Current Hepatology Reports (2019) 18:294–299
https://doi.org/10.1007/s11901-019-00477-x

DRUG-INDUCED LIVER INJURY (P HAYASHI, SECTION EDITOR)

Drug-Induced Liver Injury Due to Nonsteroidal Anti-inflammatory Drugs

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Published online: 2 August 2019
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Abstract

Purpose of Review Nonsteroidal anti-inflammatory drugs (NSAIDs) are a heterogeneous group of medications intended to treat a variety of inflammatory diseases. While they are generally regarded as safe and most known for their potential gastrointestinal and renal side effects, cases of hepatotoxicity have been reported. This review summarizes the US and international literature regarding the incidence of NSAID-induced DILI and the biochemical signature of specific NSAIDs.

Recent Findings Multiple studies have identified diclofenac as one of the more common culprits of NSAID-induced DILI. A genetic predisposition to DILI has been identified with diclofenac and lumiracoxib.

Summary While NSAID-induced hepatotoxicity is rare, the potential for serious hepatotoxicity exists especially with certain agents such as diclofenac. An improved understanding of pharmacogenomics and post-marketing surveillance/monitoring is needed to reduce the risk of this DILI.

Keywords Nonsteroidal anti-inflammatory drugs · Drug-induced liver injury · Hepatotoxicity · Idiosyncratic

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are analgesics that are commonly taken over-the-counter or as prescriptions to treat a variety of inflammatory diseases. Their mechanism of action involves inhibition of the cyclooxygenase (COX) enzyme leading to decreased synthesis of pro-inflammatory prostaglandins. It is estimated that in 2010, 29 million adults in the USA were regular users of NSAIDs, an overall increase of 41% compared to 2005 [1]. While their most notable adverse effects include gastrointestinal bleeding and renal dysfunction, serious hepatotoxicity has led to the withdrawal of several NSAIDs (bromfenac, ibufenac, benoxaprofen, and lumiracoxib) from the market.

Population-based studies have shown that NSAIDs as a group are common culprits in causing idiosyncratic drug-induced liver injury (DILI). A 2002 French study found that NSAIDs ranked as the fourth leading cause of DILI (10% of cases) behind anti-infectious (25%), psychotropic (22.5%), and hypolipidemic (12.5%) medications [2]. A more recent population–based cohort from Iceland tracked prescription medication use via nationwide pharmaceutical databases. The study showed that the most implicated drug was amoxicillin-clavulanate (22%) followed by the NSAID diclofenac (6%). The incidence of DILI from diclofenac was calculated at 1 per 9480 users [3].

In the USA, the Drug-Induced Liver Injury Network (DILIN) was established in 2003 to prospectively collect data on idiosyncratic DILI cases. DILI was defined by the following biochemical criteria: (1) aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level > 5 times the upper limit of normal (ULN) or alkaline phosphatase > 2 times the ULN (or pretreatment baseline if the baseline level is abnormal) on 2 consecutive occasions, (2) total serum bilirubin level > 2.5 mg/dL along with elevated AST or ALT or alkaline phosphatase, or (3) international normalized ratio (INR) > 1.5 with elevated AST or ALT or alkaline phosphatase. A study reporting on the first 300 cases implicated more than 100 different medications, herbal supplements, and dietary supplements. The most common drug categories included the following: antimicrobials (45.5%), central nervous system agents (15%), immunomodulatory agents (5.5%), and NSAIDs/

This article is part of the Topical Collection on *Drug Induced Liver Injury*

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muscle relaxants (5%) [4]. A more recent DILIN study looked specifically at 30 NSAID DILI cases among 1221 total DILI cases that were adjudicated between 2004 and 2014. Hepatocellular injury was the most common injury pattern and diclofenac was the most frequently implicated NSAID (16/30 cases) [5].

This review article will cover what we know about NSAID liver injury including its clinical presentation, biochemical signature, prognosis, and genetic markers that might predict the risk of hepatotoxicity.

