Enoxaparin-induced retroperitoneal haematoma in patients with renal insufficiency

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We have read with particular interest the recent article by Schmid and colleagues [1] on the use and safety of low-molecular-weight heparins (LMWH) in patients with renal insufficiency (RI). As the authors pointed out, the risk of haemorrhagic events is increased in subjects with impaired renal function, independently of the type of anticoagulant used. Low-molecular-weight heparins have been shown to cause fewer bleeding complications than unfractionated heparin (UFH) in most animal and clinical studies, although this benefit is less clear in the presence of a decreased glomerular filtration rate (GFR) [1, 2]. Parallel to its growing clinical use there has been an increased incidence of major bleeding episodes during LMWH administration in recent years, mainly at the injection or instrumentation sites (including abdominal wall or epidural haematomas) [3]. Although it is well described in the context of UFH or cumarinic anticoagulant-based therapies, only a few examples of LMWH-associated spontaneous retroperitoneal haematoma (SRH) have been described in the literature, chiefly on the basis of single case reports [3–9]. Hence we would like to take this opportunity to review our 5-year experience in the management and outcome of this complication, highlighting the role of RI in its incidence. We retrospectively analysed all consecutive patients with the diagnosis "non-traumatic retroperitoneal haematoma" (identified by ICD-10 code K66.1) seen between January 2005 and May 2009 at the University Hospital "12 de Octubre", a 1,300-bed tertiary care centre in Spain. Of a total of 109 patients we selected by chart review those undergoing LMWH therapy at the time of diagnosis. Patients with a recent history of surgical or invasive procedures were specifically excluded. GFR at the time of diagnosis of SRH was estimated according to the 4-variable Modification of Diet in Renal Disease (MDRD) study equation.

Table 1 summarises the clinical and analytical features of the 8 patients (6 males; mean age 75.5 ± 4.5 years [range: 69–83]) diagnosed with SRH in the course of LMWH therapy during the study period. Enoxaparin was the LMWH involved in all cases. It was administered at prophylactic dosage (40 mg subcutaneously every 24 hours) in one patient, the remaining receiving enoxaparin in conventional therapeutic doses (1 mg/kg body weight SC every 12 hours). Concomitant use of oral anticoagulant (acenocumarol) or antiplatelet therapy (aspirin or clopidogrel) was recorded in 4 cases. Four of the patients analysed had moderate renal impairment (GFR 30–59 ml/min) at the time when SRH was diagnosed, and 2 had severe renal impairment (GFR <30 ml/min). The mean total GFR was 44.5 ± 26.7 ml/min. The anti-factor Xa activity was not measured in any of the patients during the course of LMWH therapy. The therapeutic approach was exclusively based on supportive measures (including volume resuscitation and administration of fresh frozen plasma, platelets or packed red blood cells) in 6 cases. A single dose (100 mg/kg body weight intravenously) of recombinant activated factor VII was administered in 2 patients. In addition, one of them underwent selective embolisation of the obturator branch of the right internal iliac artery. Four of the patients died during the hospital stay, amounting to a mortality of 50%. The remaining patients recovered uneventfully.

