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Regular Article

Non-therapeutic anti-Xa levels in medical patients receiving anticoagulant therapy with enoxaparin☆,☆☆

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ABSTRACT

Introduction: Anticoagulant activity of enoxaparin is not routinely monitored even when previous studies have shown a high pharmacological variability. The aim of this study is to determine the prevalence of non-therapeutic anti-Xa levels among medical patients using enoxaparin as anticoagulant therapy and to point out potential risk factors related to the risk of having a sub-therapeutic level.
Materials and methods: Anti-Xa levels were measured in a cohort of sixty patients with medical indication for enoxaparin. Patients were categorized according to anti-Xa levels as follows: suboptimal anticoagulation (<0.5 IU/ml), optimal anticoagulation (between 0.5 and 1.2 IU/ml) or overanticoagulated (>1.2 IU/ml). Demographic and clinical variables and the use of concomitant medications were described for each group. Univariate and multivariate analysis were performed to assess the relationship between sub-optimal anticoagulation and potential predictive variables. A linear regression analysis was done to assess the relationship between anti-Xa activity, age, weight, body mass index, administered dose/weight and creatinine clearance.
Results: The mean anti-Xa activity was 0.71 ± 0.32 UI/ml. Thirty one percent of patients had anti-Xa levels out of the therapeutic range, most of them (twenty-eight percent of total population) with a sub-therapeutic level. None of the variables were associated with the risk of a sub-therapeutic anti-Xa level.
Conclusion: Almost one third of patients receiving enoxaparin had anti-Xa levels out of the therapeutic range. We need more studies to determine the clinical relevance of these findings.
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Introduction

Low-molecular-weight heparins (LWMH) are widely used in thromboembolic disorders because of their efficacy and security. After subcutaneous administration, LWMH do not bind to endothelium and exhibit a bioavailability of approximately 90% with a predictable anticoagulant response [1]. Enoxaparin sodium, a low-molecular-weight heparin, has a predictable pharmacokinetic profile allowing simplified dosing without the need for monitoring through laboratory tests, except for pregnant women, patients with extreme body weight and patients with creatinine clearance less than 30 ml/min [2,3].

However, several recent studies have shown altered pharmacokinetics of LMWH products in critically ill patients as well as in medical patients [4] leading to subtherapeutic plasma anti-Xa activity [5–8].

Moreover, a previous study reported an association between suboptimal anticoagulation with LMWH (anti-Xa activity < 0.5 IU/ml) in patients with acute coronary syndrome and an increased risk of early death and recurrent ischemic events at 30 days [9]. Similarly, several studies have revealed an increased risk of major bleeding in patients with high levels of anti-Xa [10]. For example, a study carried out in patients with an acute thromboembolic event showed an increased risk of bleeding using twice-a-day administration of enoxaparin, when anti-Xa level is above 0.8 – 1.0 IU/ml [11]. For these reasons it is possible to infer that determination of anti-Xa activity is an indirect method for the identification of patients who are at risk of bleeding or with a greater probability of new thromboembolic events.

Since many patients with medical conditions have a complex background of diseases and treatments, we hypothesized that they can exhibit a higher prevalence of non-therapeutic levels of anti-Xa than previously reported in clinical trials. These large trials have included homogeneous patients with several exclusion criteria not necessarily reflecting everyday practice.

Therefore, the aim of this prospective study was to determine the rate of patients with non-therapeutic anti-Xa levels while they are treated with enoxaparin in the context of an acute coronary syndrome and to investigate possible predictive factors influencing plasma anti-factor Xa levels.

Abbreviation: LMWH, Low-molecular-weight-heparin.

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Table 1
Baseline demographic and clinical characteristics of patients.

	All patients (n = 60)	Anti-Xa level		*P* value
		<0.5 IU/ml (n = 17)	Between 0.5 and 1.2 IU/ml (n = 41)	
Male gender (%)	32 (53.3)	10 (31.3)	22 (68.8)	0.59
Age, years	63.97 ± 15.0	62.12 ± 18.8	64.70 ± 13.4	0.55
Age > 65 years (%)	31 (51.2)	9 (29)	22 (71)	0.57
Body mass index (Kg/m2)	26.96 ± 5.4	26.53 ± 6.0	27.13 ± 5.2	0.70
Weight (Kg)	71.04 ± 15.6	70.06 ± 16.1	71.43 ± 15.6	0.76
Enoxaparin dose (mg/Kg)	0.96 ± 0.19	0.98 ± 0.22	0.96 ± 0.17	0.70
Diabetes mellitus (%)	12 (20.0)	5 (41.7)	7 (58.3)	0.25
Hypertension (%)	40 (66.7)	11 (27.5)	29 (72.5)	0.84
Prior history of myocardial infarction (%)	40 (66.7)	11 (27.5)	29 (72.5)	0.84
Cardiac failure (NYHA III-IV) (%)	7 (11.7)	4 (57.1)	3 (42.9)	0.09
Creatinine clearance (ml/min)	65.88 ± 27.9	69.58 ± 32.9	64.42 ± 25.9	0.52

