Case reports

Sulindac hepatotoxicity

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SUMMARY Two patients who developed painless jaundice while taking sulindac are described. Rechallenge in one case confirmed the association of hepatic damage with sulindac administration. Laboratory data and liver biopsy findings suggested a hepatitis with cholestatic features.

Sulindac is a recently introduced non-steroidal anti-inflammatory drug which has been associated with hepatocellular damage in three published cases.¹⁻³ We present here two cases of clinical jaundice associated with the use of sulindac. In one case both the serum transaminases and alkaline phosphatase were moderately raised. Rechallenge with sulindac caused transaminase levels to rise within 24 hours. In the other case, the predominant clinical and laboratory findings were those of cholestasis, a pattern not previously reported.

Case 1

A 70-year-old caucasian woman with a long history of osteoarthritis involving the knees, hips, back, and shoulders was admitted to the Toronto Western Hospital Surgical Service with jaundice in January 1980. The patient had been using dimethylsulphoxide (DMSO) cutaneously for over a year. Ten days before admission she was given oral sulindac.

Four days later she developed nausea, vomiting, malaise, and a fever (38°C). A day later, she visited her family doctor and jaundice was noted. The patient was treated with ampicillin, propanthelin, and maalox antacid. Because of persisting jaundice she was admitted to hospital. Notably, she denied alcohol use, was not taking any other medications, and gave no history of exposure to hepatitis.

Physical examination disclosed an afebrile, mildly jaundiced woman with a normal liver span. Laboratory data revealed a normal haemogram,

while the liver tests showed: SGOT 211 IU/l (NR 0-40), alkaline phosphatase 325 IU/l (NR 20-100 IU/l), bilirubin 54 µm/l (3.2 mg/dl), albumin 4.0 g/dl, globulin 2.9 g/dl, prothrombin time and partial thromboplastin time normal. An ultrasound of the liver, biliary tree, and pancreas was normal, as was an intravenous cholangiogram and endoscopic retrograde cholangiopancreatography.

All her medications were withdrawn on admission. Once a surgical cause for her jaundice had been excluded, a liver biopsy was performed. This was carried out 15 days after admission. This showed normal liver parenchyma except for a prominence of ceroid pigment within Kupffer cells in the centrilobular zone III areas (Fig. 1). Portal tracts were unremarkable.

The patient's liver enzymes returned to normal within a month of stopping sulindac. A further month later, the patient was prescribed sulindac 200 mg twice daily. Within 24 hours of starting the drug she complained of malaise, fever (38.3°C), and lethargy. The SGOT was raised once more from 18 IU/l the previous week to 62 IU/l the morning after the challenge. Within two days of discontinuing the drug she felt well. One month later the liver tests were normal.

Case 2

A 71-year-old woman was admitted for investigation of jaundice. She had been well until two weeks before admission when she noted the onset of malaise, nausea, dark urine, light stools, and jaundice. She had no abdominal pain or fever. Severe itching developed several days later, which improved with cholestyramine. There was no history of contact with hepatitis or blood transfusions. She

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Fig. 1 Case 1. Biopsy showing marked ceroid deposition within Kupffer cells. PAS-diastase stain, $\times 400$ (original magnification).

consumed 170 ml (6 oz) of Canadian rye whisky daily.

There was no previous history of liver disease. She had had an appendectomy, salpingectomy, and lumbar disc surgery in the remote past. There was no history suggestive of cholelithiasis.

Medications included L-thyroxin and occasional dulcolax tablets. Sulindac had been started one month before admission for back pain. She stopped taking this medication one week after developing jaundice.

Physical examination revealed jaundice with no stigmata of chronic liver disease. There was no hepatomegaly, splenomegaly, ascites, or oedema.

Laboratory investigation revealed a normal haemogram. The SGOT was 65 IU/l, the alkaline phosphatase 278 IU/l, the bilirubin 213 $\mu\text{m/l}$ (12.6 mg/dl). The albumin and thyroid indices were normal. Hepatitis markers were negative. Ultrasound examination of the liver, biliary tree, and pancreas was normal as was an ERCP. It was seven months before the patient became anicteric and her

liver enzymes returned to normal.

Liver biopsy (Fig. 2) revealed evidence of hepatocellular damage largely within the centrilobular areas (zone III). The changes included occasional acidophil bodies, focal drop-out of hepatocytes accompanied by small collections of mononuclear cells, mild small and large droplet steatosis, and heavily pigmented Kupffer cells. Portal tracts were normal, although there were numerous dilated bile canaliculi with bile plugs. These were inconspicuous on light microscopy but were prominent by electron-microscopy.

Discussion

Three cases of hepatitis associated with the use of sulindac have been described previously.¹⁻³ We have presented two women who developed

Fig. 2 Case 2. Biopsy showing zone III with terminal hepatic venule. There are focal collections of mononuclear cells associated with irregularities in the hepatocyte plates. There are numerous Kupffer cells containing ceroid pigment (curved arrows). Dilated canaliculi, often containing bile plus, were numerous (straight arrows). PAS-diastase stain, $\times 330$ (original magnification).

reversible hepatic dysfunction with sulindac. Case 1 is similar to previous reports with regard to the biochemical presentation. Case 2, however, demonstrated a predominantly cholestatic picture.

Both our patients developed malaise and jaundice. Extrahepatic obstruction was initially suspected and ruled out. It is unlikely that DMSO (which may cause liver enzyme abnormalities⁴) was responsible for the findings in case 1, as the drug was continued while the liver tests returned to normal.

There has been no previous detailed report of the liver biopsy findings in sulindac hepatotoxicity. Both our cases showed prominent pigmented Kupffer cells in zone III. In addition, case 2 had dilated bile canaliculi and evidence of mild hepatocellular necrosis, also in zone III. The biopsies were performed two weeks after discontinuing the drug and yet both provided patterns consistent with drug-induced injury and unlike those associated with extrahepatic obstruction. The relative absence of inflammatory cell infiltration may be related to the delay before biopsy.

Sulindac has now been associated with both hepatitic and cholestatic liver disease. The mechanism of hepatotoxicity is unknown. Symptomatic complaints occurred anywhere from one week to two months after initiation of sulindac therapy. In all cases described so far the liver enzymes returned to normal within a month of stopping sulindac. Case 2 in this report was unusual, as her jaundice persisted for several months. Both

our patients were otherwise healthy, but two of the three previously described cases had systemic diseases (juvenile rheumatoid arthritis¹ and systemic lupus³). In the two cases where rechallenge occurred, the rapid appearance of symptoms and liver test abnormalities (less than 24 hours) suggests a hypersensitivity reaction and probably confirms an aetiological relationship.

In summary, we have presented two cases of liver damage associated with the use of sulindac. Clinically, the patients presented with painless jaundice. Recognition of the association of cholestasis with sulindac may prevent unnecessary laparotomy or invasive investigation in the jaundiced patient.

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