The anti-factor Xa range for low molecular weight heparin thromboprophylaxis

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Abstract

Low molecular weight heparins (LMWHs) are now the mainstay option in the prevention and treatment of venous thromboembolism. In some patients receiving therapeutic doses of LMWH, activity can be measured by quantifying the presence of Anti-factor Xa (AFXa) for dose adjustment. However, currently there are no guidelines for LMWH monitoring in patients on thromboprophylactic, doses, despite certain patient populations may be at risk of suboptimal dosing. This review found that while the AFXa ranges for therapeutic levels of LMWHs are relatively well defined in the literature, prophylactic ranges are much less clear, thus making it difficult to interpret current research data. From the studies published to date, we concluded that a reasonable AFXa target range for LMWH deep venous thromboses prophylaxis might be 0.2-0.5 IU/mL.

Introduction

Low molecular weight heparins (LMWHs) have now largely replaced unfractionated heparin (UFH) in the prevention and treatment of venous thromboembolism (VTE) due to ease of administration and a more predictable pharmacokinetic profile.[1,2] However, certain patient demographics were not included in the early randomized trials of LMWHs which demonstrated the efficacy and safety of the recommended dose regimens. These groups are the obese [Body Mass Index (BMI)>50 kg/m^2], pregnant and renally impaired (creatinine clearance <30 mL/min) patient populations.[3-5] For this reason, it has been recommended to monitor the activity of Anti-factor Xa (AFXa) for dosage adjustment purposes in these patients receiving a therapeutic LMWH.[1-4,6,7] Currently, there are no guidelines to monitor LMWH in patients on thromboprophylactic doses. In adult patients, the standard fixed dosing schedule is applied to all patients with no recommendation to monitor the AFXa activity. However, several studies have suggested that a standard dose may not achieve optimal thromboprophylaxis in certain patient groups.[4,8-13] While the AFXa ranges for therapeutic levels of LMWHs are relatively well defined in the literature, prophylactic ranges are much less clear. The aim of this review is to evaluate the current data on AFXa target levels in particular in patients receiving thromboprophylactic doses of LMWH.

Anti-factor Xa assays

LMWH predominantly acts on Factor Xa, unlike UFH which exerts its effect on both Factor II and Factor Xa. For this reason, LMWH activity is monitored using serum AFXa levels instead of activated Partial Thromboplastin Time (aPTT). The Peak AFXa level is reached 3-5 hours after administration. Most laboratories use a chromogenic based assay.[1,5,14]

In this assay, a defined quantity of AFXa is added to the patient's plasma and the residual AFXa is measured using a chromogenic substrate. This is then quantified using a standard reference curve constructed using known amounts of AFXa.[14,15]

Therapeutic anti-factor Xa ranges

Target AFXa ranges for therapeutic doses of LMWHs have been relatively well defined in previous studies.[1,4,5,16-18] For twice daily and once daily dosing of subcutaneous enoxaparin, peak AFXa levels of between 0.6-1.0 IU/mL and 1.0-2.0 IU/mL have been suggested respectively.[1,4,16] It has been proposed that ranges between LMWHs may be sufficiently similar to aim for a standardized target range.[17] However, there are significant differences in target levels between various LMWHs at therapeutic doses (Table 1).

Prophylactic anti-factor Xa ranges

A target AFXa range for prophylactic doses of LMWH is not well defined due to a lack of supporting evidence.[4-6] In 1991, Leyvraz *et al.*[19] demonstrated non-inferiority between LMWH and UFH for thromboprophylaxis in post-operative orthopedic patients. Mean peak AFXa levels measured on Day 1, 3, 4 and 10 were 0.29, 0.25, 0.33 and 0.37 IU/mL respectively. In acutely ill medical patients, average AFXa levels at Day 10 were 0.21 and 0.41 when 20 mg and 40 mg enoxaparin daily were administered respectively.[20] The prophylactic range is defined to be between 0.2-0.5 IU/mL by Weitz,[21] although the reference cited only reported therapeutic AFXa levels.[16] In the review by Nutescu *et al*., a target range of 0.2-0.4 IU/mL is suggested, based on the authors' own clinical experience.[3] Similarly, several other studies utilized different ranges in various patient groups without supporting data (Table 2).[3,4,19-26]

Are prophylactic anti-factor Xa levels necessary?

As the standard fixed dosing of LMWH is

Table 1. Target anti-factor Xa ranges of therapeutic low molecular weight heparins (LMWH).

