Arguments against Monitoring Levels of Anti-Factor Xa in Conjunction with Low-Molecular-Weight Heparin Therapy

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ABSTRACT

The product monographs for some low-molecular-weight heparins (LMWHs) state that anti-factor Xa concentrations should be monitored in the treatment of deep vein thrombosis. This article reviews the pharmacological and epidemiological basis for this recommendation and finds the evidence wanting. Anti-factor Xa activity varies for each LMWH, and evidence from clinical trials using anti-factor Xa monitoring does not support a link between activity of anti-factor Xa, bleeding, and effect of the drug. Given this lack of evidence, routine monitoring of anti-factor Xa in conjunction with LMWH therapy is not recommended.

Key words: anti-factor Xa, low-molecular-weight heparin, monitoring

RÉSUMÉ

Les monographies de produit de certaines héparines de faible poids moléculaire (HFPM) indiquent que les concentrations de l'anti-facteur Xa doivent être surveillées dans le traitement de la thrombose veineuse profonde. Cet article analyse les fondements pharmacologiques et épidémiologiques de cette recommandation et trouve les données insuffisantes. L'activité de l'anti-facteur Xa varie pour chaque HFPM et les données tirées des essais cliniques qui ont eu recours à la mesure de l'anti-facteur Xa n'ont pu établir aucun lien entre l'activité de l'anti-facteur Xa, le saignement et l'effet du médicament. Compte tenu des données insuffisantes, il n'est pas recommandé d'effectuer la surveillance systématique de l'anti-facteur Xa dans le cadre d'un traitement à l'héparine de faible poids moléculaire.

Mots clés : anti-facteur Xa, héparine de faible poids moléculaire, surveillance

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INTRODUCTION

The rational basis for measuring the concentration of any drug in the blood, or for determining some surrogate marker of drug concentration, rests on certain well-founded principles. These include a known pharmacological relationship between drug concentration and clinical effect, a known statistical relationship between concentration and effect (that is, when one changes, so does the other), and, ideally, evidence from randomized trials that alteration in drug concentration causes a predictable change in effect. Overriding these principles, from a practical point of view, is the fact that greater utility is gained from measuring drug concentration than from making direct clinical observations. Typically this practical consideration applies to drugs with a narrow therapeutic index or unpredictable kinetics and to those for which there is a proven need to establish certain concentrations to achieve or avoid specific effects. This article will address each of these areas in relation to low-molecular-weight heparins (LMWHs).

PHARMACOLOGICAL PRINCIPLES

Interestingly, the pharmacological relationships between drugs for which blood concentrations are routinely measured and their therapeutic and toxic effects are rarely well understood. This is because there is an attempt to link the concentration of the drug in the blood with its effects on multiple receptors that have multiple clinical effects. Each of these effects, including effects on intended receptors (therapeutic effects) and unintended receptors (toxic effects), will have a different relationship to concentration. There are also extensions of clinical effects into side effects such as bleeding, whereby some underlying pathological condition alters these relationships (e.g., bleeding in association with anticoagulant therapy may occur more frequently in patients who have recently undergone surgery). For example, the intended pharmacological action of anticonvulsants such as phenytoin is believed to be related to ion exchange and neuronal electrical conduction, but the link between concentrations and toxicity is based on cohort studies that examined only limited aspects of toxicity (such as nystagmus), not the multitude of effects that exist for phenytoin.[1] Thus the rationale for measuring concentrations of these drugs rests much more on the ability to measure both compliance and their peculiar kinetics than on the precise relationship between drug concentration and effect. In particular, the kinetics predispose to unpredictable increases in levels of the drug for a given dose. Furthermore, the relationship between the known mode of action and the pharmacological effects is not very specific. Similarly, aminoglycosides may cause vestibular and renal damage, but the precise links between drug concentration and effects are far from clear.[2] This situation is confounded by the advent of once-daily dosing for drugs that have a half-life of 2 to 3 h in patients with normal renal function.

