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# Hepatic toxicity of antirheumatic drugs

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- **BACKGROUND** Many of the diverse group of pharmacologic agents available for the treatment of rheumatic diseases have the potential to cause serious hepatotoxicity.
- **OBJECTIVE** To identify factors associated with drug-induced hepatotoxicity in rheumatic disease.
- **SUMMARY** While mild elevations in plasma transaminase concentrations are associated with almost all nonsteroidal anti-inflammatory drugs (NSAIDs), clinically significant hepatic toxicity is very rare. NSAID-induced liver injury probably has an immunologic basis, but neither a detailed mechanism nor precise incidence rates are known. Methotrexate can cause hepatic fibrosis during chronic use, but the liver injury is poorly reflected by plasma transaminase concentrations; it is difficult to formulate monitoring recommendations when this agent is used in rheumatic disease. Gold and penicillamine have been associated with rare cases of hepatic toxicity as well.
- **CONCLUSIONS** Drug treatment of rheumatic diseases is associated with a small but well-documented risk of hepatotoxicity. Recognizing the clinical syndromes associated with liver injury by these agents facilitates the minimization of morbidity from this complication.

■ INDEX TERMS: LIVER DISEASES; ANTI-INFLAMMATORY AGENTS  
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**D**RUG-INDUCED LIVER disease is a complication of a variety of pharmacologic agents. Thus, it is not surprising that agents used in the treatment of rheumatic diseases are also associated with hepatotoxicity, although this complication is rare. An understanding of the potential for liver injury, and of the clinical pathophysiology of the hepatotoxicity, will facilitate early detection and rational management of this problem.

## MECHANISMS OF HEPATOTOXICITY

Several mechanisms of drug-induced hepatotoxicity have been identified and extensively reviewed.<sup>1,2</sup> Hepatocellular necrosis can result from a number of molecular mechanisms (Table 1). Generation of a reactive compound, either as a derivative of the drug or indirectly as an oxygen radical, can lead to covalent modification of hepatocyte proteins and subsequent hepatocellular necrosis. For example, acetaminophen-induced hepatotoxicity is the result of a reactive metabolite generated by cytochrome P-450-mediated oxidation.<sup>3,4</sup> Due to the liver's important role in whole-body fuel homeostasis, a variety of

drugs that interfere with normal intermediary metabolism can lead to hepatocyte injury. These metabolic inhibitors, such as valproic acid, often lead to the development of microvesicular steatosis.<sup>5</sup> A drug, either as the parent compound or as a metabolite, can associate with hepatocyte macromolecules to elicit an immunologic response leading to hepatocyte destruction.

Hypersensitivity reactions are usually dose-independent and reoccur with re-exposure to the drug. Diclofenac-associated liver injury has been postulated to result from host hypersensitivity (see discussion below).

Liver injury will also result if bile secretion or flow is impaired.<sup>2</sup> In cholestatic liver injury the clinical syndrome extends beyond that of simple biliary obstruction: the accumulating bile products and inflammatory response lead to hepatocellular dysfunction.<sup>2</sup> Bile acid transport and bile flow are directly impaired by estrogens, resulting in cholestatic injury. Alternatively, the biliary system can be the target of a hypersensitivity reaction leading to secondary cholestatic injury.

Other forms of liver injury associated with specific drugs include granulomatous infiltrates, diffuse fibrosis, neoplasms, and vascular syndromes. These varied lesions reflect the ability of drugs to elicit unusual immunologic responses or modify the normal biology of liver cells. An understanding of the multiple forms of drug-induced liver injury provides a framework for reviewing the effects of antirheumatic drugs on the liver.

#### NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

The nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used and effective for the symptomatic treatment of rheumatic diseases. Gastrointestinal and renal toxicities are well-recognized consequences of the systemic inhibition of cyclooxygenase caused by NSAIDs. However, the potential hepatotoxicity of NSAIDs has also been well documented for many years.<sup>6</sup> The clinical awareness of NSAID-induced hepatotoxicity has been accen-

TABLE 1  
MECHANISMS OF DRUG-INDUCED HEPATOTOXICITY

	Mechanism of injury	Example
Hepatocellular necrosis	Electrophilic metabolite	Acetaminophen
	Free radicals	Carbon tetrachloride
	Oxygen radicals	Doxorubicin
	Metabolic inhibition	Valproic acid
	Hypersensitivity	Diclofenac
Cholestasis	Altered bile transport	Estrogens
	Hypersensitivity	Chlorpromazine
Granuloma	Hypersensitivity	Quinidine
Fibrosis	Stimulation of collagen synthesis	Methotrexate

tuated by the experiences following the introduction of benoxaprofen and diclofenac in the United States.