Materials and methods

This was a single-centre, prospective, observational study carried out in hospitalized patients admitted to the cardiology and internal medicine section in San Jose, Costa Rica. The study protocol and consent form were approved by the local institutional review board and ethics committee (CLOBI-HSJD 2009-27). All subjects or an appropriate surrogate provided written informed consent before any study-related procedure was completed.

Subjects

Patients older than 18 years of age were evaluated for enrolment. We selected patients admitted for unstable angina and myocardial infarction treated with fully daily dose (1 mg/kg bid) of enoxaparin (Clexane ® Sanofi-Aventis, France). Patients were excluded from study participation if they met any of the following criteria: an estimated creatinine clearance less than 30 ml/min (assessed by the Cockcroft-Gault equation), extreme obesity defined by a body mass index greater than 50 or body weight greater than 150 kg based upon admission weight, previous use of heparin or any LMWH within 48 hours of study participation. Demographic and clinical data were collected on each patient including: age, weight, height, comorbidities, creatinine clearance and concomitant treatments.

Anti Xa activity

The anti-Xa activity was measured after patients had received at least two subcutaneous injections of enoxaparin. Blood samples for peak serum anti-Xa activity were obtained in the morning, approximately 4 h after enoxaparin injection in Vacutainer tubes containing sodium citrate 0.129 M. Samples were immediately transported to the laboratory at ambient temperature (18 – 22 °C). All of the specimens were processed within approximately 1 hour after collection.

Blood samples were centrifugated at 3000 g for 15 min at 4 °C. Plasma samples not tested immediately were separated into cryovials and stored at -70 °C until ready for testing. Plasma anti-Xa activity was determined using a colorimetric assay with the specific chromogenic substrate and bovine factor Xa as reagents (Diagnostica Stago, France).

The anticoagulation status was categorized based on previous recommendations as follows: normal therapeutic range if anti-Xa activity was between 0.5 and 1.2 IU/ml; subtherapeutic level if the anti-Xa activity was less than 0.5 IU/ml, and supratherapeutic levels if it was greater than 1.2 IU/ml.

Statistical analysis

A sample size of sixty patients was calculated based on an expected percentage of 13% of patients with an anti-Xa activity outside the therapeutic range. This sample size reaches a two-sided 95% confidence interval with a range of ± 8%. Continuous variables are presented as mean ± SD and they were compared using a t-student test. Categorical variables are presented as percentages and they were analysed by chi-square test or Fisher`s exact test when applicable. We performed a logistic regression analysis with the subtherapeutic data to assess the relationship between subtherapeutic levels of anti-Xa activity and the medical diagnosis of diabetes mellitus, age > 65 years, body mass index and a creatinine clearance < 40 ml/min as explanatory variables. We summarized overall calibration using a Hosmer-Lemeshow goodness of fit test. A stepwise approach was performed to build this

Table 2
Concomitant treatment of patients with acute coronary syndrome using enoxaparin as anticoagulant therapy.

	All patients (n = 60)	Anti-Xa level		*P* value
		<0.5 IU/ml (n = 17)	≥0.5 IU/ml and < 1.2 IU/ml (n = 41)	
Aspirin (%)	43 (71.7)	11 (25.6)	32 (74.4)	0.45
Clopidogrel (%)	45 (75)	11 (24.4)	34 (75.6)	0.25
Protom pump inhibitor (%)	7 (11,7)	0 (0)	7 (100)	0.08
Warfarin (%)	7 (11.7)	4 (42.9)	3 (57.1)	0.36
H2 antagonist (%)	44 (73.3)	13 (29.5)	31 (70.5)	0.73
Statin (%)	45 (75)	12 (26.7)	33 (73.3)	0.86
Beta blocker (%)	33 (55)	7 (21.2)	26 (78.8)	0.18
ACEI (%)	37 (61.7)	9 (24.3)	28 (75.7)	0.38
ARB (%)	12 (20)	3 (25)	9 (75)	0.54
Calcium channel blocker (%)	9 (15)	4 (44.4)	5 (55.6)	0.25
Hydrochlorotiazide (%)	7 (11.7)	2 (28.6)	5 (71.4)	0.65
Furosemide (%)	7 (11.7)	3 (42.9)	4 (57.1)	0.31

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