

CASE REPORT

Hepatitis and liver dysfunction with rifampicin therapy for pruritus in primary biliary cirrhosis

M I Prince, A D Burt, D E J Jones

Gut 2002;50:436–439

There is evidence to suggest that rifampicin is an effective second line therapy for controlling pruritus in patients with chronic cholestatic liver disease. It is most widely used as an antipruritic agent in the autoimmune cholestatic liver disease, primary biliary cirrhosis (PBC). Rifampicin has been reported as causing hepatitis in patients being treated for tuberculosis. Most reports of this have been confounded however by the concurrent use of other hepatotoxic antitubercular therapy. Here we report a single centre experience of the use of rifampicin in PBC, and describe three cases of significant hepatitis associated with rifampicin therapy. Two of these patients had significant impairment of liver synthetic function (necessitating liver transplantation in one case). These are the first reports of impaired hepatic synthetic function due to rifampicin monotherapy. Rifampicin caused significant hepatitis in 7.3% (95% confidence interval 2.5–19.4%) of patients treated for cholestatic liver disease in our centre.

Primary biliary cirrhosis (PBC) is a chronic autoimmune liver disorder characterised by slowly progressive destruction of intrahepatic bile ducts.¹ Pruritus is one of the commonest symptoms experienced by patients, and one that can significantly impair quality of life.² Pruritus is present in up to 33% of patients at the time of diagnosis of PBC and in up to 58% of patients at 10 years following diagnosis.³ The pruritus of PBC is generally unresponsive to antihistamines and often responds only poorly to bile sequestrants (which have entered widespread clinical use as first line treatment⁴ despite limited trial evidence⁵). There is little evidence to suggest that the hydrophilic bile acid ursodeoxycholic acid (UDCA) is effective in reducing pruritus, with benefit only being reported in two of 11 trials reviewed in a recent meta-analysis.⁶ There is increasing evidence (both in terms of subjective improvement in the sensation of itching and objective reduction in scratching activity) to suggest that opiate antagonist agents (such as naltrexone administered orally or naloxone administered parenterally) are effective for the management of pruritus in cholestasis.^{7–9}

A number of relatively short term clinical trials have suggested that rifampicin is effective in controlling pruritus in PBC,^{10–13} and this agent is frequently used as second line treatment in specialist clinics. Although there have been no published reports of significant additional liver dysfunction in PBC patients treated with rifampicin, concerns remain regarding its safety in PBC, given the described incidence of de novo hepatotoxicity when this agent is used as an antimicrobial.^{14–17} Following a case of severe rifampicin hepatotoxicity in our patient cohort, we reviewed the notes of all patients in our practice who had been treated with rifampicin (n=41) to study the frequency of rifampicin induced hepatotoxicity. We examined patient records to identify individuals with a 50% increase in their liver function tests

(bilirubin, alanine transaminase, or alkaline phosphatase) following commencement of rifampicin therapy. Using this approach we identified three cases of rifampicin hepatotoxicity, which are presented below.

CASE REPORTS

Case No 1

A 42 year old female company director presented to her general practitioner with a four week history of generalised pruritus. Her general practitioner initially prescribed chlorpheniramine and when this led to no improvement in her symptoms he performed a full blood count, electrolyte screen, and thyroid and liver function tests. Liver function tests (LFTs) were abnormal (albumin 40 g/l, bilirubin 17 µmol/l (normal range <17), alanine transaminase (ALT) 110 IU/l (<35), alkaline phosphatase (ALP) 610 IU/l (<120), and γ-glutamyl transferase 428 (<55)), and she was referred to secondary care.

A further clinical history gave no risk factors for liver disease. An abdominal ultrasound was normal. Further investigation revealed an elevated antimitochondrial antibody (titre 1 in 160) and a raised IgM level of 5.8 g/l (<2.8). Albumin and prothrombin time were normal. Liver biopsy showed a ductopenic process with portal fibrosis, consistent with PBC (Scheuer stage 3). She was initially treated with UDCA at doses of up to 13 mg/kg with no symptomatic improvement. She was subsequently commenced on cholestyramine therapy but could not tolerate doses above 2 g/day due to constipation while lower doses did not relieve pruritus.

