LEADING ARTICLE

TUBERCULOSIS IN PATIENTS UNDERGOING DIALYSIS — A REAPPRAISAL

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Patients with chronic renal failure on dialysis are known to have an increased incidence of tuberculosis because of a defect in cell mediated immunity. The incidence is reported to be 6–16 times higher than that in the general population (1–5) and in many of the cases, tuberculosis occurred within 6 months after starting dialysis. Some of the cases appear to be reactivation of old tuberculous lesions (3). Dialysis-associated tuberculosis is therefore of particular interest and importance to physicians in this part of the world as there is still a high incidence and prevalence of pulmonary tuberculosis in the population.

DIAGNOSIS

The diagnosis of tuberculosis in this group of patients can be difficult, as pointed out in a paper published in this issue of the journal. The disease is often not suspected in the beginning because of its protean manifestation and non-specific symptoms, eg fever, malaise, anorexia and loss of weight. In addition, when fever occurs, it is often attributed to causes other than tuberculosis, eg pyrogens in the dialyser, infection of the vascular access site or peritonitis. Negative sputum smear results for AFB and normal chest x-ray findings further contribute to the diagnostic difficulty and delay. However, there are certain features which point to the diagnosis of tuberculosis; these are a high ESR of > 100 mm/h, increased total white count, increased C-reactive protein, hepatosplenomogaly, ascites and lymphadenopathy. Another diagnostic clue is the reaction to the tuberculin test, which may be positive in some patients in spite of the defect in cell mediated immunity.

Extrapulmonary tuberculosis appears to occur more frequently in this group of patients, accounting for 40% or more of the cases diagnosed. Mortality is high especially when there is disseminated disease and involvement of the central nervous system (3).

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CHEMOTHERAPY

In renal failure, the clearance of drugs excreted by the kidney is diminished. Therefore, nephrotoxic drugs should be avoided in the therapy of tuberculosis. The 2 most effective drugs, isoniazid and rifampicin are fortunately metabolised mainly in the liver and are little affected by renal function. They can be given in standard dosages eg rifampicin 450 or 600 mg daily and isoniazid 300 mg daily. However, for patients with a glomerular filtration rate of < 10 ml/min, and especially those who are slow acetylators, a lower dosage (200 mg) of isoniazid is recommended. For patients on peritoneal diagnosis, a single dose of isoniazid 300 mg is given during dialysis, while a supplementary dose is given following haemodialysis (see table). Less isoniazid is removed during peritoneal dialysis compared with haemodialysis. A third drug ethambutol (EMB), is given to prevent the emergence of drug resistance. As ethambutol is mainly excreted by the kidney, it should be used with caution. Visual acuity and colour perception should be monitored periodically. The recommended dosage is as follows: GFR > 50 ml/min, EMB 15 mg/kg; GFR 50 – 10 ml/min, EMB 7.5 mg/kg; GFR < 10 ml/min, EMB 5 mg/kg (6). In the case of patients on haemodialysis, a dosage of 8–10 mg/kg (4) has been given (to compensate for the loss during dialysis) without the occurrence of increased drug toxicity. Ethambutol should be given for 2 months together with isoniazid and rifampicin for a total of 9 months.

Isoniazid and EMB are both removed by dialysis, while the amount of rifampicin removed is insignificant. Therefore, to simplify treatment without the need to modify dosages as a result of dialysis, all medications should preferably be given immediately after dialysis. On the other hand, if medication has to be given before or during dialysis, higher dosages or supplementary doses of isoniazid or ethambutol should be given (see table). As it is not possible to predict accurately the exact drug levels in the blood, serum levels should be measured. Monitoring the peak and trough levels will ensure therapeutic efficacy and prevent drug toxicity.

Streptomycin should be avoided because of the high risk of nephrotoxicity, vestibular disturbance and ototoxicity. Pyrazinamide can be used if there is a suspicion that the patient may have resistant organisms. Although pyrazinamide is metabolised mainly in the liver and a normal dosage (30 mg/kg/day) has been recommended (7), others have advised caution in the use of this drug (8–9), as the main active metabolite, pyrazinoic acid is excreted in the urine. A dosage up to 20 mg/kg/day was used by Andrew et al (4).

DRUG INTERACTION

It is also important to bear in mind the possibility of drug interaction between rifampicin and immunosuppressive drugs such as cyclosporine and prednisolone (10), particularly in patients who have received renal allografts. Rifampicin can reduce the efficacy of cyclosporine and prednislone leading to a rejection of the transplanted renal allograft. To prevent organ rejection, it may be necessary to increase the dose or frequency of administration of cyclosporine or in the last resort, another drug should be substituted for rifampicin.

CONCLUSION

In conclusion, early diagnosis of tuberculosis in patients with renal failure undergoing dialysis depends on a high index of suspicion and awareness of the protean manifestations of the disease. Early treatment with the appropriate drugs given in the right dosages is important in reducing the high mortality rate and preventing drug toxicity. In patients without any bacteriological evidence of tuberculosis, a therapeutic trial of antituberculosis chemotherapy based on a strong clinical suspicion is justified.

DOSAGES OF ANTITUBERCULOSIS DRUGS IN RENAL FAILURE

Drug	Usual Dose	Modification of Dosages GFR			Removed by		Dose Adjustment For DIALYSIS
		>50	50 – 10	<10	HD	PD	
Isoniazid	300 mg	NC	NC	200 mg	Y	Y	Supplementary dose after HD (200 mg/day) keep trough level < = 1 ug/ml
Rifampicin	450/600 mg	NC	NC	NC	N	N	No supplementary dose required
Ethambutol[6]	15 mg/kg	NC	7.5mg/kg	5 mg/kg	Y[1]	Y[1]	8–10 mg/kg on day of dialysis (4), serum peak level < = 5 ug/ml trough level <1–2 ug/ml
Streptomycin	15 mg/kg	24h	24 – 72h	72 – 96h	Y	N	Supplement with 5 mg/kg after HD (6) serum trough level <2 ug/ml

Figures in Superscript or within Parentheses refer to Reference Number
+ Approximately 35% of EMB is removed by HD or PD (11)
GFR = Glomerular Filtration Rate (ml/min) HD = Haemodialysis PD = Peritoneal Dialysis
NC = No change in Dosage Y = Yes N = No,h = hour

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