NIMESULIDE INDUCED CHOLESTATIC HEPATITIS

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INTRODUCTION
Non-steroidal anti-inflammatory drugs (NSAIDs) and antimicrobials are the most frequent cause of drug induced liver injury.1 Like other NSAIDs, nimesulide, a unique molecule of the sulphonanilides class, has been associated with rare and unpredictable serious hepatic adverse reactions.2,3 However validity of this association had been questioned by some authors.4 Here, we are reporting a case of nimesulide induced–cholestatic hepatitis.

CASE PRESENTATION
A 44 year old female patient, a known case of rheumatoid arthritis, came to the hospital with complaints of swelling of lower limbs since 2 months, abdominal pain and distension, weakness of lower limb. On examination, she had hepatomegaly. Liver functions were deranged. Further evaluation of patient by liver biopsy revealed cholestasis with steatohepatitis and periportal fibrosis. Patient was diagnosed as a case of drug induced cholestatic hepatitis. Nimesulide was stopped and dose of prednisolone was reduced. After eight days, liver functions were still deranged. It was only after fourteen days that patient’s general condition improved and liver functions started to come back to normal. Patient was discharged and advised to attend follow up clinic after one week.

ABSTRACT:
Forty four year old female was prescribed nimesulide and prednisolone for rheumatoid arthritis. After three months of taking these drugs, she came to the hospital with complaints of yellowish discoloration of sclera, abdominal pain, distension and weakness of lower limb. On examination, she had hepatomegaly. Liver functions were deranged. Further evaluation of patient by liver biopsy revealed cholestasis with steatohepatitis and periportal fibrosis. Patient was diagnosed as a case of drug induced cholestatic hepatitis. Nimesulide was stopped and dose of prednisolone was reduced. After fourteen days, liver functions were still deranged. It was only after fourteen days that patient’s general condition improved and liver functions started to come back to normal. Patient was discharged and advised to attend follow up clinic after one week.

KEYWORDS:
Nimesulide, rheumatoid arthritis, cholestatic hepatitis
Transaminase(ALT) = 33 IU/L, Alkaline phosphatase(ALP) = 390 IU/L with associated reversal of Albumin : Globulin(A:G) ratio. Blood tests for HBsAg, Hepatitis C were negative. Ultrasound abdomen showed hepatomegaly with fatty infiltrates and CT scan abdomen reported the presence of omental infarcts. Upper GI endoscopy confirmed the absence of any varices. Doppler scan of hepatic vein showed absence of portal or hepatic vein thrombosis and thereby ruling out the diagnosis of a Budd Chiari syndrome. For further evaluation, an ultrasound guided liver biopsy was done which showed effacement of liver architecture by extensive macrovesicular steatosis with intrahepatic cholestasis and thereby confirming the diagnosis as cholestatic hepatitis. The biopsy sample was sent for pathology review and was reported as cholestasis with steatohepatitis (Figure 2) associated with periportal fibrosis (Figure 1, 3) with absence of any bridging fibrosis or plasma cell infiltrates. Patient was diagnosed as a case of drug induced steatohepatitis with cholestasis. Tab Nimesulide was stopped on admission and Tab prednisolone was reduced to 10mg once daily. During her stay in the hospital the LFT values on the 8th day were still deranged as follows: T.Bilirubin = 8.0 mg/dL, Direct Bilirubin = 6.8 mg/dL, Aspartate transaminase(AST) = 327 IU/L, Alanine Transaminase(ALT) = 92 IU/L, Alkaline phosphatase(ALP) = 334 IU/L. On 14th day of admission as the patient started to feel symptomatically better and with the LFT values started coming to normal T.Bilirubin =6.7 mg/dL, Direct Bilirubin = 5.6 mg/dL, Aspartate transaminase(AST) = 184 IU/L, Alanine Transaminase(ALT) = 76 IU/L, Alkaline phosphatase(ALP) = 404 IU/L, the patient was discharged and was asked to visit the hospital after a week for follow up.

Fig-1: Section shows mild fibrosis of the portal tract with infiltration by chronic inflammatory infiltrate and few neutrophils
DISCUSSION

Nimesulide has not been approved for use in countries like USA, UK, Canada, Australia and New Zealand in view of concerns over its safety profile. In Southeast Asia, the drug enjoys variable regulatory status. It continues to be freely available and prescribed in India (and some European countries) with almost 70 brands in the market. Ministry of health and family welfare issued a notification and banned nimesulide use in children below 12 years vide notification No 71 dated 10th February 2011.

The incidence of nimesulide induced liver injury is low (0.1 per 100,000 patients treated). The severity of hepatotoxicity associated with nimesulide is variable and varies from hepatocellular necrosis, cholestatic hepatitis and pure cholestasis. The onset of symptoms varies between one and 15 weeks after ingestion, although a delay of up to eight months has been reported in one case report. In this case the symptoms started after two months of nimesulide.

Causality assessment using Naranjo’s scale gave a score of 7, indicating the adverse drug reaction to be probable Nimesulide induced cholestatic hepatitis.

Experimental evidence suggests that molecular mechanism of toxicity includes increased concentration of the drugs in the hepatobiliary compartment. It produces reactive intermediates that have been implicated in oxidative stress, covalent binding and mitochondrial injury. Individual variation in drug metabolism has been implicated to genetic predisposition. Elderly people are more susceptible to hepatotoxicity. Both immunological and idiosyncratic metabolic mechanisms are implicated and most likely some reactions involve interaction between reactive metabolites and an immunological response as part of
the reactive metabolite syndrome. In cholestatic liver injury normalization of alkaline phosphatase takes more time than transaminases. In the present case report, on fourteenth day as the transaminases were coming down, alkaline phosphatase was still high.

A large cohort was analyzed in Italy who were prescribed NSAIDs and observed for subsequent admission to hospital for acute non-viral hepatitis. However, authors found risk of severe liver injury was low with nimesulide than other NSAIDs. Although the rate of occurrence of minor hepatic adverse effects with nimesulide is similar to that of other NSAIDs, a significantly higher rate of serious hepatic adverse effects have been reported to the World Health Organization.

To conclude, as with other NSAIDs caution against prolonged use of Nimesulide is important. Though the severe hepatotoxicity with nimesulide is low, the history about nimesulide intake should be taken routinely especially in cases of acute liver damage.

REFERENCES:


