Drug points

Eczema after intravenous infusion of immunoglobulin

Drs C Barucha and J C McMillan (Belfast City Hospital, Belfast BT9 7AD) write: The use of intravenous immunoglobulin in high doses has become an accepted treatment for patients with autoimmune thrombocytopenia. The intravenous polyvalent pH 4 treated intact gammaglobulin concentrate prepared by the Swiss Red Cross (Sandoglobulin) has been evaluated in the laboratory,[1] and only a few minor adverse reactions have been reported in clinical trials[2 3]; the Committee on Safety of Medicines has received no reports of adverse reactions. We report the occurrence of severe extensive eczema after infusion of Sandoglobulin.

The patient was a 75 year old woman who fulfilled the criteria for idiopathic thrombocytopenic purpura when thrombocytopenia was first noted in 1982. After initially responding to steroids she became refractory, and Sandoglobulin infusions (1 g/kg daily for two days) were started in April 1986. No adverse reactions were noted, and her platelet count rose from 6×10^9/l to 158×10^9/l. She received a second infusion of Sandoglobulin seven weeks later, but at review one month after the infusion she complained of a rash, which had appeared one week previously and had been diagnosed by her general practitioner as "allergic." She was successfully treated with topical steroids and oral antihistamine. There was no history of atopy. She received a third course of Sandoglobulin after another interval of six weeks, and at review two weeks after the infusion she had a florid generalised eczematous rash. The clinical appearance was consistent with acute excoriated eczema, and a skin biopsy specimen suggested a drug reaction.

Cutaneous reactions like angio-oedema, urticaria, and pruritus are associated with blood products, while eczematous reactions are rare. Cutaneous reactions after infusion of hydroxyethyl starch have been reported.[4] The manufacturers of Sandoglobulin have received one report of a case from the United States, in which sensitisation to porcine pepsin (1:10 000 to prevent aggregates) was suspected to be due to previous exposure to insulin (E M Thompson, personal communication). Despite extensive studies we found no proof of a humoral or cellular mechanism. Our patient has required several additional infusions of Sandoglobulin, which were given with concommitant administration of hydrocortisone and chlorpheniramine together with topical steroid applications. There has been no acute exacerbation with each infusion, although she continues to suffer from widespread eczema.

1 Nydegger UE. Evaluating the quality of immunoglobulin G preparations for intravenous therapy. *Vox Sang* 1985;**49**:1-7.
2 Bussel J. Intravenous immune serum globulin in immune thrombocytopenia: clinical results and biochemical evaluation. *Vox Sang* 1985;**49**:44-50.
3 Imbach P, Wagner HP, Berchtold W, *et al*. Intravenous immunoglobulin versus oral corticosteroids in acute immune thrombocytopenic purpura in childhood. *Lancet* 1985;ii:464-8.
4 Klein RE, Mogollon G. Erythema multiforme following the infusion of hydroxyethyl starch. *Transfusion* 1984;**24**:166-7.

Calcium antagonists and psoriasis

Drs C C Harland, C M E Rowland Payne, S M Neill, and P W M Copeman (Westminster Hospital, London SW1P 2AP) write: Exacerbations of psoriasis are an important adverse effect of β blocker treatment, as Dr J Savola and colleague (12 September, p 673) remind us. In 10 of their patients psoriasis resolved after withdrawal of β blockers. In an unspecified number, however, β blockers were replaced by calcium antagonists. As calcium is implicated in the pathogenesis of psoriasis this may be pertinent. The interest in calcium and psoriasis stems from anecdotal reports. Hypocalcaemia, independent of serum albumin concentration, has been associated with exacerbations of generalised pustular psoriasis.[1] Generalised pustular psoriasis has also been precipitated by parathyroidectomy.[2] In both instances the condition improved with calcium replacement. Calmodulin, an intracellular calcium receptor protein, may have a role in plaque psoriasis. It is an activator of phospholipase A_2 and other enzymes that modify the inflammatory component of psoriasis. Calmodulin and phospholipase A_2 are increased in both lesional and non-lesional psoriatic epidermis.[3 4] Psoriasis is also characterised by increased proliferation and impaired differentiation of keratinocytes. In vitro calcium reverses these changes.[5] We wonder whether the remission of psoriasis in some of the Finnish patients should be credited not to the withdrawal of β blockers but to the substitution of calcium antagonists.

