Hydroxyurea-induced leg ulcers

J Murphy, SM Morley

DISCUSSION

Hydroxyurea is an analogue of urea that inhibits DNA synthesis. It inhibits ribonucleotide reductase, the enzyme which converts ribonucleotide diphosphates to their deoxyribonucleotide forms. This causes selective killing of cells in the S phase of the cell cycle. Hydroxyurea is well absorbed orally, has a plasma half-life of 4 hours and is mostly excreted in the urine. It is used to treat chronic myeloid leukaemia, polycythemia vera, thrombocythaemia, sickle cell anaemia and at lower doses psoriasis. It is generally well-tolerated. The most frequently encountered side-effects are nausea, vomiting and diarrhoea. The most serious side-effect, myelosuppression, is usually rapidly reversed on cessation of the drug.

Hydroxyurea has been associated with the development of leg ulcers (Best et al, 1998; Nguyen and Margolis, 1993). So far this has only been noted in patients with myeloproliferative disorders. Such ulcers have characteristic features, including a marked tendency to occur over the malleoli and are usually associated with extreme pain, requiring strong opioid analgesia. There is usually a latent period of a few months between commencement of hydroxyurea and the development of the ulcers.

Hydroxyurea has a number of other dermatological manifestations such as hyperpigmentation, alopecia, photosensitization, fixed drug eruption, brown nail discolouration, stomatitis (Boyd and Neldner, 1991) and a dermatomyositis-like skin eruption (Daoud et al, 1997).

Suspected mechanisms of actions causing ulceration include basal keratinocyte damage, inhibition of cellular DNA synthesis (Best et al, 1998), hyperviscosity and arterial microthrombi secondary to thrombocytosis and platelet dysregulation (Kido et al, 1998). Notably this patient had platelet counts within normal levels when his ulceration was at its worst. It was not until his hydroxyurea was stopped and his ulcers began to heal that his platelet count rose, suggesting that the high platelet count was not implicated. Hydroxyurea-induced leg ulcers are especially resistant to treatments including antibiotics, immunosuppressants, regular wound dressings, compression bandaging, warfarin and hyperbaric oxygen.

There have been a number of reports of successful outcomes with erythropoietin (Al-Momen, 1991) and also with a combination of prostaglandin E_1 and pentoxifylline (Kido et al, 1998).

The most appropriate management step is to stop treatment with this agent. Healing can take many months. If the myeloproliferative disorder should flare an alternative treatment such as bulsulphan should be considered. Alternatively Kennedy (1992) suggested a schedule of intermittent hydroxyurea administration (2 days each week — days 1 and 4).

It is likely that the incidence of this problem is underestimated. A lack of awareness of its existence will lead to unnecessary patient suffering. HM

CASE REPORT

A 60-year-old male caucasian presented with a 1-year history of worsening bilateral leg ulcers, occurring at the level of the ankle overlying the malleoli. They were associated with extreme pain requiring regular opioid analgesia. Their onset was insidious and they gradually deteriorated despite the prompt institution of treatment.

The patient had a history of ischaemic heart disease requiring coronary artery bypass grafting. He also suffered from osteoarthritis and benign prostatic hyperplasia. He had been diagnosed with chronic myeloid leukaemia 18 months before presentation for which he was commenced on hydroxyurea. Other causes of leg ulceration had been excluded. The patient had no history of varicose veins and there was no evidence of surrounding varicose eczema. He was not diabetic and his ankle-brachial arterial pressures were normal. A comprehensive vasculitis screen was negative. The ulcers had none of the typical features of pyoderma gangrenosum such as a purple boggy undermined edge, a more peripheral red border or a liquefying centre. Besides a pyoderma gangrenosum ulcer would be expected to improve with the commencement of an immunosuppressive agent such as hydroxyurea. His other medications at presentation were dihyrocodeine, allopurinol, aspirin, glyceryl trinitrate, lanzoprazole, diclofenac, atenolol and isosorbide mononitrate. Over the 12-month period his ulcers had deteriorated despite use of topical and systemic antibiotics, regular dressings, and compression bandaging. He was even treated empirically with dexamethasone.

As the results of investigations were negative attention focused on hydroxyurea as a cause of his ulcers. Following cessation of hydroxyurea treatment his ulcers gradually began to improve and his pain abated. However, the healing process was quite slow and it took 6 months for complete resolution to occur. His chronic myeloid leukaemia has been treated with busulphan.

Al-Momen A-KM (1991) Recombinant human erythropoietin induces rapid healing of chronic leg ulcer in a patient with sickle cell disease. *Acta Haematol* **86:** 6–8

Best PJ, Daoud MS, Pittelkow MR, Petitt RM (1998) Hydroxyurea-induced leg ulceration in 14 patients. *Ann Intern Med* **128:** 29–32

Boyd AS, Neldner KH (1991) Hydroxyurea therapy. *J Am Acad Dermatol* **25:** 518–4

Daoud MS, Gibson LE, Pittelkow MR (1997) Hydroxyurea dermopathy: a unique lichenoid eruption complicating long-term therapy with hydroxyurea. *J Am Acad Dermatol* **36:** 178–82

Kennedy BJ (1992) The evolution of hydroxyurea therapy in chronic myelogenous leukemia. *Semin Oncol* **19**(3 Suppl 9): 21–6

Kido M, Tago O, Fujiwara H et al (1998) Leg ulcer associated with hydroxyurea treatment in a patient with chronic myelogenous leukemia: successful treatment with prostaglandin E_1 and pentoxifylline. *Br J Dermatol* **139:** 1124–6

Nguyen TV, Margolis DJ (1993) Hydroxyurea and lower leg ulcers. *Cutis* **52:** 217–9

Dr J Murphy was Senior House Officer and **Dr SM Morley** is Consultant in the Department of Dermatology, Ninewells Hospital and Medical School, Dundee DD1 9SY

Correspondence to: Dr SM Morley