Piroxicam induced submassive necrosis of the liver

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Abstract

Several widely used non-steroidal anti-inflammatory drugs have been reported as causing severe hepatitis. Three cases of severe acute hepatitis have been reported in association with piroxicam. A fatal submassive necrosis that occurred in a 68 year old lady who had received piroxicam for 15 months is described. A 48 year old man who developed submassive hepatic necrosis six weeks after beginning piroxicam but was successfully treated with orthotopic liver transplantation is also reported. Piroxicam may induce submassive necrosis of the liver, probably as an idiosyncratic reaction.

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Non-steroidal anti-inflammatory drugs (NSAIDs) are increasingly being recognised as potential hepatotoxins.¹ Virtually all of those currently available have been reported to cause liver damage² which can range from minor transient abnormalities in liver function tests to fulminant hepatic necrosis. Sulindac, phenylbutazone, diclofenac, and indomethacin are reported to have a higher potential for hepatotoxicity than ibuprofen, naproxen, mefenamic acid, and piroxicam.¹ Severe, sometimes fatal, hepatitis has been most commonly reported in association with the use of diclofenac³⁻⁶ and sulindac,⁷⁻⁹ although fatalities have also been reported with the use of naproxen¹⁰ and indomethacin.¹¹

Piroxicam (Feldene) is an oxycam, unrelated chemically to other available NSAIDs. It is probably the most widely used NSAID worldwide.¹² Gastrointestinal side effects, most importantly peptic ulceration, are the most common adverse reactions seen. Although changes in liver function tests are very rare,¹³ three cases of severe acute hepatitis secondary to piroxicam have been reported. Two of these patients died^{14 15} and one survived after receiving an emergency liver transplant allograft.¹⁶ We describe two cases of fulminant hepatitis related to the use of piroxicam.

Case reports

CASE 1

A 68 year old woman was admitted to this hospital in May 1989. In December 1986 she had had a transient ischaemic attack for which she had been given enteric coated aspirin (Ecotrin 300 mg/day). On 31 December 1987 she began piroxicam (Feldene 10-20 mg/day) for pain caused by osteoarthritis of the shoulders, cervical spine, and knees. She remained well until March 1989, when she presented with generalised pruritus and fatigue. Physical

examination showed mild icterus but otherwise was entirely normal. At that time, biochemical analysis showed a bilirubin concentration of 39 $\mu\text{mol/l}$, albumin 38 g/l, alkaline phosphatase (AP) activity 235 U/l, lactate dehydrogenase (LDH) 354 U/l, aspartate transaminase (AST) 680 U/l, alanine transaminase (ALT) 1610 U/l, and gamma glutamyl transferase (GGT) 265 U/l. Her white cell count was $5.8 \times 10^9/\text{l}$, with 10% eosinophils. Both the piroxicam and aspirin were stopped. Ultrasonography showed a normal liver, gall bladder, and biliary tree. Hepatitis A and B, cytomegalovirus, Epstein-Barr virus, *Coxiella burnetii*, and leptospirosis serology were negative. Stored serum was negative for antibody to hepatitis C, using the second generation Chiron RIBA assay (Chiron Corporation, Emeryville, USA). Serum copper and ceruloplasmin concentrations were within normal limits.

Her hepatic impairment became increasingly severe, and by the end of April 1989 biochemical analysis showed a bilirubin concentration of 426 $\mu\text{mol/l}$, albumin 29 g/l, AP 187 U/l, LDH 523 U/l, AST 1854 U/l, and GGT 36 U/l. Her prothrombin time was 20 seconds. Transjugular liver biopsy on 10 May 1989 showed severe hepatitis with multiacinar necrosis (Fig 1); only occasional lobules remained. The portal areas (Fig 1) and surviving parenchyma (Fig 2) were

Figure 1: Panacinar necrosis (on right) with pronounced portal ductular hyperplasia and inflammation (on left) (haematoxylin and eosin $\times 340$).

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Figure 2: Inflammation of surviving parenchyma (haematoxylin and eosin $\times 350$).

heavily infiltrated by lymphocytes, plasma cells, and eosinophils. The appearances were consistent with submassive necrosis caused by drug toxicity. By 12 May the patient had become encephalopathic. Deterioration in her mental status and renal function occurred, and on 31 May she died, three months after the onset of her illness. Necropsy was performed and showed a

Figure 3: Panacinar necrosis (centre) with peripheral bile ductular hyperplasia (top, bottom) (haematoxylin and eosin $\times 210$).

small liver (620 g) with light microscopic changes of submassive necrosis.

