Is laboratory monitoring of low-molecular-weight heparin therapy necessary? Yes

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See also Bounameaux H, de Moerloose P. Is laboratory monitoring of low-molecular-weight heparin therapy necessary? No. This issue, pp. 551–4.

At the beginning of the clinical development of low-molecular-weight heparin (LMWH) it was expected that they produce less anticoagulation and consequently less hemorrhages compared with unfractionated heparin (UFH). This has been demonstrated in several clinical trials for treatment of venous thromboembolism (VTE). This confirms, but does not exclude the lack of a benefit, to determine the anticoagulant effects of LMWH in certain groups of patients to avoid over- or under-anticoagulation.

All studies for treatment of thromboembolism with LMWH have been performed without determination of the anticoagulant effects of LMWH except for small and detailed clinical trials. Due to the lower binding of LMWH to plasma proteins and to cell surfaces, the plasma anti-factor (F)Xa activity generated by a given dose of LMWH is more predictable than for UFH. However, there is an unexpressed agreement of avoiding an unacceptable increase of the anticoagulant effect during LMWH therapy, increasing the hemorrhagic risk [1].

Some clinical trials indicate that the interpatient variability is less pronounced for LMWHs, leading to less frequent dose adjustments in a small proportion of patients for treatment of VTE compared with UFH [2,3]. Higher doses of LMWH lead to higher anti-FXa activities and to increased incidence of hemorrhagic events, indicating a clear association between plasma activities and side-effects [4].

Anticoagulant methods

LMWH preparations inhibit preferentially FXa and only to a low extent thrombin and activated partial thromboplastin time (APTT). Accordingly, FXa assays have been developed and validated to determine the anticoagulant effect of LMWH. Of all anticoagulant methods the chromogenic assay, using bovine FXa to release para-nitroaniline from the chromogenic substrate specific for FXa, turned out to have the lowest intra- and interlaboratory variation of the anti-FXa assays during international collaborative studies. Also, fluorogen substrate assays are available. Anti-FXa clotting methods, such as hestest, have been used, but they may give different results from the chromogenic method and they may be influenced by the anti-factor (F)IIa activity of LMWHs [5].

Studies have shown that a LMWH preparation given to the patient is the best material for preparation of the standard curve [6]. The World Health Organization (LMWH) standard has been useful as a reference material for the current range of LMWH products. Its anti-Xa/anti-IIa ratio of 2.5 is in the middle of the range of 1.5–4.0 for the various products [7]. Additional standards are required for danaparoid, LMWHs with very different anti-Xa/anti-IIa ratios, fondaparinux, idraparinux and oral FXa inhibitors.

Anticoagulant effects of LMWHs

Pharmacokinetic data are available on anti-Xa activity levels relative to time of injection of therapeutic doses of all LMWH preparations [8,9]. Maximal plasma concentrations typically occur 1–5 h following administration of a dose, with the maximum peak varying slightly between LMWHs. Anti-Xa levels at 4 h after a dose (peak levels) have been measured in several studies, and the peak plasma concentrations varied rather widely. Plasma concentrations immediately prior to the administration of a daily LMWH dose averaged 0.1 IU mL\(^{-1}\). In general, measurement of a heparin level near its peak (4 h) seems to have a stronger correlation with safety and efficacy than trough levels obtained just prior to administration of a dose. Therefore, if LMWH therapy is monitored, the sample should be drawn approximately 4 h after subcutaneous administration.

Anti-FXa levels in patients treated with LMWH

The therapeutic range has not been rigorously defined for LMWH, as many of the studies performed to date have not
reported anti-Xa levels. The problem of target ranges of anti-FXa activity in plasma is indicated in clinical studies using once-daily 170 aXa U kg\(^{-1}\) tinzaparin, 200 aXa U kg\(^{-1}\) dalteparin or nadroparin [10,11]. Obviously, the peak levels of aXa activity are much higher after once-daily subcutaneous administration of higher doses of LMWH compared with twice-daily half of this dosage. Consequently, bleeding complications are related not only to anti-FXa levels, but also to concomitant medication such as vitamin K antagonists, acetylsalicylic acid, or the duration of treatment and individual risk factors of patients.

