REVERSIBLE HEPATIC AND RENAL DAMAGE FROM RIFAMPIN OVERDOSE - A CASE REPORT

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SYNOPSIS

Rifampin commonly used in the treatment of tuberculosis is reported to produce toxic effects that include jaundice, gastrointestinal symptoms and fever even at therapeutic doses. We report a case of non-fatal Rifampin overdose (9000 mg) that presented with convulsions, severe metabolic acidosis, acute renal failure, cholestatic hepatitis and thrombocytopenia. The patient was successfully treated with peritoneal dialysis. A brief review of the literature of Rifampin overdose is presented.

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CASE REPORT

A 36 year old single Chinese man was admitted to Toa Payoh Hospital in July 1986. He had a past history of tuberculosis of the left ankle for which he was put on treatment from a private doctor with Rifampin and Isoniazid in the preceding two years. He also had a background history of schizophrenia with paranoid delusions, on follow-up with a private Psychiatrist. However he frequently defaulted medication from both doctors.

On the morning of the day of admission, the patient told his relatives that he was depressed and had insomnia. He thought that his ankle was "cancerous" and wanted to die. He subsequently told his brother-in-law before passing out that he had swallowed 30 capsules of Rifampin (300mg per capsule). While still at home, he had 3 attacks of generalised fits and was brought to the hospital emergency Department in a semi-conscious state. While being examined, he had two further attacks of generalised fits lasting about one minute each, associated with uprolling of the eyes, arching of the neck and tongue biting.

He was restless and was hyperventilating. The axillary temperature was 37oC and there was no neck rigidity. His blood pressure was 130/90 mm Hg. The pulse was 120 per min. and the respiratory rate was 32 per min. He was in Coma III and the pupils were 4mm equal and reactive. The oculocephalic reflex was intact. There was bleeding from the mouth from his bitten tongue, broken dentures and 2 broken teeth. There were however no oral ulcers noted. No abnormalities were detected in the cardiovascular and respiratory systems clinically. The liver was soft, palpable 1 cm below the costal margin.

The patient was able to move all 4 limbs in response to pain and his tendon reflexes were preserved. The plantar responses were flexor bilaterally. There was a previous granulating sinus on the lateral aspect of his left ankle.

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He was admitted and stomach washout was done. The gastric returns were orange in colour and his urine was also coloured deeply orange.

Shortly after admission, he threw another 4 generalised tonic- clonic fits each lasting 30 to 70 seconds. This was finally controlled with intravenous diazepam. His fundi were normal. His arterial blood gases showed metabolic acidosis with a pH of 6.67, pO2 132mm Hg, pCO2 21.5mm Hg, HCO3 3.0mmol/l, Base Excess - 37.9mmol/l. His blood urea was 20 mg/dl, Na was 148 mmol/l, K 7.8 mmol/l, Cl 111 mmol/l, glucose 235 mg/dl. The hyperkalemia was reversed with intravenous insulin-dextrose while the acidosis was corrected with Sodium bicarbonate infusion. The blood salicylate level was negligible.

The next day the patient had turned deeply orange in complexion. His BP was 110/60 mm Hg and the pulse was 84 per minute. His prothrombin time had climbed from normal on admission to 20 sec (control = 13 sec), while his P.T.T. was 38 sec. Intravenous fresh frozen plasma 1 L was given together with I V Vitamin K. His platelet count had dropped to 53x10(9)/l. There were ecchymoses in his skin but no obvious petechiae or frank bleeding. The liver function test showed Total protein 7.9 g/dl, albumin 4.1 g/dl, bilirubin (total) 0.8 mg/dl, alkaline phosphatase 102 U/l and SGPT 39 U/l. His total urine output for the whole day had dropped to 50 ml.

His blood gases had improved to pH 7.37, p02 94 mmHg, pCO2 27.4 mmHg, HCO3 15.5 mmol/l. On the third day of admission, his conscious level improved although he remained drowsy and not responsive to commands. There was jaundice but no asterixis. It was difficult to judge the jaundice clinically as the patient had the "Red Man Syndrome". The patient's entire body and all his secretions (including his tears) were stained a deep orange in colour.

Over the next 2 days, he remained oliguric, producing between 150 to 250 ml of urine a day. The chest X-Ray showed pulmonary edema and the blood urea rose from 20 mg/dl on admission to 224 mg/dl. On the fifth day the patient was dialysed. 40 cycles at 2 l per cycle followed by another 40 cycles at 1 l per cycle of peritoneal dialysis were performed in the I.C.U.. The urea which eventually reached a maximum of 295 mg/dl fell to 184 mg/dl upon completion of dialysis. The urine output immediately increased to more than 1500 ml per day. The serum creatinine which reached a maximum of 10.9 mg/dl also

responded and fell to 4.7 mg/dl. His platelet count had improved to 107x10(9)/l.