NSAID Classification

NSAIDs are a heterogeneous group of drugs that can be divided into classes based on their chemical structure. This may in part account for the variability in the risk of hepatotoxicity and clinical phenotype. The major families include acetic acid derivatives, enolic acid derivatives, propionic acid derivatives, salicylates, selective COX-2 inhibitors, and sulfonanilides. This review will highlight the more commonly used or noteworthy drugs in these classes (see Table 1).

Acetic Acid Derivatives

Diclofenac and sulindac are members of this family. Diclofenac deserves special attention given its longstanding association with hepatotoxicity. In 2005, Rostom et al. published a systematic review of 65 randomized controlled trials of diclofenac, naproxen, ibuprofen, celecoxib, rofecoxib, valdecoxib, and meloxicam in adults with osteoarthritis or rheumatoid arthritis. Hepatotoxicity was defined as aminotransferase elevations > 3× ULN. Diclofenac had higher rates of aminotransferase elevations > 3× ULN (3.55%) than placebo or the other studied NSAIDs. However, there were no increased rates of serious hepatotoxicity, hospitalizations, or death [6]. A large prospective study by Laine et al. further examined the rate of laboratory and adverse hepatic effects of diclofenac. Patients with rheumatoid or osteoarthritis were randomly assigned to receive either diclofenac 150 mg daily or etoricoxib (60 or 90 mg daily). A total of 17,289 patients received diclofenac for a mean of 18 months. Similar to the outcome from Rostom's study, 3.1% of the diclofenac patients had ALT/AST values > 3× ULN. This was generally detected during the first 4–6 months of therapy. Clinical liver events requiring hospitalization were rare (4 cases, 0.023%). There were 2 cases (0.012%) that met Hy's law (hepatocellular jaundice). There were no reported cases of liver failure, liver transplant, or death [7].

The DILIN NSAID study helped characterize the biochemical signature of diclofenac. All 16 reported cases were hepatocellular with marked aminotransferase elevations (mean initial ALT 1508 ± 1171 U/L). There was a variable latency period ranging from 6 to 191 days. Four patients had immunoallergic features (i.e., fever, rash, facial edema, eosinophilia) and 6 patients had autoimmune features. Eight patients had severe hepatotoxicity as defined by coagulopathy (INR $\geq$ 1.5) and jaundice. Despite these concerning labs, only 1 patient died and the cause of death was attributed to septicemia and Stevens-Johnson syndrome rather than hepatic failure [5].

While much of the literature has focused on oral diclofenac toxicity, there is a recent case report describing DILI attributed to topical diclofenac. Topical NSAIDs have been used for the treatment of osteoarthritis and are thought to have negligible systemic side effects. The reported case occurred in a 79-year-old female who took diclofenac gel (1%) for bilateral knee osteoarthritis. This was started 10 months prior to documented aminotransferase elevations (peak AST 104, ALT 118 U/L). Her aminotransferases normalized within a month after diclofenac was discontinued [8].

The exact mechanism behind diclofenac hepatotoxicity is unclear. There have been no associations with HLA alleles. It is theorized that bioactivation of protein-reactive metabolites may play a role. A 2004 study demonstrated antibodies to diclofenac metabolite–modified liver protein adducts in the sera of all 7 patients with diclofenac-induced liver injury and 12/20 subjects on diclofenac without hepatotoxicity [9]. Metabolism of diclofenac is dependent on the enzyme UGT2B7 that catalyzes the formation of diclofenac acyl glucuronide (DCF-AG). Haptenization of proteins by the reactive DCF-AG can then lead to antibody formation. Prior studies have shown an association between the UGT2B7*2 allele and