LMWH	Target anti-factor Xa, IU/mL	
	Twice daily	Once daily
Enoxaparin[1,4,16]	0.6-1.0	1.0-2.0
Dalteparin[5,18]	-	0.5-1.5
Nadroparin[1,4,16]	0.6-1.0	1.3
Tinzaparin[1,4,16]	-	0.85

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Table 2. Target anti-factor Xa ranges of prophylactic low molecular weight heparins.

Study	Target AFXa	Patient group
Leyvraz (1991)[19]	Mean AFXa; day 1: 0.29 IU/mL; day 3: 0.25 IU/mL; day 4: 0.33 IU/mL; day 10: 0.37 IU/mL	Orthopaedic
Desjardins (2004)[20]	Day 10 mean AFXa; 0.21 IU/mL (enoxaparin 20 mg daily); 0.41 IU/mL (enoxaparin 40 mg daily)	Medical
Weitz (2009)[21] Lim (2010)[4]	0.2-0.5 IU/mL	All
Micromedex. DRUGDEX[26]	0.2-0.6 IU/mL	All
Nutescu (2009)[3]	0.2-0.4 IU/mL	All
Nohe (1999)[23]	0.2 -0.4 IU/mL	Pediatric
Fox (2008)[24]		
Pettila (1999)[22]	0.2-0.4 IU/mL	Pregnancy
Bates (2014)[25]	0.2-0.6 IU/mL	Pregnancy

Table 3. Target anti-factor Xa ranges for thromboprophylaxis in bariatric patients.

Study	Target AFXa, IU/mL	Low molecular weight heparin
Simoneau (2008)[13]	0.2-0.5	Dalteparin
Rowan (2008)[11]	0.18-0.44	Enoxaparin
Simone (2008)[43]	0.18-0.44	Enoxaparin
Imberti (2009)[41]	0.1-0.4	Parnaparin
Borkgren-Okonek (2008)[42]	0.2-0.4	Enoxaparin

considered safe in most adult patients (including pregnant women and patients with mild and moderate renal impairment), in general AFXa assays are not performed.[1,2,27,28] Furthermore, there is disagreement in the literature as to the clinical relevance of AFXa levels in patients receiving LMWH thromboprophylaxis.[16,29,30]

Several early studies, including large randomized trials, suggested that the correlation between clinical thromboembolic or bleeding events and AFXa levels is negligible or absent in surgical patients post-operatively.[31,32] In contrast, Levine *et al.* demonstrated a strong correlation between AFXa levels and deep venous thromboses (DVT) in post-operative orthopedic patients receiving enoxaparin thromboprophylaxis.[33]

Some studies identified a negative correlation between AFXa levels and increasing BMI and body weight.[34,35] This was disputed by the MEDENOX and PREVENT trials which investigated the enoxaparin and dalteparin thromboprophylaxis respectively and demonstrated no significant difference in efficacy between obese and non-obese patients.[36,37]

However, more recently it has been suggested that fixed dosing of LMWH for thromboprophylaxis may not be adequate in certain patient populations. Morbidly obese patients undergoing bariatric surgery (BMI>35 kg/m^2) may be one of the groups at risk of under dosing, and has been a topic of contention in the literature.[3,4,6,10-13]

Some studies recommended the use of higher doses and extended regimens of LMWH for thromboprophylaxis in these patients based upon data from AFXa levels and clinical endpoints.[11-13,38-40] Differing target AFXa ranges were utilized in the various studies (Table 3).[11-13,41-43] This lack of a well-defined prophylactic range has made it difficult to interpret research data in this area.

Despite limited evidence is available in this field, the guidelines issued by the American College of Chest Physicians (ACCP) suggest the use of increased doses of LMWH perioperatively for bariatric patients.[9]

AFXa monitoring and dose adjustment are recommended in patients with high-risk trauma and burns, who may be at risk of subtherapeutic thromboprophylaxis.[8,44,45] This approach has been shown to also decrease VTE in trauma patients.[8] Critically ill patients on inotropes may be inadequately treated with standard prophylactic dosages of LMWH, hypothesized to be due to an impaired peripheral circulation in that patient population.[46]

Conclusions

While monitoring of prophylactic AFXa levels may not be needed in the majority of patients, it may still be required in certain patient groups to optimize treatment. Due to a lack of data, the AFXa for prophylactic dosages of LMWH has not been clearly defined, and there seems to be different reference ranges used in the literature.

A standardized prophylactic AFXa range would make data from future studies in this area more comparable, and potentially improve the management of thromboprophylaxis in certain patients.

On the basis of the studies published to date, we can conclude that a reasonable AFXa target range for LMWH DVT prophylaxis may be 0.2-0.5 IU/mL, however, prospective studies are required to validate this recommendation.

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