Low Molecular Weight Heparin for the Prevention of Deep Venous Thrombosis: A Suitable Monitoring in Elderly Patients?

Isabelle Mahé^a Ludovic Drouet^b Olivier Chassany^a Anne-Sophie Grenard^a
Charles Caulin^a Jean-François Bergmann^a

^aService Médecine A, et ^bLaboratoire d'Hématologie Biologique, Hôpital Lariboisière, Paris, France

Key Words

Low molecular weight heparin · Deep vein thrombosis · Elderly · Anti-Xa activity

Abstract

Monitoring of anti-Xa activity (aXa) levels is not routinely required in patients receiving enoxaparin at prophylactic dosages, since aXa is supposed to stay below the manufacturer's recommended range in patients treated for venous thrombosis (0.5–1 IU/ml). In order to aXa in elderly subjects receiving prophylactic enoxaparin, 68 consecutive patients (mean age 82.5 ± 10.7 years) hospitalized in a medical department receiving 4,000 IU enoxaparin daily subcutaneously for the prevention of venous thromboembolic disease were studied. After the first injection of enoxaparin, the aXa of 57.4% patients was superior to 0.5 IU/ml while 69.4% had an aXa higher than 0.5 after 8.4 ± 1.2 days. A negative relationship between aXa and body weight and a trend towards a positive correlation between aXa and age but not with creatinine clearance were noted. Our findings question the opportunity to monitor aXa in elderly patients receiving 4,000 IU enoxaparin as antithrombotic prophylaxis.

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Introduction

Low molecular weight heparins (LMWH) are widely used because of the recent marked expansion of the indications and the more convenient use than unfractionated heparin. Enoxaparin 4,000 IU subcutaneously is recommended for the prophylaxis of deep vein thrombosis (DVT) in orthopedic surgical patients [1]. It is also recommended in medical high risk since the results of the MEDENOX trial, a placebo-controlled double-blind randomized trial that showed that enoxaparin 4,000 IU significantly reduced the incidence of thromboembolic events and phlebographic DVT in recently hospitalized medical patients [2]. Following the publication of several reports and surveys, the bleeding risk of prophylactic LMWH is now recognized [1, 3, 4]. Age has been identified as a predisposing factor of heparin-related bleeding [5, 6].

Anti-Xa activity (aXa) assays are the most accurate method of monitoring anticoagulant response to LMWH therapy [1]. Associations between aXa levels and antithrombotic activity have been reported, but not substantiated in all studies [7–9]. Monitoring of aXa levels is not routinely required for patients receiving LMWH therapy at prophylactic dosages since aXa is supposed to stay below the manufacturer's recommended range (0.5–1 IU/ml) generated by enoxaparin delivered at the dose required to treat a patient presenting with venous thrombosis [1].

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Dr. Isabelle Mahé
Service Médecine A, Hôpital Lariboisière
2, rue Ambroise-Paré
F-75010 Paris (France)
Tel. +33 1 49 95 63 42, Fax +33 1 49 95 84 46, E-Mail isabelle.mahé@lrb.ap-hop-paris.fr

In medical situations, the only validated efficient dose of enoxaparin is 4,000 IU, but medical patients are often old with various risk factors for hemorrhage. The present study was designed to assess the characteristics of the plasma aXa in elderly hospitalized subjects receiving enoxaparin by subcutaneous injection at the 4,000 IU dose recommended for the prophylaxis of DVT.

Patients and Methods

Sixty-eight consecutive patients hospitalized in our Department of Internal Medicine (Lariboisière Hospital, Paris, France) and requiring 4,000 IU enoxaparin daily subcutaneously for the prevention of DVT were included after informed consent. The prescription was in accordance with the approved indication of the drug. Baseline clinical and biological characteristics (creatinine clearance was calculated using the Cockcroft formula), bleeding risk factors, body weight, concomitant therapies were recorded.

Blood samples for the determination of aXa were collected at peak level (4 h after the injection of enoxaparin) [1] and analysed by the same laboratory. aXa was determined using the Stachrom-heparin™ kit fitted to an automated reader (STA) and calibration curves obtained using Heparorm HBPM (Diagnostica Stago, Asnières, France). This system is submitted to quality control and regularly checked by regional and national quality control.

aXa was measured in all patients at the beginning of the treatment (day 1 or 2) and, in subjects who were still receiving enoxaparin, after 1 week of treatment. Statistical analysis was performed using analysis of variance. A *p* value below 0.05 was considered significant.