Table 1 NSAID class and features of DILI

Class	Representative drug	Pattern of injury	Latency	Notable features
Acetic acids	Diclofenac	Hepatocellular	Variable	Can have autoimmune features
Enolic acids	Meloxicam	Hepatocellular/cholestatic	1–5 weeks	
Propionic acids	Ibuprofen	Mixed/cholestatic	3 days–3 weeks	Some cases of vanishing bile duct syndrome
Salicylates	Aspirin	Hepatocellular	Dose-dependent toxicity	Reye syndrome in children
COX-2 inhibitors	Celecoxib	Hepatocellular/cholestatic	Short	Lumiracoxib removed from market
Sulfonanilides	Nimesulide	Hepatocellular	4 weeks	Not available in the USA

diclofenac-induced DILI. A more recent study from 2018 performed enzyme kinetic analysis and unexpectedly found that the UGT2B7*2 genotype has 6-fold lower activity compared with the wild type enzyme and does not lead to increased hepatic exposure of DCF-AG. The authors speculated that a shift to oxidative metabolism in patients with UGT2B7*2 could produce more cytotoxic metabolites (quinoneimines) [10••] (see Fig. 1).

Enolic Acid Derivatives

The enolic acids include "oxicams" such as piroxicam, meloxicam, tenoxicam, and droxicam. Piroxicam was approved for use in the USA in 1982. Elevated aminotransferases can be seen in 3–18% of patients taking piroxicam although symptomatic liver disease is rare (1–5 cases per 100,000 prescriptions) [11]. The latency period is generally within 1–6 weeks and the injury pattern is primarily cholestatic. Much of the literature regarding DILI from piroxicam consists of case reports from the 1980s–1990s [12–14].

Meloxicam is a newer enolic acid derivative that was approved in the USA in 2000. Aminotransferase elevations > 3× ULN occur in 1% of patients. Rare reports of clinically significant liver injury have been published. Both cholestatic and hepatocellular injuries have been reported with short latency periods (1–5 weeks) similar to piroxicam [11]. In the DILIN NSAID study, 3 cases of meloxicam-induced DILI were reported. All three had cholestatic or mixed injury with a short latency (13–24 days). One patient had chronic cholestasis

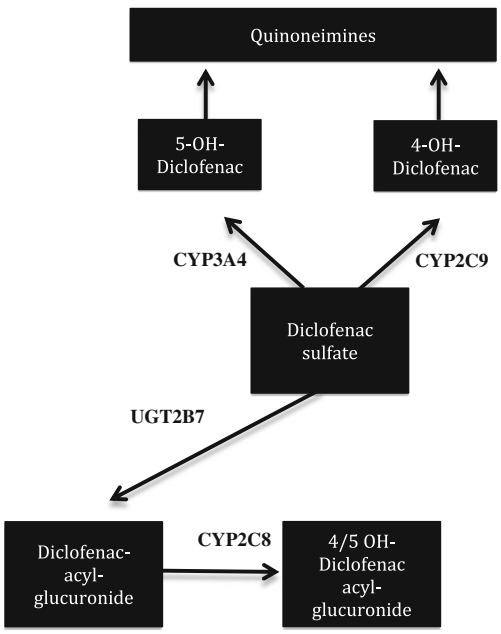

Fig. 1 Diclofenac metabolism. Reduced activity of UGT2B7 due to UTG2B7*2 genotype may shift metabolism of diclofenac toward formation of toxic quinoneimines

although alkaline phosphatase values eventually normalized 12 months after the onset of DILI [5].

Propionic Acid Derivatives

Two of the more commonly used NSAIDs in this class are ibuprofen and naproxen. Ibuprofen has been available by prescription in the USA since 1974 and was made available over-the-counter (OTC) in 1984. It is considered to be among one of the safest NSAIDs. The rate of clinically apparent liver injury is estimated to be low (1.0–1.6 cases per 100,000 prescriptions). The latency period is short (3 days to 3 weeks) and there is usually a mixed or cholestatic injury pattern. Immunoallergic features have been described [11]. Two cases of ibuprofen-induced DILI were reported in the DILIN paper. Both patients had pre-existing liver disease (one with hepatitis C and alcohol and the other with autoimmune hepatitis). Neither case had immunoallergic or autoimmune features [5]. There have been rare case reports of vanishing bile duct syndrome associated with ibuprofen, mostly in the pediatric population [15].

