between patients having abdominal or other operations. Minor operations under local anaesthesia resulted in smaller but significant increases in urinary total protein but not albumin concentrations, supporting the observation made in patients with trauma that the magnitude of proteinuria is related to the severity of injury.

We conclude that operations are associated with a rapid increase in urinary protein excretion, and major operations with microalbuminuria, and suggest that this reflects changes in vascular permeability. The usefulness of measurements of protein excretion in predicting postoperative complications needs to be established.

- 1 Winocour PH, Durrington PN, Ishola M, Anderson DC, Cohen H. Influence of proteinuria on vascular disease, blood pressure, and lipoproteins in insulin dependent diabetics. *Br Med J* 1987;294:1648-51.
- 2 Feldt-Rasmussen B. Increased transcapillary escape rate of albumin in type 1 (insulin-dependent) diabetic patients with microalbuminuria. *Diabetologia* 1986;29:282-6.
- 3 Gosling P, Sutcliffe AJ, Cooper MACS, Jones AF. Burn and trauma associated proteinuria: the role of lipid peroxidation, renin, and myoglobin. *Ann Clin Biochem* (in press).
- 4 Gosling P, Sutcliffe AJ. Proteinuria following trauma. *Ann Clin Biochem* 1986;23:681-5.
- 5 Fleck A, Raines G, Hawker F, et al. Increased vascular permeability: a major cause of hypoalbuminuria in disease and injury. *Lancet* 1985;i:781-4.

(Accepted 23 September 1987)

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Itraconazole as maintenance treatment for cryptococcal meningitis in the acquired immune deficiency syndrome

Cryptococcal meningitis is a life threatening opportunistic infection with a prevalence among patients with the acquired immune deficiency syndrome (AIDS) of 2.0-7.5%. Combination treatment with intravenous amphotericin B and oral flucytosine for six weeks is the treatment of choice.¹ Maintenance treatment is necessary subsequently as relapses often occur in immunodeficient patients.²

Itraconazole is a new antifungal triazole chemically related to drugs derived from imidazole such as ketoconazole. After induction treatment we used oral itraconazole to prevent relapse of cryptococcal meningitis in patients with AIDS.

Patients, methods, and results

Five patients positive for antibody to human immunodeficiency virus (HIV) entered the open study. In all patients *Cryptococcus neoformans* had been isolated in cultures of cerebrospinal fluid, fulfilling the diagnostic criteria of the Centers for Disease Control for AIDS. Each patient received induction treatment with amphotericin B given intravenously (0.3 mg/kg/day) and oral flucytosine (150 mg/kg/day every six hours) for six to eight weeks. In four patients (cases 1, 2, 4, 5) maintenance treatment was with oral itraconazole 100 mg twice a day. One patient (case 3) received a higher dose of itraconazole (400 mg/day) because of its interaction with rifampicin, which was being taken simultaneously. The patient in case 1 was initially given maintenance treatment with amphotericin B (20 mg intravenously once a week) for six months before receiving oral itraconazole.

During treatment the titre of cryptococcal antigen in the cerebrospinal fluid was monitored by latex agglutination (Netherlands Reference Laboratory for Bacterial Meningitis) and the presence of viable cryptococci was assessed. Patients were considered to be responding well if clinical improvement con-

Effect of maintenance treatment with itraconazole on cryptococcal infection in five patients with the acquired immune deficiency syndrome

Case No	Titre of cryptococcal antigen		Follow up (months)	Dose of itraconazole (mg/day)
	Before treatment	During treatment		
1	1/128	1/16	3	200*
2	1/2048	1/32	12	200
3	1/1024	1/32	12	400
4	1/128	1/16	10	200
5	1/32	Not done	3	200

*Maintenance treatment comprised amphotericin B 20 mg intravenously once a week for first six months after induction treatment.

tinued, cerebrospinal fluid remained or became sterile, and the titre of cryptococcal antigen in the cerebrospinal fluid declined.

Before maintenance treatment was started titres of cryptococcal antigen ranged from 1/32 to 1/2048 (table) and in all patients cultures of cerebrospinal fluid did not yield any growth, although encapsulated yeasts were still present on microscopic examination of the cerebrospinal fluid. In four patients the titre of cryptococcal antigen declined during treatment (table). One patient (case 5) refused re-examination of cerebrospinal fluid. He died three months later from a severe AIDS dementia complex without clinical evidence of relapse of cryptococcal meningitis. Another patient (case 1) died of disseminated infection with *Mycobacterium avium intracellulare* after three months of maintenance treatment, and a third patient (case 3) died after 12 months of pneumonia caused by *Pseudomonas aeruginosa*; in both cases cultures of cerebrospinal fluid were sterile before death. Two patients were still alive after 10 and 12 months of maintenance treatment.

We did not observe any side effects during treatment with itraconazole.

Comment

As with other infectious complications in AIDS that can be treated the risk of relapse of cryptococcal meningitis after an initial response to treatment is high. Maintenance treatment with amphotericin B 80-100 mg each week is now recommended,³ but it necessitates inpatient care, is often poorly tolerated, and gives frequent toxicity. Flucytosine cannot be used in maintenance treatment because of rapid development of resistance. High dose oral ketoconazole has been beneficial in preventing relapse. Itraconazole and fluconazole are new antifungal triazoles. Itraconazole has a much lower minimal inhibitory concentration for *C. neoformans* than fluconazole in vitro.⁴ In pharmacokinetic studies fluconazole penetrated the cerebrospinal fluid extremely well whereas cerebrospinal fluid concentrations of itraconazole were very low or not detectable.⁵ Both agents seemed to be equally active at similar doses in rabbits with cryptococcal meningitis.⁴

The results of this study suggest that long term treatment with oral itraconazole is effective in preventing relapse of cryptococcal meningitis in patients with AIDS. The drug can be tolerated for long periods without side effects. A clinical trial of itraconazole as induction treatment is now in progress.

- 1 Bennett JE, Dismukes WE, Duma RJ, et al. A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptococcal meningitis. *N Engl J Med* 1979;301:126-31.
- 2 Kovacs JA, Kovacs AA, Polis M, et al. Cryptococcosis in the acquired immunodeficiency syndrome. *Ann Intern Med* 1985;103:533-8.
- 3 Zuger A, Louie E, Holzman RS, Simberloff MS, Rahal JJ. Cryptococcal disease in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1986;104:234-40.
- 4 Perfect JR, Savani DV, Durack DT. Comparison of itraconazole and fluconazole in treatment of cryptococcal meningitis and candida pyelonephritis in rabbits. *Antimicrob Agents Chemother* 1986;29:579-83.
- 5 Perfect JR, Durack DT. Penetration of imidazoles and triazoles into cerebrospinal fluid of rabbits. *J Antimicrob Chemother* 1985;16:81-6.

(Accepted 9 September 1987)

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