Given this complexity of drug activity, it must be asked how the known pharmacology of LMWHs and their inhibitory activity against factor Xa might affect their therapeutic and toxic effects.

LMWHs have pentasaccharide sequences that bind to and cause a conformational change in antithrombin. This change accelerates the interaction of antithrombin with thrombin and activated factor X (factor Xa) by about 1000 times.[3] Because of the short length of the LMWH saccharide chain, fewer than half of the LMWH molecules can bind to both antithrombin and thrombin. Thus, LMWHs have greater activity against factor Xa than against thrombin.[4] However, this is not the only mechanism of action of LMWHs.

Tissue-factor-pathway inhibitor may also contribute to the inhibitory activity of LMWHs against factor Xa.[5] LMWHs release tissue-factor-pathway inhibitor from endothelium,[6,7] which forms a complex with and inactivates factor Xa; the complex then inactivates factor VIIa.[6]

Weitz[4] questioned the relative importance of inhibition of factor Xa and inhibition of thrombin in mediating the antithrombotic effect of LMWHs. He cited evidence that both are necessary but that thrombin is the more important target because inhibition of thrombin prevents feedback activation of factors V and VIII.[8,9] Thus inhibition of factor Xa may contribute to the therapeutic effect of LMWHs but is not necessarily the predominant mechanism.[10] A search of MEDLINE and personal files located no phase II correlational studies linking anti-factor Xa activity to either pharmacological effect or bleeding, which indicates that as inhibition of factor Xa changes, the pharmacological effect or the effect on bleeding changes in the same direction.

EVIDENCE FROM RANDOMIZED TRIALS

Four publications were found that reported monitoring of anti-factor Xa levels in a clinical trial setting; all of the studies involved dalteparin.

Bratt and others[11] first conducted a pilot study on 40 subjects with deep vein thrombosis and used anti-factor Xa levels to adjust the dose of both dalteparin and unfractionated heparin. The patients were from general medical or surgical wards or the emergency department. The unfractionated heparin regimen was started as a 5000-IU IV bolus followed by an infusion of 30 000 IU/24 h. The dose of dalteparin was 240 IU/kg every 12 h by IV infusion; in this patient group, 2 patients who had recently undergone surgery experienced bleeding. In the second component of the study by Bratt and others[11] (also 40 patients), the researchers compared dalteparin 120 IU/kg every 12 h with unfractionated heparin and used anti-factor Xa levels to monitor therapy in each group. In this component of the study, 2 patients receiving LMWH and 1 receiving unfractionated heparin experienced bleeding, but the sample size was too small to rule out a difference between the 2 groups. The authors stated that "it cannot, however, be assumed that the bleeding was caused by the LMWH treatment, since bleeding without anticoagulant therapy may occur in patients mobilized after orthopedic surgery". It should be added that the anti-factor Xa levels did not predict a difference in bleeding rates despite the fact that the dose of LMWH in the second component of the study was halved on

the basis of anti-factor Xa levels. Recent surgery was the best predictor of bleeding in both components of this study. All patients received unfractionated heparin or LMWH intravenously.

Both components of this study had small sample sizes, few events of interest, and poor outcome measurements (which involved an unvalidated scoring system for venograms). The authors stated that high anti-factor Xa activity was correlated with increased bleeding but did not provide a sufficient analysis to demonstrate that monitoring levels of anti-factor Xa would reduce the risk of bleeding while maintaining a therapeutic effect. They did comment that they obtained the anti-factor Xa results retrospectively, because the assay was not used routinely at their institution, but they used the results of the first component of the study to reduce the dose of dalteparin in the second component.

The same group of authors performed another study in a similar patient population, in which dalteparin 120 IU/kg every 12 h was compared with unfractionated heparin.[12] The dalteparin was adjusted to achieve anti-factor Xa levels of 0.2 to 0.4 IU/mL 4 h after the morning dose. The unfractionated heparin was adjusted on the basis of aPTT. The sample size was 120 in total. There were no cases of bleeding in the dalteparin group. However, there was no control group in which the dalteparin dose was not adjusted. Thus, it cannot be concluded that monitoring the level of anti-factor Xa alone enhanced the safety of LMWH administration.

