

## Case reports

# Fatal hepatitis associated with diclofenac

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**SUMMARY** Non-steroidal anti-inflammatory agents (NSAIDS) are a well recognised cause of hepatotoxicity. Diclofenac, a relatively new NSAID, was first introduced into the UK in 1979. Five cases of hepatitis have recently been reported, principally in the French literature.<sup>1-5</sup> We report the first fulminant case of hepatitis in the English literature in a patient taking diclofenac and indomethacin.

Diclofenac is a member of the arylalkanoic group of NSAIDS (Fig. 1). Three other agents in this group have been shown to be significantly hepatotoxic. Ibuprofen was withdrawn from circulation because of the frequent rise in transaminases,<sup>6,7</sup> the use of benoxaprofen was stopped in Britain after 10 patients died with hepatitis<sup>8,9</sup> and more recently a fatal case of hepatitis due to piroxicam has been reported.<sup>10</sup> Early reports about diclofenac showed that it caused a rise in liver function tests.<sup>11</sup> Since 1983 five reports of hepatitis caused by diclofenac have been published, including that of a 55 year old French woman, who died with fulminant hepatitis after a three week course of diclofenac.<sup>1-5</sup>

Indomethacin has been in clinical use for over 20 years and two patients have died from fulminant hepatitis caused by indomethacin.<sup>12,13</sup> Other reports of hepatotoxicity exist but are infrequent.<sup>14,15</sup> We describe a patient who developed fulminant hepatitis after one month's treatment with indomethacin followed by two months' treatment with diclofenac.

### Case report

A 56 year old farmer started treatment for osteoarthritis on 9 April, 1985. Before this he had no medical illness and was not taking any medication. He received an intramuscular injection of diclofenac (50 mg) and started indomethacin 75 mg per day for 10 days, and 50 mg per day for the following two weeks. On 2 May he received a further intramuscular injection of diclofenac (50 mg) and oral diclofenac was substituted for indomethacin. The dose was 75 mg per day for two weeks followed by

100 mg per day for five weeks. Ferrous sulphate one tablet daily was added on 16 May. The patient was admitted to hospital on 26 June. A week before this he had felt unwell with anorexia, nausea, abdominal discomfort, and dark urine. On admission he was icteric, the liver edge was palpable 4 cm below the costal margin and there were no signs of chronic liver disease. Ultrasound showed early ascites with no obstruction of the biliary tract. A week after admission he developed a maculopapular rash maximal on the trunk, diffuse lymphadenopathy, and a pyrexia of 39°C. The eosinophil count was  $399 \times 10^9/l$ . Laboratory investigations were consistent with fulminant hepatitis and serological markers for viral infection were absent (Table). The patient had no history of foreign travel, blood transfusion, alcohol abuse, exposure to toxic chemicals or

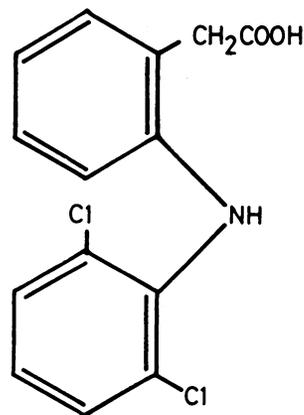


Fig. 1 Chemical structure of diclofenac.

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homosexuality. His condition gradually deteriorated. The liver reduced in size, the prothrombin time rose to 37 sec, the serum albumin fell to 23 g/l and gross ascites developed. Lactulose neomycin

and hydrocortisone were started. On 13 July asterix and foeter hepaticus were present and the patient became comatose. On 17 July urine output fell to 300 ml per day, and the platelet count was 30 000, with no laboratory evidence of disseminated intravascular coagulation. The patient died on 20 July, 24 days after admission. Necropsy showed a small liver which weighed 950 g. The histopathology was of massive hepatic cell necrosis with extensive centrilobular liver cell dropout (Fig. 2). The portal triads showed intense inflammatory infiltrate and bridging necrosis was present in the relatively better preserved areas. There was no fibrosis. Bile plugging was present in the renal tubules and the other organs were normal.

