What factors should be considered when using LMWH to treat venous thromboembolism in patients with high body weight?

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Background

It is important to ensure the correct treatment dose of a low molecular weight heparin (LMWH) for venous thromboembolism (VTE); both under and overdosing can be associated with serious adverse outcomes.

The Summaries of Product Characteristics (SPCs) for the LMWHs enoxaparin, dalteparin and tinzaparin state that the treatment dose for VTE should be based on the patient’s weight and should be administered once daily (1-3). The manufacturers of dalteparin recommend that, for patients with an increased risk of bleeding, dalteparin can be administered twice daily (2). The SPCs for enoxaparin and tinzaparin do not make a recommendation on dose capping (1, 3) but the SPC for dalteparin states that the daily dose should be no higher than 18,000 units regardless of body weight (2).

This Q&A offers guidance on what factors should be considered when calculating a LMWH treatment dose following a VTE in non-pregnant adult patients with a high body weight, defined as more than 120 kg. It focuses on enoxaparin, dalteparin and tinzaparin.

Answer

The factors to consider when using LMWH to treat VTE in high body weight patients include:

1. what weight measure to use when calculating the dose and whether the dose should be capped;
2. the frequency of LMWH dosing;
3. monitoring requirements;
4. practical issues around prescribing and administration.

1. Total body weight or lean body weight

It is generally accepted that body composition has an impact on how individuals handle drugs (4).

In general terms total body weight (TBW) has been proposed as the best single descriptor for estimating volume of distribution (Vd) and lean body weight (LBW) as a better predictor of drug clearance (5). No single body size descriptor has been accepted universally for dose adjustment in patients with high body weight and there is conflicting opinion on which descriptor is most appropriate for dose calculation of LMWHs (5).

LMWHs are hydrophilic compounds (6, 7). Their distribution tends to be confined to the intravascular space which is similar to plasma volume (8-10). Patients with high body weight normally have a higher plasma volume than the general population, so it is reasonable to accept that the Vd of LMWHs is increased in this patient population (11). However, this increase is not directly proportional to the TBW (11).

Although no robust data exist, most available evidence suggests that it is safe to use TBW when calculating treatment doses of LMWHs for high body weight patients, and that dose capping should not be used as this can lead to underdosing (10, 12, 13). This approach is off-label for dalteparin as manufacturers recommend the use of daily doses no higher than 18,000 units (2). Evidence available is limited to patients weighing up to 144 kg for enoxaparin, 190 kg for dalteparin and 165 kg for
tinzaparin (12, 13). A large proportion of evidence comes from pharmacodynamic studies (14-18). The main limitations of current evidence are the small size of study samples and the use of anti-Xa levels as a surrogate measure of efficacy and safety instead of clinical outcomes such as incidence of bleeding, VTE recurrence or mortality. One open-label retrospective study including 193 patients investigated the use of TBW for the calculation of VTE treatment doses of dalteparin and used major haemorrhage as the primary outcome measure (19). Despite the limitations of their method, the authors concluded that the bleeding rate associated with TBW dosing in patients with high body weight is comparable to that observed in other patient groups being treated with dalteparin. Although the limited evidence suggests that the use of TBW may be safe, it has been proposed by some experts that LBW is a more appropriate parameter to use for the calculation of treatment doses of LMWH in patients with high body weight because TBW does not take into account the clearance rate of these drugs in this patient group (6). The use of LBW for LMWH dose calculation in this patient population has been studied by Green and Duffull (20). They propose complex LBW calculations and twice or thrice daily dosing. This evidence is limited to pharmacodynamic studies using enoxaparin only in patients up to 160 kg (20). A conventional versus individualised dosing regimen was compared in a randomised, controlled, double blind trial (21). The study included 122 patients, 11 of whom weighed 100 kg or more. Both arms used the same dosing regimen for patients < 100 kg. For patients ≥ 100 kg, the use of TBW in the conventional arm was compared to the use of LBW. The authors concluded that the use of LBW resulted in a reduction of bleeding and major bruising in their overall patient sample, however, specific results for patients with high body weight are difficult to interpret given the small patient numbers.

In summary, it is accepted that both TBW and LBW can be used for dose calculation of LMWH in patients with high body weight. The use of TBW involves administration of large doses of LMWH whereas the use of LBW involves complex dose calculations. Evidence on both approaches remains scarce.

2. Frequency of dosing

As mentioned previously, twice daily dosing for the treatment of VTE is an off-label use of enoxaparin and tinzaparin (1, 3). The recommendation from dalteparin manufacturers is that this should be prescribed as a once daily medicine but twice daily dosing should be considered for patients with an increased risk of bleeding. (2)

The use of TBW for the calculation of LMWH treatment doses in patients with high body weight can result in the prescribing of very high individual daily doses. This raises safety concerns regarding the need to split doses to avoid excessive peaks of drug activity and injection site bruising.