A more recent study from the Spanish DILI Registry reported that ibuprofen was the most frequent causative drug (29%) among 73 DILI cases followed by diclofenac (18%). The authors pointed out that the OTC ibuprofen tablets in Spain go up to 400 mg versus 200 mg in the USA. While idiosyncratic DILI is not thought to be dose dependent, there may be a threshold dose that needs to be reached before DILI develops. The authors postulated that the availability of the 400 mg dose in Spain could account for regional differences in ibuprofen hepatotoxicity [16••].

Naproxen is another commonly used NSAID. It was approved for prescription use in the USA in 1976 and became available OTC in 1994. Clinically significant liver injury is a rare entity (1–3 cases per 100,000 users). Both hepatocellular and cholestatic injury patterns have been reported with a latency period of 1–6 weeks. Unlike ibuprofen, immunoallergic and autoimmune features are rare [11]. Recovery is usually rapid once naproxen is stopped although one case report describes chronic cholestasis with ductopenia that persisted for a decade [17].

Salicylates

Discovered in the 1890s by the chemist Felix Hoffman at Bayer, acetylsalicylic acid (aspirin) is the first NSAID and the only one in its class. Unlike other NSAIDs, aspirin is a noncompetitive and irreversible inhibitor of COX-1, accounting for its longer lasting effects. Two forms of hepatotoxicity have been described. Dose-dependent hepatotoxicity was first recognized in the early 1970s. Aminotransferase elevations have been associated with high doses of aspirin (1800–3200 mg daily) and elevated serum salicylate levels (>

25 mg/dL) [18]. The liver injury is usually mild and asymptomatic and aspirin can be used safely in lower doses in these patients.

Reye syndrome is another clinical entity associated with aspirin use. It was first described by Reye et al. in 1963, but the association with aspirin was not appreciated until 1980. Reye syndrome is characterized by lactic acidosis, microvesicular steatosis, and hepatic dysfunction that can arise in children or young adults who take aspirin for a febrile illness (usually influenza B or varicella). In the USA, the reported cases peaked at 555 in 1980. The overall fatality rate was 31%. The number of cases sharply fell after 1980 when the CDC warned physicians and parents not to give salicylates to children with viral illnesses [19].

Selective COX-2 Inhibitors

This group of NSAIDs selectively inhibits COX-2 without disrupting COX-1, which is necessary to preserve the integrity of the gastrointestinal mucosa. These agents therefore achieve anti-inflammatory effects while maintaining a more favorable GI side effect profile. Celecoxib is a first-generation COX-2 inhibitor that was approved for use in the USA in 2000. A long-term randomized controlled trial evaluated the safety profile of celecoxib compared with ibuprofen and diclofenac in patients with osteoarthritis and rheumatoid arthritis. Aminotransferase elevations were seen in 0.6% of patients on celecoxib and only 0.2% had ALT values > 3× ULN. Interestingly 97% of aminotransferase elevations in the study occurred in patients receiving diclofenac [20]. While there have been case reports of cholestatic hepatitis, vanishing bile duct syndrome, and liver failure requiring transplant due to celecoxib [21], the likelihood of clinically significant liver injury appears to be low. A pooled analysis of 41 randomized controlled trials evaluated the safety profile of celecoxib versus placebo, ibuprofen, naproxen, and diclofenac. There were significantly fewer hepatobiliary adverse events in those receiving celecoxib (1.11%) compared with diclofenac (4.24%). The safety of celecoxib was comparable to ibuprofen and naproxen [22].

A few COX-2 inhibitors (rofecoxib, valdecoxib, and parecoxib) have been withdrawn from the market due to cardiovascular adverse events. Lumiracoxib is another COX-2 that is structurally similar to diclofenac and was removed from the market in Europe, Canada, and Australia due to post-marketing evidence of serious hepatotoxicity. Post-marketing reports from Australia noted 8 cases of liver injury from lumiracoxib. Liver histology showed severe hepatic necrosis. Two patients died and another 2 required liver transplantation. Lumiracoxib is unique among the NSAIDs described in this review in that a genome-wide study identified HLA alleles associated with lumiracoxib-related liver injury. Singer et al. found that in a case-control study of 41 lumiracoxib-treated patients with liver injury and 176 controls, the HLA-DQA1*0102 allele had a sensitivity of 74% and a negative predictive value of 99% in identifying subjects at risk of developing hepatotoxicity [23].

