Cholestatic jaundice due to co-trimoxazole

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Summary

A patient developed cholestatic jaundice following therapy with co-trimoxazole. Inadvertent re-challenge with the drug resulted in further clinical and biochemical deterioration, but complete recovery ensued on stopping this drug.

Introduction

Co-trimoxazole is a combination of the dihydro-folate reductase inhibitor trimethoprim and a long acting sulphonamide, sulphamethoxazole. Jaundice is an uncommon side effect of this combination, and the authors have been unable to find a previous report of cholestatic jaundice following co-trimoxazole therapy.

Case report

A 70-year-old woman was admitted for investigation in February 1978 with a 3-month history of weight loss, anorexia, nausea, lethargy, pruritus and jaundice. The illness had started abruptly with an attack of right hypochondrial pain, associated with the passage of dark urine and pale stools. The pain had subsided within a few days, but she had remained jaundiced with increasing pruritus. She did not drink excessive amounts of alcohol and she denied taking any medication. Physical examination revealed a thin, mildly icteric woman with scratch marks on her skin. She had an early Dupuytren's contracture of her left hand. The liver was enlarged 4 cm below the right costal margin, and was slightly tender. There was no splenomegaly, and no other stigmata of chronic liver disease.

Investigations showed that the total serum bilirubin was elevated at 66 $\mu\text{mol/l}$ (normal, 6-18 $\mu\text{mol/l}$), with a moderate rise of the alanine aminotransferase to 35 i.u./l (normal 2-24 i.u./l) and a marked rise of the alkaline phosphatase to 554 i.u./l (normal 46-190 i.u./l). The total serum proteins were 64 g/l with serum albumin 41 g/l. An oral cholecystogram (performed elsewhere), ^{99}Tc sulphur-colloid isotopic liver scan, and abdominal ultrasound were normal. Antinuclear, smooth muscle and anti-mitochondrial antibodies were negative.

A diagnosis of extra-hepatic biliary obstruction

was made but percutaneous transhepatic cholangiography and possible laparotomy had to be deferred because of a chest infection. She was treated with co-trimoxazole (trimethoprim 80 mg, sulphamethoxazole 400 mg) 2 tablets twice daily and allowed home temporarily.

On readmission 7 days later, she was more deeply jaundiced with increased pruritus. Percutaneous transhepatic cholangiography failed to show dilated intra-hepatic biliary ducts. Liver biopsy showed centrilobular cholestasis with numerous bile plugs (Fig. 1). The portal tracts contained a scanty acute and chronic inflammatory infiltrate but normal bile ducts were present in all of them (Fig. 2). The appearances were those of a cholestatic jaundice and the picture was thought to be highly suggestive of a drug-induced reaction. At this stage she admitted that she had had a course of co-trimoxazole 2 tablets twice daily for 7 days just before the onset of her initial illness. The patient had originally denied this. The relationship of the liver function tests to exposure to co-trimoxazole and subsequent course is shown in Fig. 3. Six months later she was symptom free, her liver was no longer palpable, and her liver function tests had returned to normal.

Discussion

It is felt that there can be little doubt that this woman's cholestatic jaundice was due to co-trimoxazole because of the time relationship, biopsy changes and the result of the re-challenge. Dujovne, Chan and Zimmerman (1967) recommended that patients suspected of having an adverse reaction to a drug should be given a test dose of the suspect agent. This happened inadvertently with the present patient. The authors would not recommend routine drug re-challenge in cases of suspected drug-induced liver damage because of the risk of fatal hepatic necrosis known to occur with other drugs (Rehman, Keith and Gall, 1973). Whilst a re-challenge with trimethoprim or sulphamethoxazole alone, would be of considerable interest it is not felt to be justified.

Abnormalities of liver function tests ascribed to co-trimoxazole have previously been reported (Hermansen *et al.*, 1976), and Colucci and Cicero

FIG. 1. Liver biopsy showing marked centri-lobular cholestasis with numerous bile plugs present (Perl's, $\times 392$).

FIG. 2. Liver biopsy showing a portal tract with several normal bile ducts and a scanty inflammatory infiltrate (Van-Gieson, $\times 252$).

(1975) described a case of fatal toxic hepatic necrosis, also due to co-trimoxazole. However, the authors have been unable to find a similarly documented case of cholestatic jaundice in the literature. This condition as a suspected complication of co-trimoxazole therapy has, however, been reported to the Committee on the Safety of Medicines on 8 occasions (personal communication).

Trimethoprim does not appear to have a hepatotoxic effect, but sulphamethoxazole, in common with other sulphonamides, has been implicated as a cause

FIG. 3. Relationship of the liver function tests to exposure to co-trimoxazole.

of jaundice (Fries and Siragnian, 1966; Dujovne *et al.*, 1967). Macoul (1966) reported a case of hepatocellular damage, but there was no challenge, and liver biopsy was not performed. Simultaneous toxic hepatitis and Stevens-Johnson syndrome with sulphamethoxazole has also been described (Shaw and Jacobs, 1970). It seems likely therefore that this episode of cholestatic jaundice was due to the sulphonamide component of co-trimoxazole.

In the previously described cases of sulphamethoxazole jaundice the histological features of the liver biopsies showed periportal inflammation and a marked degree of hepatic necrosis suggesting that the liver lesion was part of a more severe systemic hypersensitivity reaction. These cases had a blood eosinophilia as had the patient with jaundice and a Stevens-Johnson syndrome (Shaw and Jacobs, 1970). In contrast, the present patient had no eosinophilia and the liver biopsy showed the changes of pure cholestatic jaundice, with a scanty periportal infiltrate and no hepatocellular damage. This type of cholestatic reaction may be peculiar to the trimethoprim/sulphamethoxazole combination and may not occur with sulphonamides alone.

It is felt that this case underlines the need to exclude drugs as a cause of obscure jaundice, as the causative role played by the co-trimoxazole became evident only on inadvertent challenge.

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