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Naftidrofuryl-induced acute hepatic necrosis

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Summary: **Acute hepatic necrosis is described in a 60 year old woman treated with naftidrofuryl for 5 months.**

Introduction

Naftidrofuryl oxalate (Praxilene, Lipha) is a vasodilator advocated for cerebral and peripheral vascular disease. There have been no previous reports of hepatic damage due to this drug. We now wish to report a case in which severe hepatitis was related to its use.

Case history

A 60 year old woman with a history of ischaemic heart disease presented with 5 months of nausea and one month of anorexia. She had noticed increasing jaundice, dark urine and pale stools for 10 days. She had not been in contact with viral hepatitis and had not recently travelled abroad. Her husband confirmed that she rarely took alcohol. She had been treated for leg cramps with naftidrofuryl 300 mg/day increasing to 600 mg/day for a period of 5 months, and additionally with quinine sulphate 200 mg nightly for 2 months. She was not taking any other medication. She was deeply jaundiced but with no stigmata of chronic liver disease. Her liver and spleen were impalpable. Liver function tests showed the bilirubin 295 μmol/l rising to 545 μmol/l after 2 weeks (normal 2–17), alkaline phosphatase 293 units/l (normal 40–100) and alanine aminotransferase (ALT) 1854 units/l (normal 10–40). Albumin was initially 33 g/l, falling to 29 g/l during the first week of observation, and the prothrombin time ratio was 1.6. The blood haemoglobin, total and differential leucocyte count, platelet count, sedimentation rate, urea and electrolytes were all normal. The electrocardiogram and chest radiograph were normal. Ultrasound examination showed diffusely abnormal liver parenchymal echoes. A gallstone was noted but there was no biliary dilatation. Endoscopic retrograde cholangio-pancreatography showed a normal common bile duct and pancreatic duct; multiple stones were demonstrated within the gallbladder. Liver biopsy showed extensive centrilobular necrosis with porto-central bridging (Figure 1). Serological tests for hepatitis A, hepatitis B, toxoplasma, cytomegalovirus, herpes simplex, coxiella, mycoplasma, brucella and leptospira were negative. Antibody to Epstein-Barr virus (IgG type) indicated past infection. Antimitochondrial and anti-smooth muscle antibodies were absent.

All medication was discontinued on admission and the patient made a good recovery. Four months later, her bilirubin was 23 μmol/l, ALT 57 units/l, alkaline phosphatase 178 units/l, gamma glutamyl transferase 112 units/l and albumin 37 g/l, and one year later her liver function tests were normal. She continued to take quinine sulphate intermittently despite instructions not to do so during this year and she suffered no ill effect. Twenty-two months after presentation, and with her informed consent, she was given 1 tablet of quinine sulphate (200 mg). No abnormalities of liver function occurred in the next 5 days and she remained well. These observations were repeated after the

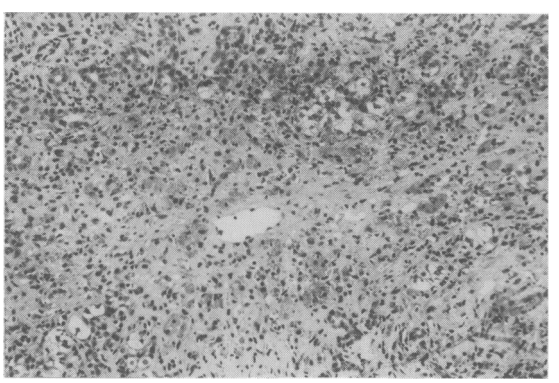

Figure 1 Liver biopsy (H.E. × 125): extensive centrilobular necrosis with a mild inflammatory cell infiltration and ceroid-containing macrophages.

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patient had taken quinine sulphate on 3 consecutive nights and no abnormalities were observed.

Discussion

The very high bilirubin, raised prothrombin time and reduced albumin indicate severe hepatitis in this case. Naftidrofuryl was launched in 1974 and since then the Committee on the Safety of Medicines has received one report of hepatitis and one of cholestatic jaundice in which this was the only drug administered. We believe that naftidrofuryl caused our patient's illness as she was taking this drug when the illness began, no alternative cause was found on investigation, and the only other drug she was taking at the time was later shown to be innocuous for her liver. A positive challenge test with naftidrofuryl would have given conclusive evidence that it was the toxic agent, but challenge tests are not entirely safe and can only be advocated where the drug is essential for the patient (Perez *et al.*, 1972). Re-exposure to a drug which has previously caused liver damage may cause fatal acute hepatic necrosis (Hoyumpa & Connel, 1973; Goldstein *et al.*, 1973) and re-challenge is not recommended if previous hepatic injury has been severe (Perez *et al.*, 1972; Hoyumpa *et al.*, 1973).

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