The frequency of LMWH dosing for the initial treatment of VTE in the general population has been the subject of a review by the Cochrane Collaboration (22). The authors concluded that overall once daily treatment is as effective and safe as twice daily treatment with LMWH, however, there was no specific analysis of results for patients with high body weight.

Only one retrospective, open-label study of 21 patients was identified comparing the same treatment dose of dalteparin given to patients with high body weight as a single or twice daily split dose (15). The dose was calculated based on the patients’ TBW. The findings suggest that twice daily dosing was more effective in producing anti-Xa activity within the target range, however, the small sample size of this study is a significant limitation. Following a large randomised, multicentre, partially blinded clinical trial, the Enoxaparin Clinical Trial Group reported that enoxaparin 1.5 mg/kg once daily and enoxaparin 1 mg/kg twice a day were clinically equivalent in the treatment of venous thromboembolic disease, despite a statistically non-significant trend of increased VTE recurrence in obese patients treated with enoxaparin once a day (n=137; 7.3%) when compared to twice a day (n=146; 3.4%) (23).

In summary, off-label twice daily dosing of enoxaparin and tinzaparin may be acceptable in certain circumstances where the total daily dose is high. Evidence for twice daily dosing of enoxaparin and tinzaparin remains scarce. Whether prescribing a once daily or twice daily regimen, if prescribing an off-label dose of LMWH it is reasonable to monitor anti-Xa levels to reduce the risk of over and under anticoagulation.
3. Monitoring of anti-Xa levels

One key aspect when adjusting LMWH doses in patients at extremes of body weight is to ensure that adequate monitoring is in place to ascertain that therapeutic levels are achieved and to monitor for drug accumulation (12, 13). Despite reservations on how well anti-Xa levels relate to clinical outcomes, this remains the best parameter available to monitor for the safety of LMWH use in ‘at risk’ patient groups (24, 25).

It is generally recommended that a peak anti-Xa level is checked 4 hours after the LMWH dose (12). Local haematology departments should be consulted to advise on monitoring requirements (e.g. when to initiate monitoring and how frequently this is required), and the most suitable target range for anti-Xa activity due to small variations in laboratory techniques.

4. Practicalities around safe prescribing and administration

If it is considered necessary to split the daily dose of LMWHs, a risk assessment must be made to ensure that increasing the frequency of dosing does not impact on other aspects of patient treatment. For example, care must be taken to avoid giving LMWHs too close to any recent or planned spinal interventions (including spinal or epidural anaesthetics, removal of epidural catheters, lumbar punctures, etc) as this can result in a serious adverse event (1-3, 26).

The complexity of dose calculations should also be taken into account and, where possible, clear dose banding advice should be produced to enable the use of pre-filled syringes (27). This may involve rounding doses up or down as necessary.

Summary

Treatment of VTE in patients with high body weight constitutes a challenge in clinical practice. Adjustments in the dose calculation may be necessary in certain circumstances and may justify the off-label use of LMWHs. This decision should however be made following careful consideration of both the clinical and practical risks introduced by changing standard practice in the prescribing of LMWHs. Monitoring anti-Xa levels is key to the safe use of these medicines in patients who receive an altered dosage regimen.

The lack of clear guidance within these product licences and the published literature may require the development of local specialist advice to support the management of these patients. Such a guideline has been developed within NHS Greater Glasgow and Clyde (available on request). It should be noted that this guidance is based on local specialist consensus and describes off-label use of LMWHs.

Limitations

This guidance is for adult patients only and it does not apply to pregnant women.
The content of this document is based on limited clinical evidence and should only be used as a guide for dosing adjustments until further data are available. This is not a comprehensive review of all LMWHs and only includes information on enoxaparin, dalteparin and tinzaparin.

References

(2) Summary of Product Characteristics – Fragmin® 18,000 IU/0.72ml solution for injection (dalteparin). Pfizer Ltd. Accessed via http://www.medicines.org.uk/emc/medicine/26892 on 13/04/2016 [date of revision of the text 01/05/2013].
(3) Summary of Product Characteristics – Innohep® syringe 20,000 IU/ml (tinzaparin). Leo Laboratories Ltd. Accessed via http://www.medicines.org.uk/emc/medicine/29741 on 13/04/2016 [date of revision of the text 06/03/2016].


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Search strategy

Embase
: exp low molecular weight heparin/ AND exp pharmacokinetics/ AND limit ‘2013-current’ AND exp obesity/

Medline
: exp Heparin, Low-Molecular-Weight/ AND exp pharmacokinetics/ AND [exp weight gain/ OR exp obesity/ OR exp obesity, morbid/] AND limit ‘2013-current’

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