REVIEW

The development and introduction of biosimilar anticoagulants – focus on enoxaparin

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Abstract: The aims of this paper are to discuss the: (1) pharmacology of low-molecular-weight heparins (LMWHs) emphasizing their synthesis, mechanism of action, and comparison with the parent compound, unfractionated heparin (UFH); and (2) recent controversial approval by the Food and Drug Administration (FDA) of a generic enoxaparin. Enoxaparin is one of several LMWHs that are currently available worldwide for clinical use. LMWHs are derived by chemical or enzymatic depolymerization of the "parent" molecule, UFH. Both UFH and LMWHs exert their primary antithrombotic effect by binding to and catalyzing the naturally-occurring anticoagulant, antithrombin. LMWHs are more effective at inhibiting factor Xa than factor IIa (thrombin). They also produce less heparin-induced thrombocytopenia and osteoporosis than UFH and are at least as effective and safe as UFH for each approved indication. They are safe and effective when given subcutaneously once or twice daily, without the need for anticoagulant monitoring, and are suitable for out-of-hospital treatment. The FDA first approved enoxaparin (Lovenox®) in March 1993. Despite its cost effectiveness, individual patients without drug insurance are often left paying for the cost of the drug. Uninsured pregnant subjects are particularly disadvantaged because they often require several months of therapy, costing several thousand dollars. To evaluate a less expensive, generic enoxaparin, the FDA chose to use the "abbreviated new drug application" because it considered enoxaparin to be a drug rather than a biologic medicine. This requires that the generic enoxaparin meets the following five criteria for "sameness": equivalence of (1) UFH source material and method of depolymerization; (2) physicochemical properties; (3) disaccharide building blocks, fragment mapping, and sequence of oligosaccharide species; (4) biological and biochemical assays; and (5) in vivo pharmacokinetic profile. Based upon meeting these criteria, and despite protests from several outside expert groups, the generic enoxaparin was approved by the FDA in July 2010.

Keywords: antithrombotic therapy, enoxaparin, unfractionated heparin, low molecular weight heparin

Background

Enoxaparin is one of several low-molecular-weight heparins (LMWHs) currently available worldwide. Over the last 30–40 years, LMWHs have been rigorously evaluated and are indicated for the prevention and treatment of arterial and venous thromboembolism.[1] The aims of this paper are: (1) to discuss briefly the pharmacology of LMWHs emphasizing their synthesis, discussing their mechanism of action, and comparing and contrasting them with the parent compound, unfractionated heparin (UFH); and (2) to discuss the recent controversial approval by the Food and Drug Administration (FDA) of a generic enoxaparin. The parent compound of all LMWHs

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is UFH, usually derived from porcine intestinal mucosa or bovine lung mucosa.[2] UFH is a glycosaminoglycan consisting of a heterogeneous mixture of polysaccharide chains with molecular weights ranging from 3000–30,000 Da.[1] These chains consist of alternating residues of D-glucosamine and uronic acid, iduronic acid, or glucuronic acid.[3] All LMWHs are prepared by enzymatic or chemical "depolymerization" of UFH resulting in chain lengths with mean molecular weights of approximately 5000 Da.[1] Both UFH and LMWHs exert their anticoagulant effect by catalyzing antithrombin, an effect that is mediated by unique and randomly distributed pentasaccharide sequences.[1,4,5] About one-third of UFH chains, compared to one-fifth of LMWHs, contain these pentasaccharide sequences. By catalyzing antithrombin, it is thought that the primary anticoagulant effects of UFH and LMWHs are mediated via antithrombin-induced inhibition of factor Xa and thrombin (factor IIa). This ternary complex of heparin, antithrombin, and factor Xa or thrombin causes an inhibition of the procoagulant effects of factor Xa and thrombin.[5] Because heparin chain length (ie, at least 18 oligosaccharide units) is vital for heparin–antithrombin-mediated thrombin, but not factor Xa inhibition, the so-called antifactor Xa/IIa ratio is 1:1 for UFH, but greater than 1:1 for all LMWHs.[6] Enoxaparin is produced by benzylation and alkaline depolymerization of UFH resulting in a LMWH with a mean molecular weight of 4200 Da and an antifactor Xa/IIa ratio of 3.8.[6] In contrast, tinzaparin has a mean molecular weight of 4500 Da and an antifactor Xa/IIa ratio of 1.9, whereas dalteparin has a mean molecular weight of 6000 Da and an antifactor Xa/IIa ratio of 2.7.[1,6]

Comparison of UFH and enoxaparin

LMWHs have virtually replaced UFH for most clinical situations in which a rapid-acting parenteral anticoagulant is indicated. This is due to several pharmacokinetic and pharmacodynamic advantages.