Rifampicin was started at a dose of 600 mg at night. Her itch resolved in the first 10 days of therapy but four weeks after starting rifampicin she developed nausea, jaundice, discolouration of urine and stool, and a worsening of pruritus. Her LFTs had significantly deteriorated (bilirubin 103 µmol/l, ALT 544 IU/l, ALP 400 IU/l). Her prothrombin time increased to 18 seconds (control 15 seconds) and albumin fell to 34 g/l. Rifampicin was immediately stopped and her LFTs and prothrombin time returned to their previous levels over the next six weeks. Her itch recurred over the next month and was eventually treated with the oral opiate antagonist naltrexone with an excellent response.

Case No 2

A 58 year old woman consulted her general practitioner with a two year history of progressively worsening pruritus. Her general practitioner performed LFTs which revealed elevated ALP (621 IU/l) and ALT (95 IU/l) and an autoantibody screen which showed a positive antimitochondrial antibody. Bilirubin, albumin, and prothrombin time were normal. She was commenced on cholestyramine (4 g/day) and referred for further investigation.

Abbreviations: PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid; LFTs, liver function tests; ALT, alanine transaminase; ALP, alkaline phosphatase.

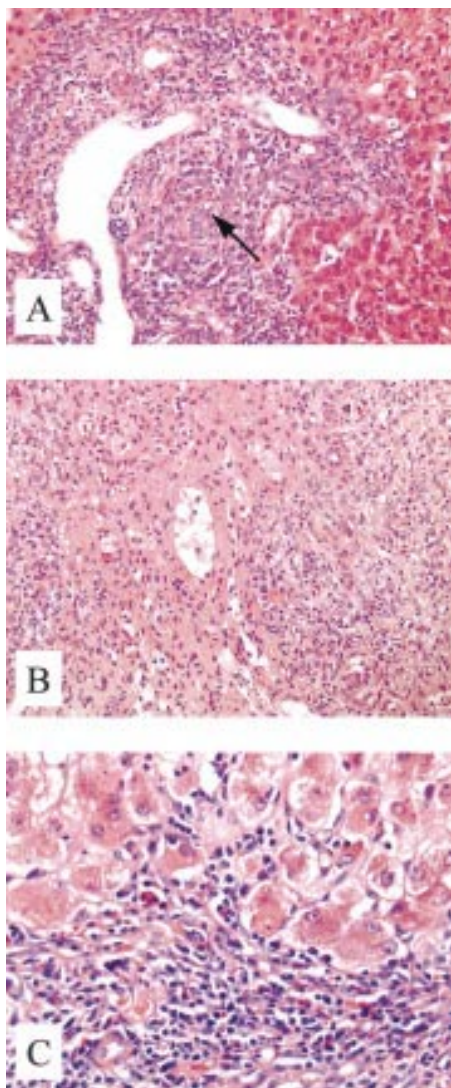


Figure 1 (A) Initial biopsy of patient No 3. Portal tract inflammation with infiltration of the bile duct by lymphocytes is evident; there is a ductular reaction and mild (lymphocytic) interface hepatitis. (B) Second biopsy (after rifampicin). Area of confluent necrosis with a prominent inflammatory infiltrate is seen. (C) Explant liver specimen. Note the marked interface hepatitis (all photomicrographs, haematoxylin-eosin stained).

