Fatal intrahepatic cholestasis associated with triazolam

I. COBDEN
M.D., M.R.C.P.

C. O. RECORD
D.Phil., F.R.C.P.

R. W. B. WHITE*
M.B. B.Chir., F.R.C.P.

Gastroenterology Unit, Royal Victoria Infirmary, Newcastle upon Tyne, and *General Hospital, Hartlepool

Summary
A 44-year-old man developed severe pruritus with jaundice which subsequently proved fatal. Liver histology showed intense cholestasis, but at post-mortem the bile ducts were patent and there was no cirrhosis, the findings being consistent with a cholestatic drug reaction. The most likely precipitant was the benzodiazepine triazolam, and surveillance is indicated for any further reactions to this recently marketed hypnotic.

Introduction
Cholestatic drug reactions are not uncommon but are usually mild and reversible. A patient is described who died as a result of an unremitting intrahepatic cholestasis which may have been related to treatment with the benzodiazepine hypnotic, triazolam.

Case report
A 44-year-old policeman presented to the General Hospital, Hartlepool, in September 1980 with a one-month history of painless jaundice and severe pruritus. In 1974 he had had a successful resection of a small ampullary carcinoma and was extremely well when finally discharged from out-patient follow-up in 1979. In April 1980 his general practitioner prescribed triazolam 0.25 mg at night for insomnia which was taken 2 or 3 times/week until presentation. In June 1980 he was found to be in atrial fibrillation and was given digoxin 0.25 mg daily and Moduretic (hydrochlorothiazide 50 mg with amiloride 5 mg) one tablet daily.

On admission he was jaundiced with many excoriations. Apart from controlled atrial fibrillation and the scar from his previous operation, there were no abnormal findings. Investigations showed an elevated bilirubin of 181 μmol/l (normal <17) with an alkaline phosphatase of 104 i.u. (normal <100) and aspartate transaminase of 97 i.u. (normal <36). Full blood count, electrolytes and clotting studies were normal. A percutaneous cholangiogram did not show any evidence of biliary tract obstruction. At laparotomy the liver, pancreas and gall-bladder were entirely normal; preoperative cholangiography showed a normal duct system with free flow into the duodenum. A wedge liver biopsy was taken. His postoperative recovery was satisfactory but his jaundice persisted. Three weeks later he was readmitted with an attack of acute pancreatitis which rapidly settled but his jaundice progressively deepened and he was transferred to the Gastroenterology Unit at the Royal Victoria Infirmary for further investigation. On admission he was cachectic and deeply jaundiced. He was drowsy with a slight liver flap and no stigmata of chronic liver disease. The biochemical evidence of cholestatic jaundice was confirmed. HBs antigen and antibody, mitochondrial antibody and other relevant autoantibodies were not detected and immunoglobulins were normal. Endoscopic retrograde cholangiography showed no abnormality of the extrahepatic or intrahepatic biliary tree and an isotope liver scan was unremarkable. Needle liver biopsy was performed. He was treated with a standard liver failure regime but terminally he developed renal impairment, gastrointestinal bleeding and a chest infection.

At post-mortem there were 2 acute duodenal erosions and evidence of previous acute pancreatitis. The gall-bladder was distended with clear fluid but the biliary tree was patent throughout and the liver was macroscopically normal apart from intense bile staining. Histology of both the surgical and needle liver biopsy specimens was essentially similar. The liver was not cirrhotic but portal tracts were expanded by collagenous tissue. There was marked pseudoductular transformation of periportal hepatocytes with some neutrophils and eosinophils. Intra-canalicicular bile plugs were seen and bile...
pigment was plentiful in Kupffer cells and hepatocytes.

**Discussion**

The clinical picture of deep painless jaundice with intense pruritus was strongly suggestive of obstruction and, although the alkaline phosphatase was only moderately elevated histology confirmed marked cholestasis. The findings are consistent with drug-induced disease. There was no history of excessive alcohol intake, large duct obstruction was ruled out and the laboratory and pathological findings make other diagnoses such as hepatitis or primary biliary cirrhosis extremely unlikely.

The relationship between the fatal liver damage and triazolam is conjectural. The authors know of no other reports of liver disease associated with the drug but it has been introduced only recently to the market. Cholestasis is a recognized association with other benzodiazepines, including chlordiazepoxide and diazepam (Davies, 1977) and flurazepam (Franks and Jacobs, 1975) but is usually a benign condition (Davies, 1977). It has not been recorded with either digoxin or Moduretic. There is one well documented case of reversible cholestasis associated with chlorothiazide treatment (Drerup et al., 1958) but these drugs have been in use for many years and diuretic-induced liver disease must be extremely rare (Davies, 1977). The authors feel that the possible association with triazolam, although not conclusive, must be taken seriously in view of the severity of the hepatic reaction.

**Acknowledgments**

We thank Dr A. Watson for the histology reports, and Mrs P. Groom for preparing the manuscript.

**References**

