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Use of Enoxaparin in Patients with Chronic Kidney Disease

Safety Considerations

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Patients with advanced chronic kidney disease (CKD) are frequently viewed as being at high risk for bleeding. This dogma has been carried through several decades and is not without an experimental and clinical basis.[1] In point of fact, however, CKD patients not only maintain a bleeding tendency but also exhibit a high frequency of thromboembolic disease. As such, cardiovascular disease ranks as the leading cause of death in patients with CKD.[2]

Given the high prevalence of coronary artery disease and acute coronary syndrome (ACS) in this population, clinicians are frequently confronted with choosing the most appropriate antithrombotic therapy in CKD patients undergoing percutaneous coronary intervention. Pivotal clinical trials such as TIMI (Thrombolysis In Myocardial Infarction) 11B[3] and ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin versus intravenous unfractionated heparin, in Non-Q-wave Coronary Events)[4] have established the superiority of enoxaparin, a low-molecular weight heparin (LMWH), over unfractionated heparin (UFH) in patients experiencing ACS. The efficacy advantage of enoxaparin relative to UFH is also supported by a more predictable pharmacokinetic profile and anticoagulant effect, and a more favourable safety profile. Regardless of these recognised advantages, CKD patients present a special circumstance in that enoxaparin carries a perceived, if not real, increased risk of adverse bleeding in these patients compared with individuals with normal renal function. Several reasons for this have been postulated, and research actively continues in this area; however, gleaning such information from trial data is daunting given the lack of covariate adjustment and the fact that CKD patients may be at risk for bleeding without anticoagulant therapy. This commentary provides a perspective on the clinical use of enoxaparin in patients with CKD.

1. Enoxaparin Administration and Clinical Pharmacokinetics

Enoxaparin sodium is prepared by the depolymerisation of porcine heparin. Once administered, enoxaparin induces a conformational change in the structure of antithrombin, which subsequently complexes with activated factor II (thrombin) and activated factor X, leading to their respective inactivation. Following its subcutaneous injection, enoxaparin is well absorbed (bioavailability >90%), and it exerts its full anticoagulant effect, as measured by antifactor Xa activity, approximately 4–6 hours after administration. Its systemic elimination is thought to occur through non-saturable reticuloendothelial/renal pathways,[5,6] with clinical data demonstrating a strong linear correlation between decreased renal

function (as determined by creatinine clearance CL_{CR}) and clearance of antifactor Xa activity.[7] The plasma clearance of enoxaparin in healthy subjects has been reported to range from 0.8 to 1.9 L/h, and the half-life of antifactor Xa activity is approximately 4 hours in healthy volunteers.[5] For the treatment of thromboembolic disorders, the standard enoxaparin dosages are 1 mg/kg subcutaneously every 12 hours or 1.5 mg/kg subcutaneously once daily,[8] with a corresponding peak antifactor Xa activity target range of 0.5–1.0 IU/mL.

2. Enoxaparin Pharmacokinetics and Pharmacodynamics in Chronic Kidney Disease

There are conflicting data regarding the pharmacokinetics of enoxaparin in CKD with regard to its half-life and accumulation kinetics in patients with moderate to severe degrees of renal insufficiency. Much of this discrepancy results from variations in study design, the degree of CKD being studied and issues of factor Xa assay methodology. Although a target range for antifactor Xa activity (0.5–1.0 IU/mL) has been proposed, few data have correlated this range with specific clinical outcomes. Anecdotally, although a patient may have a therapeutic level of antifactor Xa activity in plasma, they may still experience a bleeding event.

The lack of correlation between antifactor Xa activity and bleeding risk may relate to factor Xa being only an intermediate step in an otherwise complex clotting cascade. Another theory suggests that enoxaparin undergoes degradation into smaller, active heparin fractions that are renally cleared.[9,10] It is possible that these heparin fragments go unmeasured by the conventional antifactor Xa assay; therefore, CKD patients may have a greater anticoagulant effect for a given antifactor Xa concentration compared with patients with normal renal function. This is a promising theory when considering studies between healthy volunteers and those with CKD that have demonstrated a prolonged thrombin generation time despite similar antifactor Xa concentration-time data.[9,10]

A final consideration with enoxaparin use in patients with CKD is the early risk (within days of administration) of developing hyperkalaemia.[11] This phenomenon relates to the suppressive effect of this compound on aldosterone production and is, in part, dependent on the plasma concentration of enoxaparin.

