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Erythrodema after clodronate treatment

Drs R FURT, P LESTANG, F LLOTE, and Prof A DRYLL (Hôpital Lariboisière, 75010 Paris, France) write: The bisphosphonates, including clodronate, are powerful inhibitors of bone resorption. Until now clinical studies of clodronate have shown good tolerability and safety, with no reports of any cutaneous side effects. We report here erythrodema with lesions of the mucous membranes after oral and intravenous clodronate administration.

A 70 year old man was admitted in June 1991 for vertebral pain and hypercalcemia which led to the diagnosis of stage IIa H2 amilaminemayeloma. A single infusion of 300 mg of clodronate was given, and a course of vincristine, melphalan, cyclophosphamide, and prednisolone every four days, which was continued without reappearance of rash after the first administration and the regression of tachycardia.

Two weeks later he noticed a rash, which lasted three days. On 12 June 1991 a second administration was admitted for the 13th course of chemotherapy. At the same time he received a second infusion of intravenous clodronate 300 mg and was started on oral clodronate 800 mg daily. On 29 June he developed a generalised erythematous macular and papular rash, without pruritus, and a fever of 40°C. He also had lesions of the buccal and genital mucous membranes and a punctate keratitis. On 1 July his clinical state was unchanged. He received intramuscular betamethasone, and his clodronate was stopped.

The white blood cell count was normal, without eosinophilia; he had no infection; viral serology gave negative results. A histological examination of the skin showed epidermal changes, with a dermal lymphohistiocytic and eosinophilic infiltration strongly suggestive of toxicodema.

Within a few days the eruption gradually regressed without residual pigmentation. Other drugs were continued without reappearance of the rash.

The delay in the appearance of the rash after the first administration of clodronate, the relapse following its reintroduction, and the regression after the end of clodronate treatment all support clodronate as the cause of the erythrodema, as do the pathological features and the fact that no other drugs were involved. The cutaneous side effects of bisphosphonates are uncommon. They have been reported with pamidronate1 and tiludronate,2 but only rarely during the first 10 years' prescription of etidronate. No cutaneous reactions to clodronate have been reported to the French National Centre for Pharmacovigilance or the drug company.3

Agranulocytosis associated with cephalosporin

Drs C H Hsu and L C CHAN (Department of Pathology, University of Hong Kong, Queen Mary Hospital) write: A healthy 15 year old boy was given cefuroxime (Zinacef) 750 mg intravenously every eight hours for 17 days associated with pruritus which developed after orthopaedic surgery. As neither fever nor pneumonia improved cefuroxime was discontinued after 17 days and cefazolin substituted as a dose of 1 g intravenously twice a day. Twenty four hours later the patient had no fever and a full blood count showed haemoglobin 132 g/l, white cell count 6·30x10⁹/l with neutrophils 3·75x10⁹/l, and platelet count 379x10⁹/l. Coagulation and renal and liver function were normal.

On the seventh day of cefazolin administration fever recurred, and isolated leucopenia (white cell count 1·90x10⁹/l) associated with agranulocytosis (white cell differential 10% neutrophils, 1·25 lymphocytes, 0·61 monocytes, 0·04 eosinophils) was noted. Cefazolin was stopped and a bone marrow aspirate the next day showed a normocellular marrow with strikingly reduced myelopoiesis. Bacterial cultures and viral screen were negative. In view of the agranulocytosis, subcutaneous injection of granulocyte macrophage colony stimulating factor 1 phial daily was started. Both total white cell (4·8 x 10⁹/l) and neutrophil count (2·2 x 10⁹/l) recovered within 24 hours. Alongwith two doses of granulocyte macrophage colony stimulating factor were given, and the white cell counts remained sustained since then.

Transient leucopenia is recognised after cephalosporin administration and is more likely to occur after high doses and prolonged therapy.4 In our case we could not determine whether the agranulocytosis was due to cefazolin or cefuroxime (or both). The prompt recovery may have been due to the cessation of cephalosporin treatment rather than the granulocyte macrophage colony stimulating factor treatment. We suggest that patients should have regular full blood count while receiving cephalosporins.

Transcutaneous overdose of terbutaline

Drs G J INGAMS (Kidderminster General Hospital, Kidderminster DY10 4AB) and F B MORGAN (Aylmer Lodge Surgery, Kidderminster) write: A 15 year old mildly asthmatic boy was admitted with tachycardia (rate 130 beats/min), a labile systolic murmur at his left sternal edge, and tachypnoea. Feeling slight tightness of his chest after playing football, he had inhaled two puffs (50 µg) of terbutaline. He then discarded his inhaler and bore the aerosol to a patch of itching tinea crusts in his groin produced cooling relief and administered at least eight puffs. Ten minutes later he developed facial flush, ataxia, palpitations and an uncomfortable feeling in his chest and therefore inhaled a further two puffs.

Investigations showed hypokalaemia (2·7 mmol/l), hyperglycaemia (14·8 mmol/l), normal arterial blood gas values, and sinus tachycardia. A subsequent echocardiogram showed normal contractility and symptoms were consistent with terbutaline overdose and settled over 24 hours without specific treatment. The total inhaled dose (1 mg) was insufficient to produce a predictable clinical picture, but the total dose sprayed on to the skin (2 mg) was four times greater than the maximum dose for subcutaneous injection (500 µg).

Although transient terbutaline absorption has not been documented for β₂ agonists, the absorption of terbutaline is increased across damaged tracheal epithelium in vitro. Overdose of β₂ agonists is associated with hypokalaemia,5 which can cause sudden death.6 Transcutaneous absorption should be considered, particularly when bewildering atopic children with facial eczema and those with facial dermatitis.7

1 Jessup AR, Sundler F, Lums A, Waldeck B, Widmark E. Hydrogen peroxide-induced epilamellar damage increases terbutaline transport in guinea-pig tracheal wall implica-


