Case Report

Rifampicin-induced Renal Toxicity During Retreatment of Patients with Pulmonary Tuberculosis

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Abstract

Rifampicin is a crucial component of treatment regimens for tuberculosis and has been in use since the early 1970's. It is usually considered safe. Rarely life-threatening complications like acute renal failure or acute thrombocytopaenia may manifest during treatment with rifampicin. In our experience at the Tuberculosis Research Centre of treating more than 8000 pulmonary and extrapulmonary tuberculosis patients with rifampicin-containing regimens over the last 30 years, we are reporting 3 cases of probably rifampicin-induced acute renal failure. Despite extreme therapeutic safety of this drug the clinician must be aware of this rare complication, which if detected early is completely reversible. ©

Introduction

Rifampicin is one of the key drugs that have helped to shorten the treatment duration in tuberculosis. Serious adverse reactions due to rifampicin are uncommon. Minor side effects like nausea and vomiting can be managed with symptomatic treatment. Rarely major adverse reactions endangering life such as thrombocytopenia[1] and acute renal failure[2-4] may develop. Acute renal failure due to rifampicin therapy though uncommon has been described since 1971.[5] It is usually reversible if detected early and treated appropriately.

The Tuberculosis Research Centre (TRC) of the Indian Council of Medical Research has conducted more than 30 controlled clinical trials for the treatment of pulmonary and extrapulmonary tuberculosis since 1956. From early 1970's the TRC has been studying rifampicin-containing regimens for treating tuberculosis.[6] More than 8000 patients with pulmonary or extra- pulmonary tuberculosis have been treated with rifampicin containing regimens (daily rifampicin regimens -2000,[7,8] daily followed by intermittent rifampicin regimens -810 [8,9] and fully intermittent rifampicin - 5500[6]). Among these patients we are reporting three cases of acute renal failure, probably rifampicin-induced.

Case Reports

Case I

A 25-year-old male weighing 39 kg presented in February 1997 with fever and cough for one month. He was normotensive and had crepitations in his right lung. Chest X-ray showed infiltration of the right upper and mid-zones. Four sputum smears were positive for tubercle bacilli by fluorescent microscopy, confirmed later by positive cultures. Hepatic and renal functions were normal.

The patient was treated with a daily rifampicin-containing regimen. Dosage of rifampicin was initially 450 mg and later increased to 600 mg because the patient gained weight. Though his compliance was not satisfactory, he responded well to treatment and had negative sputum smears and cultures at the end of treatment.

Five months after completing treatment he relapsed and anti-tuberculosis treatment was restarted with thrice-weekly isoniazid 600 mg, rifampicin 450 mg, ethambutol 1200 mg and pyrazinamide 1500 mg. After 20 days he complained of vomiting, anorexia, fever and oliguria. Blood urea was 173 mg / dl and serum creatinine 17.3 mg / dl. Ultrasound scan of the abdomen showed normal kidneys with increased cortical echoes.

A diagnosis of rifampicin-induced acute renal failure was made. He was treated with 3 sessions of peritoneal dialysis along with salt, protein and fluid restrictions with close monitoring of fluid intake and output. The patient refused to consent for renal biopsy. Renal function improved and in three weeks the blood urea was 45 mg / dl and serum creatinine 1.2 mg / dl. He was discharged from the hospital after another week with blood urea of 43 mg / dl and serum creatinine of 1mg / dl. The patient was successfully treated for tuberculosis with isoniazid 300 mg, ethambutol 800 mg, pyrazinamide 1000 mg daily from March 1998 for 12 months.

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Case II

A 14-year-old male weighing 42 kg was investigated for seizures, fever and vomiting in July 1987. Computerised Tomographic (CT) scan of the brain revealed a left parieto-temporal lesion suggestive of tuberculoma with gross edema. He was treated with 3 months of isoniazid 300 mg, rifampicin 450 mg, pyrazinamide 1000 mg daily followed by 6 months of isoniazid 600 mg and rifampicin 450 mg twice-weekly along with anticonvulsants (Eptoin, mazetol). He successfully completed treatment in April 1988 and the CT scan at the end of treatment showed a decrease in the size of the hyperdense lesion with no edema. A CT scan at the end of the 48th month was normal.

In October 1999, the patient presented with dry cough, fever, loss of weight and appetite of 3 weeks duration. Chest x-ray revealed parenchymal lesion of the upper zone of the left lung. Three sputum smears were positive for acid-fast bacilli and subsequently the cultures became positive. He was started on thrice-weekly treatment with isoniazid 600 mg, rifampicin 600 mg, ethambutol 1200 mg and pyrazinamide 1500 mg.

