaneous coronary intervention; RCA Right coronary artery; TIMI Thrombolysis in myocardial infarction

(6 Fr) was inserted through a right femoral sheath. The first balloon inflation occurred 102 min after enoxaparin administration, with abciximab administered 7 min later. Thereafter, an extensive adherent thrombus was noted in the guide catheter and on guidewires and balloon shafts. All PCI equipment was removed and a bolus of intravenous enoxaparin 25.2 mg (0.3 mg/kg) was administered. New PCI equipment was inserted and the procedure was completed with stent implantation 121 min after initial subcutaneous enoxaparin.

Sample size precludes formal statistical comparison of index cases (n=3) with the overall cohort treated with primary PCI in the WEST study (n=36). The baseline characteristics and time intervals of index cases appear generally similar to the overall primary PCI cohort, although all three index cases presented earlier (from 58 min to 110 min from symptom onset to randomization) than the overall mean (144 min) (Table 1). The interval from enoxaparin administration to the start of the procedure for index cases spanned the overall median (case 1: 61 min; case 2: 73 min; case 3: 76 min; overall median 70 min).

DISCUSSION

Enoxaparin has an extensive safety and efficacy record in a variety of acute and invasive cardiac settings. Subcutaneous enoxaparin has been shown to be equivalent or superior to UFH for medical treatment of non-ST elevation ACS when combined with ASA or the platelet glycoprotein IIb/IIIa inhibitors eptifibatide and tirofiban (1-6). These and other studies have also established the safety of upstream and periprocedural, subcutaneous enoxaparin as the primary antithrombotic agent for PCI in patients with non-ST elevation ACS (7-9). In the setting of elective PCI, intravenous enoxaparin also appears to be safe and efficacious (7,10,11). A pivotal trial comparing intravenous enoxaparin with UFH for elective PCI (the Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention

Patients, an International Randomized Evaluation [STEEPLE]) recently completed enrollment. Enoxaparin has also been tested in combination with tenecteplase, the fibrinolytic agent we employed in the WEST study, and further data on enoxaparin compared with UFH plus fibrinolytics are expected to be forthcoming in the results of the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment Thrombolysis in Myocardial Infarction – Study 25 (ExTRACT-TIMI25) trial (12,13).

Enoxaparin was selected as the antithrombotic agent for the WEST study to provide consistency between treatment arms. Our subcutaneous regimen was chosen in view of concerns that excess bleeding in the Assessment of the Safety and Efficacy of a New Thrombolytic III (ASSENT-III Plus) trial (14) was related to the intravenous enoxaparin bolus. A subcutaneous agent also simplifies administration in the prehospital setting. Although a systematic evaluation of enoxaparin as the sole anticoagulant during primary PCI for evolving STEMI has not been reported, the controlled setting provided by a clinical trial (with an independent core angiographic laboratory and safety committee) was believed to be an appropriate setting for expanding its therapeutic envelope.

Although data specific to STEMI are lacking, the pharmacokinetic profile of subcutaneous enoxaparin appears to be similar in healthy individuals and those with unstable angina, with appropriate anticoagulation levels generally achieved 45 min to 60 min following administration (antifactor Xa greater than 0.5 U/mL) (15,16). The interval from enoxaparin administration until first balloon inflation exceeded these values in our index cases. However, all three cases were complex, with two patients experiencing significant hemodynamic compromise (one due to ventricular arrhythmia and the other due to progressive pump failure). It is possible that high sympathetic tone reduced cardiac output and subcutaneous vasoconstriction slowed enoxaparin absorption, resulting in inadequate serum levels when PCI procedures were commenced following a single dose.