Finally, in the statistical analysis for the first part of the first study,[11] the correlation between anti-factor Xa levels and aPTT was $r = 0.60$ ($p < 0.01$) for patients receiving unfractionated heparin and $r = 0.38$ ($p < 0.01$) for those receiving LMWH. In other words, only 14.4% (r^2) of the variance for patients receiving LMWH could be explained by the correlation between anti-factor Xa levels and aPTT. In the second part of the first study[11] the degree of correlation between anti-factor Xa levels and aPTT was the same at half the LMWH dose. The frequency of bleeding was too low to draw any meaningful conclusions.

Albada and others[13] performed a randomized trial involving 194 unselected patients in which they compared unfractionated heparin and LMWH, both administered by IV infusion. Anti-factor Xa levels, determined 4 h after each dose adjustment, were used to adjust the dose of both agents. There was a high rate of major bleeding with both regimens (13.2% with unfractionated heparin and 10.4% with LMWH). This was probably related to the inclusion of patients known to be at high risk for bleeding (defined *a priori*) and a nonstandard definition of major bleeding. The anti-factor Xa levels were kept between 0.4 and 0.6 IU/mL in both groups, which is higher than the usual 0.2 to 0.4 IU/mL.

The authors did not describe a difference in bleeding that correlated with anti-factor Xa levels. Indeed they stated that "although there is no strict relationship between anti-factor Xa levels, efficacy and bleeding risk, the results of the study suggest that anti-factor Xa levels of 0.5 units/mL Fragmin [dalteparin] are optimal levels with respect to both the risk of bleeding and the risk of recurrent or progressive thromboembolism". However, this study was not designed to test that conclusion, as anti-factor Xa level for all patients fell within the 0.4 to 0.6 IU/mL range.

Finally, Holm and others[14] used anti-factor Xa levels in a comparison of dalteparin and unfractionated heparin. There were many methodological flaws in the study (in particular small sample size, lack of blinding, and suboptimal outcomes). However, there was no bleeding in either group.

Thus, despite the suggestion by some authors that elevation of anti-factor Xa level is associated with risk of bleeding, the published literature does not support this claim.

The relationship between anti-factor Xa levels and outcomes has also been investigated in prophylaxis studies.[15–17] In a total of 1935 patients using either enoxaparin or tinzaparin, no correlations were found between anti-factor Xa levels and bleeding or thrombosis. The only significant correlation occurred in the 2 larger studies,[15,16] in which the dose correlated with body size.

UTILITY OF ANTI-FACTOR XA MONITORING

The term "utility", as used here, refers to a significant clinical advantage to performing a nonroutine laboratory test. Given this definition, the presumed advantage would result in less bleeding if the test were performed in patients receiving LMWHs.

A number of lines of reasoning can be applied to explore if the utility of the test makes it worth doing. The first is to demonstrate whether level I evidence[18] from randomized trials exists to support the routine monitoring of anti-factor Xa levels. A second is to review the randomized trials that did not monitor anti-factor Xa levels, comparing rates of bleeding in patients receiving LMWH without any monitoring and rates of bleeding in patients receiving unfractionated heparin with aPTT

monitoring. Dolovich and others[19] performed such an analysis for similar patient populations. They found no statistically significant difference in major bleeding (relative risk [RR] 0.55, 95% confidence interval [CI] 0.29–1.03, $p = 0.060$) or minor bleeding (RR 1.07, 95% CI 0.79–1.45, $p = 0.670$). Thus LMWHs without monitoring are at least as safe as unfractionated heparin with monitoring. One level I study showed that LMWH was safer than unfractionated heparin.[20]

Finally, it is worth reviewing the analysis of Hull and others,[21] who described the link between aPTT and bleeding in patients receiving unfractionated heparin. Within a randomized trial,[22] patients were stratified on the basis of their risk for bleeding, before being randomly assigned to an initial higher dose (those at low risk) or lower dose (those at high risk) of unfractionated heparin. The criteria for high risk were surgery within the previous 14 days, a history of peptic ulcer disease, bleeding into the gastrointestinal or genitourinary tract or disorders predisposing the patient to bleeding, thrombotic stroke within the previous 14 days, or a platelet count less than 150 x 106/L.

