

Is laboratory monitoring of low-molecular-weight heparin therapy necessary? No

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To cite this article: Bounameaux H, de Moerloose P. Is laboratory monitoring of low-molecular-weight heparin therapy necessary? No. *J Thromb Haemost* 2004; 2: 551–4.

See also Harenberg J. Is laboratory monitoring of low-molecular-weight heparin therapy necessary? Yes. This issue, pp. 547–50.

The issue of how and when to monitor low-molecular-weight heparin (LMWH) therapy was raised from the beginning of the clinical use of these compounds, almost 20 years ago. Laboratory monitoring of LMWH was suggested mainly because the new compounds were to replace unfractionated heparin (UFH), which definitely required monitoring. In the following, we will briefly review the reasons for monitoring drugs, the way to monitor heparins and especially LMWH, the pitfalls of such monitoring, and, finally, the evidence that monitoring does not consistently improve efficacy or safety of LMWH therapy.

Why monitoring drugs in general?

The aim of drug monitoring is ultimately to optimize dosage regimens in order to increase efficacy and/or safety. Most drugs have very little dose-related toxicity (e.g. penicillins or β -adrenergic blocking agents) and doses well in excess can be administered to maximize efficacy. Alternatively, some drugs have a smaller therapeutic index. If some effect of such drugs is easily measured [e.g. blood pressure for antihypertensive drugs, international normalized ratio for vitamin K antagonists, activated partial thromboplastin time (APTT) for unfractionated heparin, drug plasma concentration for digoxin or cyclosporin], it can be used to guide dosage, and a trial-and-error approach to optimal dosage is then used. If the plasma concentration of a drug can be accurately anticipated from the dose applied and the patient's body weight, it does not usually require monitoring, even if its therapeutic index is small.

Why and how monitoring heparins?

For decades, UFH was used as the first-line anticoagulant. Its bioavailability in a given patient cannot be predicted because

of variable binding to endothelium, monocytes as well as plasma proteins such as vitronectin, histidine-rich glycoprotein, and platelet factor 4. As a consequence, the same dose of intravenous UFH may result in highly variable anticoagulant effects in different individuals. The test that is used to assess the anticoagulant effect of UFH is the APTT. A clotting time of 1.5–2.5 times the normal mean APTT (or the patient's own baseline APTT) is said to be therapeutic. To achieve that goal, the range of daily doses to be administered is very wide and may vary by a factor of five; in addition, APTT has to be checked several times a day at the beginning of treatment to adapt the dosage and to find the maintenance dose. Once a steady dosage schedule is established, daily monitoring is sufficient. These guidelines have been followed for years. However, the evidence supporting them is based merely on the suggestion that delay in the achievement of adequate anticoagulation is associated with an increased rate of thrombosis progression or recurrence [1–3]. In addition, some patients fail to prolong their APTT despite large doses of heparin, or have a prolonged baseline APTT (due to factor deficiency or lupus-like anticoagulant) that is unreliable for heparin monitoring.

LMWH do not bind to endothelium and plasma proteins and have a very high bioavailability after subcutaneous application. The only reason to monitor them would be therefore to improve efficacy or safety, as discussed below. On the other hand, they do not prolong the APTT to the same extent as UFH does. The most widely used test that correlates with the administered dose of LMWH is the antifactor (F)Xa activity in plasma assessed by means of assays using a chromogenic substrate. Other more global tests of antithrombotic potential such as the chronometric 'Heptest' and the measurement of the 'endogenous thrombin potential' are also potentially interesting in this context, but the experience with these tests is scarce.

Pitfalls of LMWH monitoring

In 2002, the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis

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identified some limitations of the laboratory monitoring of LMWH therapy [4], including the different anti-Xa/antifactor IIa activity ratios of the various LMWH preparations, the poor comparability between commercially available anti-Xa chromogenic assays [5,6], and the importance of the timing of blood sampling in relation to that of dosing.

Indeed, Kitchen *et al.* [5] demonstrated that the selection of the anti-Xa assay method could influence patient management, since the dose required to achieve the therapeutic range would differ considerably according to the assay employed.