3. Is Enoxaparin Associated with Increased Bleeding in Clinical Trials?

In major clinical trials, enoxaparin has been associated with increased bleeding rates in CKD patients. A recent meta-analysis carefully described the available data for all LMWH products in non-dialysis-dependent CKD patients with respect to this clinical problem.[12] In the primary analysis, 4971 patients with a creatinine clearance of <30 mL/min had an increased risk of bleeding compared with those without renal insufficiency (5.0% vs 2.4%; odds ratio [OR] 2.3; 95% CI 1.2, 4.3; $p = 0.01$).[12] In a secondary product-based analysis of these same data, enoxaparin use increased the rate of major bleeding to 6.0% in CKD patients compared with 2.4% in non-CKD patients (OR 2.6; 95% CI 1.2, 4.3).[12] The likelihood of a major bleeding event was related to the enoxaparin dosing regimen used. Unadjusted standard dosing (i.e. 1 mg/kg every 12 hours) in patients with underlying CKD increased major bleeding to 8.3% versus 2.4% in non-CKD patients (OR 3.9; 95% CI 1.2, 4.3). When an adjusted-dose enoxaparin regimen was used in CKD patients, the rates of major bleeding were much less (0.9% vs 1.9% in non-CKD patients; OR 0.58; 95% CI 0.09, 3.78).

Although these data are very suggestive of an increased bleeding risk with enoxaparin therapy in the CKD patient, caution should be used in their interpretation. The studies evaluated in this meta-analysis were quite heterogeneous. For example, the analysis did not take into consideration the number of doses of enoxaparin administered, differences in the length of follow-up, how renal function was estimated and/or whether antiplatelet and antithrombin medications, such as aspirin, clopidogrel, bivalirudin, lepirudin and glycoprotein IIb/IIIa in-

hibitors were being used. Like enoxaparin, many of these drugs undergo substantial renal clearance, and it stands to reason that bleeding risk would increase with their use in CKD patients proportional to the degree of renal insufficiency.

Nonetheless, the results from this meta-analysis provide a reasonable basis on which to conclude that standard-dose enoxaparin therapy increases the risk of bleeding in patients with CL_{CR} <30 mL/min and that dose adjustment should routinely be used in this population.

4. Perspective

Based on the above findings, one would think that UFH would be a safer alternative in CKD patients. However, this has not been found to be the case. A subgroup analysis of those patients in the TIMI 11B and ESSENCE studies with severe renal impairment, found that UFH and enoxaparin carried similar risks of major bleeding.[13] Another study performed in a community hospital setting also found similar major bleeding rates regardless of whether enoxaparin or UFH was used.[14]

In light of the increased bleeding risk associated with CKD, the manufacturer of enoxaparin recently changed the dosing recommendations in the package insert. In patients with CL_{CR} <30 mL/min, the manufacturer recommends that the enoxaparin dosage be adjusted to 1 mg/kg every 24 hours.[8] Unfortunately, the manufacturer has not published details of how these recommendations were developed, but it is likely that they are linked to the decreased renal elimination of enoxaparin. Although the suggested once-daily regimen seems like a logical approach, it may be less effective because it results in a wide variation in antifactor Xa activity. Indeed, there could be relatively long periods of time when enoxaparin-treated patients would have antifactor Xa activity below the target range. To date, no studies have assessed the efficacy or safety of this particular dosing regimen.

Other authors have suggested different enoxaparin dose adjustments. Studies by Collett et al.[15,16] have shown that an enoxaparin regimen of 0.65 mg/kg twice daily results in therapeutic antifactor Xa activity without excess bleeding in patients with ACS. In another population pharmacokinetic study, Hulot et al.[17] suggested that a one-time enoxaparin dose of 1 mg/kg followed by a dosing schedule of 0.6 mg/kg twice daily should maintain antifactor Xa activity within the target range.

5. Conclusion

It is relatively clear from the data that, if therapeutic doses of enoxaparin are to be used for systemic anticoagulation in patients with CL_{CR} <30 mL/min, dose-reduction should be used. This is especially true for patients receiving concomitant antiplatelet or antithrombotic therapy. Unfortunately, what has been regarded as the most appropriate dose reduction in CKD has not been sufficiently evaluated by prospective clinical trials. Based on our experience and previous clinical trials, we believe that either UFH or adjusted-dose enoxaparin can be used safely and effectively in CKD patients; however, there are no fully tested dose-reduction regimens in CKD patients. An important advantage of UFH is that its effect can be rapidly reversed with protamine sulfate, whereas reversal of the effect of enoxaparin can prove difficult. Another advantage of UFH is that it has a relatively short half-life (minutes) compared with enoxaparin (hours). Whatever therapy is prescribed, it is imperative that judicious monitoring of the patient's haemoglobin level, as well as screening for signs of bleeding, be performed. Routine monitoring of antifactor Xa activity may help to guide therapy, but the clinician should recognise its inherent limitations.

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