Thrombi observed in our index cases were primarily characterized by thrombosis on PCI guidewires, balloons and within the guide catheters. Stouffer et al (17) observed guide-catheter thrombosis following intravascular ultrasound (IVUS) in two PCI patients pretreated with enoxaparin and eptifibatide. They subsequently demonstrated that IVUS markedly diminished antifactor Xa activity in an ex vivo whole blood model (17). IVUS was not, however, employed in our index cases. Madan et al (18) proposed differential activity against thrombus development on foreign surfaces as an explanation for three cases of enoxaparin-associated intraprocedural thrombosis observed in the Coronary disease Trial Investigating Outcome with Nifedipine GITS (ACTION). Enoxaparin has specific factor Xa inhibitory properties, a crucial factor in the contact and tissue factor activation pathways, while UFH acts with less specificity. Although an intriguing hypothesis, discrete separation of intrinsic and extrinsic pathways is artificial and has recently been questioned. Arguably, factor Xa inhibition represents an optimal intervention point because its activation is associated with a logarithmic increase in distal coagulation pathway activation (19). Enoxaparin has been shown to have an equivalent or enhanced anticoagulant effect to UFH both in vitro and ex vivo using multiple mediums (whole blood, platelet poor plasma and platelet-rich plasma) and methods of analysis (20,21). Moreover, retrospective analysis of central venous catheters in patients with hematological malignancy has demonstrated a lower rate of thrombosis with the use of low-molecular-weight heparins (16.6% catheter thrombosis with UFH versus 4.7% with enoxaparin) (22).

Limitations

We did not measure factor Xa activity in our patients. Formal assessments to rule out heparin-induced thrombocytopenia were not performed. Heparin-induced thrombocytopenia appears to be less common with low-molecular-weight heparins, and would not be expected to resolve following administration of additional enoxaparin or UFH (23). Although experienced PCI operators deemed these index cases extraordinary, attribution of the reported phenomenon of catheter-associated thrombus to the use of enoxaparin remains speculative.

CONCLUSIONS

Among 36 patients undergoing primary PCI in the WEST study, we observed three unexplained cases of thrombosis primarily that involved PCI equipment despite administration of ASA, clopidogrel, subcutaneous enoxaparin and abciximab. In response to the concerns arising, the WEST Steering Committee now strongly encourages administration of supplemental intravenous enoxaparin 0.3 mg/kg before protocol-specified primary PCI. A mechanistic substudy examining antifactor Xa levels before and after intravenous enoxaparin supplementation has been implemented.

APPENDIX: Halifax, Nova Scotia: IR Bata (MD); MV Hulan (RN); LL Magennis (RN), Queen Elizabeth II Health Sciences Centre. Edmonton, Alberta: RC Welsh (MD); AA Bjerkseth (RN), University of Alberta Hospital; PK Cheung (MD); L Kvill (RN), Royal Alexandra Hospital. Vancouver, British Columbia: JG Webb (MD); TM Kot (RN), St Paul's Hospital; CE Buller (MD); LME Tarry (RN), Vancouver Hospital. Montreal, Quebec: P Theroux (MD); N Gendron (RN), Montreal Heart Institute.

FUNDING: Funding was provided by Roche Canada and Aventis Pharma Inc.

REFERENCES

1. Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. N Engl J Med 1997;337:447-52.
2. Cohen M, Demers C, Gurfinkel EP, et al. Low-molecular-weight heparins in non-ST-segment elevation ischemia: The ESSENCE trial. Efficacy and Safety of Subcutaneous Enoxaparin versus intravenous unfractionated heparin, in non-Q-wave Coronary Events. Am J Cardiol 1998;82:19L-24L.
3. Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. Circulation 1999;100:1593-601.
4. Goodman SG, Fitchett D, Armstrong PW, Tan M, Langer A; Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment (INTERACT) Trial Investigators. Randomized evaluation of the safety and efficacy of enoxaparin versus unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes receiving the