The timing of blood sampling is also of utmost importance, because LMWH is almost exclusively administered subcutaneously and the plasma concentration (and its surrogate anti-Xa activity) is not constant during the period between two injections. Therefore, interpreting an anti-FXa level without knowing when the drug was administered may be hazardous or even misleading. For the purpose of verifying that efficacious concentrations have been achieved, blood sampling for monitoring should be performed at the peak concentration (i.e. 3–4 h after the subcutaneous injection in case of two daily applications, or 4–6 h after the injection in case of one injection a day). An additional problem resides in the different therapeutic ranges that correspond to these timings. For the purpose of ruling out the possibility of accumulation, e.g. in patients with renal insufficiency, monitoring should be performed just before application of the next dose.

Because each LMWH has its own pharmacodynamic pattern, the mean peak concentration at the doses currently recommended to treat a patient with acute venous thromboembolism will be different for each compound. Thus, a peak concentration of 1.0 anti-FXa IU mL⁻¹ may be appropriate in an enoxaparin-treated patient but may represent overdosage in a dalteparin-treated patient [7,8].

In addition, the anti-FXa activity may not be representative of the antithrombotic properties of LMWH since these compounds also have effects, e.g. on platelet function as well as on tissue factor pathway inhibitor (TFPI) release from endothelium.

In summary, measuring anti-FXa activity in LMWH-treated patients may produce flawed information and induce incorrect patient management, unless utmost attention is paid to several crucial preanalytic conditions.

Does plasma anti-FXa activity of LMWH correlate with the risk of thromboembolic recurrence?

Thousands of patients were included in clinical thromboprophylactic trials of LMWH compared with UFH in surgical and medical patients. No monitoring was performed and there is a general consensus that monitoring is not necessary in the prophylactic indication for both LMWH and UFH.

In a meta-analysis of approximately 3600 patients with established deep vein thrombosis (DVT) randomized to LMWH or UFH, Gould *et al.* [9] concluded that LMWH appears to be as effective as UFH in preventing thromboem-

bolic recurrences and to reduce mortality. While UFH-treated patients were monitored with the APTT, LMWH-treated patients received fixed weight-adjusted dosage without laboratory monitoring. Thus, at a first glance, the need for monitoring is not appealing. There is one prospective multicenter study that evaluated the potential advantage of monitoring to reduce thrombus extension or recurrence in 122 patients with acute proximal DVT who were given dalteparin (100 anti-FXa IU /kg⁻¹ b.i.d.) [7]. Plasma anti-FXa activity, measured daily in all patients, was used to adapt the dose (in order to maintain a peak activity of 0.5–1.0 IU mL⁻¹) in only half of the patients. Among the 64 patients randomized in this group, the dose remained unchanged in 44, was increased in 15 and was decreased in five. In spite of this monitoring, the mean phlebographic Marder's score reduction after 10 days of treatment was identical among the monitored patients and the 58 patients in whom no dose adjustment was made. Moreover, the mean dose that was actually delivered in the monitored patients was 103 anti-FXa IU kg⁻¹ b.i.d., which is nearly identical to the fixed dose administered in the unmonitored group.

In summary, the evidence does not support the use of laboratory monitoring to improve the efficacy of LMWH in terms of thrombus extension or recurrence.

Does plasma anti-FXa activity of LMWH correlate with the risk of bleeding?

In the previously quoted meta-analysis, Gould *et al.* [9] concluded that LMWH seems to be as safe as UFH with respect to major bleeding complications, although the LMWH-treated patients were not submitted to any monitoring. Earlier studies and meta-analyses had even suggested a slightly decreased risk of bleeding with fixed, weight-adjusted doses of LMWH compared with APTT-adjusted UFH [10]. One study examined the possible link between the occurrence of major bleedings and anti-FXa plasma activity [11]. In this prospective double-blind trial, 194 patients with acute venous thromboembolism were randomized to intravenous LMWH dalteparin or UFH. Though an increased bleeding risk was observed above a plasma concentration of 0.8 anti-FXa U mL⁻¹ (in strong relation to the dosage applied), the anti-Xa activity was not increased in the patients who experienced major bleeding. Moreover, there was no relation between the patient's highest anti-Xa level during the study period and bleeding complications. In fact, the most important independent factor predicting major bleeding in that study was the World Health Organization performance status.

In summary, the evidence does not support the use of laboratory monitoring to improve the safety of LMWH in terms of major bleeding.

Special situations

Iterative measurements of LMWH anticoagulant activity have been proposed in a few special situations, including overdosage,

pregnancy, extreme body weights, children and renal insufficiency.

Management of overdosage depends upon the clinical situation (does the patient bleed or not?), and includes watchful waiting or administration of the heparin antidote protamine chloride, whereby LMWH is less susceptible to being inhibited by this antidote than UFH. At least one-third of the LMWH molecules, those with the smallest molecular weight, will not be inhibited. Knowing the residual anti-FXa activity following protamine administration, however, will usually not guide further management.

During pregnancy, the need to adapt the LMWH dosage to the weight of the pregnant woman remains controversial and some clinicians monitor anti-FXa activity once monthly in order to adapt the dosage, but there are no firm recommendations or hard data to support this approach. Nevertheless, the situation is complex during pregnancy and may change during its course [12].

In underweight (< 50 kg body weight) or very obese (> 120 kg body weight) patients as well as in children, the typical dosage adapted to body weight may not apply because these patients were excluded from most clinical trials. Indeed, almost absent or extremely abundant subcutaneous fat tissue may influence local LMWH resorption rate and pharmacokinetics, and result in erratic anticoagulant effects. Likewise, blood volume is not directly proportional to weight and vascular space may be overestimated in the obese. Although hard data are lacking, iterative control of anti-FXa activity may be advisable in those patients. Alternatively, APTT-monitored UFH treatment might be used instead of LMWH.

According to Sutor *et al.* [13], newborns have increased and variable dose requirements with an average of 1.6 U kg⁻¹ to achieve therapeutic levels, and monitoring may be indicated in children < 2 months old [14].

Finally, because LMWH are mainly cleared via the renal route, an accumulation phenomenon may be expected in cases of reduced renal function. Renal function physiologically declines with age. Thus, 80-year-old people have half the creatinine clearance rate of young individuals. This accounts for a 1.4-fold increase in the anti-FXa peak activity after injection of most LMWH brands [15] with a risk of progressive accumulation, perhaps with the exception of tinzaparin [16], a LMWH with a higher molecular weight distribution and therefore a more significant contribution of the cellular clearance mechanism. It has been suggested that patients with a creatinine clearance < 30 mL min⁻¹ or even 45 mL min⁻¹ should be monitored while receiving therapeutic dosages of LMWH, which would result in monitoring a substantial proportion of patients aged 70 or more. This attitude has been strongly opposed by the Hamilton group based on a systematic literature review [17]. Notwithstanding this opposition, the authors admit that the pharmacokinetic response to impaired renal function may differ among LMWH preparations. A more realistic alternative would be to use APTT-adapted UFH in those patients.

Ironically, the only monitoring that is strongly indicated in LMWH- (and UFH)-treated patients is regular platelet count to prevent heparin-induced thrombocytopenia.

Conclusion

The evidence available does not support laboratory monitoring of LMWH therapy: (i) the anticoagulant activity of body weight-adjusted, subcutaneously administered, therapeutic doses of LMWH is highly predictable; (ii) the antithrombotic effect and the risk of bleeding do not consistently correlate with the anti-FXa activity measured in plasma; (iii) the safety of administering body weight-adjusted LMWH has been demonstrated in thousands of patients enrolled in clinical trials; (iv) anti-FXa measurement in plasma has definite pitfalls. Admittedly, iterative plasma measurement of anti-FXa activity following therapeutic doses of LMWH may be occasionally helpful in pregnant women, in small children, in patients with extreme body weight, or in renal insufficiency. Alternatively, administering APTT-adapted UFH may represent a more reasonable option in all these situations.

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