Hepatotoxicity of Non-Narcotic Analgesics

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The central role of the liver in drug metabolism sets the stage for drug-related hepatotoxicity. The incidence of hepatotoxicity associated with non-narcotic analgesics is low, but their widespread use—both prescription and over-the-counter—makes analgesic-associated hepatotoxicity a clinically and economically important problem. Hepatotoxicity is considered a class characteristic of nonsteroidal anti-inflammatory drugs (NSAIDs), despite the fact that they are a widely diverse group of chemicals. In fact, there are many differences in the incidence, histologic pattern, and mechanisms of hepatotoxicity between, as well as within, chemical classes. Most NSAID reactions are hepatocellular and occur because of individual patient susceptibility (idiosyncrasy). Aspirin, however, is a dose-related intrinsic hepatotoxin. Acetaminophen is also an intrinsic hepatotoxin but rarely demonstrates hepatotoxicity at therapeutic doses. It does cause hepatotoxicity with massive overdoses and with therapeutic doses in susceptible patients such as chronic users of alcohol. No hepatotoxicity has been reported to date with tramadol, another non-narcotic analgesic. Am J Med. 1998;105(1B):13S–19S. © 1998 by Excerpta Medica, Inc.

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of reactive (electrophilic) molecules that are potentially toxic. These toxic compounds are then detoxified through a third metabolic pathway involving binding by glutathione. Glutathione, which is available in limited supply, is depleted in this process and has to be replenished. Massive overloads of drugs or circumstances that deplete glutathione, such as fasting or alcoholism, predispose to hepatotoxicity—such is the case with acetaminophen. In essence, metabolic toxicity occurs when oxidation leads to the formation of toxic electrophiles. These electrophiles interact with critical cellular target molecules leading to either direct cell injury or formation of protein–drug adducts that become targets for immune mediated injury. The reactive metabolites also act as oxidizing species that can accelerate programmed cell death (apoptosis).

**MECHANISM OF DRUG-INDUCED LIVER INJURY**

The mechanism of injury in hepatotoxicity is usually classified as idiosyncratic or intrinsic. Idiosyncratic reactions occur as the consequence of individual susceptibility and may result from either metabolic idiosyncrasy or immune idiosyncrasy—both leading to cell death (Figure 1). Idiosyncratic reactions are unpredictable. They are not dose dependent and are not detected in preclinical testing. They occur with a very low incidence. A typical example of metabolic idiosyncrasy is that which is seen with valproic acid. This agent is metabolized to a 4-ene metabolite, which is toxic to the liver. Immunologic idiosyncrasy, on the other hand, results from the formation of neoantigens or drug–protein adducts. A typical example is the formation of trifluoroacetylated adducts after exposure to halothane. Another mechanism involves dysregulation of the immune system resulting in autoimmune reactions. These typically result in formation of autoantibodies such as liver and kidney microsomal (LKM) antibodies, which react against microsomal enzymes. An example is tieneolic acid, in which the LKM antibodies react against CYP2C9, and halothane, in which they react against CYP2E1. Nonspecific antibodies such as antinuclear antibodies are often present in these reactions of which α-methylidopa is an example.

Intrinsic hepatotoxicity is unique to the drug and occurs in all people if exposed to a high enough concentration of the drug. Aspirin and acetaminophen are examples of intrinsically hepatotoxic drugs.

**RISK FACTORS FOR DRUG-INDUCED LIVER INJURY**

For most drugs, the risk of hepatotoxicity is 1–10 cases per 100,000 individuals exposed. Certain factors, however, appear to increase the probability of toxic reactions (Figure 2). In general, people >40 years of age are more likely to have drug-induced liver disease. This may be influenced...
by higher exposure rates, use of multiple drugs, and altered drug disposition. Important exceptions are aspirin and valproic acid, both of which are more commonly associated with liver injury in children.

Women are predisposed to drug-induced necro-inflammatory reactions. This is especially true for diclofenac. Interestingly, men appear to be more predisposed to cholestatic reactions such as that which occurs with azathioprine.

Drug formulation may also influence toxicity. For example, erythromycin estolate appears more likely to cause toxicity than plain erythromycin—perhaps because of the higher blood levels obtained with estolate.

Patients taking multiple drugs may be more susceptible to drug-induced injury. This probably results from induction of cytochrome P-450–mediated metabolism of parent compounds to toxic metabolites. Examples of agents in this category include acetaminophen, isoniazid, and valproic acid.