Patients weighing 55–95 kg and suffering from acute proximal deep vein thrombosis (DVT) were treated with 8000 IU LMWH certoparin b.i.d. or with APTT-adjusted UFH intravenously. Baseline aXa levels ranged from 0.2 to 0.5 IU mL\(^{-1}\) during treatment with LMWH and resulted in the same aXa levels during APTT-adjusted i.v. UFH. Peak aXa levels ranged from 0.6 to 1.1 IU mL\(^{-1}\) during treatment with LMWH. Heptest coagulation assay had identical steady-state levels of FXa inhibition during UFH and LMWH therapy, when expressed in seconds: 50–80 s corresponding to 2.5–4-fold ratio of baseline levels. Peak levels during treatment with LMWH were between 80 and 120 s (Fig. 1) [12].

Using twice-a-day administration, an increased risk of bleeding was suggested at anti-Xa activities above the 0.8–1.0 IU mL\(^{-1}\) range [13]. The therapeutic range is even less clear for once-a-day dosing, but the target range will probably be higher, possibly 1.0–2.0 IU mL\(^{-1}\) (peak level) [3,6,14]. The advantage of monitoring the dose of LMWH was tested in a prospective trial [15]. Patients with acute DVT received 100 aXa U kg\(^{-1}\) b.i.d. with a target peak anti-Xa level of 0.5–1.0 IU mL\(^{-1}\). In one group of patients no dose changes were made, whereas in the other one dose change was made to maintain the target aXa level. Despite monitoring, the Marder score reduction was comparable in the two groups, but significant correlation was found between aXa levels and antithrombin levels and the Marder score reduction of patients with dose adjustment. At this point, there are insufficient data to determine if there should be individual target ranges for each individual LMWH. However, there does appear to be sufficient similarity between the commercially available LMWHs to aim for one overall target range. Thus, there is insufficient data indicating a benefit of routine monitoring of LMWH with a FXa method for patients.

**Patients who may benefit from anticoagulant monitoring**

UFH as well as LMWH is metabolized to about 30% by the liver through uptake by this scavenger receptor. Seventy percent of UFH and LMWH is excreted into the urine as uroheparin. Is is likely that the greatest amount of heparin in the urine is sulfated and 5–10% is detected as anticoagulant active heparin/LMWH [16]. Patients with reduced renal function treated with enoxaparin 1 mg kg\(^{-1}\) body weight subcutaneously b.i.d. obtained peak blood levels of anti-Xa concentrations 4 h post dose of 0.9 IU mL\(^{-1}\) and 1.34 IU mL\(^{-1}\), if creatinine clearance was above or below 30 mL min\(^{-1}\), respectively [17,18].

Patients receiving therapeutic levels of LMWH for prolonged periods of time (1 mg kg\(^{-1}\) enoxaparin b.i.d. or 100 IU kg\(^{-1}\) dalteparin o.d. [19]) may benefit from monitoring to prevent excessive or insufficient anticoagulation. This includes patients with malignancy and long-term treatment, patients with thrombosis refractory to warfarin as in myeloproliferative disorder or in antiphospholipid antibody syndrome, and patients unable to take warfarin. The latter would include pregnant women and patients with allergic reactions to coumarins. Pregnancy may require monitoring because of the need for an increased dose in the third trimester of pregnancy [20]. Long-term prophylaxis of VTE during pregnancy demonstrated that 5000 IU of dalteparin once daily subcutaneously in women weighing 50–70 kg at entry had chromogenic anti-FXa levels between 0.2 and 0.4 IU mL\(^{-1}\) plasma 3 h post injection [21]. During long-term treatment with 70–100 IU kg\(^{-1}\) body weight o.d. LMWH peak aXa levels ranged between 0.2 and 0.6 IU mL\(^{-1}\) [22].

