SHORT REPORTS

Antazoline-induced allergic pneumonitis

Asthma and acute or chronic interstitial pneumonitis may be induced by several drugs^{1,2} but antazoline has not been incriminated. We therefore report a case of antazoline-induced acute interstitial pneumonitis and rash that was confirmed by a challenge test.

Case report

A 35-year-old woman who smoked 20 cigarettes daily developed erythema at the injection site of an immunoglobulin preparation given for chronic rhinitis. The erythema was treated with antazoline hydrochloride (Antistin-Privine), 50 mg six-hourly. Seven hours after the second dose she complained of fever, rash, and dyspnoea, which subsided spontaneously. Three weeks later she was given 400 mg antazoline hydrochloride daily for two days. Because of dyspnoea, cough, fever, and an exanthematous rash, mainly on the anterior surface of the arms and legs, she was admitted to this hospital.

No immunoglobulin preparations were given. Her temperature was 37.5°C. No rales were heard. Chest radiography showed alveolointerstitial shadows in the lower lung fields. White cell count (WCC) was $31 \times 10^9/l$ ($31\,000/mm^3$), with 87% segmented neutrophils, 9% band neutrophils, 2% monocytes, 2% lymphocytes, and no eosinophils. Rheumatoid factor was not detected but antinuclear factor antibody titre was 1/10 by indirect immunofluorescence. Concentrations of IgG, IgA, IgM, IgE, C3, and C4 were normal. Lung function values were: carbon monoxide transfer factor (T_LCO) 2.3 ml/min/kPa (17.2 ml/min/mm Hg) (standard temperature and pressure dry; STPD) (normal value over 2.8 ml/min/kPa; 21 ml/min/mm Hg); vital capacity (VC) 2.3 l (normal: 3.3 l); and forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) was normal (85%). Two days later she had improved and radiography showed only a linear atelectasis at both lung bases. After a week her radiographs were normal and she was discharged. One month later she consented to return for a challenge test (figure). After basal lung function tests and radiography, placebo was given with no effect, and 24 hours later (time zero) 50 mg antazoline hydrochloride was administered. This was repeated 48 hours after placebo. Eight hours after the first dose she complained of mild dyspnoea. Seven hours after the second dose dyspnoea increased and fever (38°C) and rash appeared. Chest radiographs were similar to those seen on first admission. Total WCC count progressively increased but there were no eosinophils. Complement concentrations were unaltered. Lung function tests showed rapid decrease in VC and T_LCO but FEV_1/FVC was unchanged (figure). She improved rapidly with 40 mg methylprednisolone, and eight weeks later her lung function and radiographs were normal.

Changes in lung function values and clinical course after antazoline.

Conversion: SI to traditional units— T_LCO : 1 ml/min/kPa $\approx$ 7.5 ml/min/mm Hg.

Comment

Antazoline hydrochloride (2-[N-benzyl-antinomethyl] imidazoline hydrochloride) is commonly used for allergic reactions. Side effects include thrombopenia,³ cardiac arrhythmia, haemolytic anaemia, and acute renal failure.⁴ Our studies show that antazoline may also cause

acute interstitial pneumonitis. A similar type of acute reaction after a short course of treatment with nitrofurantoin has been described; an immunocomplex vasculitis was suggested as the cause.⁵ Other drugs such as sulphonamide, sulphasalazine, and aminosalicilic acid are well known causes of pulmonary reactions associated with eosinophilia, usually after long courses. The mechanism of these reactions has not been clearly defined, though features of both the immediate anaphylactic (type I) reaction and the intermediate Arthus (type III) reaction are present. In our patient the delayed reaction to challenge suggests a mechanism similar to that of extrinsic alveolitis because of immunocomplexes (type III), though serum complement concentrations remained normal. The normal concentrations of IgE and absence of eosinophilia tend to exclude a type I reaction.

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Palpable spleen and bleeding oesophageal varices

Upper gastrointestinal endoscopy may not have changed the prognosis of patients bleeding from the upper gastrointestinal tract, but those few bleeding from varices require special management and need to be identified early. We have therefore tested the hypothesis that a spleen that is palpable, without implying its size, indicates that varices are the source of the haemorrhage.

Patients and results

During the five years 1973-7 22 patients at St Thomas's Hospital were examined endoscopically because of upper gastrointestinal bleeding and were found to have oesophageal varices. Out of the 22 patients 16 had cirrhosis (12 alcoholic, one primary biliary, and three cryptogenic), one had portal vein thrombosis, one had congenital hepatic fibrosis, and in four the cause of the portal hypertension was not determined. Sixteen of the 22 patients were bleeding from their varices, and 14 of these 16 had a palpable spleen, one had had a splenectomy, and the last had such gross ascites that no abdominal organs were palpable but the spleen was enlarged on scintiscan. The remaining six patients were bleeding from a lesion other than varices (a peptic ulcer in five, aspirin-induced gastric erosions in one). None of these six patients had a palpable spleen. Analysis of the routine liver function tests (serum bilirubin, alkaline phosphatase, aspartate aminotransferase and albumin concentrations, and prothrombin time ratio before treatment with vitamin K) showed no significant difference between the groups.