A liver biopsy confirmed the diagnosis of PBC (stage 1) and she was commenced on UDCA (gradually increased to 12 mg/kg) with no improvement in her symptoms. Her pruritus responded to an increased dose of cholestyramine (6 g/day). Her itch recurred two years later despite continuing on this regimen. This symptomatic relapse was not associated with deterioration of LFTs (bilirubin 8 $\mu\text{mol/L}$, ALP 592 IU/L, ALT 51 IU/L, albumin 43 g/l). Rifampicin was introduced at 150 mg at night. The patient was reviewed fortnightly and reported a significant improvement in pruritus. Seven weeks after commencing therapy her LFTs deteriorated (bilirubin 8 $\mu\text{mol/L}$, ALP 537 IU/L, ALT 353 IU/L). Her prothrombin time and albumin remained normal. These results were discussed with the patient who elected to continue with rifampicin given her symptomatic improvement. She was monitored closely for signs of further deterioration. Her LFTs were stable for eight more months (ALT 303–385 IU/L with bilirubin level and synthetic function remaining normal).

The patient self presented to clinic 11 months after starting rifampicin complaining of jaundice and nausea. Her LFTs had

deteriorated (bilirubin 116 $\mu\text{mol/L}$, ALP 142 IU/L, ALT 419 IU/L, albumin 29 g/l). Her prothrombin time was elevated to 19 seconds. Rifampicin was stopped and her LFTs returned to their previous levels within seven weeks (bilirubin 12 $\mu\text{mol/L}$, ALP 154 IU/L, ALT 52 IU/L, albumin 35 g/l). Her pruritus remains under control seven months after stopping rifampicin.

Case No 3

A 39 year old woman presented to her general practitioner with an eight month history of pruritus and dry mouth and eyes. Her mother had been diagnosed as having PBC six years earlier. Initial LFTs confirmed a combined cholestatic and hepatic abnormality (bilirubin 31 $\mu\text{mol/L}$, ALP 258 IU/L, ALT 311 IU/L, albumin 40 g/l, prothrombin time 16 seconds). PBC was confirmed by an antimitochondrial antibody (titre 1 in 640) and liver biopsy showed lymphocytic destruction of medium sized bile ducts and a moderate ductular reaction with minimal fibrosis. Portal tract inflammation included lymphocytes, eosinophils, and epithelioid macrophages; there was mild interface hepatitis but negligible intra-acinar hepatitis (fig 1A). The appearances were those of PBC stage 2 (Scheuer). There were no serological features suggestive of an autoimmune hepatitis crossover syndrome (IgG levels were normal and the patient was antinuclear and smooth muscle antibody negative). She was treated with cholestyramine and UDCA (10 mg/kg) with good control of her pruritus.

Despite continued therapy, a distressing level of pruritus returned three years later. Her LFTs had improved on UDCA (bilirubin 27 $\mu\text{mol/L}$, ALP 288 IU/L, ALT 149 IU/L, albumin 40 g/l, prothrombin time 15 seconds). The patient was already on the maximum tolerated dose of cholestyramine. UDCA was increased to 13 mg/kg with no improvement in symptoms. Rifampicin was started at 150 mg at night which controlled her itch within six weeks. Fourteen months after starting rifampicin her LFTs deteriorated again (bilirubin 91 $\mu\text{mol/L}$, ALP 151 IU/L, ALT 389 IU/L, albumin 38 g/l, prothrombin time 18 seconds). Repeat liver biopsy showed progression to stage 4 disease but, in addition, severe interface hepatitis and a marked intra-acinar hepatitis with areas of confluent and bridging necrosis were found (fig 1B). The patient was unable to tolerate withdrawal of rifampicin because of severe recurrent pruritus. Her LFTs deteriorated (bilirubin 120 $\mu\text{mol/L}$ and prothrombin time 22 seconds). She was assessed for transplantation on the grounds of severe liver impairment with uncontrollable symptoms off rifampicin. She underwent liver transplantation and made a good recovery. Histological examination of the explanted tissue confirmed the presence of an established biliary type cirrhosis but again showed severe interface hepatitis and intra-acinar inflammation (fig 1C)