#### Benoxaprofen

Benoxaprofen is a propionic acid derivative that was introduced in the United States in 1982. Although the drug was introduced with high expectations, clinical reports published in the United Kingdom and the United States after approval identified several cases of severe renal and hepatic toxicity, the latter characterized by severe cholestasis.<sup>7,8</sup> Elderly patients, particularly women, appeared to be most susceptible.<sup>6,7</sup> In one series of five elderly patients with benoxaprofen-associated cholestatic jaundice, all four patients for whom data were available also had preexisting renal insufficiency.<sup>7</sup> The identification of several fatal cases of toxicity resulted in withdrawal of benoxaprofen from the market in 1982.

The pharmacokinetics of benoxaprofen are unusual: it has a long half-life (35 hours) that is further prolonged in elderly patients, and substantial biliary excretion of the drug occurs.<sup>9,10</sup> Additionally, benoxaprofen's toxicity can be identified using *in vitro* liver systems.<sup>11</sup> Thus, the severe liver injury observed in a very small minority of patients taking benoxaprofen was attributed to unique properties of the compound instead of a more general potential for liver injury with NSAIDs.

#### Diclofenac

Diclofenac is a phenylacetic acid derivative that has been widely used in Europe since 1974. Introduced in the United States in 1988, diclofenac was believed to be minimally toxic based on extensive European experience and on a pharmacokinetic

profile that was viewed as unusually safe.<sup>12</sup> In American clinical development trials, diclofenac was associated with a 15% incidence of asymptomatic elevations in plasma transaminase concentrations but no clinically significant hepatotoxicity.<sup>13</sup> Thus, the report in 1990 of seven cases of severe diclofenac-associated hepatitis in the United States was initially surprising.<sup>14,15</sup> Hepatotoxicity appeared within 1 to 6 months of initiating diclofenac therapy in patients 46 to 69 years old and was associated with dosages ranging from 75 to 150 mg per day. Six of the seven patients recovered when the drug was discontinued, but one patient died and one patient who received diclofenac after recovering experienced recurrent hepatotoxicity. Other cases of diclofenac-associated hepatitis were reported from Europe.

Histologically, diclofenac-associated liver injury appears as hepatocellular necrosis with minimal inflammatory response. While the mechanism of hepatotoxicity is unknown, it is presumably the result of hypersensitization or of idiosyncratic metabolism of the drug. Observations of elevated IgE concentrations and eosinophilia with diclofenac-associated hepatotoxicity support the hypothesis of a hypersensitive reaction. Evidence of generation of diclofenac-derived toxic metabolites was supported by work with another phenylacetic acid derivative, alclofenac. *In vitro* studies with alclofenac demonstrated destruction of cytochrome P-450, and formation of an epoxide intermediate was postulated.<sup>16</sup> However, alclofenac contains an unsaturated side chain that diclofenac lacks, which would influence oxidative metabolism of the compound. Since four of the patients who recovered from diclofenac-associated hepatotoxicity were subsequently treated with other NSAIDs without toxicity, cyclooxygenase inhibition does not appear to be involved.

The dramatic experiences with benoxaprofen and diclofenac highlighted the potential for other NSAIDs to induce liver disease as a rare complication. In fact, almost all NSAIDs have been associated with some form of liver injury.<sup>6,17,18</sup> The incidence of elevated plasma transaminase concentrations during NSAID use is much higher than the incidence of clinically significant hepatotoxicity. Thus, patients with increased plasma transaminase concentrations may not need to stop taking NSAIDs if there is a strong clinical indication for its continued use. However, a pattern of increasing transaminase concentrations or elevated transaminase concentra-

tions associated with other indices of hepatic injury (ie, elevated plasma bilirubin concentration) strongly suggests that the NSAID be discontinued.