Comment

Endoscopy in cases of acute upper gastrointestinal haemorrhage is generally agreed to be safe and accurate¹ but the information it gives has not been shown to improve the prognosis. Our survey clearly shows that when the spleen is palpable upper gastrointestinal bleeding is possibly from varices while, conversely, an impalpable spleen is

Published evidence on interrelationships between upper gastrointestinal haemorrhage and oesophageal varices, portal venous pressure and splenic enlargement.

strong evidence that the bleeding is from another site. It may therefore be appropriate to endoscope urgently only those patients in whom the spleen is palpable, while endoscopy could reasonably be postponed when the spleen is impalpable. This may be particularly appropriate in hospitals where experienced endoscopists are not on immediate recall.

In our study 27% of those who bled did so from a site other than their varices. This agrees with other British studies and also confirms that this group is smaller than in North America, where more patients bleed from gastric erosions. The relationships between the height of the portal venous pressure, the presence and size of oesophageal varices, bleeding from the varices, and the size of the spleen are not clear (figure). Oesophageal varices seen on barium swallow examination are more likely to bleed if they are large² but, surprisingly, the portal pressure is poorly correlated with the size of varices,^{2,3} with the occurrence of bleeding,⁴ or with the size of the spleen.⁵ Our findings now link a palpable spleen with variceal bleeding. We conclude that even when varices are known to be present the absence of a palpable spleen in a patient who has an upper gastrointestinal haemorrhage and does not have gross ascites makes it unlikely that the bleeding is from varices.

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Hypercalcaemia after tamoxifen for breast cancer: a sign of tumour response?

Hypercalcaemia occasionally occurs as an acute event in patients with advanced breast cancer after hormone treatment.¹ Tamoxifen, a non-steroidal oestrogen antagonist, is widely used for advanced breast cancer,² and over the past two years we have treated 62 such patients with tamoxifen. We describe the course of four patients who became hypercalcaemic after starting tamoxifen.

Case reports

Case 1—A 57-year-old woman was admitted with advanced breast cancer and bone metastases. Tumour oestrogen receptor concentration was 95 fmol (2 bfg)/mg protein and serum calcium concentration was normal. Tamoxifen

was given (20 mg twice daily), and after four days she complained of nausea, vomiting, and weakness. Her serum calcium concentration was 4.0 mmol/l (16.2 mg/100 ml). Tamoxifen was discontinued and she was treated with intravenous fluids and steroids. A few days later serum calcium concentration was 2.7 mmol/l (10.6 mg/100 ml). Tamoxifen was reinstituted after 10 days. Five months later serum calcium concentration was normal, she was symptom-free, and radiography showed sclerosis of previous lytic lesions.

Case 2—A 61-year-old woman was admitted with a mass in the breast and widespread osteolytic metastases. Tumour oestrogen receptor concentration was 381 fmol (103.8 fg)/mg protein and serum calcium concentration was normal. Tamoxifen was given (10 mg twice daily), and after four days she became confused. Serum calcium concentration was 2.9 mmol/l (11.5 mg/100 ml). Tamoxifen was discontinued and she was treated with fluids and prednisone. Three days later her condition was improved. Her serum calcium concentration was 2.5 mmol/l (10.2 mg/100 ml). Cytotoxic chemotherapy was tried and achieved temporary control.

Case 3—A 68-year-old woman with breast cancer and bone metastases was admitted because of confusion and vomiting. Serum calcium concentration was 3 mmol/l (12.3 mg/100 ml) but was normal after administration of fluids and prednisone. Tamoxifen was given (20 mg twice daily), and after five days she developed weakness, and serum calcium concentration had risen to 3.0 mmol/l (12.0 mg/100 ml). Tamoxifen was stopped, and serum calcium concentration fell to 2.5 mmol/l (9.8 mg/100 ml) after fluids and steroids were administered. Cytotoxic chemotherapy was given but without response.

Case 4—A 60-year-old woman presented with stage IV breast cancer and pulmonary and bone metastases. Serum calcium concentration was normal. Tamoxifen, 20 mg twice daily, and intermittent adriamycin and cyclophosphamide were given, and two weeks later she developed confusion and bone pain. Serum calcium concentration was 3.7 mmol/l (15.0 mg/100 ml) but became normal when she was treated with fluids, diuretics, prednisone, and oral phosphate. Her bone pains disappeared. Two months later radiography showed sclerosis of the bone metastases. Tamoxifen, adriamycin, and cyclophosphamide were continued throughout this period.

Comment

Four out of 26 patients with breast cancer and bone metastases developed acute hypercalcaemia when treated with tamoxifen (figure).

Changes in serum calcium concentration after beginning tamoxifen.

This occurred four to five days after starting tamoxifen in three patients and after two weeks in the fourth. None of the 36 patients with advanced breast cancer without bone metastases developed hypercalcaemia when treated with tamoxifen. During the study period 112 patients with advanced breast cancer were treated with cytotoxic chemotherapy and 48 underwent oophorectomy; none developed acute hypercalcaemia after treatment. We conclude that tamoxifen-induced hypercalcaemia occurs only in patients with breast cancer and bone metastases and that cytotoxic chemotherapy or oophorectomy does not cause this complication.

A recent review of 36 patients with breast cancer who became hypercalcaemic after treatment with tamoxifen showed a prevalence of hypercalcaemia of under 0.1%.³ Our findings suggest that this complication may be more common. Two of our patients who became hypercalcaemic after tamoxifen had high tumour oestrogen receptor concentrations, and two showed objective tumour responses with continued treatment. Hall *et al*⁴ recorded tumour responses in three out of six patients who became hypercalcaemic while taking oestrogens.