Azathioprine shock

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Summary: Azathioprine has been used as an immunosuppressant for over 20 years in cancer chemotherapy, organ transplantation and diseases with confirmed or suspected immune mechanisms. A hypersensitivity reaction manifesting as fever, rash, myalgia and a neutrophil leucocytosis occurring about 2 weeks after exposure is well documented and has been confirmed by challenge testing. Hypotensive reactions are less common but potentially fatal; a case is reported where repeat exposure resulted in profound circulatory collapse responding only to intervention with inotropic agents.

Introduction

Hypotensive reactions to azathioprine are well recognized though uncommon. A further case is reported where this life-threatening response followed re-exposure to the drug after an initial hypersensitivity reaction.

Case report

A 31 year old man with multiple sclerosis but no incapacitating neurological disabilities, was commenced on azathioprine 50 mg three times daily. Two weeks later he became unwell with fever, headache, breathlessness, abdominal pain and a rash. He discontinued azathioprine on the advice of his neurologist and was treated with penicillin by his general practitioner. The symptoms necessitated him being confined to bed for 5 days over the course of which he made a complete symptomatic recovery. Two days later his general practitioner suggested that the illness had been incidental and he recommenced azathioprine.

After the second dose, his symptoms recurred in a more severe form and he presented to hospital. He had a pyrexia of 39°C, injected conjunctivae, and an erythematous macular rash covering the extensor aspect of the upper arms, the legs and the back. Central to the macules were pinhead sized white vesicles some of which appeared older and were crusted. The initial haematological and biochemical investigations were normal apart from a mildly elevated blood urea of 12.6 mmol/l and he was admitted for observation.

A few hours after admission, he complained of severe central chest pain and faintness, and became extremely anxious. He was peripherally cyanosed with

a core temperature of 36.5°C, had a systolic blood pressure of 60 mmHg and a heart rate of 120/min.

Arterial blood gas analysis revealed an oxygen tension of 8.5 kPa (64 mm Hg), carbon dioxide tension of 3.5 kPa (26 mm Hg) and a pH of 7.45. The electrocardiogram and chest radiograph were normal but his white count had risen to $14.2 \times 10^9/l$ (94% neutrophils). Central venous pressure was -3 cm H₂O reference the sternal angle and rose to +1 cm after rapid infusion of 1500 ml fluid. Blood pressure remained low despite intravenous corticosteroids (hydrocortisone 400 mg) and he was then commenced on dopamine (5 µg/kg/min) and dobutamine (10 µg/kg/min). Systolic blood pressure rose to 100 mm Hg and soon after was followed by a diuresis. There was a rapid improvement in his well being and the oxygen tension rose to 13.9 kPa (104.3 mm Hg). In view of the leucocytosis he was commenced on intravenous ampicillin but this was discontinued after 2 days.

Six hours later he was able to eat and drink but remained presyncopal when elevated from recumbency. Inotropic support was only able to be withdrawn finally 24 hours later. Scrapings from skin lesions revealed numerous pus cells but no organisms on conventional or electron microscopy and histology revealed non-specific features with a few perivascular eosinophils. Cultures of blood, urine and skin lesions were all sterile. The leucocytosis peaked at $30.6 \times 10^9/l$ on the third day and the erythrocyte sedimentation rate rose to 36 mm in 1 hour. There were raised levels of aspartate aminotransferase (478 IU/l), alkaline phosphatase (945 IU/l), and lactate dehydrogenase (998 IU/l). Serum creatine phosphokinase and complement levels were normal. Serum bilirubin was elevated to 23 µmol/l and creatinine peaked at 238 µmol/l. Corticosteroids were continued for 5 days whereafter he was discharged; by this time his rash was fading, the leucocytosis had subsided and renal and hepatic function had returned to normal.

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Discussion

This patient had a severe reaction on re-exposure to azathioprine with evidence of hepatic and renal dysfunction as well as circulatory collapse. The hypersensitivity response is well documented occurring about 2 weeks after exposure with varying combinations of fever, myalgia, arthralgia, rash, nausea, vomiting, diarrhoea, oliguria, hypotension and bronchospasm. A neutrophil leucocytosis is a constant finding while elevated transaminases, amylase and creatinine have been variably reported (King *et al.*, 1972; Davis *et al.*, 1980; Cunningham *et al.*, 1981). The reaction may mimic reactivation of the underlying disease process as in Crohn's disease (Davis *et al.*, 1980) and dermatomyositis (Goldenberg & Stor, 1975) and even simulate rejection in renal transplantation (King *et al.*, 1972). The differentiation from septicæmia may be difficult particularly in patients who are already immunocompromised by the underlying disease process or by immunosuppressant therapy. In this patient pyrexia, oliguria and a rash resembling a septic exanthem together with a neutrophil leucocytosis initially created diagnostic difficulty.

The nature of the symptoms occurring 1 to 3 weeks after exposure and which recur within a few hours of challenge, support a hypersensitivity reaction. The mechanism of the hypotension which may occur is uncertain; postulates include fluid loss from severe gastrointestinal upset or pancreatitis (Pozniak *et al.*, 1981). Where pancreatitis has been reported hypotension has not been a feature and amylase levels are usually only two to three times the laboratory level of normal (Nogueira & Freedman, 1972; Sturdevant *et al.*, 1979; Davis *et al.*, 1980; Pozniak *et al.*, 1981). Five reported cases with severe circulatory collapse have responded fairly quickly to treatment with fluid replacement, corticosteroids and antibiotics (Cunningham *et al.*, 1981; Keystone & Schabas, 1981; Zaltzman *et al.*, 1984). One patient, with clinically unrecordable blood pressure, profuse vomiting and diarrhoea,

elevated transaminases but normal serum amylase, responded rapidly to fluid replacement on two separate occasions (Zaltzman *et al.*, 1984). The patient reported here did not develop diarrhoea or vomiting to account for fluid loss while fluid replacement and intravenous corticosteroids alone did not correct the hypotension. It was only when inotropic therapy was commenced that it was possible to stabilize the circulation. Hypotension responding to fluids, steroids and inotropes is suggestive of peripheral vasodilatation, increased capillary permeability, and poor cardiac contractility. This is in keeping with a generalized reaction which would account for the varying clinical and biochemical features.

Deaths from hypotension after azathioprine reactions have not been reported although some may have been mistaken for disease progression or septicæmia. One patient with severe nephritis developed oliguria during a reaction which subsequently proved to be fatal (King *et al.*, 1972). The need for careful supervision of any challenge testing has been recorded previously (Cunningham *et al.*, 1981). It has even been suggested that a suspicion of azathioprine hypersensitivity should contraindicate a challenge (Keystone *et al.*, 1981), doses as low as 12.5 mg having caused profound hypotension in susceptible patients (Zaltzman *et al.*, 1984). However, if doubt exists as to whether the patient is experiencing a flare up of his disease process or having a hypersensitivity reaction, and it is felt strongly that alternative therapy is not possible, challenge testing should be performed with extreme caution. A small dose should be administered initially and facilities for resuscitation should be readily available.

The indications for azathioprine therapy have widened and more patients with less severe disease are likely to be treated. Patients, particularly when commencing treatment on an outpatient basis, should be aware of the possible reaction. Those developing hypersensitivity reactions need to be warned about the dangers of repeat exposure.

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