Acute sulphasalazine hepatotoxicity

P.E. Jennings, R.L. Blandford and F.D. Rosenthal

The Leicester Royal Infirmary, Leicester LE1 5WW, UK.

Summary: We describe a case of severe sulphasalazine hepatotoxicity. The features described are those of an acute hypersensitivity reaction which responded to drug withdrawal alone as steroids were withheld. Supportive treatment only is recommended for this potentially fatal condition.

Several reports have appeared of an association between sulphasalazine use and acute hepatotoxicity. The most severe form of liver damage occurs in a hypersensitivity reaction which may be fatal. There is scanty evidence to suggest that this rare condition will respond to steroids. Nevertheless, most cases previously reported have been treated with steroids. We report here on a case of severe sulphasalazine induced hepatotoxicity which responded to withdrawal of the drug alone.

Case report

In February a 37 year old school master presented to his general practitioner with bloody diarrhoea. Sigmoidoscopy showed an inflamed mucosa and the biopsy findings of crypt abscesses with a leucocyte infiltrate, although not diagnostic, were consistent with ulcerative colitis. Sulphasalazine 4 g/day was started from presentation. A barium enema showed disease limited to the rectum and sigmoid colon. After 14 days on treatment an itchy erythematous rash appeared on his trunk and the sulphasalazine dosage was halved. There was no improvement in the rash but because of worsening diarrhoea the original dosage was recommenced. He was referred to the hospital due to the deterioration in his condition in early March. Twenty-three days after starting treatment he was complaining of the rash together with jaundice, arthralgia, oral ulceration and malaise although his diarrhoea had settled. On examination he was pyrexial (39.8°C) and jaundiced with general lymphadenopathy and a generalized confluent erythematous rash with pharyngeal ulceration but no conjunctival or urethral involvement. He was drowsy, disorientated and dehydrated with a tachycardia and tender hepatomegaly but no splenomegaly. Investigations on

admission revealed grossly abnormal liver function tests with a hepatic picture, alanine transaminase (ALT) 1994 IU/l (normal 2–53), γ -glutamyl transferase 174 IU/l (normal 0–50), alkaline phosphatase 271 IU/l (normal 40–130) and bilirubin 119 μ mol/l (normal 3–17). He had a normal full blood count and differential white cell count initially.

His sulphasalazine was stopped and apart from fluids, nutritional support and a bland emulsifying cream to his skin no other therapeutic agents were used. During his first 2 days in hospital his condition deteriorated with the patient lapsing into coma as his liver enzymes elevated. The maximum ALT became 2712 IU/l with bilirubin reaching 134 IU/l and alkaline phosphatase 430 IU/l. The prothrombin time became prolonged at 27 seconds (control 14). By this time his haemoglobin had fallen to 9 g/dl and the platelet count fell from normal to 14×10^9 /l over the next 7 days. He also had a raised total white cell count of 18.3×10^9 /l, a 14% eosinophilia and 44% activated lymphocytes.

Despite falling numbers of platelets his fibrinogen and fibrin degradation products were normal. Viral studies were repeatedly negative for hepatitis A and B, cytomegalovirus, toxoplasma, leptospira and Epstein-Barr virus. There existed a polyclonal increase in total IgG to 28.7 g/l (normal 5–18) and total IgA to 6.0 g/l (normal 0.9–4.5). Serum complement was reduced with a C3 of 0.75 g/l (normal 1.01–1.98) and a C4 of 0.14 g/l (normal 0.16–0.39). Auto-antibodies were not detected and DNA binding was negative. Bone marrow aspiration showed reactive hypercellular marrow with increased megakaryocytes. Isotope liver scan revealed an enlarged liver with uniformly diminished uptake and a normal spleen. Liver biopsy was not performed due to the clotting and platelet abnormalities.

After 7 days his mental state improved, his liver enzymes started to fall and the rash desquamated. Gastro-intestinal bleeding occurred due to the thrombocytopenia and he was transfused. Eventually in April he was discharged home with normal haematological results and only mild elevation in liver

Correspondence: F.D. Rosenthal, M.D., F.R.C.P.
Accepted: 2 July 1985

enzymes, which returned to normal 4 months after his admission. He has had no further diarrhoea, his rectal mucosa now appears normal sigmoidoscopically and he is on no medication.

Discussion

This severe reaction is compatible with sulphonamide hypersensitivity (Dujovne *et al.*, 1967). Our patient showed the majority of features previously described with sulphasalazine, namely, onset within a month of starting treatment, rash, fever, arthralgia, hepatitis, eosinophilia and hypocomplementaemia (Mihas *et al.*, 1978). This multi-system disorder has also been shown to affect the kidneys and nervous system (Chester *et al.*, 1978; Smith *et al.*, 1982). Abnormalities of liver enzymes seen in ulcerative colitis may be unrelated to medication. There is a well recognized association between chronic colitis and fatty infiltration, focal necrosis and cirrhosis of the liver as well as the rarer complication of sclerosing cholangitis. These conditions should be considered in the differential diagnosis of abnormal liver enzymes associated with ulcerative colitis. However, the rapid onset of symptoms developing within a few weeks of starting therapy and an itchy erythematous rash should lead to the diagnosis

of an acute drug reaction. Liver biopsies have been performed in this condition and correspond to that described in sulphonamide-induced hepatotoxicity (Dujovne *et al.*, 1967). Ballooning degeneration of the hepatocytes, focal necrosis with eosinophilic infiltration and mild intracanalicular cholestasis are the commonest histological features, with a granulomatous hepatitis occurring occasionally.

The latency period for this acute hypersensitivity reaction appears to be between 11–28 days, from the review by Losek & Werlin in 1981, and it can occur in patients already on systemic steroids. However, one case has been described of hepatotoxicity occurring after 15 years successful treatment with sulphasalazine (Lennard & Farndon, 1983).

There is no good evidence that steroids alter the course of this hypersensitivity reaction. From the details of the 7 cases reviewed by Losek & Werlin (1981) in only 2 cases were steroids withheld and these patients had a mild form of hepatitis. In our case there was severe systemic upset and steroids were not given. It is extremely doubtful in our opinion that the administration of steroids would have had any beneficial effects on this patient. It was not felt that drug rechallenge was advisable. Patients who develop hepatitis whilst taking sulphasalazine should have the drug withdrawn.

References

- CHESTER, A.C., DIAMOND, L.H. & SCHREINER, G.E. (1978). Hypersensitivity to salicylazosulfapyridine: renal and hepatic toxic reactions. *Archives of Internal Medicine*, **138**, 1138.
- DUJOVNE, C.A., CHAN, C.H. & ZIMMERMON, J.H. (1967). Sulphonamide hepatic injury. *New England Journal of Medicine*, **277**, 785.
- LENNARD, T.W.J. & FARNDON, J. (1983). Sulphasalazine hepatotoxicity after 15 years successful treatment for ulcerative colitis. *British Medical Journal*, **287**, 96.
- LOSEK, J.D. & WERLIN, S.L. (1981). Sulphasalazine hepatotoxicity. *American Journal of Diseases in Childhood*, **135**, 1070.
- MIHAS, A.A., GOLDENBERG, D.J. & SLAUGHTER, R.L. (1978). Sulphasalazine toxic reactions: hepatitis, fever, skin rash, with hypocomplementemia and immune complexes. *Journal of the American Medical Association*, **239**, 2590.
- SMITH, M.D., GIBSON, G.E. & ROWLAND R. (1982). Combined hepatotoxicity and neurotoxicity following sulphasalazine administration. *Australian and New Zealand Journal of Medicine*, **12**, 76.