Jaundice associated with naproxen

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Summary

Hepatic injury in association with naproxen therapy is described and documented by liver biopsy in one patient. Histological findings were consistent with a drug-induced hepatitis, and cessation of therapy led to reversal of the clinical and biochemical changes. Circumstantial evidence is in favour of a hypersensitivity response to the drug rather than direct hepatotoxicity. Increased awareness of clinicians of this probably rare side effect of naproxen may help prompt identification of similar cases.

Introduction

Naproxen ((+)-6 methoxy 2-naphthaleneacetic acid), a non steroidal anti-inflammatory agent, is currently widely used in rheumatic conditions. Slight and transient changes in serum transaminase levels, regressing despite continued therapy, have been reported by Frenger and Norbach (1973) and more recently jaundice was suggested as a possible side effect of naproxen (Bass, 1974; Law and Knight, 1976). These 2 case reports were not histologically documented. The authors now present what, to their knowledge, is the first histologically documented case of jaundice associated with naproxen.

Case report

A 66-year-old Angolan black male presented with a 2-year history of mild back pain and a diagnosis of spinal osteoarthritis. No treatment was given until January 1977 when he was started on naproxen 250 mg twice/day and Neurobion (vitamin B₁, B₆ and B₁₂) injections twice/week. One month after commencing this treatment he developed fever for 4 days with malaise and this was followed by appearance of dark urine and marked jaundice. He had

no complaints of abdominal pain, pruritus or rash, no history of contact with cases of viral hepatitis and no alcohol consumption preceding the episode. Excluding the vitamin preparation during the preceding month, he had had no injections or transfusions in the 2 previous years. After the appearance of jaundice, naproxen was stopped and 10 days later he was admitted to hospital for investigation.

Physical examination at this time revealed marked jaundice, a slightly tender liver palpable 5 cm below the costal margin and no other positive findings.

Laboratory tests showed a normal Hb, blood film, haematocrit, blood urea nitrogen, glucose, electrolytes and prothrombin time. Erythrocyte sedimentation rate was 15 mm in 1st hr (Westergren). Serum aspartate transferase, 102 u. (normal range 5-40 u.). Total bilirubin, 99.2 µmol/l. Alkaline phosphatase, 19 Bodansky u. (normal range 1.5-5.0 u.). Cholesterol, 5.98 mmol/l. HBs antigen and anti-nuclear, antimitochondrial and antismooth muscle antibodies were all negative.

Percutaneous liver biopsy was then performed. The histological appearances revealed preservation of normal architecture. The most prominent abnormal normal feature was the accumulation of PAS positive pigment in clumped Kupffer cells and portal tract phagocytes providing evidence of previous liver cell death (Fig. 1). A mild degree of steatosis with small and medium sized vacuoles (Fig. 2) and rare and small foci of mononuclear cell infiltration, scattered through the parenchyma, were present. Portal tracts were sharply limited and moderately enlarged with oedema and infiltration by mononuclear cells and some eosinophils (Fig. 3). The changes were interpreted as those of a resolving acute hepatitis-type lesion. In 2 weeks the hepatomegaly disappeared and the patient was discharged with a mild residual jaundice and almost complete regression to normal of liver function tests: serum aspartate transferase, 17 u., total bilirubin, 37.6 µmol/l.

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FIG. 1. Liver biopsy showing Kupffer cells and portal tract phagocytes with intensely PAS-positive pigment (MC. Manus, $\times 130$).

FIG. 2. Liver biopsy showing mild steatosis (HE, $\times 250$).

and alkaline phosphatase, 7.0 Bodansky units. Ten days later jaundice had resolved.

Discussion

One month after starting naproxen the patient developed jaundice which resolved after stopping the drug. There were no epidemiological data in

favour of viral hepatitis A and HB_s antigen was negative. Lack of alcohol consumption preceding the episode and the histological appearances excluded alcoholic hepatitis. In fact, the liver biopsy findings were those of a resolving acute hepatitis-type lesion. The presence of eosinophilic infiltration and steatosis, which is not usual in viral hepatitis, in

FIG. 3. Liver biopsy showing portal tract enlargement with oedema and cellular infiltration including some eosinophils (HE, $\times 150$).

conjunction with the temporal sequence and the exclusion of the above mentioned aetiologies led to the diagnosis of a drug-induced hepatitis. The use of a challenge test was not done in view of the initial severity of the clinical picture, together with the fact that naproxen was not essential to this patient's management. Finally, the clinical picture was in several aspects similar to the 2 previously reported cases (Bass, 1974; Law and Knight, 1976).

The presence of a relatively fixed sensitization period (one to 6 weeks) in the 3 reported cases, the apparent rarity of this side effect, together with the sudden onset of fever and the presence of eosinophils in the infiltrate in this case, are all circumstantial evidence supporting a hypersensitivity response to the drug rather than a direct hepatotoxic effect. Also the recent report of accidental ingestion of 25 g of naproxen without liver abnormalities (Fredell and Strand, 1977) and the study on pharmacokinetics of naproxen by Runkel, *et al.* (1976), provide further evidence against direct hepatotoxicity.

Thus, naproxen-associated jaundice is probably a rare event limited to sensitive individuals. Increased awareness by clinicians of this side effect may help in the prompt identification of similar cases and prevent continuing liver damage by early withdrawal of the drug.

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