glycoprotein IIb/IIIa inhibitor eptifibatide. Circulation 2003;107:238-44.
5. de Lemos JA, Blazing MA, Wiviott SD, et al. Enoxaparin versus unfractionated heparin in patients treated with tirofiban, aspirin and an early conservative initial management strategy: Results from the A phase of the A-to-Z trial. Eur Heart J 2004;25:1688-94.
6. Blazing MA, de Lemos JA, White HD, et al. Safety and efficacy of enoxaparin vs unfractionated heparin in patients with non-ST-segment elevation acute coronary syndromes who receive tirofiban and aspirin: A randomized controlled trial. JAMA 2004;292:55-64. (Erratum in 2004;292:1178).
7. Lee DS, Bhatt DL, Moliterno DJ, Peacock WF, Ellis SG, Topol EJ. The combination of enoxaparin, glycoprotein IIb/IIIa inhibitors and an early invasive approach among acute coronary syndrome patients. J Invasive Cardiol 2004;16:46-51.
8. Collet JP, Montalescot G, Lison L, et al. Percutaneous coronary intervention after subcutaneous enoxaparin pretreatment in patients with unstable angina pectoris. Circulation 2001;103:658-63.
9. Ferguson JJ, Antman EM, Bates ER, et al. Combining enoxaparin and glycoprotein IIb/IIIa antagonists for the treatment of acute coronary syndromes: Final results of the National Investigators Collaborating on Enoxaparin-3 (NICE-3) study. Am Heart J 2003;146:628-34.
10. Choussat R, Montalescot G, Collet JP, et al. A unique, low dose of intravenous enoxaparin in elective percutaneous coronary intervention. J Am Coll Cardiol 2002;40:1943-50.
11. Rabah MM, Premmereur J, Graham M, et al. Usefulness of intravenous enoxaparin for percutaneous coronary intervention in stable angina pectoris. Am J Cardiol 1999;84:1391-5.
12. Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: The ASSENT-3 randomised trial in acute myocardial infarction. Lancet 2001;358:605-13.
13. Antman EM, Louwerenburg HW, Baars HF, et al. Enoxaparin as adjunctive antithrombin therapy for ST-elevation myocardial infarction: Results of the ENTIRE-Thrombolysis in Myocardial Infarction (TIMI) 23 Trial. Circulation 2002;105:1642-9. (Erratum in 2002;105:2799).
14. Wallentin L, Goldstein P, Armstrong PW, et al. Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS randomized trial in acute myocardial infarction. Circulation 2003;108:135-42.
15. Gerotziafas GT, Zafiropoulos A, Van Dreden P, et al. Inhibition of factor VIIa generation and prothrombin activation by treatment with enoxaparin in patients with unstable angina. Br J Haematol 2003;120:611-7.
16. Argenti D, Hoppensteadt D, Heald D, Jensen B, Fareed J. Pharmacokinetics of enoxaparin in patients undergoing percutaneous coronary intervention with and without glycoprotein IIb/IIIa therapy. Am J Ther 2003;10:241-6.
17. Stouffer GA, Pathak A, Whinna HC, Ohman EM. Effect of multielement intravascular ultrasound on the anticoagulant potency of enoxaparin. Am J Cardiol 2004;93:1453-4.
18. Madan M, Radhakrishnan S, Reis M, et al. Comparison of enoxaparin versus heparin during elective percutaneous coronary intervention performed with either eptifibatide or tirofiban (the ACTION Trial). Am J Cardiol 2005;95:1295-301.
19. Buller HR. Factor Xa is a superior target to factor IIa for antithrombotic therapies. Semin Thromb Hemost 2003;29(Suppl 1):37.
20. Samama MM, Bara L, Gerotziafas GT. Mechanisms for the antithrombotic activity in man of low molecular weight heparins (LMWHs). Haemostasis 1994;24:105-17.
21. Fareed J, Hoppensteadt D, Walenga J, et al. Pharmacodynamic and pharmacokinetic properties of enoxaparin: Implications for clinical practice. Clin Pharmacokinet 2003;42:1043-57.
22. Cortelezzia A, Fracchiolla NS, Maisonneuve P, et al. Central venous catheter-related complications in patients with hematological malignancies: A retrospective analysis of risk factors and prophylactic measures. Leuk Lymphoma 2003;44:1495-501.
23. Fung KC, Chandar S, Brieger D. Heparin-induced thrombocytopenia. N Engl J Med 2001;345:619.