

Anti-factor Xa Activity of Enoxaparin for Thromboprophylaxis in Nonsurgical Patients Is Dependent on Body Mass

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OBJECTIVE: Thromboprophylaxis with fixed doses of low molecular weight heparin is recommended for hospitalized acutely ill medical patients. The purpose of this study was to assess whether the anti-factor Xa (anti-Xa) activity of enoxaparin prescribed for venous thromboembolism prophylaxis depends on body mass index (BMI) in patients hospitalized for an acute respiratory disease.

PATIENTS AND METHODS: All patients admitted by the respiratory medicine department (January-December 2006) for an acute respiratory disease, and for whom pharmacologic thromboprophylaxis was indicated, were included in the study. Anti-Xa activity was measured 4 hours after administration of enoxaparin on the third day of hospitalization. The primary outcome was anti-Xa activity in relation to BMI.

RESULTS: One hundred twelve patients were enrolled. Mean anti-Xa activity decreased with each BMI quartile (0.28, 0.23, 0.15 and 0.13 U/mL for quartiles 1, 2, 3, and 4, respectively). In the multivariate analysis, BMI was the only predictor of inadequate anti-Xa activity (odds ratio, 1.14; 95% confidence interval, 1.05-1.24; $P < .002$) after adjustment for age, sex, and serum creatinine concentration. Two episodes of symptomatic proximal deep vein thrombosis were observed in the month after hospitalization; both were in patients who had inadequate anti-Xa activity.

CONCLUSIONS: Anti-Xa activity is dependent on BMI in hospitalized acute medical patients receiving enoxaparin for thromboprophylaxis.

Key words: Enoxaparin. Thromboprophylaxis. Acute medical condition.

La actividad anti-Xa depende del peso en pacientes médicos que reciben tromboprofilaxis con enoxaparina

OBJETIVO: Se recomienda la tromboprofilaxis con heparina de bajo peso molecular a dosis fijas en pacientes médicos agudos que requieran ingreso hospitalario. El objetivo de este estudio ha sido determinar si la actividad antifactor Xa de la enoxaparina depende del peso corporal cuando se administra a pacientes hospitalizados por un proceso respiratorio agudo como profilaxis de la enfermedad tromboembólica venosa.

PACIENTES Y MÉTODOS: Se incluyó prospectivamente en el estudio a todos los pacientes ingresados en el Servicio de Neumología entre enero y diciembre de 2006 por un proceso respiratorio agudo con indicación de tromboprofilaxis farmacológica. Se determinó la actividad anti-Xa 4 h después de la administración de la enoxaparina, en el tercer día de ingreso hospitalario. El criterio de evaluación principal fue la actividad anti-Xa en función del índice de masa corporal (IMC).

RESULTADOS: Se incluyó a 112 pacientes en el estudio. La actividad anti-Xa media disminuyó a medida que aumentaban los cuartiles de IMC (0,28, 0,23, 0,15 y 0,13 U/ml para los cuartiles 1, 2, 3 y 4, respectivamente). En el análisis multivariable, el IMC fue la única variable predictora de actividad anti-Xa insuficiente (*odds ratio* = 1,14; intervalo de confianza del 95%, 1,05-1,24; $p < 0,002$), después de ajustar por la edad, el sexo y la creatinina sérica. Hubo 2 episodios sintomáticos de trombosis venosa profunda proximal en el mes posterior al ingreso hospitalario, ambos en pacientes con actividad anti-Xa insuficiente.

CONCLUSIONES: La actividad anti-Xa de la enoxaparina depende del IMC en los pacientes que reciben tromboprofilaxis por un proceso médico agudo que requiera hospitalización.

Palabras clave: Enoxaparina. Tromboprofilaxis. Proceso médico agudo.

Introduction

Low molecular weight heparins (LMWHs) are now the treatment of choice for venous thromboembolic disease.¹ Peak anti-factor Xa (anti-Xa) activity occurs 3 to 5 hours after subcutaneous injection of LMWHs and the efficacy and safety of these drugs, unlike the effect of unfractionated heparin, rest on the predictability of their action when dosages are adjusted for weight.²

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Two clinical trials have shown that hospitalized acutely ill medical patients have a risk of venous thromboembolism that is not negligible, and that administering a fixed dose of a LMWH (not based on weight) significantly reduces that risk.^{3,4} In those trials, however, the benefits of pharmacologic thromboprophylaxis were not maintained in the subgroups of obese patients.^{5,6} Moreover, although such treatment is not given to a considerable proportion of nonsurgical patients,⁷ in fact most thrombotic episodes occur in patients who are so treated but in whom preventive measures have failed.⁸

LMWHs have a limited ability to prolong activated partial thromboplastin time,^{9,11} and that variable is therefore not recommended for monitoring the effect of therapy. The measurement that is recommended for confirming anticoagulant response to LMWH treatment is anti-Xa activity.¹² It has been suggested that levels should be monitored in patients who are obese, pregnant, or suffering from renal insufficiency.¹³⁻¹⁶

We therefore proposed to carry out a pharmacokinetic study in patients hospitalized for an acute respiratory disease who were receiving enoxaparin for thromboprophylaxis in order to assess variations in anti-Xa activity according to weight. We also aimed to identify factors associated with that variability.

