Renal Failure and Low Molecular Weight Heparins. A Dangerous Liaison? The Case of Retroperitoneal Hematoma

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Low molecular weight heparins have been shown to be effective and safe for the treatment of thromboembolic disease [1,2]. The LMWH differ in their mechanism of action from unfractionated heparin by their inhibitory effect against factor Xa and thrombin. In addition, due to their better bioavailability, longer half-life and dose-dependent clearance, the LMWH produce a predictable anticoagulation response, eliminating the need for laboratory monitoring. These advantages have made LMWH an attractive choice for the treatment of acute venous thromboembolism [3]. However, parallel to its increasing popularity and widespread use, there has been an increased incidence of bleeding, specifically of abdominal wall hematoma [4], spinal and epidural hematoma [5], thigh hematoma [6] and retroperitonal hematomas [7–15]. In this edition of *IMAJ*, Kruzel-Davila and co-workers [16] report on four hemodialysis patients who developed a retroperitoneal hematoma after treatment with enoxaparin. Two patients died from bleeding complications. Three patients received full-dose enoxaparin, 1 mg/kg twice daily, for the treatment of deep vein thrombosis, and the fourth patient was treated prophylactically with 1 mg/kg once daily after fixation of a lower limb fracture. Anti-factor Xa activity was not evaluated.

Several questions arise from this report concerning the safety of LMWH, and specifically of enoxaparin, in patients with renal insufficiency. First, is LMWH associated with a greater risk of bleeding as compared with unfractionated heparin in patients with renal failure? Since enoxaparin is entirely excreted by the kidneys, the manufacturers warn against its use in patients with renal insufficiency. Despite these warnings, enoxaparin has been used widely as anticoagulation therapy for patients with varying degrees of renal insufficiency. In a retrospective cohort study, Thorevska et al. [17] compared the bleeding rates in patients with renal insufficiency who had received anticoagulation therapy with either UFH or enoxaparin. Overall, the frequency of bleeding increased with worsening renal insufficiency, irrespective of the agent used. However, minor bleeding was significantly more common with enoxaparin than with UFH in the subgroup with severe impairment (68 vs. 27 minor bleeds per 1,000 person-days) [17]. Although this study is limited by its retrospective cohort design, minor (but not major) bleeding was significantly more common with enoxaparin than with UFH among patients with severe renal insufficiency. A similar higher risk for major and any bleeding was associated with severe renal impairment in patients treated with UFH or enoxaparin for acute coronary syndrome [18]. In a meta-analysis of randomized trials, LMWH was found to be as safe and effective as UFH, when used as anticoagulant during hemodyalysis in patients with end-stage renal disease [19]. But as the authors point out, inferences from these trials assessing anticoagulation for patients who undergo hemodialysis will continue to be weak until larger, more rigorous randomized trials are conducted.

Second, are there specific risk factors or predictors of major bleeding complications among renal insufficiency patients treated with LMWH? Several studies suggest that the risk factors for LMWH-associated bleeding are similar to those linked to bleeding induced by UFH, and include age above 70 years, recent trauma or surgery, and concomitant use of aspirin, glycoprotein IIb/IIa inhibitor, and thrombolysis [20,21]. In addition, worsening renal insufficiency (serum creatinine above 1.5 mg/dl) and female gender have also been associated with an increased risk of bleeding [17]. Duration of treatment may also influence the risk for bleeding; in one study, patients receiving anticoagulation therapy for more than 3 days experienced a 180% excess risk of major bleeding compared with patients receiving anticoagulation therapy for 1–3 days. For enoxaparin, whereas only 3.1% of patients treated for 1–3 days had a major bleed, 15.5% of those treated for >3 days had bleeding (relative risk 5.0, 95% confidence interval 1.9 to 12.9). In contrast, for heparin, 48.6% of major and 65.3% of minor bleeding events occurred in the first 3 days of anticoagulation therapy [17]. Interestingly, in this same study, a strong association was found between the degree of renal insufficiency and in-hospital all-cause mortality ($P < 0.0001$).

Third, can safety measures be applied to decrease the risk of bleeding? Can a safer dose be recommended? Reports on excessive drug accumulation and increased half-life of different LMWH in renal insufficiency have led to conflicting recommendations regarding the dose adjustment requirement [22,23]. In December 2003 the official prescribing information for enoxaparin changed to reflect data from new research on enoxaparin pharmacokinetics. For patients with creatinine clearance above

LMWH = low molecular weight heparins
UFH = unfractionated heparin

Table 1. Retroperitoneal hematoma case reports and associated risk factors

Age (yr)	Indication	Dose (mg x 2/day)	RF	Concomitant treatment	Outcome	Author, year [ref]
67	DVT Px	30	No	ASA	Recovered	Klein, 1997 [6]
69	DVT	80	Yes	ASA	Died	Montoya, 1999 [7]
68	DVT	80	Yes		Recovered	Dabneyi, 2001 [8]
46	DVT	60	Yes		Recovered	
74	DVT	80	No	ASA	Recovered	Kumar, 2001 [9]
58	Susp PE	70		ASA	Recovered	Mrug, 2002 [10]
83	NQMI	1 mg/kg		ASA	Died	Chan-Tack, 2003 [11]
70		80	Yes	ASA	Recovered	Melde, 2003 [12]
71		80	Yes	ASA+OAC	Recovered	
77	DVT	100	No	OAC	Died	Vaya, 2003 [13]
76	NSTEMI	1 mg/kg	No	ASA+inh gpIIb/IIIa	Recovered	Aydin, 2003 [14]
70	PE	NS	No	OAC	Recovered	Topgul, 2005 [15]
71	DVT PX	1 mg/kg x1	Yes		Died	Kruzel-Davila, 2005 [16]
72	DVT	1 mg/kg	Yes		Died	
70	DVT	1 mg/kg	Yes		Recovered	
68	DVT	1 mg/kg	Yes		Recovered	

RF = renal failure, DVT = deep vein thrombosis, Px = prophylaxis, PE = pulmonary emboli, NQMI = non-Q wave myocardial infarction, NSTEMI = non-ST elevation myocardial infarction, ASA = aspirin, OAC = oral anticoagulant

30 ml/min the new prescribing information recommends reduced doses of 30 mg once daily for DVT prophylaxis, and 1 mg/kg once daily for treatment of venous thromboembolism, unstable angina, and non-Q-wave myocardial infarction. Standard doses are still recommended for patients with milder degrees of renal impairment. In addition, although prospective studies are needed to evaluate the role of anti-Xa activity monitoring in patients with severe renal insufficiency, it seems a prudent measure. Furthermore, as the bleeding risk increases in patients older than 70 years, until future studies permit solid recommendations dose reduction may be a sensible option.

Finally, although retroperitoneal hematoma is a rare complication of LMWH treatment, in addition to the four cases presented in this issue of *IMAJ* 12 cases had previously been published. Table 1 summarizes these cases of retroperitoneal hematoma and their association with the risk factors.

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DVT = deep vein thrombosis

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