1 Copeman PWM, Bold AM. Generalised pustular psoriasis (von Zumbusch) with episodic hypocalcaemia. *Proc R Soc Med* 1965;**58**:425-7.
2 Stewart AF, Battaglini-Sabetta J, Millstone L. Hypocalcaemia-induced pustular psoriasis of von Zumbusch. *Ann Intern Med* 1984;**100**:677-9.
3 Tucker WFG, MacNeil S, Bleehen SS, Tomlinson S. Biologically active calmodulin levels are elevated in both involved and uninvolved epidermis in psoriasis. *J Invest Dermatol* 1984;**82**: 289-9.
4 Forster S, Ilderton E, Norris JFB, Summerly R, Yardley HJ. Characterisation and activity of phospholipase A_2 in normal human epidermis and in lesion free epidermis of patients with psoriasis or eczema. *Br J Dermatol* 1985;**112**:135-47.
5 Van Erp PEJ, Mier PD. Calcium. In: Mier PD, van de Kerkhof PCM, eds. *Textbook of psoriasis*. Edinburgh: Churchill Livingstone, 1986:141.

Life threatening interaction between tamoxifen and warfarin

Drs R Lodwick and B McConkey and Mr A M Brown (Dudley Road Hospital, Birmingham B18 7QH) and Dr Linda Beeley (Queen Elizabeth Hospital, Birmingham B15 2TH) write: The *British National Formulary* lists more than 50 drugs or groups of drugs that may interact with warfarin. Tamoxifen is not among them. We report a life threatening interaction between tamoxifen and warfarin.

A 65 year old woman had been receiving anticoagulant treatment with warfarin for 11 years since an aortic valve replacement; the total weekly dose had varied between 27 mg and 28·5 mg, producing a prothrombin time of 23 to 34 seconds (control 12 seconds). In October 1986 she had had a mastectomy for breast carcinoma. Histology showed an infiltrating duct carcinoma with no affected nodes. There was no evidence at this time, or subsequently, of metastatic disease. Treatment with tamoxifen 10 mg twice daily was started on 5 October 1986; her warfarin dose remained unchanged. When she was discharged from hospital on 8 October her prothrombin time was 39 seconds (control 14 seconds). Three weeks later, in an anticoagulant clinic elsewhere, her prothrombin time was found to be 75·6 seconds (control 14 seconds). This was assumed to be due to a five day course of cotrimoxazole that she was taking for a respiratory infection, and the dose of warfarin was left unchanged. On 21 November, six weeks after she was discharged from hospital, she was readmitted with a three day history of haematemesis, abdominal pain, and haematuria. Her prothrombin time was found to be 206 seconds (control 14 seconds). She gave no history of ingestion of any other drugs, and there was no evidence of metastatic disease. Renal and hepatic function, as assessed by conventional biochemical tests, was normal. She was treated with fresh frozen plasma, and anticoagulant treatment was withdrawn until her prothrombin time had returned to within the therapeutic range. The haematuria ceased within 12 hours of admission, and she had no further haematemesis; upper gastrointestinal endoscopy yielded normal results. Treatment with warfarin was restarted on the fifth day after admission, and when she was discharged her weekly warfarin dosage had fallen to 17·5 mg and her prothrombin time was stable at 34 to 37 seconds (control 14 seconds). She continued to take tamoxifen throughout this time.