Chronic ethanol ingestion lowers the threshold for injury possibly by inducing the microsomal enzyme system as occurs with acetaminophen and perhaps with isoniazid, niacin, and methotrexate.

The nutritional state of the patient also affects toxicity. Obesity, for example, increases susceptibility to halothane hepatitis and perhaps methotrexate fibrosis, whereas fasting increases susceptibility to acetaminophen toxicity, probably due to glutathione depletion.

Genetic polymorphism of the cytochrome P-450 system may predispose to toxic injury. For example, 10% of the population has a relative deficiency of CYP2D6, which leads to propranolol and quinidine toxicity. Finally, it appears that patients with certain diseases are predisposed to toxicity. This is the case with aspirin hepatotoxicity, which is more common in patients with systemic lupus erythematosus, juvenile rheumatoid arthritis, and rheumatic fever.

**NSAID HEPATOTOXICITY**

NSAID-induced liver injury is rare, occurring with an incidence of <0.1%, but results in 2.2 hospitalizations per 100,000 population per year. Due to the widespread use of these drugs (15 million users per year in the United States), however, the accompanying medical and economic cost is high. The issue of NSAID hepatotoxicity came into focus after the introduction of benoxaprofen in April 1982. Striking cholestatic reactions, usually considered benign, were observed; 11 of 14 patients in the United States and >70 patients around the world died. Benoxaprofen was withdrawn from the US market a few months after its introduction. Other NSAIDs (e.g., cinchophen, ibufenac) had also been withdrawn from the market because of unacceptable levels of hepatotoxicity and, as a result, NSAID–associated liver toxicity was reviewed by the US Food and Drug Administration (FDA) Arthritis Advisory Committee. When it became apparent that virtually all NSAIDs were associated with some liver injury, hepatotoxicity was designated a class characteristic of NSAIDs. This designation, however, is an oversimplification for several reasons. First, many different...
chemical classes with little in common comprise the NSAIDs (Table 1). There is no clear correlation between chemical class and the risk of hepatotoxicity—the rates of hepatotoxicity vary markedly within chemical classes. For example, benoxaprofen has a high incidence of hepatotoxicity, and ibuprofen, which is chemically similar, has a very low incidence. Similarly, the adjusted odds ratio for hepatotoxicity with sulindac has been estimated at almost twice that of indomethacin (5.0 vs 2.6, respectively) despite their being in the same chemical class. Several groups have reviewed the published cases, as well as unpublished cases, reported to the FDA and estimated the relative incidence of NSAID hepatotoxicity inferred from that data.  

Second, the histologic type of injury varies within, as well as between, chemical classes (Table 2). Hepatocellular injury is the most common, but cholestatic injury and mixed injury are also seen as well as steatosis and granulomatous changes. Autoimmune injury, as occurs with diclofenac, has also been reported. Different types of injury have also been reported with the same drug. For example, sulindac causes both cholestatic and hepatocellular reactions.

Finally, there is no consistent mechanism of liver injury for NSAIDs (Table 3). With the exception of aspirin, most are associated with idiosyncratic toxicity mediated either immunologically (immune idiosyncrasy) or as the consequence of toxic metabolites (metabolic idiosyncrasy). Nevertheless, most NSAID-induced injury is hepatocellular and idiosyncratic. Unlike the gastrointestinal and renal effects of NSAIDs, liver injury is not related to prostaglandin inhibition. Of the 18 NSAIDs approved for use in the United States, all except ketorolac and meclofenamate have been reported to be hepatotoxic.

**Diclofenac Hepatotoxicity**

Significant hepatotoxicity occurs in approximately 1–5 per 100,000 exposed patients. This injury is more common in women. It is idiosyncratic and probably the consequence of drug metabolism since inhibition of CYP2C reduces cell injury. However, protein adducts are also formed and may be involved with immune-mediated toxicity. A chronic autoimmune type injury also occurs. Fatalities have been reported.

**Sulindac Hepatotoxicity**

Sulindac is one of the most commonly reported causes of NSAID hepatotoxicity. Approximately 75% of the patients are female, usually >50 years of age. Injury typically occurs within 8 weeks of initiating therapy. Most of the reactions are cholestatic (50%) but 25% are hepatocellular and 12% are mixed. Immune features are present in most patients. Deaths have been reported typically in the presence of a hypersensitivity reaction. The mechanism is immunologic idiosyncrasy.