Anticoagulant monitoring

When used in full treatment doses (eg, for treatment of acute venous thromboembolism), most centers administer UFH by continuous intravenous infusion, whereas LMWHs (for treatment and prophylaxis) and prophylactic UFH are usually administered by subcutaneous injection. UFH must be monitored with a coagulation test, such as the activated partial thromboplastin time,[7] because of the wide interpatient variability of heparin dose requirements, whereas LMWHs (for most patients) don't require lab monitoring. This is due to several factors:

1. The presence – in variable amounts – of heparin-binding proteins, such as fibronectin, vitronectin, and histidine-rich glycoprotein, which bind to and neutralize UFH.[8] These plasma proteins are present in increased concentration in sick patients. LMWHs bind far less than UFH to these proteins.
2. UFH binds to endothelial walls, whereas LMWHs bind very little.[9]
3. UFH binds to macrophages more than LMWHs resulting in a dose-independent clearance mechanism, part of the reason why LMWH have a longer half-life than UFH.[1]

Consequently, the majority of patients receiving LMWH do not require anticoagulant monitoring, whereas those receiving full-dose UFH do. One group of patients in whom caution must be shown with LMWH is those with impaired renal function. If renal function is impaired, some experts avoid LMWH and use intravenous UFH, whereas others empirically reduce the dose of LMWH and/or measure antifactor Xa levels.

Heparin-induced thrombocytopenia

This is a dreaded immune-mediated complication of heparin therapy and is associated with limb- or life-threatening arterial and venous thrombosis. It is a relatively common complication of UFH (~1%–3%) that is less common (<1%) with LMWH.[10]

Heparin-induced osteoporosis

This is a potential problem in patients who receive long-term ($\geq$1 month) heparin. This can present with symptomatic fractures or with subclinical reduction in bone density that is probably not totally reversible.[11,12] The largest group of patients that receives long-term heparin is pregnant women who have a high risk of arterial or venous thromboembolism and some subgroups of pregnant women with prior multiple pregnancy losses. There are convincing data that osteoporosis is less common in LMWH-treated patients than UFH-treated patients.[11,12]

Comparison of efficacy and bleeding of UFH and LMWH

Several large randomized trials have compared LMWHs (including enoxaparin) and UFH for the treatment of acute venous thromboembolism, including patients whose primary presentation was with a lower extremity deep vein thrombosis or with pulmonary embolism.[13,14] To summarize, the studies show that 1.5 mg/kg (ie, 150 antifactor Xa units/kg) once daily or 1.0 mg/kg twice daily of subcutaneous enoxaparin

is as effective and safe as intravenous UFH. Moreover, patients could be treated outside of hospital when receiving enoxaparin. However, UFH – because of the need for intravenous infusion and frequent activated partial thromboplastin time monitoring – is unsuitable for outpatient treatment. In contrast, because of the amenability of subcutaneous injection to out-of-hospital treatment and the lack of need for activated partial thromboplastin time monitoring, most patients with deep vein thrombosis and many patients with pulmonary embolism can be treated out of hospital with enoxaparin.

Approved indications for enoxaparin

These, along with the appropriate dose regimens, are summarized in Table 1. Based upon a concern by the FDA about the risk of epidural hematomas with epidural analgesia associated with initiation of LMWHs (and all heparin-related compounds) preoperatively, they issued a "black box" warning (Table 2).

Generic enoxaparin

The FDA first approved enoxaparin (Lovenox®; Sanofi SA, Paris, France) in March 1993. In view of the widespread use of Lovenox (Table 1), despite its cost effectiveness from a societal point of view, individual patients are often left paying for the cost of the drug depending on whether they have

Table 1 Enoxaparin dosage and administration

Indication	Standard regimen
VTE prophylaxis in abdominal surgery	40 mg SC once daily for up to 12 days
VTE prophylaxis in knee replacement surgery	30 mg every 12 hours for up to 14 days
VTE prophylaxis in hip replacement surgery	30 mg SC every 12 hours or 40 mg SC once daily for up to 14 days
VTE prophylaxis in medical patients	40 mg SC once daily for up to 14 days
Inpatient treatment of acute DVT with or without pulmonary embolism	1 mg/kg SC every 12 hours or 1.5 mg/kg SC once daily (with warfarin) for up to 17 days
Outpatient treatment of acute DVT without pulmonary embolism	1 mg/kg SC every 12 hours (with warfarin) for up to 17 days
Unstable angina and non-Q-wave MI	1 mg/kg SC every 12 hours (with aspirin) for 2–8 days
Acute STEMI in patients < 75 years of age	30 mg single IV bolus plus 1 mg/kg SC dose followed by 1 mg/kg SC every 12 hours for at least 8 days (with aspirin)
Acute STEMI in patients > 75 years of age	0.75 mg/kg SC every 12 hours (no bolus) for at least 8 days (with aspirin)

Note: Adjust the dose for patients with severe renal impairments.
Abbreviations: DVT, deep vein thrombosis; IV, intravenous; MI, myocardial infarction; SC, subcutaneous; STEMI, ST-segment elevation myocardial infarction; VTE, venous thromboembolism.

