CORRESPONDENCE

Treatment of Deep Vein Thrombosis in the Pelvis and Leg

by Prof. Dr. med. Viola Hach-Wunderle, Prof. Dr. med. Markus Düx, Anja Hoffmann, Dr. med. Florian Präve, Prof. Dr. med. Max Zegelman, Prof. Dr. med. Wolfgang Hach in volume 1–2/2008

Variability of the Intravascular Space

I would like to point out a number of errors and make a few comments. In table 1, the approved low-molecular-weight heparins (LMWH) are listed; in the adjacent column, it is stated that LMWH should be given in doses adapted to the patient's body weight. This is not true of all LMWH, however: certoparin is approved for the treatment of deep vein thrombosis in a dosage of 8000 IU anti-Xa b.i.d., independently of body weight. In general, it seems to me that the authors fail to address the issue of body-weight-adjusted administration of LMWH in a critical manner. This type of administration is often inappropriate from the pharmacological point of view. The authors do, indeed, write that an abnormal body weight should be taken into account, among other factors, but they do not explain why. The reason can be stated simply enough: LMWH are strongly hydrophilic substances that are distributed exclusively in the intravascular space once they are absorbed after subcutaneous injection. The size of the intravascular space, which is the smallest distributive space in the body, depends only in part on body weight. It indeed increases with increasing muscle and organ mass, but not with an increase in body weight due to fatty tissue. Thus, two patients of identical weight, but different heights, can have intravascular spaces of very different sizes. It follows that, despite the relatively wide therapeutic window of LMWH, dosing them exclusively on the basis of the patient's body weight would lead to overdosing of short but markedly overweight patients, which would then be likely to produce hemorrhagic complications. This risk of overdose can be avoided by basing the LMWH dose not on the patient's body weight per se, but rather on his or her normal weight – or else by using an LMWH preparation that can be given in a dose that is independent of body weight. This is not a new idea, by the way; I read it for the first time in 1983, in my pharmacology textbook (1). DOI: 10.3238/arztebl.2008:0344a

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Evaluate Thrombophilia First

In this otherwise excellent CME article, one important fact is missing that would be essential for treating physicians to know. The once-daily dosing of nadroparin as recommended in table 1 seems not to be applicable to the thrombophilic patient without serious implications, according to the product's Summary of Product Characteristics (European Medicines Agency) and „Fachinformation“ (Bundesinstitut für Arzneimittel und Medizinprodukte). Both agencies are cautioning against a once-daily administration "in patients with thrombophilia", where "a twice daily administration of nadroparin should be considered", instead. It follows, therefore, that a single daily dose of nadroparin is an unsuitable means of providing immediate and effective anticoagulation to a large percentage of patients with thromboses, because time-consuming screening for thrombophilia would have to be evaluated first if this drug was to be given in compliance with the above recommendations. This limitation does not apply to any other low-molecular-weight heparin. DOI: 10.3238/arztebl.2008:0344b

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Severe Renal Insufficiency

The molecular-weight-dependent risk of accumulation of low-molecular-weight heparins (LMWH) in the setting of renal failure is widely accepted. Unfortunately, the attribution of diagram 2 was omitted (from the work of S. Alban). Fondaparinux is discussed in the article as if it were comparable to enoxaparin; one must realize, however, that the cited study by Büller et al. (1) excluded patients with an elevated creatinine concentration – yet it is precisely these patients who so often present for treatment, among others, in everyday practice.

A look at the information for physicians with regard to fondaparinux reveals that even a moderate degree of renal insufficiency led to hemorrhagic complications in 6.6% of patients, while severe renal insufficiency did so in 14.5%. The figures for enoxaparin are similar; this clearly indicates that low molecular weight, renal function, and hemorrhagic tendency are closely associated with one another. Fondaparinux is absolutely contraindicated in patients with severe renal insufficiency. For enoxaparin, an adjustment of the dose is recommended, yet treating physicians often will not even know whether renal insufficiency is present, let alone how severe it is. Protamine is available as an antidote for low-molecular-weight

heparins, but no such antidote is available for fondaparinux. In view of these facts, I think it is rather bold to call fondaparinux "a good alternative" to heparins. At most, one can say that it might be an alternative if there is a reason why low-molecular-weight heparins cannot or should not be given.

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In Reply:

We are grateful for the many positive reactions to our article and are glad to provide the following answers to the critical remarks that were expressed.

Dr. Spannagel points out that the low-molecular-weight heparin (LMWH) certoparin is particularly useful in view of the fact that it can be given in a fixed daily dose, independently of the patient's body weight. This can also be seen from our table 1. If this drug is used, it should be borne in mind that patients weighing less than 60 kg should be carefully monitored, as they are at an increased risk of hemorrhage. This recommendation implies that the ideal dosing of certoparin also depends, to some extent, on body weight.

The information we gave about the dosing of low-molecular-weight heparins corresponded to the doses in which they were approved. There is no adequate evidence to date regarding dose adjustment by normal weight (1, 2).

Dr. Rippich raises the issue of a possible limitation of the approval of nadroparin in a single daily dose for the treatment of acute venous thrombosis if the patient is known to have thrombophilia, or if a diagnostic evaluation for thrombophilia has not yet been performed. This supposition is incorrect. Nadroparin is explicitly approved for the treatment of acute venous thrombosis. The information for physicians states, "The administration of nadroparin in two doses per day should be considered in patients with thrombophilia, complicated deep vein thrombosis, or an elevated risk of hemorrhagic complications." This means merely that, if the physician knows that thrombophilia or a very severe or extensive thrombosis is present, a twice-daily application of LMWH can be considered because of its better pharmacokinetics, with a more evenly distributed effect over a 24-hour period.

Dr. Trieb once again gives a stern warning, from the urological point of view, about the accumulation of low-molecular-weight heparins, and fondaparinux as

well, in patients with renal failure, leading to a risk of hemorrhage. Here we can only agree. In patients with acute venous thrombosis, the serum creatinine concentration should be determined as part of the initial laboratory testing, and, if the creatinine clearance is impaired, the dose of the medication should be adjusted, or else it should be switched to unfractionated heparin.

The relation between the molecular weight of LMWH and their accumulation in renal failure was published by Professor Dr. S. Alban of the Pharmacology Department at the University of Kiel (3).

In the rare case of uncontrollable hemorrhage, LMWH can be partially antagonized with protamine. If fondaparinux was used for anticoagulation, recombinant factor VII could be considered in order to counteract bleeding.

Fondaparinux is, indeed, a good alternative to LMWH for the treatment of acute venous thrombosis. This is indicated by the extensive study data that are now available, by its simultaneous approval for the treatment of pulmonary embolism, and by the obviated need for regular checking of the platelet count because of the very low risk of an immune reaction.

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