HIT/HITT and alternative anticoagulation: current concepts

Editor—I read with interest the review article by Pravinkumar and colleagues on current concepts of alternative anticoagulation for patients with HIT/HITT.

Heparin is the most commonly used anticoagulant drug in clinical practice. Unfortunately, a small group of patients develop heparin-induced thrombocytopenia type II (HIT II) as a complication of heparin therapy. This group of patients poses a management problem for the clinician should they need further anticoagulation therapy.

I note in the section on hirudin (Lepirudin), that the authors advised changes in the rate of its infusion based on the activated partial thromboplastin time (aPTT). Several authors have shown that aPTT was not sufficiently sensitive to monitor the plasma hirudin level. Pötzsch and colleagues demonstrated from in vivo experiments a poor correlation between the prolongation of the aPTT and the concentration of recombinant hirudin (r-hirudin), and Nowak found that high levels of r-hirudin can not be confidently monitored by aPTT, with inconsistencies in single measurements and in normal values. Other studies have also suggested that aPTT is not of adequate specificity to provide an accurate measurement of the anticoagulation effect of r-hirudin. However, the use of the ecarin clotting time (ECT) assay was more sensitive, as was cited in the review, and produced more reliable results which may lead to its wider use and safer practice.

Secondly, I feel you have overlooked a useful anticoagulation strategy that has been successfully used in a subpopulation of patients with HIT II. HIT antibodies reach an undetectable level about 100 days after termination of heparin therapy. Pötzsch and colleagues concluded that since HIT antibody levels start to rise in the circulation only after the plasma heparin concentration becomes undetectable, and HIT antibodies are not thrombogenic in a heparin-free circulation, patients with a history of HIT II who are antibody negative can safely have a single exposure to heparin. This approach has been successfully used only for anticoagulation during cardiopulmonary bypass in open heart surgery. However, the drawback of such an approach is that further exposure to heparin must be avoided and if necessary alternative anticoagulants should be used.

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Editor—We would like to thank Mr Saad for the interest shown in our review, which addresses an important issue in clinical practice. We accept that neither the aPTT nor aPTT ratio is ideal for monitoring direct thrombin inhibitors such as hirudin and recombinant hirudin (Lepirudin). However, these tests are not only recommended in the product insert, and the British National Formulary (BNF), but their use for monitoring has been discussed in various trials.

Unlike unfractioned heparin, plasma hirudin levels do not correlate well with aPTT or the aPTT ratio. Its limitation is particularly evident with higher doses of lepirudin, as they show no linear correlation with plasma concentrations of hirudin and there are marked interindividual differences. However, its correlation with plasma hirudin is linear for hirudin concentrations in the low to normal therapeutic range (up to 1 µg ml⁻¹), depending on the aPTT reagent used. This raises the possibility of using plasma hirudin levels for therapeutic monitoring and dose adjustment rather than aPTT. There are other tests that can be used to monitor hirudin.

Activated clotting time (ACT) has been evaluated for monitoring hirudin therapy, especially during cardiothoracic surgery and extracorporeal circulation. However, ACT lacks reproducibility and does not correlate with plasma hirudin levels. Thrombin time (TT) lacks a linear dose–response relationship with hirudin plasma concentrations. Quantitative thrombin time (QTT) has no interference with hirudin, lupus anticoagulant, low fibrinogen, clotting factors, and fibrin degradation products (FDP). Although suitable for monitoring hirudin concentrations between 1 and 7 µg ml⁻¹, it is not sensitive to concentrations less than 1 µg ml⁻¹, and furthermore QTT has not been evaluated in clinical studies. Immunochemical assays using mono- and polyclonal antibodies are more sensitive than QTT and have good reproducibility. They are used in monitoring both high and low plasma hirudin concentrations. The drawback is the prolonged assay time (>1.5 h) and its availability. More sensitive assays include chromogenic substrate-based assay and ECT. The chromogenic assay has a good linear correlation over a wide range of plasma hirudin concentrations. The assay can be done with a small sample volume and no interindividual differences are observed. The test is relatively fast (<15 min) and cost effective (<£1.00 per test), and has been shown to be reliable in clinical studies. We have highlighted the importance of ECT, which can be expressed in seconds, as an ECT ratio, or as hirudin concentration. The assay has an excellent linear correlation over a large range of plasma hirudin concentrations. It not only allows monitoring of therapeutic plasma levels but also the monitoring of under- and over-dosing of hirudin. The assay is fast (<5 min), cheap (<£1.00 per test), free from various interferences except FDP, and is available as a bedside test.
Although ECT has been studied in only a few clinical trials, the results are encouraging.

We have already addressed the issue of heparin use in patients with a history of HIT II undergoing cardiopulmonary bypass surgery in our response to the letter by Lakshmanan and colleagues. We would once again take issue with the suggestion that heparin could be considered in patients who had HIT II, especially when there are other alternative anticoagulants. Direct thrombin inhibitors such as lepirudin and argatroban have been used for HIT II patients requiring CPB surgery. Saad, like the previous author, quotes the same correspondence that appeared in the New England Journal of Medicine, which was criticized for reporting unpublished data. We are equally concerned and would be against researchers using the correspondence section of journals for projecting unpublished and invalidated research data.

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DOI: 10.1093/bja/aeg619