Table 2 Black box warning: spinal/epidural hematoma

Epidural or spinal hematomas may occur in patients who are anticoagulated with low-molecular-weight heparin or heparinoids and are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:
- Use of indwelling epidural catheters
- Concomitant use of other drugs that affect homeostasis, such as nonsteroidal anti-inflammatory drugs, platelet inhibitors, and other anticoagulants
- A history of traumatic or repeated epidural or spinal punctures
- A history of spinal deformity or spinal surgery

Monitor patients frequently for signs and symptoms of neurological impairments. If neurological compromise is noted, urgent treatment is necessary

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis

insurance to pay for the drug and depending on the location (in hospital or out of hospital) of drug therapy. Uninsured pregnant subjects are particularly disadvantaged because they often require several months of therapy, which could cost several thousand dollars. The economic burden falls not only on patients, but also on nationally funded healthcare services such as those in the United Kingdom. Because the drug is expensive, the impetus to approve a less expensive, generic version of enoxaparin grew. There are two major pathways for approval of "generic" drugs by regulatory agencies: (1) the abbreviated new drug application, and (2) the biosimilar pathway. The former is used for drugs and is generally associated with more rapid evaluation and approval, whereas the latter is used for biologic medicines. The FDA considers enoxaparin to be a drug rather than a biologic medicine. This is the easier of the two routes and requires that the generic meets the following five criteria for "sameness":

1. Equivalence of UFH source material and method of depolymerization.
2. Equivalence of physicochemical properties.
3. Equivalence in disaccharide building blocks, fragment mapping, and sequence of oligosaccharide species.
4. Equivalence in biological and biochemical assays.
5. Equivalence of in vivo pharmacokinetic profile.

On July 23, 2010, the FDA approved the abbreviated new drug application by Sandoz Inc (Princeton, NJ) for a generic enoxaparin as the agency was satisfied with the active ingredient "sameness" and the interchangeability of Lovenox with this generic version. This caused considerable controversy and confusion. The European Medicines Agency views them as biologic medicines and will therefore

regulate copies of LMWHs via a biosimilar pathway because only similar copies can be manufactured. They also require well-designed clinical trials to establish that the biosimilars have comparable efficacy and safety as the branded LMWHs.

The approval by the FDA of generic enoxaparin was met with many negative reviews. It came on the heels of many adverse patient experiences with UFH and case reports of adverse experiences with the use of generic enoxaparin. In the United States, there were as many as 140 deaths from anaphylaxis caused by UFH contaminated with chondroitin sulfate.[15] This led many groups of experts to heavily criticize the FDA for relatively lax approval of generic enoxaparin by obviating the need for clinical trials of this agent; many expressed the need for a broad consensus defining the minimum attributes of copies of LMWHs, particularly those required for efficacy and safety.

In July 2010, the FDA responded to a citizen petition (and many addenda) submitted on behalf of Sanofi between 2004 and 2009. In brief, the petition asked for the FDA to hold off on approving generic enoxaparin unless the manufacturers of the generic could show that their manufacturing process was equivalent to that of Sanofi or until properly designed clinical trials showed equivalent safety and efficacy of the generic compound to Lovenox. The petition also requested that the generic enoxaparin contains the 1,6 anhydro ring structure at the reducing ends of 15%–25% of its saccharide chains. The FDA agreed with the latter but denied other requests by the citizens' petition.

This abbreviated new drug application flew in the face of several other groups of thrombosis experts and the European Medicines Agency, who required clinical trial proof of equivalence as a minimum prior to approval.[16] Part of the difficulty is because of the lack of a predictive biomarker that correlates well with clinical outcomes. Although antifactor Xa levels have been used to approximate the blood concentration of enoxaparin, a therapeutic range using this assay has yet to be established. The disasters with generic UFH have raised red flags, underlining the need for close scrutiny of the manufacturing process for any generic enoxaparin. In addition, the diseases that are treated with enoxaparin (venous thromboembolism, acute coronary syndromes) are sufficiently dangerous that inadvertent over- or underdosing could have dire consequences. It is somewhat ironic that the United States, which has a very high rate of successful "class action" law suits against pharmaceutical companies when patients suffer adverse experiences, should be fairly aggressive in approving generic enoxaparin. Until the generic

enoxaparin has a sufficient "track record" to gauge its efficacy and safety, as well as to ensure the manufacturing process is similar to that of Lovenox, it is probably prudent for clinicians prescribing the drug to explain that they are receiving a generic substitute.

In defense of the FDA, the probability that the generic enoxaparin prototype is as safe and effective as Lovenox is high. In addition, since enoxaparin is used in multiple clinical settings, clinical trials demonstrating equivalence would require thousands of patients, cost of millions of dollars, and probably result in a significant increase in the cost of the generic enoxaparin.

Disclosure

The author reports no conflicts of interest in this work.

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