In the absence of apparent trauma, retroperitoneal haemorrhage most frequently results from a ruptured abdominal aortic aneurysm or bleeding from an underlying renal or adrenal condition [3]. SRH represents an infrequent but potentially fatal complication of LMWH therapy, with a wide spectrum of clinical presentations (ranging from leg pain or paraesthesias to catastrophic haemorrhagic shock), and requires a high level of suspicion for diagnosis [3, 7]. In spite of aggressive management the associated mortality remains high, as our case series exemplifies. Analysis of previous case reports of enoxaparin-induced SRH reveals certain common predisposing risk factors, such as age over 70 years, concomitant administration of oral anticoagulant or antiplatelet agents and, specifically, the presence of RI [6, 9]. Is a well-known fact that renal function impairment causes a delay in the clearance of enoxaparin, resulting in inappropriately elevated levels of anti-factor Xa activity [8, 9]. Some pharmacokinetic analyses of anti-Xa activity suggest dose alterations even in mild to moderate RI (that is, a GFR between 30 and 59 ml/min) [10]. As Schmid and colleagues comment, the efficacy and safety of enoxaparin in the setting of renal function impairment has been sufficiently studied and empirical dose reduction is usually recommended according to established guidelines [1]. On the other hand, both age-related sarcopenia and decline in creatinine clearance may contribute to misdiagnosis of RI in interpretation of serum creatinine levels alone. Our experience therefore illustrates the crucial role of RI in the aetiopathogenesis of enoxaparin-associated SRH, and underpins the need to make regular use of GFR prediction equations when evaluating renal function in elderly patients, before as well as during treatment with LMWH. Although prospective studies are needed to assess the reliability and cost-effectiveness of monitoring anti-factor Xa activity in patients with RI, it seems to be a reasonable measure in preventing such a potentially ominous complication.

Table 1

Clinical features, therapeutic approaches, and outcomes in 8 patients with enoxaparin-associated spontaneous retroperitoneal haematoma (SRH).

Sex / age (years)	Enoxaparin indication	Concomitant treatment[a]	Enoxaparin dose	GFR[b]	Management	Outcome
F / 73	Atrial fibrillation	–	40 mg/12 h	19 ml/min	Supportive	Recovered
M / 69	Atrial fibrillation	–	80 mg/12 h	71 ml/min	Supportive	Died
M / 77	Atrial fibrillation	–	60 mg/12 h	32 ml/min	Supportive	Died
F / 83	NSTEMI	Aspirin and clopidogrel	60 mg/12 h	31 ml/min	Supportive, recombinant activated factor VII	Recovered
M / 71	Atrial fibrillation	Aspirin	80 mg/12 h	53 ml/min	Supportive, recombinant activated factor VII, arterial embolisation	Died
M / 77	DVT prophylaxis	Clopidogrel	40 mg/24 h	18 ml/min	Supportive	Recovered
M / 81	Atrial fibrillation	OAC and clopidogrel	60 mg/12 h	32 ml/min	Supportive	Recovered
M / 73	Atrial fibrillation	–	60 mg/12 h	100 ml/min	Supportive	Died

F: female; GFR: glomerular filtration rate; M: male; NSTEMI: non-ST elevation myocardial infarction; OAC: oral anticoagulant. DVT: deep vein thrombosis.

[a] Denotes concomitant administration of anticoagulant or antiplatelet agents.

[b] GFR (estimated by MDRD-4) at diagnosis of SRH.

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The case series by Fernández-Ruiz and Guerra-Vales documents bleeding complications in eight patients treated with enoxaparin [1] similar to those reported in many previous publications, which place the emphasis on evaluation of the individual patient's risk factors such as age, renal function, known bleeding diathesis and co-medication before starting and during anticoagulation. The authors again emphasise that renal function cannot be evaluated using creatinine alone. Elderly patients and patients with at least moderate renal insufficiency represent a significant subpopulation even in a tertiary care hospital [2].

Two of the four reported fatal complications occurred in patients with normal renal function [1]. There is no dose adjustment reported for patients with even severe renal insufficiency. Duration of anticoagulation is not reported and anti-Xa activity was not measured [1], making it difficult to evaluate whether the complications were related to true bioaccumulation of low-molecular-weight heparin (LMWH). Among the 109 patients with "non-traumatic retroperitoneal haematoma" only eight were treated with enoxaparin (7.3%), and there were thus other causes in more than 90%. Patients with a recent history of surgical or invasive procedures were excluded from the analysis.

Anticoagulation is associated with an increased risk of bleeding which needs to be balanced against the benefit of preventing or treating thromboembolic disease. The proper use of anticoagulants leads to a significant reduction in morbidity and mortality [3–5]. However, the physician responsible must base his choice of the specific drug and dose on the assessment of risk factors for individual patients and according to current knowledge, in order to minimise the risk of bleeding and thromboembolic events [6].

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