Practical prescribing of intravenous unfractionated heparin

Intravenous unfractionated heparin is sometimes poorly managed in NHS hospitals. This article investigates why this is so and reviews the evidence for optimal unfractionated heparin prescribing, using it to make some suggestions as to how doctors can improve this.

Unfractionated intravenous heparin has been used for many years in the treatment of venous, arterial and cardiac thrombosis. Numerous studies have documented its efficacy in this regard (Barritt and Jordon, 1960; Theroux et al, 1988; Heik et al, 1994).

In the authors' experience, prescribing unfractionated heparin is fraught with difficulty because of the complicated pharmacokinetics of the drug and the practical difficulties that it produces in the busy hospital environment. A survey of NHS trusts in England has shown that there are widely varying dosing nomogram protocols being used by different hospitals (Sado et al, 2008). As a result of the above problems, the authors have found in audit work that the anticoagulation produced by unfractionated heparin is often sub- or supratherapeutic.

Over-anticoagulation with unfractionated heparin in patients with acute coronary syndromes results in higher risks of bleeding and transfusion (Melloni et al, 2008; Wang et al, 2008). The occurrence of bleeding during the treatment of acute coronary syndromes significantly increases mortality (Sobieraj-Teague et al, 2008). This underlines the importance of trying to avoid over-anticoagulation with unfractionated heparin.

This review discusses the evidence base for unfractionated heparin dose-prescribing nomograms and makes some suggestions aimed at improving anticoagulation control.

Pharmacokinetics of unfractionated heparin

The pharmacokinetic profile of unfractionated heparin is complicated and beyond the scope of this article. However, it results in widely differing dosage requirements for individual patients. This necessitates regular monitoring of the activated partial thromboplastin time (APTT) to ensure that the correct level of anticoagulation is achieved. If not, the dose administered will need to be adjusted. The unpredictability of the response to unfractionated heparin and the logistical problems of performing regular blood tests make this drug suboptimal.

The logistical problems with unfractionated heparin

Most NHS hospitals have a protocol for unfractionated heparin prescribing which suggests that APTT is measured 4–6 hours after a 24-hour infusion of the drug has commenced. Following venesection, in most cases, the sample will need to be sent to the laboratory for analysis and calculation of the APTT. There may rarely be equipment on the ward which can be used to calculate the APTT.

The process of venesection and laboratory calculation of the APTT is likely to take at least 45 minutes in the authors' experience. Following this, the result needs to be reviewed, usually via a computer system, and acted upon using the dosing nomogram. In the authors' experience, this is usually performed by a junior doctor, except on high dependency or coronary care units, where the nursing staff will carry it out.

One problem identified by audit work performed in three hospitals was significant delays (often many hours) in the taking of blood for the APTT and then the review of the result. This was particularly true when the job was tasked to a junior doctor outside of normal working hours. In contrast to this, nurse-led unfractionated heparin prescribing was far prompter at each stage. While this audit only looked at 33 patients, it confirmed the authors' suspicions from their clinical experience and is likely to be applicable to most NHS hospitals.

Have low molecular weight heparins replaced unfractionated heparin?

Low molecular weight heparins were first evaluated in the 1980s. These are administered subcutaneously and have a much more predictable pharmacokinetic profile than unfractionated heparin (Bara and Samama, 1988), so there is usually no requirement for blood test monitoring. Low molecular weight heparins have a long duration of action and so only need to be administered once or twice per day, depending upon the preparation and indication for use. Compared to unfractionated heparin, low molecular weight heparins have at least similar if not

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greater efficacy in the treatment of ST elevation and non-ST elevation myocardial infarction and venous thromboembolism (Bassand et al, 2007; De Luca and Marino, 2007; Segal et al, 2007).

The efficacy and logistical benefits of low molecular weight heparins have led to their widespread use in thromboembolic conditions in preference to unfractionated heparin. However, low molecular weight heparins have yet to acquire a licence in anticoagulation of mechanical heart valve prostheses. They also have a long duration of action and reversal of their effect is difficult – this is a potential problem in patients at risk of bleeding. In addition, their effect is more difficult to predict in patients with renal impairment. As a result of these issues, unfractionated heparin continues to be prescribed under certain circumstances.

The evidence base for unfractionated heparin nomograms

In 1991, Cruickshank et al published the first evidence-based unfractionated heparin nomogram to guide the drug doses that should be prescribed and how they should be titrated according to the APTT. This nomogram was not, however, based on the weight of the patient, which had previously been shown to be the best single predictor of unfractionated heparin dosing requirement (Cipolle et al, 1981). Raschke et al (1993) therefore hypothesized that a weight-based nomogram would allow therapeutic levels of heparin to be achieved more quickly and consistently. Their randomized controlled study confirmed that using a weight-based nomogram was associated with earlier achievement of a therapeutic APTT.