Patients and Methods

Design, Patients, and Inclusion Criteria

A prospective cohort study was carried out in a tertiary university hospital from January through December 2006. All patients admitted by the respiratory medicine department for acute respiratory disease, and for whom prophylactic enoxaparin was indicated, were enrolled.¹⁷ Patients requiring curative anticoagulation therapy were excluded. Also excluded were patients with contraindications for LMWH therapy (eg, active bleeding or at high risk of bleeding). The study was approved by our hospital's ethics committee and all patients gave their consent to participation.

Interventions

All patients received a daily subcutaneous injection of 40 mg of enoxaparin (Clexane, Sanofi-Aventis, Barcelona, Spain). The mean (SD) prescribed duration of enoxaparin therapy was 10 (4) days. Anti-Xa activity was measured 4 hours after administration¹⁰ on the third day of hospitalization. Doses were not adjusted on the basis of the results of anti-Xa testing.

Anti-Xa Activity

Blood was extracted into a citrate collection tube, centrifuged at 2000g for 20 minutes, and stored at -20°C. Anti-Xa activity was assessed using a Berichrom heparin kit (Dade-Behring, Liederbach, Germany). The anti-Xa range for prophylaxis was considered to be between 0.2 and 0.6 U/mL; the therapeutic range was defined as between 0.6 and 1.0 U/mL.¹⁸⁻²⁰

Episodes Analyzed

The main variable of interest was the relationship between anti-Xa activity and body mass index (BMI). Of secondary interest were the incidences of objectively confirmed thrombotic

episodes and significant bleeding in the month following hospitalization.

Statistical Analysis

Continuous variables were expressed as mean (SD) and compared using the *t* test for paired or unpaired data. Categorical variables were expressed as percentages and compared with the χ^2 test or the Fisher exact test if required. BMI, age, sex, and serum creatinine values were entered into a logistic regression model for multivariate analysis. Values of *P* < .05 were considered to be statistically significant. The analyses were performed with the SPSS statistical package for Windows, version 13 (SPSS Inc, Chicago, Illinois, USA).

Results

Patients

We enrolled 112 patients who were admitted to the respiratory medicine department of Hospital Ramón y Cajal from January through December 2006 because of an acute respiratory disease. All met the criteria for pharmacologic prophylaxis. The patients' baseline characteristics are shown in Table 1. Their mean age was 72 years and 25% were aged over 80 years. Most were men. Twenty-one percent were obese and on admission 9% had renal insufficiency (serum creatinine concentration >1.5 mg/dL). The mean duration of thromboprophylaxis was 7 days.

Anti-Xa Activity

Anti-Xa activity was below the level considered adequate for thromboprophylaxis in 62 of the 112 patients (55%). Mean anti-Xa activity (Table 2) was significantly lower in patients in the highest BMI quartile (*P* < .001). This relationship persisted when the patients were grouped by BMI deciles, although the data did not adopt a U-shaped pattern on distribution (Figure).

TABLE 1
Baseline Characteristics of the 112 Patients^a

Age, y	
Mean (SD)	72 (13)
Median	75
Sex, women	28 (25%)
Weight, kg	
Mean (SD)	70 (15)
Median	70
Obesity, BMI >30 kg/m ²	24 (21%)
Serum creatinine, mean (SD), mg/dL	1.16 (0.3)
Risk factors for bleeding	
Hypertension	68 (61%)
Diabetes	22 (20%)
Cancer	18 (16%)
Concomitant medication	
Antiplatelets	32 (29%)
Corticosteroids	75 (67%)
Nonsteroidal anti-inflammatory drugs	6 (5%)
Duration of prophylaxis, d	
Mean (SD)	7 (2)
Median	6

Abbreviation: BMI, body mass index.

^aData are numbers of patients and percentages unless otherwise indicated.

TABLE 2
Mean Anti-factor Xa Activity by Body Mass Index Quartiles^a

	Body Mass Index, kg/m ²			
	1st Quartile (<23.04)	2nd Quartile (23.04-25.95)	3rd Quartile (25.96-29.61)	4th Quartile (>29.61)
No. of patients	29	29	26	28
Age, y	72 (14)	76 (12)	70 (13)	71 (14)
Sex, female, n (%)	8 (28)	4 (14)	8 (31)	8 (29)
Serum creatinine, mg/dL	1.19 (0.30)	1.22 (0.43)	1.08 (0.16)	1.13 (0.25)
Anti-factor Xa activity, U/mL	0.28 (0.23)	0.23 (0.35)	0.15 (0.09)	0.13 (0.11)

^aData are presented as the mean (SD) unless otherwise indicated.

