

## Review

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# Hepatocellular damage from non-steroidal anti-inflammatory drugs

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## Summary

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the management of rheumatological disorders, and as analgesics and antipyretics. Hepatotoxicity is an uncommon, but potentially lethal complication, which usually occurs within 12 weeks of starting therapy. It can occur with all NSAIDs, but appears to be more common with diclofenac and particularly sulindac. Female patients aged >50 years, with autoimmune disease, and those on other potentially hepatotoxic drugs, appear to be particularly susceptible. Liver function test abnormalities generally settle within 4–6 weeks of stopping the causative drug. However, some patients may develop acute liver failure and successful orthotopic liver transplantation may be undertaken in such patients. Recent *in vitro* animal

studies have shown that the mechanism of diclofenac toxicity relates both to impairment of ATP synthesis by mitochondria, and to production of active metabolites, particularly n,5-dihydroxydiclofenac, which causes direct cytotoxicity. Mitochondrial permeability transition (MPT) has also been shown to be important in diclofenac-induced liver injury, resulting in generation of reactive oxygen species, mitochondrial swelling and oxidation of NADP and protein thiols. Physicians and hepatologists must be vigilant to the hepatotoxic potential of any NSAID, as increased awareness, surveillance and reporting of these events will lead to a better understanding of the risk factors and the pathophysiology of NSAID-related hepatotoxicity.

## Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are the centrepiece of pharmacotherapy for most rheumatological disorders, and are used in large numbers as analgesics and antipyretics, both as prescription drugs and over the counter purchases. The epidemiological risk of clinically apparent liver injury is low (1–8 cases per 100 000 patient years of NSAID use), but when it occurs, it can be serious and can cause diagnostic confusion.<sup>1–4</sup> However, use of ibuprofen rose rapidly between 1998 and 2000,<sup>5</sup> and as Neurofen was the number one branded medication sold over the counter in the

UK by value in 2002 (personal communication Information Resources, www.infores.com), annual exposure of the population to NSAIDs is enormous.

A systematic literature search was performed using Medline, Embase and Toxline for all relevant articles published in French or English between 1966 to date. The search strategy consisted of (Intoxication OR Poisoning OR Overdose OR Adverse Drug Reaction) AND (exp NSAID) AND (exp Hepatotoxicity).

Few trials use uniform diagnostic criteria for hepatotoxicity, and the incidence rate of adverse

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liver events is greatly dependent on such criteria, confounding attempts to compare data on the incidence of hepatotoxicity between trials on different NSAIDs. Clinical trials that use routine monitoring of liver function have the highest likelihood of ascertainment of any liver function abnormalities, but the usefulness of these studies is often limited by small numbers of patients and limited exposure times, as hepatotoxicity may be asymptomatic.<sup>6</sup> Nearly all of the NSAIDs have been implicated in causing liver injury, and tend to be hepatocellular in nature: the mechanism is thought to be immunological idiosyncrasy.<sup>7,8</sup> Diclofenac, and particularly sulindac, are reported to be more commonly associated with hepatotoxicity.<sup>3,9</sup> In one study, sulindac use was associated with a 5–10 fold higher incidence of hepatic injury than other NSAIDs.<sup>3</sup>

Although reports of serious liver toxicity with ibuprofen are rare, subacute hepatic failure requiring orthotopic liver transplantation has been reported in a 59-year-old female taking ibuprofen 600 mg tds.<sup>10</sup> Riley<sup>11</sup> reported a case series of three hepatitis C patients who developed a greater than five-fold increase in liver transaminases following ingestion of therapeutic doses of ibuprofen. One of these patients had a mirror rise in transaminases following a subsequent two-day re-exposure to the drug. Several NSAIDs have been withdrawn from clinical use because of associated hepatotoxicity.<sup>12–14</sup> The new more selective COX-2 inhibitors (e.g. celecoxib, rofecoxib, nimesulide) are also associated with hepatotoxicity,<sup>15–18</sup> although celecoxib is said to have less potential for hepatotoxicity.<sup>19</sup>