Since Raschke's landmark study, weight-based nomograms have been assessed for use on coronary care and intensive care units and in the treatment of stroke, acute coronary syndromes and venous thromboembolism (Hassan et al, 1995; Paradiso-Hardy et al, 1996; Brown and Dodek, 1997; Becker et al, 1999; Hochman et al, 1999; Toth and Voll, 2002). These studies have all found that weight-based nomograms are safe and the most effective way to manage unfractionated heparin dosing.

In both the studies by Wang et al (2008) and Melloni et al (2008), over-anticoagulation was found to be most common in underweight and female patients when non-weight-based protocols were used. These patients were then found to be at the highest risk for developing bleeding and needing blood transfusion.

National and international guidelines for unfractionated heparin nomograms

As a result of the evidence base discussed above, a variety of American and European specialty guidelines now recommend the use of weight-based nomograms to guide unfractionated heparin therapy for both venous and arterial thromboembolism (Campbell et al, 2003; Hirsh and Raschke, 2004; Baglin et al, 2006; Anderson et al, 2007; Bassand et al, 2007). The authors were unable to find any current guidelines that do not recommend the use of weight-based nomogram prescribing.

Current practice in the NHS

Despite the evidence base and guidelines, in the authors' survey only 32% of NHS trusts in England use weight-based unfractionated heparin dosing nomograms. Furthermore, one of the most commonly used junior doctor handbooks suggests a non-weight-based approach (Longmore et al, 2007).

In a further questionnaire sent to haematology consultants, it was apparent that many were unaware of the evidence base and guidelines endorsing weight-based unfractionated heparin nomograms.

How can we improve UK practice?

Low molecular weight heparins have virtually replaced unfractionated heparin as the antithrombotic therapy of choice in NHS hospitals. However, in patients requiring anticoagulation but also with a high risk of bleeding, unfractionated heparin is often preferred as the infusion can be stopped and the effect reversed quickly if haemorrhagic complications occur. In such patients, it is crucial that unfractionated heparin dosing is managed in an optimal manner to try to reduce the risk of thrombotic or bleeding problems.

The evidence base and resultant national and international guidelines are clear that optimal unfractionated heparin nomograms should give dose titration on the basis of the weight of the patient. However, this has only been embraced by 32% of NHS trusts in England (Sado et al, 2008). It seems that this is partly a result of a percentage of unfractionated heparin protocols being written many years ago and hence being out of date and also some haematology consultants being unaware of the evidence base, most of which was published in the 1990s.

Ideally there should be a national, cross-specialty, weight-based nomogram which all NHS hospitals use. Having the same protocol in all hospitals would be of great help to junior doctors rotating through different trusts. The authors feel that the different guidelines in use by varying hospitals only encourage confusion in junior doctors. Furthermore, with the unanimous evidence base and guidelines, all hospitals and handbooks should be endorsing the weight-based approach.

The next problem is the logistical issues of managing patients on unfractionated heparin. In the authors' clinical experience and audit work this is performed more efficiently by nurses than on call junior doctors, who are often very busy and covering many wards throughout the hospital. The authors believe that unfractionated heparin could be managed in an equivalent way to diabetic sliding scales and, in most cases, be entirely nurse led (on some wards the nurses may not be trained to

perform venesection and hence may require some junior doctor input). This will require clear guidelines and then training explaining the importance of good APTT control and how best to achieve this using the protocol provided.

Conclusions

Unfractionated heparin prescribing in NHS hospitals is suboptimal in some trusts. Although this is a difficult drug to manage well, the use of weight-based nomograms and nurse-led prescribing would increase the chances of achieving good anticoagulation control.

The authors believe that all of the NHS hospitals not currently using weight-based nomograms should reconsider their protocols in light of the evidence presented above. **BJHM**

Conflict of interest: none.

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KEY POINTS

- The pharmacokinetics of unfractionated heparin are complicated and result in widely differing dose requirements for individual patients.
- A randomized controlled study confirmed that using a weight-based nomogram was associated with the earlier achievement of a therapeutic activated partial thromboplastin time (APTT).
- A variety of American and European guidelines now recommend the use of weight-based nomograms to guide unfractionated heparin therapy for both venous and arterial thromboembolism.
- Only 32% of trusts in England use a weight-based unfractionated heparin prescribing nomogram in their protocol.
- The authors believe that ideally there should be a national, cross-specialty weight-based nomogram that all NHS hospitals use.
- Unfractionated heparin could be managed in the equivalent way to diabetic sliding scales and, in most cases, be entirely nurse led.