Peer reviewed article

Spontaneous leg haematoma in a patient anticoagulated with nadroparin for suspected pulmonary thromboembolism

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Fixed-dose, subcutaneous Low Molecular Weight Heparin (LMWH) is as effective and safe as adjusted-dose, intravenous unfractionated heparin (UFH) for the initial management of venous thromboembolism and symptomatic pulmonary thromboembolism [1–4]. Clinical experiences indicate that bleeding is a major side effect, not only of UFH, but also of LMWH [5].

An 81-year-old woman (60 kg) was admitted with a clinically suspected pulmonary embolism (SPE) with a 2-day history of pleuritic chest pain and dyspnoea. Her past medical history showed congestive heart failure, atrial fibrillation (AF) and hyperthyroidism, immobilisation due to femoral head fracture 7 years previously. Propylthiouracilcoumadin, aspirin, perindopril, spironolactone, and digoxin were started in May 2000 and propylthiouracil and coumadin was discontinued after 3 months follow-up. Owing both to SPE and chronic AF she was started on nadroparin subcutaneously twice daily 5700 UI AXa/0.6 ml. The ventilation/perfusion scan of the lung was reported as having low probability of pulmonary embolism and a duplex ultrasound of the lower limbs was negative for DVT the night after the symptoms started. Despite these findings anticoagulant treatment was continued due to the chronic AF. Except for slightly raised white blood cells and a raised creatinine on admission her laboratory results and coagulation parameters were within normal limits. Two days after anticoagulant treatment, she complained of sudden onset of left leg pain with the finding of a tender haematoma (measuring 5×10×25 cm). There was no history of trauma. Together with nadroparin aspirin was also discontinued.

Initially she was managed conservatively, nonetheless the haematoma progressed further over 8 days. Immediate surgical intervention was considered applicable owing to severe systemic co-morbidity of the patient. Subsequently, however, the significant increase in dimensions of the haematoma and accompanying risk of impairment in the vascular supply of the extremity was accepted as the indication for surgery. General anaesthesia was preferred. Surgical exploration revealed 600 ml of organised clot located in the anterolateral compartment of the proximal ⅓ of the leg. Sudden death of unknown cause was observed two days after operation. Anti Xa determination was not carried out at the time of the clinical event due to a lack of laboratory facilities. No autopsy was performed due to family refusal.

Bleeding is the most important side effect of LMWH therapy. LMWHs, including nadroparin, have been shown in multiple studies to be associated with some haemorrhagic complications (spontaneous suprachoroidal bleeding, subcutaneous haematoma, intrahepatic haemorrhage, psoas haematoma after lumbar plexus block and an increase in the incidence of postoperative intracranial haemorrhage in patients treated prophylactically for deep venous thrombosis (DVT) being operated on for brain tumours) [6]. Subcutaneous haematoma, wound and injection site haematoma are relatively common adverse effects of therapy with LMWH including nadroparin [7].

The bleeding due to LMWHs seems to be effected by age of patients, concomitant use of medicines, side effects of LMWH itself, dose given, renal function and additional medical problems.

In clinical trials conducted in older patients (mean age usually >60 years), nadroparin was at least as effective and even more safe as UFH in preventing DVT and pulmonary embolism after major general or orthopaedic surgery, and in bedridden patients [8]. The frequency of major bleeding was similar in the prophylaxis of DVT in patients undergoing general surgery with nadroparin in three different studies (0.4, 4.9 and 5.3 percent, respectively) [9].

The concomitant use of medicines affects haemostasis, such as non-steroidal anti-inflammatory drugs (ibuprofen, ketorolac and aspirin), platelet inhibitors or other anticoagulants.

Heparin-induced thrombocytopenia (HIT) is a severe adverse effect of heparin therapy. Although most cases occur in patients receiving unfractionated heparin, HIT can arise in venous thrombosis prophylaxis with nadroparin [10]. In this particular patient no thrombocytopenia was observed as a predisposing factor for this complication.

Thery et al. performed a dose ranging study with nadroparin and compared the results with a regimen of dose adjusted UFH. The highest doses (5700 to 9500) resulted in an unacceptable high rate of bleeding complication. No major bleeding was observed in the lowest dose (1900 to 3800 IU) [11]. In another prospective study no bleeding events occurred in the patients given the lower dose compared with two major haemorrhages in those given the higher dose. According to both studies the risk of bleeding complications with LMWH is dose dependent [12].

In a study a significant accumulation of the anti-factor Xa activity was observed in the healthy elderly and in the patients but not in the healthy young subjects. There was also significant correlation between the clearance of creatinine and the clearance of the anti-factor Xa activity. Together with ageing, the low creatinine clearance of our case might have caused a significant accumulation of the anti-factor Xa activity [13].

Even if anti Xa determination and autopsy are lacking in our case the haematoma should most probably be regarded as a complication of nadroparin as it arose 2 days after use of nadroparin, and the other coagulation parameters were normal at the time of event.

A complication of this type offers new evidence on the safety hazards in the treatment and prevention of thromboembolism in elderly patients.

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