### Salicylates

Salicylates are associated with two forms of hepatotoxicity.<sup>6</sup> The first form is a hepatocellular injury characterized by elevated plasma transaminase concentrations, hepatocellular degeneration, and necrosis on pathologic examination.<sup>6,18</sup> While salicylate-associated elevations in transaminases are common (up to 50% in some series,<sup>18</sup>), clinically significant hepatic injury or death with therapeutic use of salicylates is rare. However, due to the nonspecific nature of the hepatic findings, salicylate-induced hepatitis has been confused with chronic active hepatitis.<sup>19</sup> When liver injury is secondary to salicylate use, it typically reverses after discontinuation of the drug.<sup>6,19</sup> The hepatocellular injury appears to be related to the plasma salicylate concentration, as hepatotoxicity is usually associated with plasma salicylate concentrations above 25 mg/dL.<sup>6,18,19</sup> These salicylate concentrations are similar to those that affect mitochondrial function in laboratory studies,<sup>20</sup> suggesting that the hepatic injury may result from altered liver energy transformations secondary to the high salicylate concentrations.<sup>6</sup>

The second form of hepatotoxicity associated with salicylates is Reye's syndrome, which, based on epidemiologic data, has been associated with the use of aspirin.<sup>21</sup> Reye's syndrome is characterized by fulminant hepatic failure following a viral illness in children.<sup>21</sup> While the cellular basis of Reye's syndrome is unknown, children with viral syndromes should not be treated with aspirin because of the epidemiologic evidence and the known potential of salicylate to modify mitochondrial function.<sup>22</sup>

Of the nonsalicylate NSAIDs currently marketed in the United States, sulindac, diclofenac, and phenylbutazone have been the subject of most case reports of hepatotoxicity at therapeutic doses.<sup>6,17,18</sup> However, the true incidence of NSAID-induced hepatotoxicity is not known for any of the NSAIDs, and only tolmetin and the fenamates have not been the subject of case reports suggesting hepatotoxicity.

With the exception of the salicylates, the mechanism of NSAID-induced injury is unknown. Both hepatocellular and cholestatic pathologic injuries have been seen; the mechanism is most likely hypersensitivity. A hypersensitive mechanism would

be consistent with the rare nature of the toxicity and would also explain cross-sensitivity between structurally similar NSAIDs,<sup>23</sup> but not between structurally distinct NSAIDs.<sup>14,24</sup> However, we cannot exclude idiosyncratic metabolism of an NSAID to yield a metabolite that is directly toxic, accumulates in bile, or is strongly antigenic. New insights into quantitatively minor metabolic pathways for the NSAIDs<sup>25</sup> and into the role of Kupffer cell-generated metabolites as potential antigens or toxins<sup>26</sup> may clarify these issues in the future.

### Strategy for NSAID use

The potential hepatotoxicity of the NSAIDs further emphasizes the need to define clear goals of therapy when initiating treatment. Based on these individualized goals, the clinical use of an NSAID can be limited to the minimum necessary to achieve the therapeutic objectives. Both duration of therapy and dose need to be assessed to avoid unnecessarily intensive therapy. Because NSAID-induced liver disease usually occurs during the first 6 months of therapy, plasma transaminase concentrations should be monitored monthly in those patients anticipated to require chronic NSAID administration. Progressive elevation in plasma transaminase concentrations should be considered an indication for discontinuing therapy, though a trial of an NSAID of a structurally distinct class could be considered.

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## DISEASE-MODIFYING AGENTS

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### Methotrexate

Methotrexate is efficacious in the treatment of rheumatoid arthritis.<sup>27</sup> Nevertheless, chronic use of methotrexate is associated with a risk of hepatic toxicity. Use of methotrexate in the treatment of psoriasis has been associated with the development of hepatic fibrosis, which progresses to cirrhosis in severe cases.<sup>28</sup> The mechanism of the fibrosis is unknown, but it has been postulated that methotrexate stimulates collagen biosynthesis by hepatic Ito cells.<sup>18,29</sup> Clinical experience in patients with psoriasis has facilitated identification of risk factors for methotrexate-induced fibrosis; these include daily methotrexate dosing, long-term methotrexate therapy, ethanol abuse, obesity, and decreased renal function. As methotrexate is excreted largely unchanged in the urine, doses should be reduced in patients with renal dysfunction to compensate for the decreased clearance. Co-administration of an

NSAID has been associated with severe methotrexate toxicity, presumably secondary to an NSAID-induced decrease in glomerular filtration and inhibition of renal tubular secretion of methotrexate, both of which result in decreased methotrexate clearance.<sup>30</sup> Clinical monitoring for methotrexate hepatic toxicity is difficult because the plasma transaminase concentration is a poor indicator of hepatic fibrosis. Thus, in patients with psoriasis, diagnostic liver biopsies have been recommended following a cumulative dose of 1.5 g or after 1.5 to 2 years of treatment.<sup>28</sup>