## Clinical features of hepatotoxicity due to NSAIDs

Hepatotoxicity from NSAIDs can occur at any time after drug administration, but like most adverse drug reactions, most commonly occurs within 6–12 weeks of initiation of therapy.<sup>20</sup> In one series of 180 patients with diclofenac related hepatotoxicity, 33% were detected as a result of routine laboratory analyses and 67% were detected by symptoms (of these 67% were jaundiced); 79% were female and 71% were over 60 years of age. Hepatic injury was apparent by 1 month after starting the drug in 24%, by 3 months in 63%, and by 6 months in 85% of cases.<sup>21</sup> Acute liver failure occurs in a tiny proportion of individuals exposed and is often not recognized as a possible adverse event until the post-marketing stage.<sup>14,16,22,23</sup>

There are two main clinical patterns of hepatotoxicity due to NSAIDs.<sup>8,20</sup> The first is an acute hepatitis with jaundice, fever, nausea, greatly elevated transaminases and sometimes eosinophilia. The alternative pattern is with serological (ANF-positive) and histological (periportal inflammation with plasma and lymphocyte infiltration and fibrosis extending into the lobule) features of chronic active hepatitis. In one series of 44 patients with drug-induced hepatotoxicity, three (7%) presented with hepatic failure, 24 (54%) presented with jaundice, and 17 (39%) were asymptomatic and were picked up because of abnormal liver function tests performed as part of routine investigations.<sup>20</sup> At follow-up at a median of 5 years later, eight had persistently abnormal liver function tests,<sup>20</sup> although in another series (as in our clinical experience) liver function test abnormalities generally resolved within 4–8 weeks of discontinuing the causative drug.<sup>24</sup> One of the patients in this latter series died from acute liver failure, and there are many other isolated case reports of NSAID-related acute liver failure leading to liver transplantation or death.<sup>23,25,26</sup>

## Mechanism of hepatotoxicity of NSAIDs

Two main mechanisms are responsible for injury: hypersensitivity and metabolic aberration. Reported risk factors for NSAID-induced idiosyncratic hepatotoxicity include female sex, age >50 years and underlying autoimmune disease.<sup>1,4</sup> However, whether these are true risk factors or merely represent the population taking NSAIDs, remains to be established. In one retrospective cohort study, NSAID users with rheumatoid arthritis had a ten-fold increased risk of NSAID-related hepatotoxicity when compared with NSAID-users with osteoarthritis.<sup>1</sup> Another risk factor is concomitant exposure to other hepatotoxic drugs.<sup>27</sup> Patients who have experienced hepatotoxicity to one NSAID, often have the same reaction if the drug is restarted or a sister drug is given, particularly if the sister drug is structurally similar, e.g. diclofenac and tiaprofenic acid. Hypersensitivity reactions often have significant anti-nuclear factor or anti-smooth muscle antibody titres, lymphadenopathy and eosinophilia. Rechallenge with the drug results in a repeat increase in anti-nuclear factor titres. A recent rechallenge from an error caused by generic and non-generic prescribing of diclofenac resulted in a liver transplantation for one patient.<sup>26</sup>

Metabolic aberrations can occur as genetic polymorphisms and alter susceptibility to a wide range of drugs. It may account for the incidence

ratio of 1–8 per 100 000 prescriptions of NSAIDs. *In vitro* metabolism of aceclofenac reflects phenotypic variability amongst donor liver cells.<sup>28</sup>

Recently, a number of *in vitro* animal models have been used to investigate the possible mechanisms of NSAID-related hepatotoxicity. Studies using rat liver mitochondria and freshly isolated rat hepatocytes showed that diphenylamine, which is common in the structure of NSAIDs, uncouples oxidative phosphorylation, decreases hepatic ATP content and induces hepatocyte injury.<sup>29,30</sup> Incubation of mitochondria with diphenylamine, mefenamic acid or diclofenac caused mitochondrial swelling. In addition, a spectral shift of the safranin-binding spectra to mitochondria occurred, indicating the loss of mitochondrial membrane potentials (one of the characteristics of uncoupling of oxidative phosphorylation). Addition of oligomycin, which blocks ATPase, protected against cell injury.<sup>29</sup> In diclofenac-induced toxicity in hepatocytes, no significant oxidative stress (decrease in glutathione and lipid peroxidation) or increase in intracellular calcium concentration was seen.<sup>30</sup>