Table Laboratory data on admission

Liver function tests	Normal range
Albumin	36 g/l (34–48 g/l)
Prothrombin time	22 secs (14–16 sec)
Alkaline phosphatase	321 U/l (30–115 U/l)
Bilirubin	115 $\mu$ mol/l (0–17 $\mu$ mol/l)
Alanine aminotransferase	2110 U/l (0–45 U/l)
Viral screen	
Hepatitis A – IgM	Negative
Hepatitis B – sAg	Negative
Hepatitis B – IgM – cAntibody	Negative
Cytomegalovirus	Negative
Ebstein-Barr virus	Negative
Herpes Simplex virus	Negative
Autoantibodies	
Nuclear	Negative
Mitochondrial	Negative
Smooth muscle	Negative
White cell count $5.7 \times 10^9/l$	
Neutrophils	65%
Lymphocytes	28%
Eosinophils	7%

### Discussion

This patient died from fulminant hepatitis, as shown by the absence of clinical, or histological evidence of previous liver disease, the occurrence of hepatic encephalopathy three weeks after the onset of jaundice, the abnormal prothrombin time and the massive hepatic cell necrosis. There are three possible causes: non-A non-B hepatitis, indomethacin, and diclofenac. The diagnosis of non-A non-B hepatitis is one of exclusion. In this patient all

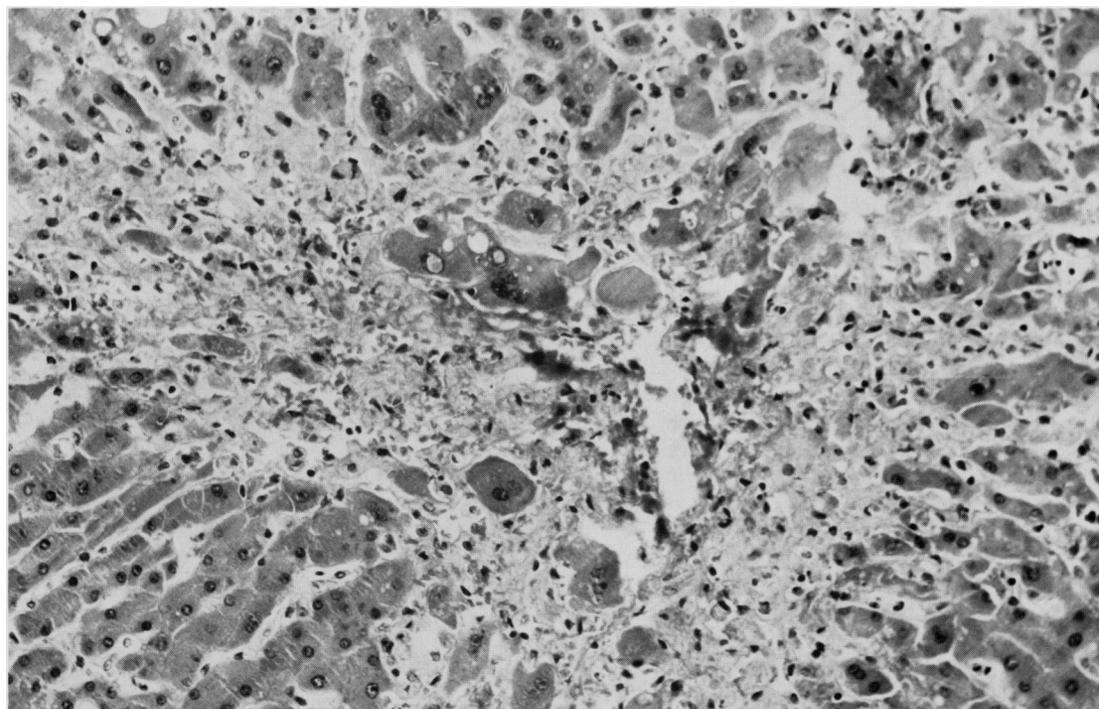


Fig. 2 Microscopy of liver showing centrilobular necrosis.