Sulfonanilides

Nimesulide is the only NSAID in the sulfonanilide class. It has preferential COX-2 activity. It was initially approved in Italy in 1985 and was never approved for use in the USA. Some European and Latin American countries withdrew the medication due to concerns about hepatotoxicity. Donati et al. published a case-control study that was conducted at nine Italian hospitals between 2010 and 2014. They found the annual incidence of DILI induced by NSAIDs to be 2 cases per 100,000 inhabitants. Thirty cases (17%) and 184 controls (10%) were exposed to nimesulide; the adjusted risk of acute and serious liver injury was 2.10 (95% CI, 1.28–3.47). Aside from nimesulide, only ibuprofen was associated with a statistically significant increased risk of liver injury. Despite restrictions in indications and treatment duration, nimesulide remained the fourth most prescribed NSAID in Italy in 2013 [24].

Acute Liver Failure

Large registry studies evaluating drug-induced acute liver failure (ALF) have implicated some NSAIDs. Bjornsson et al. reported on data collected by the Swedish Adverse Drug Reactions Advisory Committee collected from 1966 to 2002. There were 103 cases of suspected adverse drug reactions with fatal outcomes. NSAIDs were the fourth most common type of drugs associated with a fatal outcome (9%) behind antibiotics (29%), analgesics (paracetamol and dextropropoxyphene, 16%), and anesthetics (16%). Among NSAIDs, there were 4 fatal cases from diclofenac with a median duration of treatment of 97 days. There were 3 fatal cases from naproxen with a median duration of 8 days [25].

Data on DILI gathered from 1994 to 2004 from a Spanish registry was published in 2005. There were 461 cases of DILI and 18 patients who met criteria for ALF. Twelve of the ALF patients died and 6 underwent liver transplantation. In terms of specific NSAIDs, there were 3 cases of ibuprofen induced ALF and 2 cases of nimesulide. There were 12 cases of diclofenac-induced DILI including 6 that required liver-related hospitalization, but no ALF cases were reported [26]. The US Acute Liver Failure Study Group more recently published data on prospectively collected drug-induced ALF cases between 1998 and 2007. There were 133 total cases with a poor 3-week transplant-free survival of 27.1%. Antimicrobials accounted for 46% of ALF cases. There were 7 cases of NSAID-induced ALF and bromfenac was the biggest culprit (4 cases). Of note, bromfenac was withdrawn from

the US market in 1998. Other implicated NSAIDs included diclofenac (2 cases) and etodolac (1 case) [27].

Conclusions

Since their introduction over 100 years ago, NSAIDs have been commonly used medications both in prescription form and over-the-counter for a variety of inflammatory conditions. Pre-marketing data suggested a low risk of aminotransferase elevations although this is not a reliable predictor of clinically significant liver injury. In many circumstances, concerning reports of hepatotoxicity were not apparent until post-reporting data was gathered. This led to the withdrawal of several different NSAIDs including more recently marketed COX-2 inhibitors. Since the incidence of idiosyncratic reactions is low, it is imperative to have appropriate surveillance and monitoring after new NSAIDs are approved for use.

Over the past 15 years, there has been interest in identifying genetic risk factors for DILI through pharmacogenomic studies. To date, a genetic predisposition to developing DILI has been identified with diclofenac and lumiracoxib, as discussed previously. Moving forward, mitigating the risk of NSAID DILI will likely depend on both advancements in pharmacogenomics and improvement in post-marketing surveillance and reporting.

Compliance with Ethical Standards

Conflict of Interest Paul A. Schmeltzer declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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