In patients with acute coronary syndrome multivariable analysis demonstrated that the creatinine clearance was the predominant factor in determining the pharmacokinetic profile in contrast to weight, sex, body mass index, leukocyte count, hemoglobin, hematocrit, platelet count and creatinine level. The creatinine and LMWH clearance of enoxaparin correlated with \(r = 0.85\). Patients with creatinine clearance < 40 mL min\(^{-1}\), 40–80 mL min\(^{-1}\), and > 80 mL min\(^{-1}\) were older and lower in body weight with decreasing creatinine clearance. Absolute peak anti-FXa levels in patients with normal creatinine clearance were 1.25 ± 0.44. These levels increased to 1.53 ± 0.54 in patients with creatinine clearance > 80 mL min\(^{-1}\) and > 40 mL min\(^{-1}\). Major hemorrhage occurred more frequently in patients who were older, lighter in body weight and with reduced creatinine clearance. Peak anti-Xa activities were distributed equally among patients with and without new myocardial infarctions [23].

![Fig. 1. Heptest coagulation values (s, mean, SEM) during treatment of patients with acute deep venous thrombosis with activated partial thromboplastin time (APTT)-adjusted intravenous unfractionated heparin (UFH) or 2 × 8000 IU low-molecular-weight heparin (LMWH) Certoparin (through and peak levels) (from [12], with permission).](image-url)
Patients at high risk of bleeding, such as postoperative patients or those with a likelihood of thrombotic recurrence, may also benefit from monitoring to avoid periods of over- and under-anticoagulation.

Patients with very low body weight may also benefit from intermittent monitoring due to differences in the pharmacokinetics compared with patients with an ideal body weight.

Newborns and children may also require different dosage schemes from adults, and monitoring may be necessary to assure adequate therapy. This is based on a study with newborns requiring 1.6 mg kg\(^{-1}\) enoxaparin b.i.d. to achieve a target range of 0.5–1.0 IU mL\(^{-1}\) compared with older children requiring the adult dose of 1.0 mg kg\(^{-1}\) b.i.d. to obtain the same target range [24]. Dose finding studies demonstrated that children over 5 kg body weight required 30 IU kg\(^{-1}\) s.c. b.i.d. and children ≤5 kg required 50 IU kg\(^{-1}\) s.c. b.i.d. to achieve the target range of 0.1–0.3 IU mL\(^{-1}\) 3 h after s.c. injection [25]. During 3 months’ prophylaxis of VTE with subcutaneous LMWH, 5.6% of children had recurrent VTE or death and another 5.6% major bleedings compared with UFH and oral anticoagulation (10.0% and 12.5%, respectively). However, there was no relation between anti-FXa activity and the occurrence of severe events [26].

**Indications for monitoring LMWH**

The recommendations of the College of American Pathologists Conference XXXI on laboratory monitoring of anticoagulant therapy with LMWH are based on the levels of evidence from the clinical studies (Table 1) [27], and can be summarized as follows:

1. Laboratory monitoring using an anti-FXa assay may be of value in patients with reduced creatinine clearance, over- and underweight, prolonged therapy including pregnancy (level 1) and an increased need of LMWH in the third trimester of pregnancy (level 2).

2. Pediatric patients receiving LMWH should be monitored (level 1).

3. When LMWH is monitored, the sample should be obtained 4 h after subcutaneous injection (level 2).

4. The target concentration for the peak LMWH levels in patients treated with twice-daily dosing should be 0.5–1.1 IU mL\(^{-1}\) when measured by an anti-FXa method (level 1) and by heptest assay between 82 and 120 s for UFH and LMWH (level 2). Target peak levels for once-daily doses of LMWH should range from 0.8 to 1.6 IU mL\(^{-1}\) (level 2).

5. The chromogenic anti-FXa method (level 1) and the heptest assay (level 2) are recommended.

6. A calibrated LMWH should be used to establish the standard curve for the assay to measure LMWH (level 1).

7. Chromogenic and heptest assays have peak aXa levels during prolong therapy with LMWH range between 50 and 75% of the therapeutic dose depending on the applied dosage (level 2).

8. Over-anticoagulation leads to major hemorrhage (level 2).

**Table 1** Levels of evidence for consensus recommendations [27] (modified)

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
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<tbody>
<tr>
<td>Level 1</td>
<td>The recommendation is based on well-designed prospective studies, preferably more than one</td>
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<tr>
<td>Level 2</td>
<td>The recommendation is based on a prospective study or multiple anecdotal studies that reach consensus</td>
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<tr>
<td>Level 3</td>
<td>The recommendation is based on anecdotal studies or the consensus of expert practitioners</td>
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