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**Table 1. Nonsteroidal Anti-inflammatory Drugs (NSAIDs) by Chemical Class**

<table>
<thead>
<tr>
<th>Chemical Class</th>
<th>NSAIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicylates</td>
<td>Aspirin, diflunisal, ibuprofen</td>
</tr>
<tr>
<td></td>
<td>Diclofenac, indomethacin, phenylbutazone, etodolac</td>
</tr>
<tr>
<td>Propionic acids</td>
<td>Benoxaprofen, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, naproxen, oxaprozin, piroxicam, sulindac, tolfenamic acid</td>
</tr>
<tr>
<td></td>
<td>Diclofenac, flurbiprofen</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>Flurbiprofen, nabumetone, piroxicam, etodolac, diflunisal</td>
</tr>
<tr>
<td>Phenylacetic acids</td>
<td>Diclofenac</td>
</tr>
<tr>
<td></td>
<td>Diclofenac, flurbiprofen</td>
</tr>
<tr>
<td></td>
<td>Flurbiprofen, nabumetone, piroxicam, etodolac</td>
</tr>
</tbody>
</table>

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**Table 2. Histologic Types of Liver Injury Associated with Selected Nonsteroidal Anti-inflammatory Drugs (NSAIDs)**

<table>
<thead>
<tr>
<th>Histology</th>
<th>Associated NSAIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular</td>
<td>Aspirin, diclofenac, indomethacin, phenylbutazone, etodolac, nabumetone, oxaprozin, ibuprofen</td>
</tr>
<tr>
<td>Cholestatic</td>
<td>Diclofenac, flurbiprofen, sulindac, nabumetone, naproxen, piroxicam, etodolac</td>
</tr>
<tr>
<td>Mixed</td>
<td>Sulindac, diflunisal</td>
</tr>
<tr>
<td>Steatosis</td>
<td>Aspirin, indomethacin, ibuprofen</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>Diclofenac</td>
</tr>
<tr>
<td>Granulomatous</td>
<td>Phenylbutazone</td>
</tr>
</tbody>
</table>

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**Table 3. Intrinsic Versus Idiosyncratic Hepatotoxins**

<table>
<thead>
<tr>
<th>Type of Hepatotoxicity</th>
<th>Associated NSAIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrinsic</td>
<td>Aspirin, phenylbutazone(?)</td>
</tr>
<tr>
<td>Idiosyncratic (immunological)</td>
<td>Ibuprofen, sulindac, phenylbutazone, piroxicam, diclofenac</td>
</tr>
<tr>
<td>Idiosyncratic (metabolic)</td>
<td>Benoxaprofen, diclofenac, indomethacin, naproxen</td>
</tr>
</tbody>
</table>

NSAIDs = nonsteroidal anti-inflammatory drugs.

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**Salicylate Hepatotoxicity**

Aspirin causes dose-dependent toxicity and thus, is an intrinsic hepatotoxin. This is supported by experimental studies demonstrating that aspirin is a dose-related toxin in animals and cell culture. The exact mechanism of injury is unknown, but probably related to mitochondrial injury. Toxicity usually occurs with blood levels near or above the upper therapeutic concentration of 25 mg/dL. The injury is hepatocellular and usually mild with 3–5-fold increases in aminotransferase enzymes. Jaundice is
unusual. Patients with juvenile rheumatoid arthritis, systemic lupus erythematosus, and rheumatic fever appear to be more susceptible. The nonacetylated salicylates, sodium and choline salicylate as well as diflunisal, a difluorophenyl derivative, have also been implicated with hepatotoxicity although these reactions are probably immune idiosyncrasy.

Of special concern with aspirin is its apparent association with Reye’s syndrome in patients being treated for influenza or varicella. Aspirin should not be used in such patients, especially in children.