Other studies have shown that ferrous iron release from rat liver microsomes contributes to naproxen-induced microsomal lipid peroxidation.<sup>31</sup> Furthermore, diclofenac is more cytotoxic to drug-metabolizing cells than to non-metabolizing cell lines (HepG2, FaO).<sup>30</sup> Toxicity thus relates both to impairment of ATP synthesis by mitochondria and to drug metabolism, and is reduced by the addition of cytochrome P450 inhibitors (prothiaden and ketoconazole) to culture medium.<sup>30</sup> The *in vitro* cytotoxicity correlated well with the formation of 5-hydroxydiclofenac and particularly the *n*,5-dihydroxydiclofenac metabolite—the latter in particular can inhibit ATP synthesis.<sup>30</sup> Mitochondrial permeability transition (MPT) has also been shown to be important in diclofenac-induced liver injury, resulting in generation of reactive oxygen species, mitochondrial swelling and oxidation of NADP and protein thiols.<sup>32</sup>

## Implications for clinical practice

NSAID-induced hepatotoxicity must be considered in the differential diagnosis of all patients presenting with a spectrum of disease, ranging from isolated deranged liver function tests in an otherwise well patient, to fulminant hepatic failure. Because of the availability of these drugs over the counter, many patients will not disclose their use of these agents to their doctor as they do not perceive them to be 'prescribed' medication. The quoted incidence of NSAID-induced hepatotoxicity is likely to represent

significant under-reporting of the condition, as many cases are subclinical and are never detected, or are detected fortuitously as part of a routine biochemical work-up and may not be correctly ascribed to their true aetiology.

In the investigation of apparent NSAID-induced hepatotoxicity, it is critical to consider viral causes (hepatitis A, B, C, HIV, CMV) and other liver diseases (autoimmune chronic active hepatitis, haemochromatosis, primary biliary cirrhosis, Wilson's disease).<sup>33</sup> Successful orthotopic liver transplantation may be undertaken in patients with acute<sup>23,25</sup> or subacute<sup>10</sup> liver failure due to NSAIDs.

Patients who develop NSAID-induced hepatotoxicity must be advised to stop taking NSAIDs permanently. Paracetamol remains the analgesic drug of choice for these patients, even if they are jaundiced.<sup>34,35</sup> They may also safely use aspirin in the future. This is because the toxicity of NSAIDs relates to their diphenylamine ring molecular structure, which aspirin does not have.<sup>13</sup> This is an important finding, given the widespread use of aspirin as an anti-platelet agent in cardiovascular and cerebrovascular disease. Aspirin-related hepatotoxicity has been reported, but this is a dose-related phenomenon related to intrinsic salicylate hepatotoxicity, and generally only occurs when aspirin is used in full anti-inflammatory doses (i.e. not the 75–300 mg used in anti-platelet indications) and there is no evidence that this is more common in patients who have had an episode of NSAID-related hepatotoxicity.<sup>34,36,37</sup>

There are no published data to suggest that patients who have developed NSAID-induced hepatotoxicity exhibit cross-reactivity to any other group of drugs, although drugs which can be hepatotoxic in therapeutic doses should be avoided in these patients. The role of steroids in the management of NSAID-induced hepatotoxicity remains to be clarified. Empirically, there may be a place for the judicious use of steroids in patients who are ANF-positive and in whom a viral aetiology has been excluded. However, to date there are no published studies addressing this issue.

## Conclusions

Recent *in vitro* animal studies have gone some way towards demonstrating the mechanisms of NSAID induced hepatotoxicity but further work is required to fully understand the pathogenesis. Currently there are no markers to identify those at risk of NSAID-induced hepatotoxicity, nor to identify those likely to develop hepatic failure as opposed to deranged liver function tests. While hepatotoxicity related

to NSAIDs is an uncommon adverse effect, it is important to be vigilant to the hepatotoxic potential of any NSAID, as increased awareness, surveillance and reporting of these events will lead to a better understanding of the risk factors and the pathophysiology of NSAID-related hepatotoxicity. Idiosyncratic reactions due to hypersensitivity or metabolic aberration are responsible for toxicity in the vast majority of cases and at-risk groups for idiosyncratic hepatotoxicity have been identified. Although hepatotoxicity is listed as a class warning for NSAIDs, diclofenac and sulindac seem most commonly associated with the problem.

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