Adverse drug reaction of the month

Heparin-induced thrombosis

Neil JL Gittoes, Jonathan T Wilde, Michael C Sheppard, Robin E Ferner

Thrombocytopenia is a well-recognised adverse effect of heparin therapy. We describe a case of fatal thrombosis associated with this complication of heparin therapy.

Case report

A 47-year-old woman with Graves' disease had become euthyroid following treatment with radioactive iodine five months previously. However, her thyrotoxicosis relapsed with free thyroxine of 30.8 (normal 11.0–24.0) pmol/l, free tri-iodothyronine of 12.6 (normal 3.4–7.2) pmol/l and thyrotropin fully suppressed to less than 0.1 (normal 0.30–4.50) mU/l. She had rapidly developed a large toxic multinodular goitre and she showed classical signs of superior vena caval obstruction due to the retrosternal extension of the goitre. She was admitted to hospital and treated with propylthiouracil at a dose of 600 mg daily by mouth and with heparin 30 000 units every 24 hours by continuous intravenous infusion, to prevent thrombosis of the superior vena cava. Routine biochemical and haematological investigations were normal on admission; the platelet count was $199 \times 10^9/l$. Radiography, including computed tomography of the thoracic inlet and mediastinum revealed a large retrosternal goitre which was compressing and displacing the trachea.

The patient remained ambulant whilst awaiting definitive surgery and the intravenous heparin infusion was continued to maintain an APTT ratio of around 1.9. Seven days following admission, the patient developed acute onset of pain in both lower limbs in association with clinical signs of arterial occlusion at the level of the bifurcation of the aorta. Platelet

count at this time had dropped to $37 \times 10^9/l$. Embolectomy was initially successful in re-establishing the peripheral circulation to the left leg but a below knee amputation of the right leg was required. The patient was treated with warfarin as an alternative to heparin and the platelet count quickly recovered. Despite this, however, continuing arterial insufficiency and poor healing of wounds in both lower limbs necessitated bilateral above knee amputations. The patient succumbed to overwhelming sepsis from wound infections three months after her initial admission. The toxic multinodular goitre and signs of superior vena cava obstruction had all resolved with continuing propylthiouracil therapy.

Discussion

Approximately 5% of patients treated with unfractionated heparin develop thrombocytopenia (platelet count less than $150 \times 10^9/l$) making it the most common cause of drug-induced thrombocytopenia.¹ Two types of heparin-induced thrombocytopenia (HIT) have been characterised (box 1). Type I HIT, which accounts for the majority of cases, results from the direct aggregatory effect of heparin on platelets. It usually occurs within the first four days of heparin therapy and the platelet count usually remains above $100 \times 10^9/l$. The thrombocytopenia is not associated with any clinical sequelae and no specific treatment is required. Heparin does not need to be discontinued and the thrombocytopenia often resolves while heparin is continued.

Type II HIT, the form occurring in our patient, is induced by the action of antibodies against multimolecular complexes of heparin and its natural neutralising agent, platelet factor 4.² The immune complexes bind to platelet-membrane-bound crystallisable fragment receptor type II³ via the crystallisable fragment component of the antibodies and induce intravascular platelet activation resulting in platelet thrombus formation.⁴ It is associated with the paradoxical development of major arterial or venous thromboembolism resulting in major vessel occlusion causing limb ischaemia, cerebrovascular accidents, myocardial infarction and pulmonary embolism. The condition has a reported mortality rate of 30%.^{5,6}

In a recent study,⁷ type II HIT was identified in nine of 332 (2.7%) patients receiving unfractionated heparin. Eight of these patients developed thrombotic events, which were mainly venous. Type II HIT usually occurs

Queen Elizabeth
Hospital,
Birmingham B15
2TH, UK
Department of
Medicine
NJL Gittoes
MC Sheppard
Department of
Haematology
JT Wilde

West Midlands
Centre for Adverse
Drug Reactions
Reporting, City
Hospital, Birming-
ham B18 7QH, UK
RE Ferner

Mechanisms of heparin-induced thrombocytopenia (HIT)

Type I HIT

- direct aggregatory effect of heparin on platelets
- occurs within four days of commencing therapy
- mild effect on platelet count
- no change to heparin treatment required

Type II HIT

- immune complex mediated
- occurs after five days of heparin therapy
- platelet count usually $< 50 \times 10^9/l$
- associated with fatal arterial and venous thromboses
- requires termination of heparin therapy

Box 1

Accepted 20 March 1997

six to 14 days after commencing heparin therapy but can occur sooner in previously sensitised individuals. The platelet count usually falls below $50 \times 10^9/l$ and the development of the condition is independent of the route of heparin administration and the dose given. Low-molecular-weight heparin preparations have been reported as having a substantially lower risk of developing type II HIT. In the study of Warkentin *et al.*,⁷ none of 333 patients treated with low-molecular-weight heparin developed thrombocytopenia.

