Fourteen days later she presented with a sudden onset of general malaise, fever (38°C) rigors, and relative hypotension (115/70 mm Hg). No focal signs of infection were found, and blood and urine cultures were negative. There was no leucocytosis or eosinophilia. Azathioprine was stopped on admission. Intravenous antibiotics and 100 mg hydrocortisone six hourly were started. The fever and symptoms resolved within 12 hours, and the usual dose of prednisolone was resumed. Because of the possibility of an azathioprine reaction, the patient was rechallenged with a 50-mg dose two weeks later. Within two hours, nausea, vomiting, and mild diarrhoea developed, followed by profound hypotension (60 mm Hg systolic, pulse 120/min), oliguria, and peripheral cyanosis. No fever, rash, or bronchospasm occurred. Once again cultures were negative, and the patient recovered over 24 hours with intravenous fluids, 100 mg hydrocortisone six hourly, and intravenous frusemide.

Case 2—A 51-year-old woman who had had seropositive erosive rheumatoid arthritis for 17 years was started on azathioprine 50 mg daily for increasing disease activity. She had previously developed proteinuria when treated with gold. Other medication consisted of prednisolone 6 mg and naproxen. After four weeks the dose of azathioprine was increased to 75 mg daily, and after a further four weeks the patient presented to her local doctor with sudden onset of vomiting and dizziness and was found to be profoundly hypotensive (blood pressure 60/40 mm Hg) but with no fever. Initially gastroenteritis was diagnosed, and the patient recovered rapidly with intravenous fluids, cessation of azathioprine, and 100 mg hydrocortisone six hourly. A second similar episode occurred when azathioprine 50 mg was started a few days later and again with a similar rechallenge in hospital. The last episode was milder (blood pressure 100/60 mm Hg, less vomiting) and resolved spontaneously. Blood and urine cultures were negative, and there was no associated rash or bronchospasm.

Comment

The well-known side effects of azathioprine are dose-dependent and usually reversible after withdrawal of the drug.¹ Patients with azathioprine hypersensitivity have been described as having similarities to a viral illness or serum sickness² with fever, diffuse erythematous rash, myalgia, arthralgia, tachycardia, and, less commonly, jaundice² and interstitial nephritis.³ The diagnostic difficulties that might occur in patients undergoing renal transplant where the clinical features may suggest septicaemia or graft rejection have been emphasised. Other hypersensitivity reactions reported have had some features of anaphylaxis⁴—namely, bronchial asthma, laryngeal oedema, and urticaria, which were relieved by antihistamine treatment and recurred on rechallenge.

The cases we report here have the distinguishing and potentially serious feature of hypotension, which could not be attributed to infection, fluid loss, or cardiac disease and which recurred when the patients were rechallenged with the drug. The clinical features of anaphylaxis and rashes were not present, and the mechanism of the hypotension remains obscure. Both patients were also receiving prednisolone in stable and only moderate doses and developed the syndrome some weeks after starting azathioprine.

Septicaemia must be excluded in immunosuppressed patients presenting with sudden onset of shock, with or without fever. Possibly this drug-related syndrome is more common than reported and may be ascribed to septicaemia. The apparent response of hypotension and fever to intravenous fluids, antibiotics, steroids, and azathioprine withdrawal (temporary or permanent) may be taken as clinical evidence of septicaemia despite negative cultures, whereas the important factor in response is the withdrawal of azathioprine.

Extreme caution is suggested with rechallenge, as the first of our patients became profoundly ill after this. Fortunately, both patients recovered completely.

¹ Meyler L, ed. *Side effects of drugs*. Vol 7. Amsterdam: Excerpta Medica, 1972.

² Davis M, Eddleston AL, Williams RW. Hypersensitivity and jaundice due to azathioprine. *Postgrad Med J* 1980;56:274-5.

³ King JO, Laver MC, Fairley KF, Ames GA. Sensitivity to azathioprine. *Med J Aust* 1972;2:939-41.

⁴ Michot F. Erfahrungen in der Langzeitbehandlung von Kollagenkrankheiten mit Azathioprin (Imuran). *Med Klin* 1968;63:1262-6.

⁵ Stollenwerk R, Schilling F. Imurek fever. *Verh Dtsch Ges Rheumatol* 1980;6:473-4.

(Accepted 9 June 1981)

Department of Rheumatology, Royal Melbourne Hospital, Parkville, Victoria 3050, Australia

T CUNNINGHAM, MB, BS, rheumatology registrar
D BARRACLOUGH, FRACP, assistant rheumatologist
K MUIRLEN, MD, FRACP, head, rheumatology unit

Dominant inheritance of intracranial berry aneurysm

Autosomal dominant inheritance of intracranial berry aneurysm has been suggested in some families.¹⁻³ Associations with polycystic kidney, Ehlers-Danlos syndrome, pseudoxanthoma elasticum, and coarctation of the aorta have also been reported.⁴ We describe a family with four proved and two clinically suggestive cases of berry aneurysm with no evidence of such associated conditions. Families have been described with aneurysm in two generations, but this family and that of Hashimoto³ where consanguinity was present, have members affected in three generations, providing strong evidence for an autosomal dominant mode of inheritance.

