Prolonged cholestasis associated with short-term use of celecoxib

SUMMARY
Drug-induced liver injury due to celecoxib, a first generation Cox-2 inhibitor, has been rarely reported. We describe one case of severe and prolonged cholestasis after treatment with celecoxib for 12 days in a young woman with no evidence of other causes of liver disease or allergy. Jaundice lasted for 3 months, pruritus and abnormal liver biochemistries persisted for 18 months after stopping the drug. Liver biopsy specimens showed a cholestatic pattern of liver injury with only minimal mononuclear infiltrate in the portal tracts. This case report supports the notion that celecoxib may cause bland, long term cholestasis.

Case report
A 32 year-old woman presented with complaints of yellow skin discoloration, dark urine, acholic stools and severe and diffuse pruritus of approximately 2 weeks duration. Twenty four days before the onset of jaundice she had received celecoxib (Celebrex®) 200 mg per day for 12 days for pain following an operation for hallux valgus performed under local anaesthesia. There were no other medical problems in the patient's history. One year earlier, she had not developed cholestasis of aspartate aminotransferase was 83 U/L (normal < 35), alanine aminotransferase was 69 U/L (normal < 43), alkaline phosphatase was 613 U/L (normal < 111), γ-glutamyltransferase was 16 U/L (normal 4-37) and total serum bilirubin was 337 µmol/L (normal 6-17) (conjugated bilirubin 259 µmol/L (normal 1-6)). Serum creatinine was normal. Evaluation for viral, autoimmune hepatitis and metabolic liver diseases were negative. Abdominal ultrasound and computerized tomography showed normal pancreas, biliary tract and liver except for the presence of a small hepatic angioma of 8 mm. Magnetic resonance cholangiopancreatography showed no evidence of intra- or extra-hepatic bile duct dilatation, filling defects or primary sclerosing cholangitis. Twenty three days after the onset of jaundice, a liver biopsy was performed revealing marked canalicular and hepatocellular cholestasis with the formation of numerous bile plugs without bile duct injury and hyperplasia. Minimal mononuclear infiltrate in some of the portal triads was present (figure 1). Jaundice disappeared after 3 months, but pruritus persisted for 18 months. Evaluation of serum bilirubin and alkaline phosphatase are shown in figure 2. A second liver biopsy performed 12 months after discontinuation of the drug showed marked improvement of hepatocellular and canalicular cholestasis and the presence of a few paucicellular hepatoocyte necrosis foci associated with mild mononuclear infiltration and slight fibrosis of the portal tracts (figure 1).

Discussion
We describe a case of severe celecoxib-induced cholestatic liver injury. Several lines of evidence strongly suggest that celecoxib was responsible for this cholestatic liver injury. First our patient developed severe icteric cholestasis 24 days after starting celecoxib. Second, there was no evidence of viral, autoimmune hepatitis, metabolic liver diseases, biliary lithiasis, sclerosing cholangitis or any history of familial cholestasis. Third, histology was consistent with drug-induced liver injury; and the involvement of paracetamol is unlikely due to the ingested dose, the duration of treatment and the type of hepatitis. Finally, spontaneous improvement of cholestasis occurred slowly after stopping the drug. To our knowledge six cases of celecoxib induced acute
Celecoxib induced cholestasis have been reported [2-7] (table I). Frank cholestasis was present in four of them [3, 4, 6, 7]. Our case was characterized by a very prolonged evolution which was sometimes noted in previous reports of drug-induced cholestasis [8-10]. A previous allergy to sulfamoiety was mentioned in two cases [2, 3]. A liver biopsy was performed in 3 cases and in all of them the hepatic lesion consisted of hepatocellular cholestasis associated with a mild mononuclear infiltrate, sometimes including eosinophils in the portal tracts. In our case, low serum γ-glutamyltransferase activity was consistent with the lack of bile duct injury. A low level of γ-glutamyltransferase has been described in other cases of drug induced-cholestasis, in particular those caused by natural and synthetic estrogens [9].

Drugs can impair the formation of bile by interfering with any or all of the various hepatocellular and biliary mechanisms and structures involved in this process. At least three distinct forms of cholestatic liver injury are recognized, namely noninflammatory (bland) cholestasis, inflammatory cholestasis and ductopenic cholestasis. In the two latter forms inflammation is conspicuous and accompanied by bile duct inflammation and...
destruction [10, 11]. In the former, the lesion displays a bland accumulation of bile in cells and canaliculi. Histologic features of inflammation and necrosis are minor or absent. This pattern characterizes cholestasis caused by sex hormones [9]. This reported case as well as one well documented case [7] in the literature are typical of bland cholestatic injury.

In conclusion we have described a case of severe and prolonged cholestasis following 12 days of celecoxib administration which confirms the notion that this drug may be responsible for cholestatic liver injury.

REFERENCES