There seems no doubt that treatment with tamoxifen led to this patient's overanticoagulation. This is surprising because there have been reports of venous and arterial thrombosis associated with tamoxifen.[1] There has been one report to the manufacturer (ICI), however, of a patient whose prothrombin time increased from 20-22 seconds to 50-60 seconds one month after treatment with tamoxifen was started. This patient was also taking phenobarbitone and phenytoin. The mechanism of the interaction is unclear, but inhibition of warfarin metabolism is a possibility. Inhibition of the cytochrome P450 enzyme system by tamoxifen has been shown in animals.[2] Increased digitoxin concentrations after administration of tamoxifen have also been reported,[3] and digitoxin is probably metabolised by the same enzyme system as warfarin. Alternatively, oestrogens increase concentrations of clotting factors and, therefore, theoretically an antioestrogen might reduce them. Tamoxifen may produce an acquired factor VIII deficiency,[4] but there was no evidence of this in our patient.

1 Dahan R, Epie M, Mignot L, Houlbert D, Chanu B. Tamoxifen and arterial thrombosis. *Lancet* 1985;i:638.
2 Al Turk WA, Stohs SJ, Roache EB. Effect of tamoxifen treatment on liver, lung and intestinal mixed-function oxidases in male and female rats. *Drug Metab Dispos* 1981;**9**:4.
3 Middeke M, Remien C, Lohmoller G, Holzgrere H, Zöllner N. Increased serum levels of digitoxin with tamoxifen. *Klin Wochenschr* 1986;**64**:1211.
4 Barlas AH. Acquired factor VIII deficiency in an elderly woman on tamoxifen. *J Am Geriatr Soc* 1986;**34**:318-20.

Severe rombergism due to gentamicin toxicity

Drs Roderick Duncan and Ian D Melville (Institute of Neurological Sciences, Southern General Hospital, Glasgow G51 4TF) write: Symptoms of rombergism (unsteadiness in the dark or when washing the face) occur due to gentamicin toxicity, but Romberg's test is usually negative.[1] We report a case in which rombergism was a dominating feature and Romberg's test was highly positive.

A 71 year old man received two courses of intramuscular gentamicin for perineal infection, lasting eight days and six days, both at a dose of 80 mg three times a day. During the second course he complained of nausea and dizziness. Serum gentamicin concentration was 13·6 mg/l, and the drug was discontinued. He was also taking frusemide 80 mg day orally, metronidazole, ampicillin, dihydrocodeine, and temazepam. On becoming mobile after his illness he noted difficulty in maintaining his balance in the dark. He experienced abnormal sensations of motion while in bed and had bobbing oscillopsia while walking. He had no hearing loss, tinnitus, or vertigo. Neurological examination showed no impairment of posterior column sensation or of coordination of the arms. On closing his eyes he had complete ataxia of trunk and legs and could neither sit nor stand upright. There was no positional vertigo or nystagmus and no response to maximal caloric stimulation in either ear. Audiometry was normal. A magnetic resonance imaging scan showed minimal cerebellar atrophy. Closing the eyes removes one of the three inputs to postural control. If posterior column sensation is also absent the remaining input from the vestibular apparatus is insufficient, and the patient will fall. Presumably the same applies when vestibular function is absent and only posterior column sensation remains. Why then is rombergism not a more common result of gentamicin toxicity? While it is preferentially vestibulotoxic, and tends to leave cochlear function intact,[2] gentamicin may be even more specifically toxic to the semicircular canals, leaving otolith function relatively intact.[3] Since output from the otolith organs is mainly tonic, there remains a vestibular input to postural control with the head static, allowing maintenance of posture with the eyes closed. This case illustrates that gentamicin toxicity may present with rombergism with no hearing loss and no overt features of vestibular dysfunction. The Committee on Safety of Medicines lists only two cases of vestibular disturbance due to gentamicin between 1964 and 1986, although Ramsden and Ackrill report 15.[1]

1 Ramsden RT, Ackrill P. Bobbing oscillopsia from gentamicin toxicity. *British Journal of Audiology* 1982;**16**:147-50.
2 Ballantyne J. Ototoxicity. In: Oosterveld WJ, ed. *Otoneurology* Chichester: Wiley, 1984.
3 Keene M, Hawke M, Barber HO, Farkashidy J. Histopathological findings in clinical gentamicin ototoxicity *Arch Otolaryngol* 1982;**108**:65-70.