Case reports

Case I 2—A previously healthy 39-year-old woman suddenly began snoring while sleeping and died one hour later without awakening. No necropsy was performed.

Case II 1—A 59-year-old known hypertensive woman collapsed while shopping and died within 24 hours. Postmortem disclosed a ruptured berry aneurysm.

Case II 4—A 41-year-old hypertensive farmer was found collapsed in his field after earlier complaining of severe headache. He died within two hours. The certified cause of death was "apoplexy".

Pedigree of family studied

Case II 5—The proband, an asymptomatic 53-year-old woman, underwent elective angiography at her own request because of her family history. Berry aneurysms were found bilaterally and these were subsequently clipped and wrapped.

Case II 8—A known hypertensive 39-year-old man collapsed at work and died without regaining consciousness. Necropsy disclosed a ruptured berry aneurysm.

Case III 1—A 25-year-old woman presented with headache of acute onset. Two left sided berry aneurysms were subsequently clipped at operation. She was left with residual hemiparesis. Investigations performed six years later after further severe headaches showed a right-sided aneurysm. Further operations were not recommended.

Cases II 6, II 7, III 15, and III 16 all underwent elective angiography without evidence of berry aneurysm.

Comment

Six affected members occurred in three generations of this family, with a pattern of segregation which strongly suggests dominant inheritance. The incidence of aneurysms of the internal carotid artery and middle cerebral artery tends to be higher in familial cases,³ though there was no evidence of such preferential distribution in this family. At their own request five asymptomatic relatives were investigated with cerebral angiography and one of them was found to be affected and subsequently treated (Case II 5). A negative angiographic result in a family member still in the twenties does not preclude the later development of aneurysm, especially as symptomatic members in

this family have all presented over the age of 35. Because of this uncertainty, angiography, an invasive procedure with a definite morbidity, should perhaps be reserved for people with symptoms and older relatives who request the investigation. Computerised axial tomography with contrast enhancement is an alternative investigation for such cases. It must be emphasised, however, that, though less hazardous, this is not an accurate method of diagnosing aneurysms and that negative investigation does not rule out the condition.

The benefits of surgery for symptomatic cases of berry aneurysm are well established. The long-term results of major surgery for the treatment of asymptomatic people are not known. In experienced hands the surgery of operable unruptured aneurysms should carry a mortality and morbidity of well below five per cent. The technical difficulties in such cases are much less, making the procedure safer and simpler. The alternative is to reserve surgery for symptomatic cases or for those in whom precipitating factors such as hypertension develop. When a choice is made, it should be remembered that the first haemorrhage from an aneurysm carries an appreciable immediate mortality. The asymptomatic proposita in this family, because of the rapid death of so many of her relatives, had no doubts that she wanted elective surgery.

We suggest that a detailed family history should always be taken in cases of berry aneurysm. If other cases are found or strongly suspected in the family, angiography should be considered but due attention given to the relative risks of angiography compared with simple observation. If berry aneurysms are found, however, surgical intervention may have to be offered.

Pope *et al*⁵ recently showed type III collagen deficiencies in skin biopsy preparations from some patients with congenital cerebral aneurysms. In future collagen patterns may be helpful in identifying individuals at risk in families where cerebral aneurysm appears to be segregating as a dominant trait.

¹ McKusick VA. *Mendelian inheritance in man: catalogs of autosomal dominant, autosomal recessive and X-linked phenotypes*. 5th ed. Baltimore, London: Johns Hopkins Press, 1978.

² Jain KK. Familial intracranial aneurysms. Review of literature and presentation of six new cases. *Acta Neurochir* 1974;**30**:129-37.

³ Hashimoto I. Familial intracranial aneurysms and cerebral vascular anomalies. *J Neurosurg* 1977;**46**:419-27.

⁴ Thierry A, Ballivet J, Dumas R, *et al*. Les cas familiaux d'aneurysmes intra-cranies. *Neurochirurgie* 1972;**18**:267-76.

⁵ Pope FM, Nicholls AC, Narcisi P, Bartlett J, Neil-Dwyer G, Doshi B. Some patients with cerebral aneurysms are deficient in Type III collagen. *Lancet* 1981;*ii*:973-5.