After 10 days the patient developed low back pain, anorexia and vomiting. He had renal angle tenderness. Blood urea was 77 mg / dl and serum creatinine 3.8 mg / dl. Renal biopsy showed diffuse mesangial proliferation with patchy interstitial inflammation. The glomeruli showed mild increase in mesangeal cellularity. The basement membrane was not thickened. Tubules appeared unremarkable. The interstitium showed focal round cell infiltrates and blood vessels were mildly thickened. Acute renal failure was diagnosed and rifampicin was stopped; anti-TB treatment was continued with isoniazid 150 mg, ethambutol 800 mg and pyrazinamide 750 mg daily on the advice of the nephrologist. The renal failure was managed with peritoneal dialysis along with fluids, salt and protein restriction. Renal functions returned to normal after five days with blood urea of 25 mg / dl and serum creatinine of 1mg / dl. The patient successfully completed anti-tuberculosis treatment with isoniazid 300 mg, ethambutol 800 mg, pyrazinamide 1500 mg followed by isoniazid 300 mg and ethambutol 800 mg daily for 13 months. He responded well to treatment with negative sputum smears and cultures.

Case III

A 25-year-old male weighing 46 kg presented in May 1996 with cough and fever for one month. He had taken irregular treatment for pulmonary tuberculosis elsewhere with a rifampicin-containing daily regimen for 5 months about a year before. He had crepitations and rhonchi in both lungs. Chest X-ray showed infiltration left mid-zone and right lower zone. Two sputum smears were positive for tubercle bacilli and subsequently the cultures became positive.

He was started on thrice-weekly isoniazid 600 mg, rifampicin 450 mg, ethambutol 1200 mg and pyrazinamide 1500 mg. After 10 days he complained of oliguria, facial puffiness, pedal edema and vomiting for 4 days. His blood urea was 168 mg / dl and serum creatinine level 12.8 mg / dl. He refused consent for renal biopsy. A diagnosis of acute renal failure was made and rifampicin was stopped. With peritoneal dialysis and supportive measures renal function became normal in a month with blood urea level of 39 mg / dl and serum creatinine of 1 mg / dl. Anti-tuberculosis treatment was continued with isoniazid 600 mg, ethambutol 600 mg and pyrazinamide 1500 mg daily. The patient subsequently developed resistance to streptomycin and isoniazid and he is now being treated with kanamycin 1g, amoxycillin + clavulanic acid 625 mg, ethambutol 800 mg, clofazamine 100mg and pyrazinamide 1500mg. He continues to be sputum positive.

Discussion

Rifampicin-induced acute renal failure is sometimes encountered in the treatment of tuberculosis. More than 100 cases have been reported in the literature and a recent review from Chennai reported a series of 25 cases.[2]

All three patients reported here had been previously treated with daily rifampicin-containing regimens. They developed acute renal failure following re-treatment with an intermittent rifampicin regimen. The initiation of an intermittent rifampicin-containing regimen after an interval ranging from 5 months to 11 years, led to acute renal failure, which manifested within 10-20 days of starting re-treatment. Although we did not measure rifampicin dependent antibody levels in these patients the sequence of events was highly suggestive of rifampicin-induced acute renal failure. On withholding rifampicin and providing dialysis and supportive care the renal insufficiency reversed to normal.

It has been observed that serious adverse reactions to rifampicin, though rare, manifest more commonly in patients who are taking rifampicin intermittently or resume the drug after an interval.[10] The cause of such reactions is postulated to be due to rifampicin-dependent antibodies.[5] The mechanism postulated for the development of immune induced rifampincin toxicity is that sufficient quantity of antibodies accumulate during antigen-free interval when there is a gap in treatment or during intermittent dose regimen, and when rifampicin is readministered an intense immune reaction takes place.[10] The immune complexes get deposited in the blood vessels or interstitium and cause glomerular endotheliosis leading to tubular injury thereby decreasing renal function.[2] This may possibly be the cause of renal failure in all three of our patients. The I antigen expressed on tubular epithelium through which immune complexes lead to tubular cell destruction was demonstrated by De Vriese *et al.*[3]

The histological feature of the biopsy in our patient was suggestive of immune complex deposition in the interstitium and blood vessels and is consistent with the predominant pattern observed by Muthukumar et al[2] in renal biopsy of 12 patients with rifampicin-induced acute renal failure. Fynn *et al*[4] reported a similar picture of interstitial edema in the renal biopsy of an oliguric patient after intermittent rifampicin therapy. According to De Vriese et al acute tubular necrosis is the predominant pattern in renal biopsies during acute renal failure attributed to intermittent rifampicin therapy.[3] Chan *et al*[11] explained that immune complex deposition with compliment fixation leads to glomerular endothelial swelling which causes obstruction to the blood flow causing tubular ischemia.

Rifampicin therapy is a milestone in the treatment of pulmonary tuberculosis and is usually extremely safe. At TRC we have treated more than 8500 pulmonary and extrapulmonary tuberculosis patients with rifampicin-containing regimens in clinical trials. The regimens included daily and intermittent dosing. All patients were closely monitored for adverse drug events as part of the clinical trials protocols. We have not had a single case of renal failure in these patients during primary treatment. However during re-treatment with an intermittent rifampicin-containing regimen in 3 patients who had been previously treated with a daily rifampicin regimen we encountered acute renal failure. Our experience reinforces the fact of the extreme renal safety of this important drug, but still the physician must be aware of this rare life-threatening complication, which if detected early is completely reversible.

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