Heparin-associated skin necrosis

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Summary: A case of skin necrosis at the sites of injection of subcutaneous heparin is described. The patient went on to develop heparin-induced thrombocytopenia and pulmonary embolism. Review of the previously described cases of heparin-associated skin necrosis reveals that this sequence of events is not uncommon.

Introduction

Low-dose subcutaneous heparin administration to prevent deep venous thrombosis and pulmonary embolism in surgical patients is of proven value.¹ Other than an increase in usually minor haemorrhagic problems, this is associated with few side effects. Among the rarer but more serious side effects are skin necrosis at the site of injection of subcutaneous heparin, first reported by O'Toole in 1973,² and thrombocytopenia, which can be profound.³ Here we report a case in which these two problems coincided.

Case report

An otherwise healthy 59 year old woman was admitted for elective cholecystectomy. She was obese (weight 71 kg, ideal weight 54 kg) but had no other risk factors for thromboembolic disease. She received sodium heparin 5,000 U (Uniparin, CP Pharmaceuticals) subcutaneously with her anaesthetic premedication, and twice daily for 8 days postoperatively. No postoperative complications were noted, and she was discharged well on the eighth postoperative day.

She was readmitted 3 days later, complaining of pleuritic chest pain and abdominal bruising. On examination there was no clinical evidence of either deep venous thrombosis or pulmonary embolism. Abdominal inspection revealed two areas of skin necrosis at the sites of previous injection, the larger of which was 3 × 2 cm in size. Both were surrounded by an erythematous, eczematous zone of a few further cm, and an outer-zone of bruising. Further areas showing only an erythematous zone with surrounding bruising, and areas of bruising alone were also seen (Figure 1). These areas all

healed spontaneously over subsequent days, and no new ones developed.

Ventilation/perfusion scan was unequivocally positive for pulmonary embolism, and heparin therapy by intravenous infusion was commenced with a bolus of 5,000 U followed by 24,000 U per 24 hours, increasing to 32,000 U per 24 hours over the next 2 days as appropriate. The KCCT ratio to control was in the range 1.7–2.9 throughout therapy. The patient experienced a brief episode of malaise approximately one hour after commencing intravenous heparin, and continued to complain of occasional pleuritic chest pain, but there were no other symptoms or signs of note. Bilateral ascending venography was normal. Platelet count had been 403×10^9 /litre preoperatively and 434×10^9 /litre on day 5. It fell steadily during heparin therapy to 71×10^9 /litre by the sixth day of infusion. On this day the patient experienced a further episode of back and pleuritic chest pain, and became pale and sweaty. She became mildly hypotensive (blood pressure 90/60 mmHg) and developed a tachycardia, and her arterial PO_2 fell over the course of this event from 96 mmHg to 78 mmHg. Electrocardiogram and chest X-ray were unchanged. A clinical diagnosis of continuing pulmonary thromboembolism was made and a Greenfield filter was inserted. Heparin therapy was discontinued but warfarin, commenced the previous day, was continued. The patient made an uneventful recovery thereafter and warfarin therapy was stopped after 3 months. Antithrombin III and protein C levels were checked after cessation of warfarin therapy and found to be normal (antithrombin III antigen = 0.30 g/l; protein C antigen = 101%).

Discussion

Skin necrosis is an uncommon complication following administration of subcutaneous heparin – Ulrick *et al.*, reviewing the subject in 1984, found

Figure 1 The areas of skin necrosis on the abdominal wall, surrounded by bruising.

only 16 reported cases⁴ and since then, to our knowledge, only one more has been added.⁵ These 17 cases include 7 males and 10 females, ranging in age from 27 to 79 years. In all but one case skin changes occurred after 6 to 14 days, and they have been associated with both bovine and porcine heparins. Eight patients have required debridement of necrotic tissue and three skin grafting. The pathogenesis is uncertain, although the results of histological studies have suggested that it is a hypersensitivity reaction. This may take the form of heparin-induced immune aggregation of platelets, resulting in ischaemia,⁶ or an Arthus type reaction with the formation of antigen-antibody complexes.⁷ A further, non-immunological mechanism might be responsible, where there is incorrect intradermal administration of the heparin, with local haemorrhage in a tense dermis leading to pressure on small blood vessels and subsequent ischaemic necrosis of the overlying skin.⁵ The patient in whom this occurred developed necrosis after 2 months of heparin therapy, and there were no further problems after correction of injection technique.

Heparin-associated thrombocytopenia is relatively common, the quoted incidence varying between 1 and 5% in more recent prospective studies.³ A mild fall in the platelet count is probably even more common, possibly related to the temporary sequestration of platelets.⁸ However, the more severe form of thrombocytopenia appears to have an auto-immune basis – several groups having described a heparin-dependent IgG against platelets.⁹ This generally occurs 7 to 10 days after the start of heparin therapy, but may appear earlier in those who have previously received heparin (as in

our case). It is well-recognized that heparin-associated thrombocytopenia may be complicated by arterial or venous thrombosis,⁸ and it is therefore necessary to stop the heparin as soon as the diagnosis is made.³ Oral anticoagulants can, however, be started as there seems to be no cross-reaction between heparin- and coumarin-induced thrombocytopenia (or skin necrosis,¹⁰ that associated with coumarins being related to pre-existing protein C or protein S deficiency).¹¹ A fibrinolytic agent can be used, but the risk of bleeding complications must be borne in mind, especially soon after surgery. Caval interruption is another option that should be seriously considered in these patients.

That our patient, who developed skin necrosis, went on to develop thrombocytopenia and uncontrolled embolism is not unprecedented, as intravenous administration of heparin appears to be especially hazardous in patients who have manifested skin necrosis. Four previously reported patients have received intravenous heparin after the cessation of subcutaneous therapy because of skin necrosis. Of these four, one subsequently developed progressive enlargement of the necrotic skin area; another developed a suspected deep venous thrombosis, leg ischaemia and worsening asthma; a third became hypotensive immediately after starting intravenous heparin; and the fourth developed cerebral and myocardial infarction.⁴ In all, 4 of the 17 previously reported patients with heparin-associated skin necrosis have had thromboembolic complications, and thrombocytopenia has been recorded in 3. The relationship between heparin-associated skin reactions and such haemostatic complications is not known but it is tempting

to suggest a common immunological mechanism.

We conclude that it is important to avoid the use of intravenous heparin in patients who develop

heparin-associated skin necrosis, and to be aware that there is an increased risk of thrombocytopenia and thrombotic complications in this situation.

References

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