In the analysis by Hull and others[21] of data gathered in the randomized trial,[22] it became clear that bleeding was not related to the aPTT but to the risk for bleeding that existed before the patient entered the trial (e.g., recent surgery). In other words, patients known to be at high risk for bleeding (who had lower aPTT levels) experienced bleeding more often than those known to be at low risk for bleeding (who had higher aPTT values). Thus, the *a priori* risk of bleeding was a more important predictor of bleeding than the standard laboratory aPTT test.

The question could be raised whether it should be routine to monitor anti-factor Xa levels in patients receiving LMWHs who are known to be at high risk for bleeding. However, even in these patients, close clinical monitoring for bleeding is essential. Lowering the dose of the LMWH on the basis of anti-factor Xa levels cannot be recommended because, theoretically at least, less LMWH might be given, which might result in a lower therapeutic effect and potentially fatal pulmonary embolism.

However, in cases of renal failure and obesity, studies might be justified to explore the usefulness of anti-factor Xa monitoring.

From the results of all of the studies reviewed here, several conclusions can be drawn: (1) there is considerable variability among patients in anti-factor Xa levels when LMWHs are given on a weight-adjusted basis, peak anti-factor Xa levels ranging from 0.3 to 1.2 IU/mL; (2) patients whose anti-factor Xa levels were in the upper range did not have a greater risk of bleeding than those whose anti-factor Xa levels were lower; and (3) patients whose anti-factor Xa levels were in the lower range did not have a greater risk of recurrent thromboembolism than those whose anti-factor Xa levels were higher. None of the studies distinguished between peak and trough levels.

CONCLUSIONS

No pharmacological or epidemiological evidence exists to support anti-factor Xa monitoring in conjunction with LMWH therapy. Furthermore, data could be located for only one type of LMWH (dalteparin), and those data were not helpful. Given the lack of helpful data and the myriad of trials showing that LMWH therapy without monitoring is safe and effective for the treatment of deep vein thrombosis and pulmonary embolism, routine monitoring of anti-factor Xa is not justified. Adjusting doses on the basis of anti-factor Xa levels is therefore even less tenable.

References

1. Rosenbloom D, Upton ARM. Drug treatment of epilepsy: a review. *CMAJ* 1983;128:261-70.
2. McCormack JP, Jewesson PJ. A critical reevaluation of the "therapeutic range" of aminoglycosides. *Can J Infect Dis* 1992; 14:320-39.
3. Rosenberg RD, Bauer KA. The heparin–antithrombin system: a natural anticoagulant mechanism. In: Colman RW, Hirsch J, Marder VJ, Salzman EW, editors. *Hemostatasis and thrombosis: basic principles and clinical practice*. 3rd ed. Philadelphia: JB Lippincott; 1994. p. 837-60.
4. Weitz JI. Low-molecular weight heparins. *N Engl J Med* 1997; 337:688-98.
5. Abildgaard U, Lindahl AK, Sandset PM. Heparin requires both antithrombin and extrinsic pathway inhibitor for its anticoagulant effect in human blood. *Haemostasis* 1991;21:254-7.
6. Sandset PM, Abildgaard U, Larsen ML. Heparin induces release of extrinsic coagulation pathway inhibitor (EPI). *Thromb Res* 1988;50:803-13.
7. Broze GJ Jr. Tissue factor pathway inhibitor. *Thromb Haemost* 1995;74:90-3.
8. Ofosu FA, Hirsh J, Esmon CT, Modi GJ, Smith LM, Anvari N, et al. Unfractionated heparin inhibits thrombin-catalysed amplification reactions of coagulation more efficiently than those catalysed by factor Xa. *Biochem J* 1989;257:143-50.
9. Beguin S, Mardiguian J, Lindhout T, Hemker HC. The mode of action of low molecular weight heparin preparation (PK10169) and two of its major components on thrombin generation in plasma. *Thromb Haemost* 1989;61:30-4.
10. Barrowcliffe TW, Merton RE, Havercroft SJ, Thunberg L, Lindahl U, Thomas DP. Low-affinity heparin potentiates the action of high-affinity heparin oligosaccharides. *Thromb Res Suppl* 1984;34:125-33.

