Letter to the Editors

A case of acute liver failure due to etodolac

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Etodolac is a cyclooxygenase 2 (COX-2)-specific non-steroidal anti-inflammatory agent, used predominantly in the management of musculoskeletal disease and arthritis. Dyspepsia, headache, dizziness, rash and pruritus are the commonest side effects.

Hepatic impairment is extremely rare, occurring in less than 0.3% of patients [1, 2]. Liver failure has been reported only once, in a patient with underlying alcohol related chronic liver disease and cocaine abuse, contributing to the presentation [3]. We report the first case of etodolac induced acute liver failure in the absence of confounding factors such as chronic liver disease or concomitant use of other hepatotoxic agents.

Case report

A 73-year-old female with a background of inflammatory polyarthritis was admitted to our unit with a 2 week history of worsening jaundice, malaise and non-specific abdominal pain. Etodolac 600 mg twice daily, her only medication, had been commenced 6 months prior, for the management of arthritis and was discontinued 1 week before admission on the advice of the patient's general practitioner. No additional risk factors for liver disease were identified, including excess alcohol or obesity. The patient denied any additional courses of medication within the previous year, and was not using herbal remedies or over the counter preparations. No transfusion, contact or travel history could be elicited and there was no history of previous drug reaction. Multiple records of the patient's liver function tests prior to admission revealed no abnormality.

Physical examination revealed severe jaundice in the absence of stigmata of chronic liver disease. Laboratory blood tests on admission were as follows: haemoglobin 15.6 g dl⁻¹ (normal range 11.5–16.0 g dl⁻¹), white cell count 9.0×10^9 l⁻¹ (4.0 – 11.0×10^9 l⁻¹), platelet count 236×10^9 l⁻¹ (150 – 400×10^9 l⁻¹), urea 4.5 mmol l⁻¹ (2.5 – 7.8 mol l⁻¹), creatinine 72 µmol l⁻¹ (49 – 90 µmol l⁻¹), bilirubin 525 µmol l⁻¹ (<21 µmol l⁻¹), alanine aminotransferase (ALT) 1400 IU l⁻¹

(5 – 38 IU l⁻¹), alkaline phosphatase (ALP) 274 IU l⁻¹ (25 – 140 IU l⁻¹) and prothrombin time 16.7 s (9.8 – 12.6 s). Early during admission, the patient developed grade II encephalopathy. Hepatic Doppler ultrasound and abdominal computed tomography with arterial and portal venous phase imaging were both unremarkable. Acute (IgM) serologies for hepatitis A, B, E, CMV, EBV and toxoplasma were negative. Hepatitis C and E RNA polymerase chain reactions (PCR) were also negative. Serum concentrations of immunoglobulin, α_1 -antitrypsin and caeruloplasmin were within normal range and liver auto-antibodies were negative. Percutaneous liver biopsy revealed severe acute portal and lobular hepatitis with confluent necrosis and bridging collapse without specific features, compatible with drug-induced liver injury (Figure 1). Spontaneous clinical recovery ensued, liver function returned entirely to normal within 3 months of drug cessation and has remained stable 2 years on.

Etodolac induced liver failure, defined as hepatic impairment associated with encephalopathy and coagulopathy, has been reported once [3]. The patient described had a history of alcohol excess with clinical and radiological evidence of chronic liver disease. Diagnostic limitations at the time meant that viral hepatitis was excluded only on the basis of negative serology for hepatitis A, B and C. Spontaneous improvement following discontinuation of etodolac would have been a strong indicator of drug-induced hepatotoxicity; however the patient deteriorated and died. The reporting team acknowledged that other causes could not be fully excluded and underlying chronic liver disease contributed to the outcome. The patient described here had extensive laboratory, histopathological and radiological investigations. Together with spontaneous recovery following drug withdrawal these findings strongly support a diagnosis of etodolac induced acute liver failure.

The pathogenesis of COX-2 inhibitor induced liver injury has been described for lumiracoxib, which has been subsequently withdrawn. Hepatotoxicity appears to be precipitated by a specific HLA haplotype. Lumiracoxib or its

Figure 1

Photomicrograph of the liver histology revealing severe acute portal and lobular hepatitis with confluent necrosis and bridging collapse, without specific features (haematoxylin and eosin $\times 10$)

metabolites interact with HLA complexes to trigger an immune response. Hepatocellular damage typically manifests 100–200 days following initiation of the drug [4, 5]. The mechanism of etodolac induced hepatotoxicity remains unclear. Etodolac is a weak inhibitor of the cytochrome P450 system, targeting CYP2C9 [6]. However, extensive hepatocellular damage resulting in acute liver failure is not theoretically likely on the basis of this interaction. Liver injury develops as a delayed event, 180 days and 120 days post initiation of therapy in the case described here and by Mabee *et al.*, respectively. The timing of presentation and the absence of rash or eosinophilia mean a hypersensitivity reaction is unlikely [4]. A similar pathogenetic mechanism to lumiracoxib may therefore exist.

We conclude that acute liver failure is a rare but potentially life-threatening complication of etodolac. Presentation may be delayed, in this case developing 6 months after the onset of treatment. We propose regular monitoring of liver function in all patients receiving etodolac, within 1 month after initiation of the drug and continuing at extending intervals over a year, to facilitate early identification of adverse hepatic effects.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (avail-

able on request from the corresponding author) and declare no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

REFERENCES

- Schattenkirchner M. An updated safety profile of etodolac in several thousand patients. *Eur J Rheumatol Inflamm* 1990; 10: 56–65. PMID: 2146132.
- Latrive JP, Combaux D, Crépin P, Barbare JC. Acute hepatitis associated with etodolac therapy. *Thérapie* 1992; 47: 82–3. PMID: 1387992.
- Mabee CL, Mabee SW, Baker PB, Kirkpatrick RB, Levine EJ. Fulminant hepatic failure associated with etodolac use. *Am J Gastroenterol* 1995; 90: 659–61. PMID: 7717333.
- Tujios S, Fontana RJ. Mechanisms of drug-induced liver injury: from bedside to bench. *Nat Rev Gastroenterol Hepatol* 2011; 8: 202–11. PMID: 21386809.
- Singer JB, Lewitzky S, Leroy E, Yang F, Zhao X, Klickstein L, Wright TM, Meyer J, Paulding CA. A genome-wide study identifies HLA alleles associated with lumiracoxib-related liver injury. *Nat Genet* 2010; 42: 711–4. PMID: 20639878.
- Nakamura A, Tougo K, Kitazumi H, Yamada T, Honjou K, Zinno A, Nonaka K, Mukai H. Effects of etodolac on P450 isoform-specific activities in human hepatic microsomes. *Arzneimittelforschung* 2005; 55: 744–8. PMID: 16430028.

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