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SHORT REPORTS

Microproteinuria: response to operation

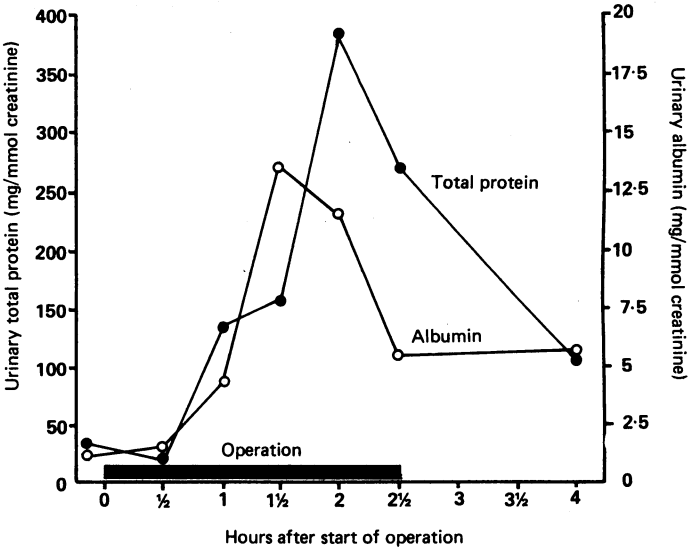
Microalbuminuria is accepted as a sensitive indicator of diabetic nephropathy. In diabetes proteinuria is associated with a greater incidence of arterial disease and higher mortality,[1] and microalbuminuria with a general increase in vascular permeability.[2] A transient increase in urinary excretion of protein and albumin occurs within four hours after burns and trauma.[3] It is proportional to the severity of injury, recurs with complications such as sepsis, and may reflect a general increase in vascular permeability as part of the acute phase response.[3,4] Vascular permeability increases within three hours of the start of operations[5] and might therefore be accompanied by an increase in urinary protein excretion. To establish whether this was so we measured protein excretion in patients before and after various operations.

Patients, methods, and results

We studied 33 patients, of whom 21 had indwelling bladder catheters. Eleven patients were having intraperitoneal operations (elective repair of an aortic aneurysm (five), resections of the large bowel (five) and cholecystectomy (one)); 13 were having extraperitoneal operations (femorodistal arterial reconstruction (11) and repair of an inguinal hernia (two)); and nine were having high ligation of the saphenous vein under local anaesthesia. Urine was obtained within the two hours before and three hours after the operation in all patients. Urinary total protein and albumin excretion was measured as described previously[4] and expressed as mg/mmol creatinine to correct for changes in dilution.

After operation the urinary total protein concentration increased in all 33 patients and urinary albumin concentration increased in 29 patients (four patients undergoing ligation of the saphenous vein did not show an increase). The geometric mean urinary total protein concentration increased 4·37-fold (95% confidence interval 2·28 to 8·34; geometric mean 6·5 (range 0·9-55·7) mg/mmol creatinine before operation and 28·6 (2·5-462) mg/mmol after). The geometric mean urinary albumin increased 3·10-fold (95% confidence interval 1·69 to 5·66; geometric mean 1·3 (range 0·4-8·5) mg/mmol before operation and 4·1 (0·3-62·6) mg/mmol after). The arithmetic mean urinary total protein concentration in the nine patients operated on under local anaesthesia increased from 4·4 (range 0·9-12·6) mg/mmol creatinine before operation to 7·2 (2·5-23·0) mg/mmol after operation, ($p<0·05$, Wilcoxon's signed rank test). The arithmetic mean urinary albumin concentration in these nine patients did not change significantly (mean 0·9 (range 0·2-2·4) mg/mmol creatinine before and 0·8 (0·3-2·0) mg/mmol after operation).

In two patients undergoing resections of the large bowel, one elective repair of an aortic aneurysm, and one axillobifemoral grafting with bilateral femorodistal arterial reconstruction urine samples were collected 15 minutes before the operation and every 30 minutes after the start of the operation. The mean time to significant increase in urinary total protein or albumin concentration was 1·5 (range 0·5-2·5) hours. The figure shows serial urinary concentrations of total protein and albumin in a 62 year old man with Crohn's disease who underwent resection for an enteroenteric fistula.



Excretion of urinary total protein and albumin during laparotomy and bowel resection. (Mean total protein and albumin concentrations in 20 healthy subjects were 3·9 (SD 1·3) and 0·5 (0·6) mg/mmol creatinine respectively.)

Comment

All 33 patients showed increases in urinary total protein concentration, and 29 in urinary albumin concentration, by three hours after their operation; the figure shows the rapidity and magnitude of the changes. Measurement of urinary proteins in four patients before and after catheterisation and induction of general anaesthesia showed no change in concentration. Three patients who had major operations but did not have catheters inserted showed appreciable increases in urinary total protein and albumin concentrations, suggesting that the phenomenon is independent of catheterisation. There were no differences between men and women or

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.

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

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.

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.

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