CASE 2

A 48 year old man developed stiffness in his joints and lethargy in December 1987, and was begun on piroxicam (Feldene 10 mg). His arthralgia resolved but six weeks later he developed jaundice, dark urine, and pale stools. Examination at this time showed a firm, enlarged liver. On 16 February 1988 his bilirubin concentration was 243 $\mu\text{mol/l}$, albumin 28 g/l, international normalised ratio 2.4, AST 1860 U/l, alkaline phosphatase 87 U/l, LDH 471 U/l, and GGT 133 U/l. Ultrasonography and endoscopic retrograde cholangiopancreatography were normal. Serology for hepatitis A and B, cytomegalovirus, and Epstein-Barr virus and an autoantibody screen were negative. Stored serum from this time has subsequently been shown to be negative for antibody to hepatitis C (RIBA assay, Chiron Corporation). Serum copper and ceruloplasmin concentrations, iron studies, and ferritin were all within normal limits. On 22 February 1988 he developed grade II hepatic encephalopathy and ascites. Acute renal impairment (creatinine 0.37 mmol/l) developed on 26 February 1988 and his encephalopathy worsened to grade IV.

Orthotopic liver transplantation was performed on 28 February 1988. Histology showed submassive necrosis (Fig 3). Sixteen days after liver transplantation a deterioration in liver function tests occurred and liver biopsy showed cytomegalovirus inclusion bodies. His platelet count began to fall and bone marrow biopsy showed viral haemophagocytic syndrome. The patient was treated with intravenous ganciclovir. He recovered promptly and has had no further problems 30 months after transplantation.

Discussion

We believe that the submassive necrosis in these two patients was caused by piroxicam. Metabolic and infectious causes of submassive necrosis are unlikely in view of the negative biochemical and serological tests. Importantly, hepatitis C serology was negative. Sporadic reports of hepatitis associated with widely used drugs have been criticised in the past, because of inability to exclude non-A, non-B hepatitis.¹⁷

Aspirin was also used by the elderly woman in the first case. Aspirin has been reported to cause hepatotoxicity in recent years. Most patients affected have been young women with connective tissue disorders who receive aspirin regularly in high dosage.² Their liver damage is usually mild, dose dependent, and reversible when the drug is stopped. Several case reports of severe liver damage, some with encephalopathy resembling Reye's syndrome, have been reported with aspirin usage but these have all been in children.² We believe that there is no good evidence that aspirin is responsible for our patient's fulminant liver disease in view of her age and the dosage of aspirin she ingested.

Severe liver damage caused by NSAIDs is usually attributed to 'hypersensitivity' or

'idiosyncrasy'. This also seems to be the mechanism of piroxicam induced liver damage. There does not seem to be a consistent dose related hepatotoxic effect, even in overdose. Normal liver function tests were recorded after a reported ingestion of 1800 mg piroxicam.¹⁸ Previous case reports of piroxicam induced submassive necrosis have described the onset of jaundice three days¹⁴ and three weeks¹⁵ after beginning piroxicam. Our second patient fits this pattern, with an onset of jaundice approximately six weeks after piroxicam was begun. Most other cases of severe hepatic injury associated with NSAIDs have occurred within weeks to months of starting treatment.³⁻¹¹

The first patient we described presented with jaundice 15 months after beginning piroxicam. There is precedence for this long duration between introduction of the drug and the development of hepatitis. The NSAIDs pirofen, benoxaprofen, and diclofenac caused fatal hepatitis 9, 10, and 11 months respectively after starting therapy.¹⁹⁻²¹ In a large study of isoniazid associated hepatitis, 54% of patients presented after having received the drug for more than two months and several received the drug for more than 12 months before presentation.²²

Two of the three previously reported cases of severe hepatitis caused by piroxicam occurred in women in their 60s.^{14,15} Treatment with corticosteroids was begun in each of these without success, with death occurring 105 and 53 days respectively after the onset of jaundice. Our first patient, also in her 60s, survived three months after the onset of jaundice. She was not treated with corticosteroids. It seems clear that only hepatic transplantation will save such patients with severe hepatic failure. As previously mentioned, there is a report of successful liver transplantation in a 36 year old man with acute hepatic failure related to piroxicam usage.¹⁶ The long term prospects of the 48 year old man who

underwent liver transplant are good. We recommend liver transplantation as the only treatment likely to be successful in drug related submassive necrosis of the liver.

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