**Acetaminophen**

Acetaminophen is one of the most commonly used drugs in the United States. It inhibits both isoforms of the cyclooxygenase enzyme, COX-1 and COX-2, but has little, if any, anti-inflammatory activity and is used for its analgesic and antipyretic properties. It is a dose-related hepatotoxin that can cause fulminant hepatic necrosis but rarely does so at therapeutic doses. Hepatotoxicity is seen most frequently with massive overdoses. Under normal circumstances, acetaminophen undergoes direct glucuronidation and sulfation. However, approximately 5–15% of acetaminophen is metabolized through oxidation by the cytochrome P-450 isoenzymes 2E1 and 1A2 to form a toxic metabolite, N-acetyl-p-benzoquinoneimine (NAPQI) (Figure 3), and hepatic injury from acetaminophen is due primarily to this metabolite. NAPQI is a reactive species that can covalently bind nucleophilic proteins in the cell leading to hepatic necrosis. At normal therapeutic doses of acetaminophen, NAPQI is detoxified by binding with glutathione to form mercapturic acid, a stable metabolite excreted in urine. Hepatic necrosis occurs when the formation of NAPQI exceeds the binding capacity of glutathione. This occurs whenever the glutathione stores are reduced or excess NAPQI is formed. There are several reports of acetaminophen-induced liver injury occurring with apparently therapeutic doses in the setting of chronic alcohol ingestion, so-called “therapeutic misadventure.” In fact, most of these cases have occurred with acetaminophen doses greater than the recommended 4 g/day, albeit at doses less than those ordinarily considered hepatotoxic. Nevertheless, it is now clear that chronic alcohol ingestion enhances susceptibility to acetaminophen injury. It does this by 2 mechanisms: (1) chronic alcohol use enhances acetaminophen hepatotoxicity by inducing CYP2E1 isoenzyme, leading to excess formation of NAPQI; and (2) alcohol depletes glutathione stores, which compromises the detoxification mechanism. Patients who take enzyme-inducing drugs such as isoniazid, omeprazole, phenobarbital, phenytoin, or carbamazepine also may be at increased risk. Cimetidine, by inhibiting CYP2E1, and acute alcohol ingestion, by substrate competition for 2E1, probably reduce acetaminophen hepatotoxicity.

The clinical presentation of acetaminophen toxicity is characterized by an initial several hours of anorexia, nausea, and vomiting followed by 1–2 days of being relatively symptom free (although biochemical changes start occurring during this period and there may be right upper quadrant discomfort). This is followed by overt hepatic injury in which the aminotransferase enzyme levels are typically in the thousands. Hepatic failure with jaun-
by T. J. Schnitzer in this Supplement.)

No hepatotoxicity has been reported to date. (See article thesis and does not possess anti-inflammatory activity. Tramadol is a pure analgesic that does not affect prostaglandin synthesis. Indeed, its therapeutic response leading to further sodium retention.\textsuperscript{33,34}

holic patients who present with aminotransferase levels >1,000 U/L, since acute alcoholic hepatitis alone rarely presents with enzyme levels >300 U/L. Such patients should have acetaminophen levels measured and be treated appropriately.

Acetaminophen injury should be suspected in alcoholic patients who present with aminotransferase levels >1,000 U/L, since acute alcoholic hepatitis alone rarely presents with enzyme levels >300 U/L. Such patients should have acetaminophen levels measured and be treated appropriately.

**Tramadol**

Tramadol is a centrally acting, non-narcotic analgesic that has been available in the United States since 1995. It is a pure analgesic that does not affect prostaglandin synthesis and does not possess anti-inflammatory activity. No hepatotoxicity has been reported to date. (See article by T. J. Schnitzer in this Supplement.)

**HEPATOTOXICITY IN PATIENTS WITH PRE-EXISTING LIVER DISEASE**

In general, pre-existing liver disease does not enhance susceptibility to drug-induced liver disease. Important exceptions include methotrexate toxicity, alcoholic cirrhosis, alcohol in the presence of chronic hepatitis C, vitamin A use concurrent with alcoholic liver disease and, perhaps, halothane in patients with alcoholic liver disease. NSAIDs, however, enhance the renal disease associated with cirrhosis. Such patients are predisposed to retaining fluid, in part, due to their vasodilated state, which decreases arterial blood flow and thus renal blood flow with subsequent activation of the renin–angiotensin system leading to sodium and water retention. The normal adaptive response to this state is the release of prostaglandins which cause natruresis. NSAIDs inhibit this adaptive response leading to further sodium retention.\textsuperscript{33,34}

**SUMMARY AND CONCLUSIONS**

All of the available non-narcotic analgesics—with the exception of ketorolac, meclofenamate, and tramadol—have been associated with hepatotoxicity. Furthermore, NSAIDs have enhanced nephrotoxicity in the presence of liver disease and alcohol enhances the susceptibility to acetaminophen toxicity. There continues to be a need for the development of new drugs for the treatment of patients with underlying liver disease.

**REFERENCES**