Hepatitis and non-steroidal anti-inflammatory drugs

Hepatotoxicity is an uncommon but sometimes serious side effect of treatment with non-steroidal anti-inflammatory drugs (NSAIDs). Virtually all NSAIDs have been reported to cause liver damage on occasion and cross reactivity between the propionic acids, naproxen and fenoprofen, has been reported. The true incidence of NSAID induced hepatitis is unknown because this information is derived mainly from the reporting of adverse drug reactions. Mild reactions may not come to clinical attention and the association of an adverse reaction with any particular drug may be difficult to prove. Single case reports draw attention to particular and peculiar side effects and assume importance when the incidence of the noted side effect is low. Although most NSAID induced hepatitis is reversible when the drug is stopped, benoxaprofen was withdrawn from the market because of a high incidence of adverse reactions, including hepatotoxicity, with deaths in elderly patients.

Salicylates in regular high dosage (greater than 50 mg/kg daily) cause a mild, reversible, dose dependent hepatitis, becoming evident within four weeks of starting treatment. Most patients affected are young women with connective tissue disease such as rheumatoid arthritis, Still's disease, acute rheumatic fever, systemic lupus erythematosus, and dermatomyositis. In a combined series of 500 patients with acute inflammatory arthritis receiving salicylates nearly 50% had evidence of hepatitis shown by increased aminotransferase activity. Although it is widely considered that patients with connective tissue diseases have an increased susceptibility to the hepatotoxic effects of salicylates, hepatitis has been reported with an equal incidence in healthy subjects taking 3-6 g of aspirin daily for 12 days. Reye's syndrome, characterised by impaired liver function, hypoglycaemia, acidosis, and encephalopathy, occurs almost exclusively in children and young adults, usually associated with a viral-type illness. The role of salicylates has been debated, but they may be implicated as a factor leading to the syndrome. Moderate increase of plasma aminotransferase activity is common, but jaundice is characteristically absent or minimal.

According to case reports virtually all the newer, non-salicylate NSAIDs may cause hepatotoxicity. Clinically significant episodes of hepatitis are rare but they may be fatal. All classes of NSAIDs have been incriminated and although cross reactivity has been reported, this is not predictable and may not occur on further exposure to another NSAID of the same chemical class as the initial offending drug. The true incidence of NSAID induced hepatitis is unknown. One large retrospective cooperative study reports 56 patients with NSAID induced liver injury occurring over a 12 month period, but the total number of patients exposed to NSAIDs was not recorded. Cases were classified according to the ratio of aminotransferase to alkaline phosphatase activities into acute cytolitic hepatitis (24 cases), acute cholestatic hepatitis (nine cases), and mixed pattern (15 cases). Asymptomatic rises in aminotransferase and alkaline phosphatase activities were noted in an additional four cases each.

Liver biopsy has shown variable histological changes, ranging from mild toxic hepatitis to cholestasis. My review of case reports suggests that acute reactions occurring early in treatment are more likely to be associated with fever, rash, malaise, and upper abdominal pain. Hepatocellular enzymes are increased and histology indicates portal and periportal infiltration with mononuclear cells and occasionally eosinophils. Hepatic necrosis is noted, but cholestasis may also be present. The latter is not normally a prominent feature of salicylate induced hepatitis. The more gradual, delayed onset of anorexia, pruritis, and jaundice is more compatible with a cholestatic hepatitis, sometimes associated with chancrular bile plugs. The mechanisms of NSAID induced hepatotoxicity remain poorly understood. Perhaps surprisingly there seems to be no evidence incriminating inhibition of prostaglandin synthesis. Dose dependent toxicity is recognised with salicylates and may occur with sulindac. The overall rarity of clinically significant hepatitis, together with the associated sudden onset of fever and an eosinophilic component to the hepatic infiltrate, has led to the suggestion of a hypersensitivity reaction rather than a direct hepatotoxic effect. The production of reactive intermediate metabolites, as might have been the case with benoxaprofen, may also be a mechanism that initiates a toxic response in the liver. It has been suggested that sulindac toxicity also may involve such metabolites. It should be remembered that NSAIDs are not the only potential cause of hepatitis in patients with rheumatic diseases. For example, intermittent illness with the hepatic viruses and concomitant treatment, particularly with methotrexate and sulphasalazine, may cause liver enzyme abnormalities. D-Propoxyphene alone, or in combination with aspirin or paracetamol, has been reported to cause cholestatic jaundice. Increase of serum alkaline phosphatase of hepatic origin is a common feature of inflammation itself and concentrations are not influenced by NSAIDs. Not all enzyme rises are hepatic in origin and bony alkaline phosphatase may be raised owing to bone disease—for
example, Paget’s disease or a healing fracture. Fractionation or isoenzyme analysis indicates the bony or hepatic origin
of the alkaline phosphatase. It has been noted that hepatic
alkaline phosphatase is raised, sometimes markedly so, in
patients with constrictive pericarditis.10
Overall, the outcome of NSAID induced hepatitis is
excellent with clinical, biochemical, and histological features
reverting rapidly and completely to normal after withdrawal
of the offending drug. Salicylate elimination can be increased
by haemodialysis or haemoperfusion. Occasional fatalities
have occurred, however, and rechallenge is contraindicated.
After NSAID induced hepatotoxicity it is preferable to
substitute an NSAID of a different class if possible.

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