11. Bratt G, Törnebohm E, Granqvist S, Åberg W, Lockner D. A comparison between low molecular weight heparin (KABI 2165) and standard heparin in the intravenous treatment of deep venous thrombosis. *Thromb Haemost* 1985;54:813-7.
12. Bratt G, Aberg W, Johansson M, Törnebohm E, Granqvist S, Lockner D. Two daily subcutaneous injections of Fragmin as compared with intravenous standard heparin in the treatment of deep venous thrombosis (DVT). *Thromb Haemost* 1990;64:506-10.
13. Albada J, Nieuwenhuis HK, Sixma JJ. Treatment of acute venous thromboembolism with low molecular weight heparin (Fragmin). Results of a double-blind randomized study. *Circulation* 1989;80:935-40.
14. Holm HA, Ly B, Handeland GF, Abildgaard U, Arnesen KE, Gottschalk P, et al. Subcutaneous heparin treatment of deep venous thrombosis: a comparison of unfractionated and low molecular weight heparin. *Haemostasis* 1986;16(Suppl 2):30-7.
15. Bara L, Planes A, Samama MM. Occurrence of thrombosis and haemorrhage, relationship with anti-Xa, anti-IIa activities, and D-dimer plasma levels in patients receiving a low molecular weight heparin, enoxaparin or tinzaparin, to prevent deep vein thrombosis. *Br J Haematol* 1999;104:230-40.
16. Kovacs MJ, Weir K, MacKinnon K, Keeney M, Brien WF, Cruickshank MK. Body weight does not predict for anti-Xa levels after fixed dose prophylaxis with enoxaparin after orthopedic surgery. *Thromb Res* 1998;91:137-42.
17. Bara L, Leizorovicz A, Picolet H, Samama M. Correlation between anti-Xa and occurrence of thrombosis and haemorrhage in post-surgical patients treated with either Logiparin® (LMWH) or unfractionated heparin. *Thromb Res* 1992;65:641-50.
18. Guyatt G, Schünemann H, Cook D, Jaeschke R, Pauker S, Bucher H. Grades of recommendation for antithrombotic drugs. *Chest* 2001;119(1 Suppl):3S-7S.
19. Dolovich LR, Ginsberg JS, Douketis JD, Holbrook AM, Cheah G. A meta-analysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of venous thromboembolism: examining some unanswered questions regarding location of treatment, product type, and dosing frequency. *Arch Intern Med* 2000;160:181-8.
20. Hull RD, Raskob GE, Pineo GF, Green D, Trowbridge AA, Elliott CG, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. *N Engl J Med* 1992;326:975-82.
21. Hull RD, Raskob GE, Rosenbloom D, Lemaire J, Pineo G, Bayli B, et al. Optimal therapeutic level of heparin therapy in patients with venous thrombosis. *Arch Intern Med* 1992;152:1589-95.
22. Hull RD, Raskob GE, Rosenbloom D, Panju AA, Brill-Edwards P, Ginsberg JS, et al. Heparin for 5 days as compared with 10 days in the initial treatment of proximal venous thrombosis. *N Engl J Med* 1990;322:1260-4.

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