screening for viral infection was negative. Two injections with sterile disposable needles and syringes were administered, but transmission of non-A non-B hepatitis by this route seems most unlikely. The manifestations of hypersensitivity favour a drug aetiology rather than non-A non-B hepatitis.<sup>16</sup> The predominance of centrilobular necrosis also favours a drug aetiology.<sup>17</sup>

Reports of hepatotoxicity with indomethacin are rare. Two deaths due to fulminant hepatitis have been published.<sup>12-13</sup> On both occasions treatment was with 100 mg per day for two and a half and seven months respectively, and treatment was in progress when the hepatitis occurred. This patient had a smaller dose of indomethacin for a much shorter period, and treatment had stopped two months before the onset of hepatitis. There were no adverse effects or signs of a hypersensitivity reaction during treatment with indomethacin. Those that did occur were unlikely to have been caused by a drug administered two months previously.<sup>17</sup>

Diclofenac is the most likely cause of hepatitis in this patient. Hepatitis including fulminant hepatitis due to diclofenac is well established.<sup>1-5</sup> It usually occurs after an average of three months' treatment and may be associated with signs of a hypersensitivity reaction. This patient had taken two months' treatment with diclofenac and hepatitis occurred while taking the drug. The signs of a hypersensitivity reaction and the temporal relationship between the onset of hepatitis and treatment with diclofenac, in the absence of convincing evidence of another cause, supports diclofenac as being the offending agent.

The mechanism of arylalkanoic derivative induced hepatitis is not clear. Dunk and Danan favour a metabolic rather than a hypersensitivity mechanism.<sup>1-10</sup> They base this on the absence of hypersensitivity signs in some patients, the initial delay in the onset of hepatitis from the start of treatment, and the late response to readministration of the drug.<sup>1-5, 18</sup> Alclofenac, another arylalkanoic derivative, has been shown to form unstable epoxides which destroy cytochrome P-450.<sup>19</sup> This mechanism may be at the basis of other arylalkanoic derivative induced hepatotoxicities, in view of the similarity of chemical structure and metabolism of these agents.<sup>20</sup>

The early onset of ascites is thought to reflect portal hypertension. This has recently been reported with ketoconazole induced hepatitis using wedge and free hepatic venous pressures.<sup>21</sup> Diffuse adenopathy associated with arylalkanoic derivative induced hepatitis has not been documented before, though cervical adenopathy has been reported on one occasion with ibuprofen.<sup>22</sup> Renal failure fre-

quently accompanies hepatitis caused by benoxaprofen and fenclofenac is now known to cause interstitial nephritis.<sup>8, 9, 23</sup> This patient, however, developed oliguria as a terminal event, and necropsy failed to show any specific findings suggestive of a drug induced nephropathy.

Review of the five published reports of diclofenac hepatitis, shows that four patients were women, and the mean age was 56.8 years (range 45-72). The mean duration of treatment was 14.2 weeks (range 3-24). Two patients had eosinophilia and one patient had a skin rash. On withdrawing the drug, three patients showed rapid correction of liver function tests, and the other two patients died from hepatic failure, one five weeks and the other five months, after starting treatment. Three authors suggest toxic metabolic mediated liver damage, and one author suggests an immunoallergic mechanism. We consider the latter to be the most likely mechanism in this patient, in view of the presence of signs of hypersensitivity, and the exceptional nature of the liver damage. The eosinophil count was at the upper limit of the normal range, and thus neither supports nor excludes this mechanism.

The recent increase in reports of hepatotoxicity induced by NSAIDs warrants attention. This is the first report in the English literature of fulminant hepatitis induced by diclofenac. Fortnightly assessment of liver function for the first six months' treatment with these new agents is advisable.

Immediately stopping treatment on finding raised liver function tests or at the onset of symptoms such as nausea, anorexia, or abdominal discomfort, is obligatory. Corticosteroid treatment was not successful in this patient and its role in diclofenac induced hepatitis has yet to be evaluated.

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