DISCUSSION

Rifampicin is a semisynthetic antibiotic derived from the rifamycins, a group of antibacterials produced by *Streptomyces mediterranei*. Rifampicin was initially developed to treat tuberculosis but more recently has been used against other bacteria. The beneficial effect of rifampicin on pruritus was initially discovered serendipitously. Four formal studies (three of which were randomised controlled trials) have suggested a subjective effect of rifampicin on itch severity.^{10–13} These studies also suggested that rifampicin was better at relieving itch than other hepatic enzyme inducing agents such as phenobarbitone.¹⁰ A single small study failed to confirm the effectiveness of rifampicin for subjective itching in cholestatic liver disease (including three patients with PBC).¹⁸ All of these studies used subjective measures of itch severity (for example, visual analogue scales). To our knowledge no trial of rifampicin in cholestasis has examined efficacy in terms of objective changes in scratching activity,¹⁹ an outcome measure which should now be regarded as the “gold standard” for

assessment of pruritus in cholestasis.³ None of the patients in these studies of rifampicin (total n=64) developed drug induced hepatitis although treatment was not continued for a prolonged period (range seven days to eight months). In all studies the majority of patients showed an improvement in alkaline phosphatase levels during therapy.

The mechanism by which rifampicin alleviates pruritus is unknown; two mechanisms have been postulated although conclusive data supporting either are limited. The first suggests that rifampicin acts as an inducer of microsomal enzymes leading to increased metabolism of endogenous pruritogenic compounds.²⁰ Intriguingly, it has been reported that introduction of rifampicin can induce a withdrawal reaction in individuals taking methadone.²¹ One interpretation of this observation is that endogenous opiates are among the "pruritogens" retained in cholestasis whose metabolism is increased by rifampicin. If this were the case it would suggest that rifampicin and opiate antagonists mediate their therapeutic effects through interaction on the same endogenous opiate pathway. The second postulated mechanism of action of rifampicin is by inhibition of bile salt uptake by hepatocytes leading to a reduction in bile salt mediated disruption of hepatocyte membranes causing release of "pruritogens".²²

"Rifampicin hepatitis" was originally described by Scheuer *et al* in 1974 in a case series of 11 patients.¹⁴ Ten of these patients developed abnormal LFTs within six weeks of starting rifampicin therapy. These patients were found to have a wide range of histological changes ranging from isolated steatosis through varying degrees of portal inflammation with a neutrophil or mononuclear infiltrate, to confluent necrosis. All 11 of these patients however had received rifampicin for tuberculosis, and were also treated with other antibiotics which are also known to be hepatotoxic (isoniazid and streptomycin in all patients and p-aminosalicylic acid in three patients). It is therefore difficult to distinguish the potentially toxic effects of rifampicin from those of other drugs. Indeed, eight of the 10 patients who survived the initial hepatotoxicity were rechallenged with rifampicin and only two of these developed further liver problems (both of whom were also rechallenged with isoniazid). It is therefore possible that some or most of these cases of "rifampicin hepatitis" were in fact due to the effects of isoniazid. Other case series of possible rifampicin induced hepatotoxicity have also been confounded by use of other antitubercular agents.^{15, 16} Rothwell and Richmond described one case of renal failure and jaundice occurring in a patient taking rifampicin intermittently (three doses of 450 mg over five weeks) for tuberculosis.¹⁷ Although the patient suffered symptoms of nausea and "chills" immediately following rifampicin, it is not clear whether the patient also took PAS which had been coprescribed.

A Medline literature search identified only two previous cases of hepatitis occurring in patients treated with rifampicin in the absence of other hepatotoxic agents. Bachs *et al* described two cases of rifampicin hepatitis in women treated for PBC.²³ These cases were drawn from a cohort of 16 PBC patients who were treated with rifampicin for a mean of 12 months. Their incidence of rifampicin hepatitis (12.5% (95% confidence interval (CI) 3.5–36.0)) was therefore not dissimilar to ours (7.3% (95% CI 2.5–19.4)). In common with cases 1 and 2 above (and 10 of the cases reported by Scheuer), both patients reported by Bachs *et al* developed problems within two months of starting therapy. Although both cases reported by Bachs *et al* developed elevated ALT levels (1624 IU/l and 819 IU/l) and jaundice (maximum bilirubin 162 µmol/l and 64 µmol), neither was reported to suffer deterioration in hepatic synthetic function.

