

LIMITATIONS OF THE LABORATORY MONITORING OF HEPARIN THERAPY

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Heparin is the most widely used anticoagulant for the prevention and initial treatment of venous thromboembolism, for haemodialysis and cardiopulmonary bypass procedures and, with aspirin, for the management of acute coronary syndromes. In venous thrombosis and coronary disease low molecular weight heparins (LMWHs) have been demonstrated to be at least as effective and safe as unfractionated heparin (UFH) and the use of LMWH is rapidly increasing.

Most of the available LMWHs are depolymerised porcine mucosal heparin preparations prepared by chemical or enzymatic digestion. This process results in a variety of lower molecular weight products (mainly of molecular mass between 4 and 8 kDa) and reduces the anti-IIa activity, in relation to anti-Xa activity. However this relationship varies between LMWH preparations, as do other potentially important properties including interaction with platelet factor 4 and heparin cofactor II. Furthermore, the mechanism of the antithrombotic action of LMWH is not fully understood and probably does not only depend upon anti-Xa and anti-IIa activities. For example, UFH and LMWH release Tissue Factor Pathway Inhibitor (TFPI) from vascular sites and this could explain some of the antithrombotic effect of subcutaneously administered LMWH (Hoppensteadt et al, 1995).

The activated partial thromboplastin time is used to monitor therapeutic doses of UFH in venous thromboembolism. A target ratio versus mid-point of normal range of 1.5 to 2.5 is typically employed. This is principally based on evidence that delay in the achievement of adequate anticoagulation is associated with an increased rate of thrombosis recurrence or progression. It is, however, clear that the sensitivity of the test to heparin is highly reagent and instrument dependent and ideally local calibration of the APTT should be employed (Brill-Edwards et al, 1993; D'Angelo et al, 1990). Sample collection systems, sample anticoagulants and storage conditions also have clinically important effects on the results (Contant et al, 1983; Ray, 1991; Van den Besselaar et al, 1987).

The inconvenience and limited precision of monitoring of UFH therapy has contributed to the increasing use of LMWH preparations, as several randomised studies have demonstrated their efficacy and safety when administered in fixed dosage and without laboratory monitoring (Lensing et al, 1995). Despite this positive development there is still debate over the need to monitor treatment with LMWH in certain subgroups. This arises in part because most clinical trials have excluded subjects at increased risk of bleeding, as well as children, pregnant women, the very obese and others in whom the antithrombotic and prohaemorrhagic responses may be less predictable, such as patients with severe renal failure. Where

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monitoring is performed the anti-Xa assay is generally employed, but there are crucial considerations in relation to the interpretation of results:

- Anti-Xa (and anti-IIa) activity represents the amount of heparin present but not necessarily the antithrombotic function of LMWH, because the same concentration of heparin may have varying effects in different plasmas and patients (above).
- LMWH have been standardised ultimately against the 4th International Heparin Standard. This may have resulted in an overestimation of the anti-Xa and underestimation of the anti-IIa activity (Hemker and Béguin, 1993; Peyrou et al, 1997)
- Relative anti-Xa and anti-IIa activities vary between preparations (Eriksson et al, 1995; Fareed et al, 1998), and the antithrombin activity appears to be the more important action in kinetic studies (Hemker et al, 1986; Béguin et al, 1988, 1989a, 1989b, 1992; Béguin and Hemker, 1990)
- The comparability between commercially available anti-Xa chromogenic assays is poor (Kitchen et al, 1999; Kovacs et al, 1999). Assays should preferably be LMWH, method and equipment specific.
- The timing of blood sampling in relation to that of dosing with LMWH is crucial for interpretation of the pharmacokinetics.
- Anti-Xa level has not been demonstrated to be a good predictor of bleeding risk and antithrombotic efficacy in thromboprophylaxis with LMWH (Leizorovicz et al, 1993; Alhenc-Gélas et al, 1994)
- Anti-Xa level has not been demonstrated to be a good predictor of bleeding during treatment with LMWH. The clinical status (WHO stage) of the patient and dose administered are more informative (Nieuwenhuis et al, 1991).

Consideration of these factors, and of the good results obtained in clinical trials where LMWH has been administered without monitoring as venous thromboprophylaxis and treatment, leads to the conclusion that routine monitoring by anti-Xa assay is not currently indicated. Furthermore, whilst anti-Xa assays may provide some clue to LMWH pharmacokinetics in individual subjects, such as the obese, the underweight, pregnant women and infants, only limited information on antithrombotic effect and bleeding risk can be deduced from this measurement. If anti-Xa assay is employed for monitoring in these clinical situations the limitations of the information generated must be borne in mind. Although more global tests of antithrombotic potential, such as the 'Heptest' and measurement of the 'endogenous thrombin potential' (area under the thrombin generation curve; Wielders et al, 1997) are interesting they are not yet fully evaluated in the setting of studies of efficacy and safety of anticoagulation with heparins.

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