Adverse drug reaction of the month

Spontaneous retromammary haemorrhage during warfarin therapy

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A 70-year-old woman was admitted as a medical emergency with central chest pain radiating into the right arm. She had not previously had chest pain but had rheumatic fever as a child, received a Lilliehei-Kaster mitral prosthetic valve in 1978, and had been taking warfarin since that time. She had rheumatoid arthritis, principally affecting the hands. Her other drug therapy was co-amlofruse 80 mg bid, thyroxine 150 µg od and prednisolone 5 mg od (for the past 6 months for her rheumatoid arthritis). Examination revealed her to be in controlled atrial fibrillation, and to have slight bruising on her left breast; electrocardiogram (ECG) showed T inversion in her lateral chest leads. Her haemoglobin and full blood count, urea and electrolytes and creatine kinase were all normal. Her International Normalised Ratio (INR) on admission was 3.5 on warfarin 2.5 mg daily, with no evidence of recent difficulties in anticoagulant control. A provisional diagnosis of unstable angina was made.

By the next day, the bruising on her left breast was much more noticeable, the breast was swollen and tender and the right breast and chest wall were also affected (figure). Vitamin K, 0.5 mg, was given intravenously and her INR fell to 2.5 after 24 hours. The pain and bruising initially settled somewhat but her haemoglobin fell to 8 g/dl and she was given packed red cells; her warfarin dose was adjusted to maintain a target INR of 2.5 and a maximum INR of 3.0.

After discharge her left breast remained swollen and again became tender. Mammography revealed no evidence of breast disease but a large hyper-echoic area behind the left breast and in front of the pectoral muscle. More than 500 ml of blood was evacuated from this site under local anaesthetic. A second aspiration of 300 ml of blood-stained fluid was performed before the pain settled and the haematoma resolved.

Discussion

Although haemorrhage is an important adverse effect of oral anticoagulant therapy, most episodes occur from pathological lesions or as a result of trauma.¹ The patient consistently denied sustaining even minor trauma and mammography revealed no evidence of intrinsic breast disease. We have been unable to find any previous report of spontaneous retromammary haemorrhage, although haemorrhagic necrosis of the skin and subcutaneous tissue of the breast has been reported frequently. The

latter normally occurs within 5 days of starting warfarin, is sometimes associated with protein C or S deficiency and may be associated with areas of necrosis elsewhere.² Our patient had no evidence of tissue necrosis, however, and had been receiving warfarin for nearly 20 years without adverse effects. Apparently spontaneous haemorrhage from other sites has been reported in patients receiving anticoagulant therapy. Intramural oesophageal haematoma,³ small bowel haematoma,⁴ pulmonary⁵ and mediastinal haematoma,⁶ thoracic intramedullary haematoma,⁷ and abdominal wall haematoma⁸ have all been described. The INR was often but not always raised in these cases. It is, of course, not possible to be certain that the sites from which the bleeding occurred were definitely normal and bleeding into tissues may be related to the atrophic changes that occur with increasing age. The corticosteroid treatment this lady received for rheumatoid arthritis may have contributed to this process since this can cause atrophic changes in tissues. She received only a small dose of prednisolone for a relatively short period, however.

The risk of bleeding with anticoagulants is non-linearly related to the INR.⁹ Thus, the risk of bleeding rises three-fold between an INR of 2 and 3 and a further three-fold between 3 and 4.⁹ The optimum target INR is therefore the lowest consistent with protection from thrombosis in the particular indication. The thrombogenicity of first-generation valves such as the Lilliehei-Kaster is such that a range of 3-4.5 is recommended. This patient developed haemorrhage while in this range, however. The second-generation bi-leaflet or disc valves are associated with lower levels of valve thrombosis or systemic embolism and a lower range of

Figure The breasts of the patient, 7 days after admission and before aspiration of the left retromammary haematoma

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Guidelines for management of excessive anticoagulation¹¹ (based on INR and clinical state)

Life-threatening haemorrhage: immediately give phytonadione (vitamin K₁) 5 mg by slow intravenous injection and a concentrate of factors II, IX and X (with factor VII concentrate if available). If no concentrate is available, fresh frozen plasma should be infused (approximately 1 litre for an adult) but this may not be as effective.

Less severe haemorrhage, eg, haematuria and epistaxis: withhold warfarin for one or more days and consider giving phytonadione (vitamin K₁) 0.5–2 mg* by slow intravenous injection

INR 4.5–7 without haemorrhage: withhold warfarin for 1 or 2 days then review

INR > 7 without haemorrhage: withhold warfarin and consider giving phytonadione (vitamin K₁) by slow intravenous injection

*usually 1 mg is adequate and should be given if INR greater than desired: higher doses will prevent oral anticoagulants from acting for several days or even weeks

Box 1

INRs between 2.5 and 3 is recommended by the European Society of Cardiology for such valves.¹⁰

Reversal of anticoagulation requires great care in patients with prosthetic heart valves, as in other circumstances where the implications of thromboembolism are potentially devastating. Full reversal of anticoagulation will increase the risk of thromboembolism and should only be considered when the consequences of haemorrhage are profound and outweigh the risks of recurrent thromboembolism.¹¹ For less serious haemorrhage, small doses of vitamin K (eg, 0.5 mg intravenously) will partially reverse the anticoagulant effect after around 24 hours, without producing the subsequent warfarin resistance that can occur after larger doses.¹² When bleeding is only minor, temporary discontinuation of warfarin may be all that is required.¹¹ These

Learning points

- although anticoagulant-associated bleeding normally occurs from a site of pathology, apparently spontaneous haemorrhage can occur elsewhere
- anticoagulant-associated bleeding sufficiently severe to be life-threatening or to result in hospitalisation (like all serious reactions to established drugs) should be reported to the Committee on Safety of Medicines
- bleeding risk increases non-linearly with increased INR so that the target range should be chosen for the particular indication
- all patients who bleed while taking warfarin should be investigated for an underlying cause, whatever the INR at the time of the incident

Box 2

guidelines are now in the British National Formulary and are shown in box 1.

Haemorrhage while taking warfarin should always be investigated, whatever the INR at the time of the incident. The diagnosis of spontaneous haemorrhage can only be made when pathological causes and trauma have been excluded, as in this case. Major bleeding occurs most frequently from the gastrointestinal tract, followed by wounds and other areas of trauma and from the vagina.¹ A cause of bleeding was found in only 50 to 60% of episodes,^{1 13} although the absence of a definitive diagnosis after full investigation of the gastrointestinal tract carried a good prognosis.¹³

This case illustrates that apparently spontaneous haemorrhage can occur in patients receiving warfarin, even when the INR is within the accepted therapeutic range. The diagnosis is one of exclusion, however, and all such patients should be investigated for an underlying cause. The risk of serious haemorrhage is disproportionately related to the INR and good control within the target range for the particular indication is one of the most important factors in reducing the risk of bleeding.

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