The importance of rifampicin dose on the frequency and severity of hepatic side effects is not clear. The first patient described above, who suffered the most severe reaction, was

started on what we would now consider to be a high initial dose of rifampicin. All 11 patients in the series described by Scheuer *et al* were prescribed 450–600 mg daily.¹⁴ The two patients described by Bachs *et al* received an initial dose of 10 mg/kg/day.²³ To our knowledge there have been no reports of the effect of rifampicin dose on hepatotoxicity in monotherapy. In the absence of a clear evidence basis for dosing of rifampicin in PBC, and given the fact that a significant proportion of cases of hepatotoxicity appear to have occurred in patients taking relatively high doses of rifampicin, we consider it prudent to start patients on a daily dose of 150 mg with subsequent increase in the dose to a daily maximum of 600 mg based on clinical need.

To our knowledge the cases described here are the first reports of significant impairment of hepatic synthetic function associated with rifampicin monotherapy. In each case of impairment of synthetic function, rifampicin was continued after the onset of abnormal LFTs because of the presence of otherwise uncontrollable severe pruritus; a factor which may explain the severe clinical pattern. Case No 3 presented unusually late after starting rifampicin. Scheuer *et al* described one case of "rifampicin hepatitis" starting 52 weeks after transplantation.

Only a limited number of patients receiving rifampicin therapy for pruritus in PBC appear to develop significant hepatotoxicity. However, the cases described here clearly demonstrate that the process of liver damage induced by rifampicin can progress from the stage of the previously described elevation in transaminases to significant impairment of liver synthetic function. The majority of patients who develop hepatotoxicity will probably do so in the first two months of therapy and LFTs should be monitored regularly during this period. Continuation of rifampicin therapy after the initial development of a transaminitis can result, as the cases described here demonstrate, in the development of progressive liver dysfunction with impairment of synthetic capacity. If rifampicin hepatitis develops this will usually resolve with cessation of therapy.

There is however a broader issue to be addressed. Given the potential for rifampicin to induce significant hepatotoxicity, and the advent of seemingly more effective (and better characterised) second line antipruritic agents such as the oral opiate antagonists, it is unclear whether the use of rifampicin should still be recommended, other than perhaps as an agent of last resort in patients who have failed to respond to or tolerate all other agents (including oral opiate antagonists).

Authors' affiliations

M I Prince, A D Burt, D E J Jones, Centre for Liver Research, University of Newcastle, Newcastle, UK

Correspondence to: Dr M Prince, Centre for Liver Research, 4th Floor William Leach Building, Newcastle University Medical School, Framlington Place, Newcastle NE2 4HH, UK; Martin.prince@ncl.ac.uk

Accepted for publication 3 July 2001

REFERENCES

- 1 Neuberger JM. Primary biliary cirrhosis. *Lancet* 1997;**350**:875–9.
- 2 Jones EA, Bergasa NV. The pruritus of cholestasis. *Hepatology* 1999;**29**:1007–12.
- 3 Prince M, Howell D, Metcalf JV, *et al*. Time profile of symptom development and prognosis in 770 patients with PBC. *Hepatology* 2000;**32**:171A.
- 4 Verma A, Jazrawi RP, Ahmed HA, *et al*. Prescribing habits in primary biliary cirrhosis: a national survey. *Eur J Gastroenterol Hepatol* 1999;**11**:817–20.
- 5 Datta DV, Sherlock S. Cholestyramine for long term relief of the pruritus complicating intrahepatic cholestasis. *Gastroenterology* 1966;**50**:323–32.
- 6 Goulis J, Leandro G, Burroughs AK. Randomised controlled trials of ursodeoxycholic-acid therapy for primary biliary cirrhosis: a meta-analysis. *Lancet* 1999;**355**:657–58.

