

## ADVERSE DRUG REACTION

# A case of two adverse reactions

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Low molecular weight heparins are now widely prescribed in the treatment of thromboembolic disease and acute coronary syndromes. Anaphylaxis is a recognised but rare potentially life threatening side effect of heparin.

Common clinical features of anaphylaxis are cardiovascular collapse, bronchospasm, cutaneous symptoms, angioedema, generalised oedema, or gastrointestinal symptoms. It is extremely rare, however, for patients to experience such dramatic and potentially life threatening consequences as seen in the case reported here. It has been shown that patients may be tolerant of certain low molecular weight heparins but sensitive to others.

Adrenaline is regarded as the most important drug for any severe anaphylactic reaction. Administration by the intramuscular route produces significantly higher peak plasma concentrations compared with subcutaneous injection, which is clearly beneficial in the critically compromised patient. Current UK Resuscitation Council guidelines support the use of 0.5 ml of 1:1000 adrenaline to be administered intramuscularly.

A 78 year old man with a history of ischaemic heart disease (positive exercise test at end of stage 1 of Bruce protocol) was referred to the coronary care unit by his general practitioner. He had been having increasing frequency and severity of angina for one week. His admission was precipitated by an episode of severe pain unrelieved by sublingual glycerine trinitrate spray.

Past medical history included treated hypertension, carcinoma of prostate, and a femoral deep venous thrombosis. He had been treated three years previously with tinzaparin (without any adverse effects) followed by anticoagulation with warfarin.

His medications on admission included atenolol 100 mg once a day, frusemide 40 mg once a day, amlodipine 10 mg once a day, fosfestrol tetrasodium 120 mg twice a day, goserelin by injection every three months, isosorbide mononitrate 40 mg twice a day, cyclizine 50 mg three times a day, aspirin 75 mg once a day, and lisinopril 2.5 mg once a day. He was known to have had a previous sensitivity reaction to pethidine, but there was no previous history of angioedema.

On admission, his pain had lessened after having diamorphine already administered by his general practitioner and was fully relieved by 3 mg sublingual buccal suscard. The paramedic crew had given 300 mg aspirin. Admission 12 lead electrocardiogram (ECG) showed anterolateral ischaemia (fig 1).

The patient was started on intravenous nitrate and subcutaneous enoxaparin at treatment dose (1 mg/kg body weight twice daily). Thirty minutes later, the patient himself noted marked tongue swelling. Following review by the attending senior house officer he was given oxygen, 200 mg hydrocortisone and 10 mg chlorpheniramine intravenously. The patient continued to develop worsening angioedema. He

developed a bradycardia and hypotension despite the nitrate infusion having been stopped. He was prescribed 1 ml of 1:1000 adrenaline, given subcutaneously. The administration of adrenaline had rapid clinical effect and haemodynamic stability was regained. The angioedema had fully resolved within two hours from onset.

After resolution of the angioedema, the patient developed severe chest pain, requiring large doses of intravenous nitrates and diamorphine. His ECG showed more marked widespread ST depression (fig 2). Electrocardiographic changes persisted for four hours after the administration of adrenaline. Troponin I was raised at 18.9 µg/l (>1.0 high risk) at 12 hours.

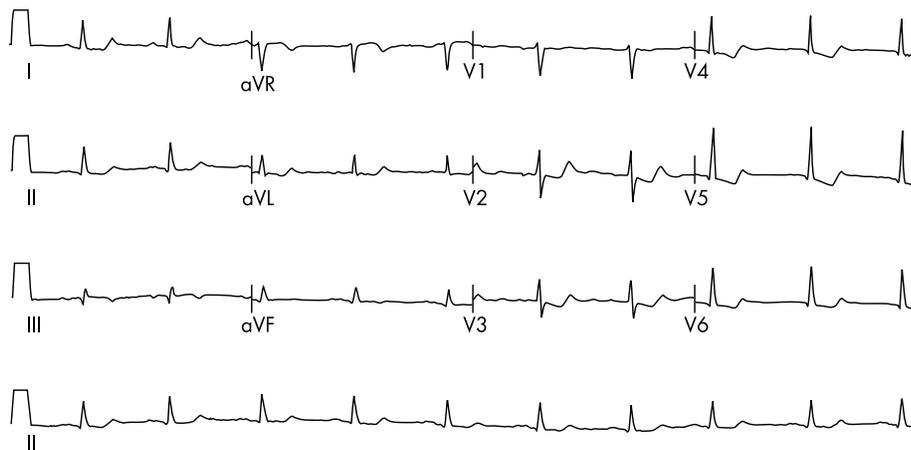
He was referred to a tertiary centre where he underwent coronary angiography, which showed triple vessel disease with an occluded right coronary artery, circumflex, left main stem stenosis, and severe left anterior descending artery disease. The pattern of disease was deemed unsuitable for revascularisation by percutaneous intervention or surgical grafting. The patient was optimised on medical treatment. He successfully completed cardiac rehabilitation after discharge and remained well at outpatient review six months later. Unfortunately he suffered a further cardiac event and died one year after the episode of angioedema. This suspected adverse drug reaction to enoxaparin was reported to the Committee on Safety of Medicines.