(Accepted 9 June 1981)

University Department of Neurosurgery, Manchester Royal Infirmary, Manchester M13 9WL

T W EVANS, BSC, MB, house officer (present appointment: senior house officer Professorial Medical Unit, Royal Hallamshire Hospital, Sheffield)
M C VENNING, PHD, BM, house officer (present appointment: senior house officer, Renal Unit, Guy's Hospital, London SE1 9RT)
F A STRANG, FRCS, consultant neurosurgeon

St Mary's Hospital, Manchester M13 0JH

DIAN DONNAI, MRCP, DCH, consultant clinical geneticist

Toxic hepatitis during ketoconazole treatment

Ketoconazole, a synthetic imidazole-piperazine compound, is a new oral broad-spectrum antimycotic drug for the treatment of superficial and systemic fungal infections. The side effects reported have been minor and mostly subjective, such as nausea, itching, headache, and dizziness. Liver toxicity as shown by raised serum enzyme activities has been reported in a few cases.¹ We report a case of hepatotoxicity with clinical symptoms associated with ketoconazole.

Case report

A 68-year-old woman who had had severe recalcitrant dermatophytosis (*Trichophyton rubrum*) of feet and toe-nails for 35 years was admitted to a multicentre study of ketoconazole. She underwent clinical investigation including liver function and blood tests every three weeks. Treatment was

started with 200 mg ketoconazole daily, which she received for 12 weeks, after which the dose was increased to 400 mg owing to lack of improvement. After two weeks on this dose she developed pruritus and rhinorrhoea and felt tired and dizzy. Three days later dark urine and pale faeces were observed, and she was admitted to a regional surgical department. Intravenous cholecystography showed no abnormality. Results of liver function tests, including serum alanine aminotransferase and serum alkaline phosphatase activities and serum bilirubin concentration, were compatible with parenchymal liver damage (see figure). A liver biopsy specimen showed preserved lobular architecture. The portal tracts were enlarged, with slight bile duct proliferation and moderate infiltration with mononuclear cells. Focal necroses were seen in the parenchyma. The centrilobular area showed condensation of the reticulin and increased amounts of seroid in Kupffer's cells, indicating recent necroses. Proliferation of Kupffer's cells was pronounced.

Serum alanine aminotransferase activity during two periods of ketoconazole treatment with different doses.

Normal range of serum alanine aminotransferase activity is 10-40 u/l.

Ketoconazole treatment was stopped and her symptoms disappeared. Results of liver function tests returned to normal. Seventeen weeks later ketoconazole treatment with 200 mg daily was restarted. After two weeks of treatment the symptoms reappeared and results of the liver function tests were again abnormal. A liver biopsy specimen showed enlarged portal tracts, but the parenchymal changes were less prominent. Necroses were rare and Kupffer's cell proliferation was absent. After ketoconazole treatment was stopped her symptoms again disappeared and the results of liver function tests returned to normal, and have remained normal now for eight months.

Results of tests for hepatitis B surface antigen and antibodies to hepatitis B virus and to hepatitis A virus were negative. Haematological values remained normal, and eosinophilia was not found. She did not receive other drugs. A third liver biopsy specimen six months after ketoconazole was withdrawn showed only rather enlarged portal tracts with moderate mononuclear infiltration.

Comment

In clinical trials of more than 2000 patients ketoconazole was shown to be effective and reliable in the treatment of candida, dermatophytes, and fungi causing deep mycoses.^{2,3} It was also effective compared with other systemic antimycotics—for example, griseofulvin.^{3,4}

Imidazole-piperazine compounds either stimulate or inhibit liver enzyme production⁵ and therefore the side effect reported here is not surprising. The liver histology was like that seen in methyl dopa-induced hepatitis—that is, enlarged portal tracts with mononuclear cell infiltration and piecemeal necrosis as seen in chronic active hepatitis. The fact that the liver impairment reappeared shortly after ketoconazole treatment was restarted strongly supports the evidence for ketoconazole-induced liver damage. In animal experiments liver toxicity has not been found.² So the type of hepatotoxicity seen in our case must be classified as a type II reaction (National Institutes of Health classification)—that is, the hepatotoxicity of ketoconazole cannot be predicted from animal experiments, it is rare in humans, and it is dose-independent.

¹ Petersen EA, David WA, Kirkpatrick H. Treatment of chronic mucocutaneous candidiasis with ketoconazole. *Ann Intern Med* 1980;**93**:791-5.

² Symoens J, Moens M, Dom J, *et al*. An evaluation of two years of clinical experience with ketoconazole. *Reviews of Infectious Diseases* 1980;**2**:674-87.

³ Hay RJ, Wells RS, Clayton YM, Wingfield HJ. Treatment of chronic mucocutaneous candidosis with oral ketoconazole: a study of 12 cases. *Reviews of Infectious Diseases* 1980;**2**:600-5.