The liver function continued to deteriorate with a total protein of 4.8 g/dl, Albumin of 2.8 g/dl, bilirubin increasing to 10.7 mg/dl, alkaline phosphatase to 170 U/l and SGPT to 412 U/l on Day 7.

A liver biopsy was performed on Day 12 and there was focal necrosis with presence of bile in the cytoplasm of the hepatocytes. Morphologically it was a picture of cholestatic hepatitis with centrilobular cholestasis, compatible with Rifampin toxicity.

The patient refused a renal biopsy.

Post dialysis his urea hovered around 170 mg/dl and his serum potassium remained normal. His uric acid climbed to 16.6 mg/dl while the serum calcium fell to 7.7 mg/dl and serum phosphate rose to 11.3 mg/dl.

On the sixteenth day his liver function test had improved. The total protein was 5.6 g/dl, albumin was 2.9 g/dl, alkaline phosphatase was 103 U/l, Bilirubin was 2.0 mg/dl and SGPT was 42 U/l. His platelet count had risen to 447x10(9)/l.

Both his liver and renal functions improved after 27 days. The prothrombin time had also returned to normal. On review 3 weeks later in the Outpatient's the patient was clinically well and his serum biochemistry was entirely normal.

DISCUSSION

Rifampin is an important and widely used drug especially in the treatment of tuberculosis and leprosy. Its toxic side effects both in therapeutic and toxic doses are well recognised and include fever, gastrointestinal disturbances, jaundice, hepatic and renal dysfunction, leukopenia, thrombocytopenia and convulsions. In massive overdose, fatality can occur as was first reported in 1978 by Broadwell and Broadwell(1). Our patient is the first to be described in the local literature and had features of metabolic acidosis, transient thrombocytopenia, cholestatic hepatitis, oliguric renal failure and the "Red Man Syndrome".

The patient ingested a total of 9000 mg of Rifampin. It has long been established that anuric tubular nephritis with acute renal insufficiency can occur in Rifampin toxicity(2). It has also been noted that renal impairment is mediated by immune mechanisms(3). The reactions usually occur in patients who have undergone previous long term treatment with Rifampin, especially if given intermittently and symptoms occur after readministration of the first dose of their second course of therapy. Zeana, Banica et al reported in all their three cases, indirect Coomb's test was positive for anti Rifampin antibodies (IgM Class)(4) and the histopathology revealed extensive lesions including necrosis of the tubules. Mauri, Fort et al(4) reported that in their 5 patients with acute renal failure, there was no correlation between severity of clinical manifestations and the total dose taken. IgM antibodies were detected in their patients. Two of their patients had renal biopsies and these showed non specific Acute tubular necrosis very similar to ischemic damage, further supporting the possibility of vascular-mediated damage triggered by immunoallergic mechanisms. Others have detected IgG antibodies in association with intravascular hemolysis(5). However IgG antibodies result in non oliguric Acute renal failure usually not requiring dialysis.

The most significant risk factor for Rifampin induced renal insuffiency is intermittent or interrupted therapy(6). It seems therefore our patient's renal impairment was related more to his previous treatment with Rifampin and made worse by his poor compliance. Our patient refused a renal biopsy but typical renal biopsies as reported by others(7) include acute interstitial nephritis, normal glomerular histology, effacement of glomerular epithelial cell foot processes and electron dense deposits in mesengial matrix, subendothelial and paramesangial sites.

The hepatotoxicity in contrast seems to be dose dependent however, as shown by O' Brien R. J., et al(8). The damage would be more prominent if there is underlying liver disease.(9) Features of centrilobular cholestatic hepatitis with focal spotty necrosis were seen in our patient. Fatty change and centrilobular necrosis were however absent.

The patient developed the typical features of the "Red Man Syndrome"(10). This is a striking glowing red discoloration of the skin and facial or periorbital edema described as the hallmarks of acute Rifampin toxicity. It is in contrast to side- effects of Rifampin from therapeutic doses. Our patient also had severe acidosis on admission. The acidosis was also observed by Spalding, Buss et al(1). The transient thrombocytopenia observed in our case has also been reported in the literature(12).

We successfully treated the patient's acute renal failure by peritoneal dialysis. A similar case of peritoneal dialysis treatment for Rifampin induced kidney failure was reported by Kirsten, Schmidt et al in 1982(13). Others have not been so successful in treating their patients who eventually perished from their overdose(14)(15).

Facilities for measuring serum or urinary levels of Rifampin are not available in Singapore at the present. The toxicological findings are best investigated by determining the concentrations of Rifampin and its 2 major metabolites 25-desacetylrifampicin and 3-formylrifamycin in blood, urine, bile and liver using a high performance liquid chromatographic method described in the Archives of Toxicology(16).

It is important to recognise that since Rifampin is widely used, its side effects should be carefully sought. In cases of massive overdose, prompt and vigorous treatment directed at the correction of metabolic, renal, liver and hematological abnormalities may avert fatality.

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