### DISCUSSION

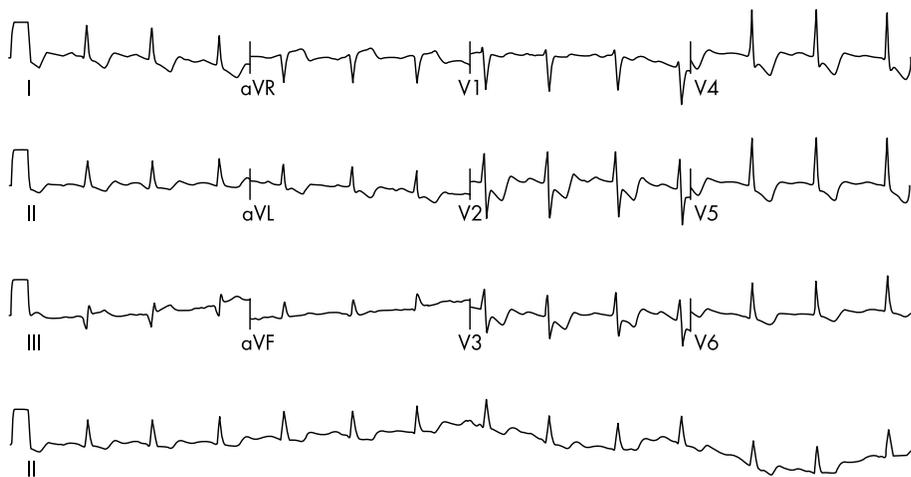
Low molecular weight heparins are now widely prescribed in the treatment of thromboembolic disease and acute coronary syndromes. Side effects include haemorrhage, eczematous plaque formation at the injection site,<sup>1</sup> skin necrosis,<sup>2</sup> thrombocytopenia, and hypersensitivity reactions (including urticaria,<sup>3</sup> angioedema,<sup>3</sup> and anaphylaxis<sup>4</sup>). It is extremely rare, however, for an individual to experience such a dramatic and potentially life threatening adverse reaction to heparin as seen in the case that we report.

Angioedema is a rare (incidence 0.1%–0.2%; with a threefold risk in the black population) adverse reaction to angiotensin converting enzyme (ACE) inhibitors. Most reactions occur within a few hours or in the first week after therapy, although delayed onset of months or years has also been described. Certain drugs such as ciprofloxacin, amoxicillin, mefenamic acid, and injection of lignocaine as a local anaesthetic have been postulated as co-factors in cases having a delayed onset.<sup>5</sup> It was felt that this man's adverse reaction was probably not due to the ACE inhibitor. It is not known whether he was taking an ACE inhibitor when treated with tinzaparin as his general practitioner records were unavailable and the deep venous thrombosis had been treated elsewhere. He had no further episodes of angioedema, having continued on and been discharged on lisinopril. At the tertiary unit, he was anticoagulated with lepirudin (a recombinant hirudin). He declined any further investigation

**Abbreviations:** ACE, angiotensin converting enzyme; ECG, electrocardiogram



**Figure 1** Admission ECG showing ST segment depression in the anterolateral leads.



**Figure 2** ECG two hours after administration of adrenaline showing increased ST segment depression in the anterolateral leads.

regarding the adverse reaction to enoxaparin and the incident was clearly recorded in his hospital records.

Cross reactivity between low molecular weight heparins (dalteparin sodium and enoxaparin) has been reported, manifesting as a skin reaction<sup>6</sup> during prophylactic treatment for thromboembolism during pregnancy. Since neither product contains preservatives it is clearly due to the heparin component alone. Enoxaparin has been used safely after adverse reaction to unfractionated heparin (rash). This is surprising as enoxaparin is derived from porcine unfractionated heparin.<sup>7</sup> It has been shown that patients may be tolerant of certain low molecular weight heparins but sensitive to others.<sup>1</sup> It is recommended to confirm the diagnosis of true hypersensitivity that a patch, prick, or intradermal test should be performed initially for safety reasons. If these are negative, a subcutaneous test is necessary as it is the most reliable modality.

Anaphylaxis results from the rapid degranulation of mast cells and basophils. The term encompasses reactions that are IgE mediated (anaphylaxis) and those that are non-immunologically mediated (anaphylactoid). There is no clinical relevance between the two types of reaction. Reactions may be triggered by antibiotics, insect stings, foodstuffs, drugs, blood products, and anaesthetic agents.

Anaphylaxis may progress slowly or rapidly. Clinical expression is variable. Most common features are cardiovascular collapse, bronchospasm, cutaneous symptoms, angioedema, generalised oedema, or gastrointestinal symptoms. Diagnosis should be followed by removal of the inciting agent where

possible. Prompt treatment with intramuscular adrenaline should follow. Supportive measures include airway support, oxygen therapy, intravenous antihistamine, and corticosteroids. Intravenous fluid and inotrope support may be required.

Adrenaline is regarded as the most important drug for any severe anaphylactic reaction. There is no international consensus on the recommended dose of adrenaline.<sup>8</sup> Current UK Resuscitation Council guidelines support the use of 0.5 ml of 1:1000 adrenaline to be administered intramuscularly.<sup>9</sup> It is unclear as to why the attending doctor chose to prescribe the specified dose of adrenaline by the specified route.

The prescribed dose may need to be repeated on more than one occasion if clinical improvement is absent or if improvement is transient. It has been shown in trials that the intramuscular route produces significantly higher peak plasma concentrations compared with subcutaneous injection.<sup>10</sup> The action of adrenaline can be detrimental by increasing myocardial oxygen consumption causing increased angina, myocardial ischaemia, and risk of myocardial infarction.<sup>11</sup>

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