Only BMI was significantly associated with anti-Xa activity (odds ratio, 1.14; 95% confidence interval, 1.05-1.24; $P < .002$) after adjustment for age, sex, and serum creatine concentration.

Thrombotic and Hemorrhagic Episodes

No major bleeding occurred during the follow-up period. Two episodes of proximal deep vein thrombosis were recorded in the month after hospitalization. Both occurred in patients for whom measured anti-Xa activity had been classified as inadequate.

Discussion

Two main conclusions can be drawn from this study. The first is that the anti-Xa activity of enoxaparin bears an inverse relation to the BMI of patients receiving thromboprophylaxis while hospitalized for an acute respiratory disease. The second is that anti-Xa activity is

lower than the level considered to be preventive when the patient's BMI is above 26 kg/m².

The relationship between the pharmacokinetic parameters of LMWHs and body weight is well known in the context of treatment for venous thromboembolic disease.¹ However, this relationship has been less studied in nonsurgical patients receiving these drugs as a preventive measure. Our results indicate that the anti-Xa activity of enoxaparin administered in this setting is dependent on body mass. These results are similar to those of a study in obese surgical patients²¹ and another study in patients admitted to an intensive care unit.²² However, a statistically significant correlation does not necessarily mean there is a clinically significant effect.

Results from clinical studies have been inconsistent with regard to the correlation between anti-Xa activity and clinical events in patients receiving LMWHs either for prophylaxis or for treatment of thromboembolic disease.²³⁻²⁸ In patients receiving prophylactic treatment for hip replacement surgery, Levine and coworkers²⁷ saw a

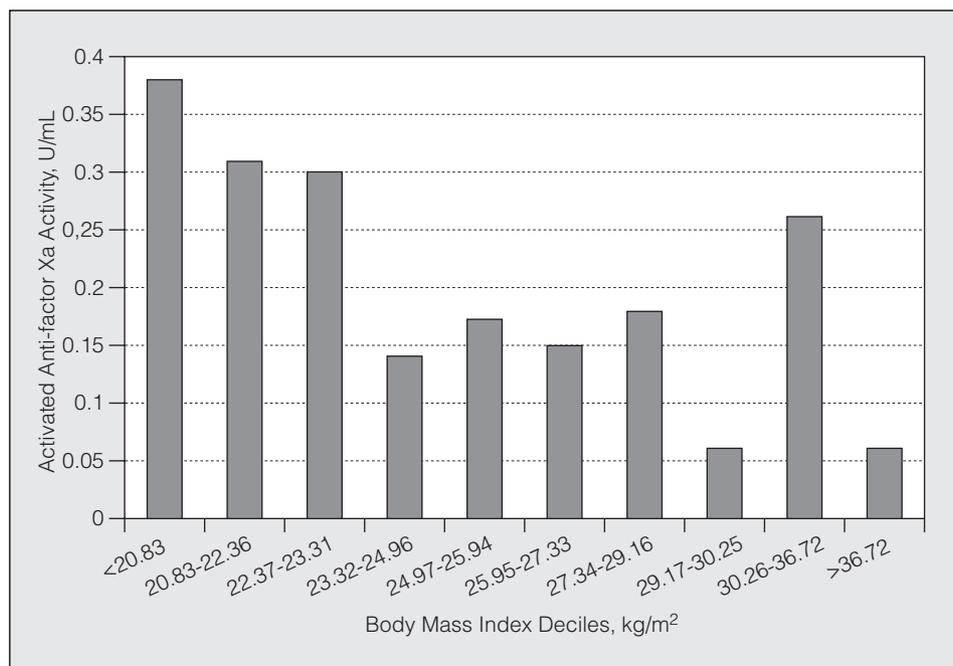


Figure. Anti-factor Xa activity distributed by body mass index deciles.

significant association between anti-Xa activity and the incidence of deep vein thrombosis detected by venography or surgical wound hematomas. Other authors have demonstrated very weak associations when studying patients who underwent general surgery,^{25,26} and some have seen no correlation at all.^{23,29}

Our study has certain limitations to consider. The ranges we set for effective anti-Xa activity for the prevention and treatment of venous thromboembolism with enoxaparin have not been validated in prospective studies. Furthermore, our patient series was small and few clinical events were recorded, so it was not possible to determine whether the lower anti-Xa activity observed in obese patients actually increased their risk of thrombosis. Finally, most patients in this study had normal kidney function. Our results therefore cannot be generalized to patients with low creatinine clearance.

In conclusion, the anti-Xa activity of enoxaparin administered for prophylaxis depends on the BMI of acutely ill patients. Well-designed studies are needed to analyze whether this finding implies there is likely to be a higher incidence of thrombotic episodes in such patients.

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