- 7 **Bergasa NV**, Alling DW, Talbot TL, *et al.* A controlled trial of naloxone infusions for the pruritus of chronic cholestasis. *Gastroenterology* 1992;**102**:544–9.
- 8 **Bergasa NV**, Schmitt JM, Talbot TL, *et al.* Open-label trial of oral nalmefene therapy for the pruritus of cholestasis. *Hepatology* 1998;**27**:679–84.
- 9 **Wolffhagen FHJ**, Sternieri E, Hop WCJ, *et al.* Oral naltrexone for cholestatic pruritus—a double-blind, placebo-controlled study. *Gastroenterology* 1997;**113**:1264–9.
- 10 **Bachs LP**, Pares A, Elena M, *et al.* Comparison of rifampicin with phenobarbitone for treatment of pruritus in biliary cirrhosis. *Lancet* 1989;**1**:574–6.
- 11 **Loginov AR**, Petrakov AV. The treatment of primary biliary cirrhosis with rifampicin. *Terapevticheskii Arkhiv* 1993;**665**:57–62.
- 12 **Podesta AL**, Terg P, Villamil R, *et al.* Treatment of pruritus in primary biliary cirrhosis with rifampicin. *Dig Dis Sci* 1991;**36**:216–20.
- 13 **Ghent CN**, Carruthers SG. Treatment of pruritus in primary biliary cirrhosis with rifampicin. Results of a double-blind, crossover, randomised trial. *Gastroenterology* 1988;**94**:488–93.
- 14 **Scheuer P**, Ladel S, Summerfield J, *et al.* Rifampicin hepatitis. *Lancet* 1974;**i**:421–5.
- 15 **Lees AW**, Allan GW, Smith J, *et al.* Toxicity from rifampicin plus isoniazid and rifampicin plus ethambutol therapy. *Tubercle* 1971;**52**:182–90.
- 16 **Hollins PJ**, Simmons AV. Jaundice associated with rifampicin. *Tubercle* 1970;**51**:328–32.
- 17 **Rothwell D**, Richmond D. Hepatorenal syndrome with self-initiated rifampicin therapy. *BMJ* 1974;**ii**:481–2.
- 18 **Woolf GM**, Reynolds TB. Failure of rifampicin to relieve pruritus in chronic liver disease. *J Clin Gastroenterol* 1990;**12**:174–7.
- 19 **Talbot TL**, Schmitt JM, Bergasa NV, *et al.* Application of piezofilm technology for the quantitative assessment of pruritus. *Biomed Instrument Technol* 1991;**25**:400–3.
- 20 **Miguet JP**, Mavier P, Soussy CJ, *et al.* Induction of hepatic microsomal enzymes after brief administration of rifampicin in man. *Gastroenterology* 1977;**72**:924–6.
- 21 **Kreek MJ**, Garfield JW, Gutjahr CL, *et al.* Rifampicin-induced methadone withdrawal. *N Engl J Med* 1976;**294**:1104–6.
- 22 **Galezzi R**, Lorenzini I, Orlandi F. Rifampicin induced elevation of serum bile acids in man. *Dig Dis Sci* 1980;**25**:108–12.
- 23 **Bachs LP**, Elena M, Piera M, *et al.* Effects of long-term rifampicin administration in primary biliary cirrhosis. *Gastroenterology* 1992;**102**:2077–80.



Want to extend your search?

Cross journal searching

If you can't find what you are looking for in *Gut* you can extend your search across many of the more than 200 journals available for selection. You can restrict your search to specific subject areas (eg, clinical medicine, basic research), or select specific journals, or search all available titles.

www.gutjnl.com