Due to the severe consequences of type II HIT, we recommended that patients treated with heparin for longer than five days, have frequent platelet counts. Heparin must be stopped if type II HIT develops, especially if accompanied by the presence of new thromboembolic events. Warfarin must be commenced immediately if not already started. Although less antigenic, low-molecular-weight heparin preparations do cross-react with the type II HIT antibodies,⁸ hence substitution of these for unfractionated heparin is not recommended. If anticoagulation is essential prior to full warfarinisation, an alternative anticoagu-

Learning points

- perform frequent platelet counts on all patients receiving heparin for longer than five days
- it is always important to report serious adverse reactions, even to well-established drugs – reports can act as signals to warn that the risks and benefits of a drug need to be re-assessed

Box 2

lant, danaparoid sodium (Oregaran) may be used; it has low cross-reactivity with heparin antibodies.⁸ In the presence of established arterial thrombosis, embolectomy is indicated. Fibrinolytic therapy may also be considered in life-threatening situations.

Type II HIT is an uncommon but life-threatening paradoxical complication of heparin therapy which, if major sequelae are to be avoided, needs to be recognised early and managed appropriately.

Keywords: heparin, adverse reaction, thrombosis

- 1 Warkentin TE, Kelton JG. Heparin-induced thrombocytopenia. *Prog Hemost Thromb* 1991; **10**: 1–34.
- 2 Greinacher A, Potzsch B, Amiral J, Dummel V, Eichner A, Mueller-Eckhardt C. Heparin-associated thrombocytopenia: isolation of the antibody and characterisation of a multimolecular PF4-heparin complex as the major antigen. *Thromb Haemost* 1994; **71**: 247–51.
- 3 Chong BH, Fawaz I, Chesterman CN, Berndt MC. Heparin-induced thrombocytopenia: mechanism of interaction of the heparin-dependent antibody with platelets. *Br J Haematol* 1989; **73**: 235–40.
- 4 Warkentin TE, Hayward CPM, Boshkov LK, *et al.* Sera from patients with heparin-induced thrombocytopenia generate platelet-derived microparticles with procoagulant activity: an explanation for the thrombotic complications of heparin-induced thrombocytopenia. *Blood* 1994; **84**: 3691–9.
- 5 King DJ, Kelton JG. Heparin-associated thrombocytopenia. *Ann Intern Med* 1984; **100**: 536–40.
- 6 Chong BH. Heparin-induced thrombocytopenia. *Blood Rev* 1988; **2**: 108–14.
- 7 Warkentin TE, Levine MN, Hirsch J, *et al.* Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med* 1995; **332**: 1330–5.
- 8 Keeling DM, Richards EM, Baglin TP. Platelet aggregation in response to four low molecular weight heparins and the heparanoid ORG 10172 in patients with heparin-induced thrombocytopenia. *Br J Haematol* 1994; **86**: 425–6.

Books received

Proceedings of the Royal College of Physicians of Edinburgh. pp 277. Royal College of Physicians of Edinburgh, Edinburgh, 1977. Paperback

Facing death and finding hope. A guide to the emotional and spiritual care of the dying. C Longaker. pp 262. Century, London, 1997. £14.99, hardback

Imaging handbook for house officers, P M Silverman, D J Quint, eds. pp 455. Wiley-Liss, New York, 1997. £29.95, paperback

Patient pictures. Gastroenterology, P Neild, B Gazzard. pp 30, illustrated. Health Press, Oxford, 1997. £10.95, paperback

Patient pictures. Gynaecology, M Stafford. pp 34, illustrated. Health Press, Oxford, 1996. £10.95, paperback

Fast facts. Osteoporosis, J E Compston, C J Rosen. pp 63, illustrated. Health Press, Oxford, 1997. £10.95, paperback

Fast facts. Urology highlights 1996, J Shah ed. pp 80, illustrated. Health Press, Oxford, 1997. £10.95, paperback

On-the-job training for surgeons, D H Hargreaves, M G Bowditch, D R Griffin. pp 132, illustrated. Royal Society of Medicine Press, London, 1997. £17.50, paperback

Prevention and control of pain in children. Royal College of Paediatrics & Child Health, pp 116. BMJ Publishing Group, London, 1997. £15.95, paperback

Resuscitation of babies at birth. Royal College of Paediatrics & Child Health, pp 61, illustrated. BMJ Publishing Group, London, 1997. £10.95, paperback

ABC of clinical genetics, HM Kingston. pp 75, illustrated. BMJ Publishing Group, London, 1997. £14.95, paperback

Communication skills in medicine, CRK Hind, ed. pp 161, illustrated. BMJ Publishing Group, London, 1997. £14.95, paperback

Quality of life assessment in medicine, M Tamburini. Glamm Interactive srl Milan, Italy, 1997. CD ROM