The manufacturer's recommended range of aXa for patients on enoxaparin for thrombosis is 0.5–1 IU/ml. We hypothesized that to observe a significant proportion of patients (30%) on this regimen with aXa levels higher than 0.5 IU/ml, 60 subjects would be necessary.

Results

Sixty-eight patients participated in the study (mean age 82.5 ± 10.7 years, mean body weight 59.6 ± 13.3 kg, mean creatinine clearance 95.7 ± 57.5 ml/min). The first aXa measurement was performed 4 h after the first or the second injection of enoxaparin; the mean duration of enoxaparin therapy was 1.5 ± 0.9 days. Mean aXa was 0.52 ± 0.20 IU/ml. The percentage of patients with aXa greater than 0.5 IU/ml was 57.4% while 2 patients had an aXa superior to 1 IU/ml. The individual values of aXa are given in figure 1 and 2.

The second aXa measurement was performed in 36 patients after a mean duration of enoxaparin therapy of 8.4 ± 1.2 days. Mean aXa was 0.61 ± 0.18 IU/ml. The proportion of patients with aXa greater than 0.5 IU/ml was 69.4% and aXa was above 1 IU/ml in 1 patient. Thirty-two patients had only 1 aXa measurement for the fol-

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Fig. 1. Correlation between aXa and body weight.

Fig. 2. Correlation between aXa and age.

lowing reasons: change in the enoxaparin dosage (*n* = 8), discontinuation of the therapy (*n* = 20), death (*n* = 2), hemorrhagic event (*n* = 2).

A negative relationship between aXa and body weight (*p* = 0.0009) (fig. 1) and a trend towards a positive correlation between aXa and age (*p* = 0.09) were noted (fig. 2), but not with the corrected creatinine clearance (*p* = 0.20).

Discussion

The main finding of our study in an elderly population is that soon after the initiation of enoxaparin (1.5 ± 0.9 days) at a prophylactic dosage (4,000 IU), peak aXa was higher than 0.5 IU/ml in nearly 60% of the patients (and 1 IU/ml in nearly 3% of patients). Several factors might contribute to explain these high aXa levels: lower body weight, renal dysfunction, age [3, 4]. These results are not

in accordance with the aXa measurements performed in a subset of patients included in the MEDENOX trial ($n = 68$): mean aXa at the end of the treatment (day 10 ± 4 days) in the enoxaparin 4,000 IU group was 0.41 IU/ml with no patient with aXa above 0.5 IU/ml [10].

As other authors reporting on LMWH at prophylactic dosages, we found that aXa might inversely correlate with body weight [11–13]. Although a physiological reduction in renal function related to aging is reported to induce accumulation after repeated administration of LMWH [12], no correlation between aXa and creatinine clearance could be established in our study as in the MEDENOX trial. This may be due to the fact that the rate of accumulation remains moderate in elderly subjects who have normal renal function for their age and is believed to have no clinical relevance [14].

The age of patients receiving LMWH might be important to consider because it is associated with an increased hemorrhagic risk [5, 6]. Some authors reported a tendency to accumulate aXa in elderly subjects [14, 15]; we observed a tendency to a correlation between aXa and age, while no correlation could be established in a subset of patients included in the MEDENOX trial. This might be due to the different characteristics of the patients included in the studies: both were medical patients who were going to stay in the hospital for at least 6 days,

but the age was quite different (74.1 ± 10.6 in the MEDENOX trial vs. 82.5 ± 10.7 years in our study). Put together this suggests that higher aXa levels might occur with increasing age.

Our findings suggest that the modalities of an optimal prophylactic treatment for thromboembolism in elderly patients may have to be revised. In the MEDENOX study, 4,000 IU was the only efficient dosage of enoxaparin for the prevention of DVT [2] while inducing a dose-dependent increase in aXa independently of other factors [10]. Our study performed in older patients shows that there is a wide interindividual variability of aXa in patients receiving enoxaparin 4,000 IU for 2 days. The fact is that in a substantial subset of patients (more than 60%) aXa reaches the range which is usually recommended if the patient is receiving enoxaparin to treat a DVT; these patients might be at increased hemorrhagic risk. On the other hand, reducing the dose of enoxaparin in elderly patient might reduce the therapeutic benefit observed.

Older patients are at increased risk for both thromboembolic and hemorrhagic events. Although it is currently not recommended to monitor aXa in patients receiving LMWH for the prevention of DVT, our results suggest that aXa should indeed be monitored in elderly subjects to avoid overdose.

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