However, projecting the experience with methotrexate in patients with psoriasis to patients with rheumatoid arthritis is a matter of conjecture. The dosages of methotrexate used in rheumatoid arthritis are usually lower than those used in psoriasis (30 to 75 mg/wk in psoriasis vs 10 mg/wk in rheumatoid arthritis), and clinicians are now cautious about using the drug in patients who abuse ethanol. Additionally, only rare cases of methotrexate-induced cirrhosis during treatment of rheumatoid arthritis have been reported.<sup>31</sup> A recent study of 62 patients (12 of whom underwent liver biopsies) receiving methotrexate for juvenile rheumatoid arthritis demonstrated no clinically significant liver disease or fibrosis on biopsy.<sup>32</sup>

The challenge of monitoring rheumatoid patients during methotrexate therapy is further complicated by the results of work by Rau et al.<sup>33</sup> These investigators examined, in a blinded manner, biopsies from patients with rheumatoid arthritis who were initiating methotrexate therapy and from patients who had been taking the drug for 2 to 4 years. Evidence of fibrosis was found in 25% of the patients, but no difference was identified between the two groups. Therefore, the finding of fibrosis may be unrelated to methotrexate therapy in a patient with rheumatoid arthritis, and it would be difficult for a clinician to make management decisions based on it.

While plasma transaminase concentrations correlate with hepatic histologic grade in patients with rheumatoid arthritis who take methotrexate, this correlation is relatively weak ( $r = .5$  to  $.6$ )<sup>34</sup>; therefore, the utility of these measurements for decision-making in individual patients is limited. However, concomitant use of salicylates with methotrexate increases the incidence of elevations of plasma transaminase concentrations,<sup>35</sup> and as discussed earlier, NSAIDs do increase the clinical risk of methotrexate-associated hepatic disease. Thus, it is inter-

esting to note that the use of hydroxychloroquine during methotrexate therapy of rheumatoid arthritis decreases the frequency of plasma transaminase elevations,<sup>35</sup> though the relationship between this observation and clinically significant hepatic fibrosis is unknown.

Further, the natural history of fibrosis in patients who continue to take methotrexate is also unknown; both histologic progression and reversal of changes have been reported.<sup>27</sup> Case reports provide examples of continued benefit of methotrexate therapy following an abnormal biopsy finding without progression of liver disease.<sup>33</sup> Thus, while meta-analysis confirms the risk of hepatic toxicity in patients with rheumatoid arthritis (at a lower risk than patients with psoriasis),<sup>36</sup> the cost and morbidity rates associated with liver biopsies make their use controversial in clinically stable patients. Consensus-panel recommendations support performing biopsies at 2-year intervals or after a 1.5-g cumulative dose, particularly in the high-risk psoriasis population.<sup>37</sup> While these recommendations can be challenged in the light of the newer data, recent reviews and editorials continue to support the use of diagnostic liver biopsies in patients with rheumatoid arthritis who receive methotrexate.<sup>18,38</sup> However, the current state of the available data precludes definitive conclusions, and it appears probable that routine biopsies are of limited utility in the absence of risk factors for fibrosis.

## Gold

It has long been recognized that the use of gold salts in the treatment of rheumatoid arthritis is associated with a risk of cholestatic jaundice.<sup>39,40</sup> At one time it was postulated that gold-induced jaundice was causally linked to the drug's efficacy.<sup>39</sup> Prior to the recognition of gold as a hepatotoxic agent, several patients were subjected to laparotomy due to the severity of their cholestasis.<sup>40</sup>

The presentation of gold-induced liver disease frequently includes pruritus, rash, fever, and abdominal pain.<sup>41,42</sup> Most cases of gold-induced liver disease present during the first month of the first course of therapy,<sup>41</sup> but at least one case has been reported that occurred after many years of therapy.<sup>43</sup> The liver disease usually reverses after gold therapy has been discontinued. While chelation therapy will accelerate renal excretion of gold, there is no clinical basis for the use of chelating agents in the treatment of acute gold-induced cholestasis.<sup>41</sup>

The mechanism of gold-induced cholestasis is unknown. The systemic manifestations and eosinophilia often observed suggest an immune-mediated injury.<sup>17,44</sup> However, the gold salt clearly is not the antigen; gold presumably causes an endogenous protein to denature, eliciting an immune response. Whether the rarity of gold-induced liver disease reflects idiosyncratic hepatic handling of gold or heterogeneity in response to the postulated gold-induced antigen presentation is unknown.

## Penicillamine

Hypersensitivity reactions are a frequent side effect of penicillamine therapy, and the liver is a rare target of the immunological injury.<sup>45</sup> While initial case presentations suggested that liver injury was reversible with discontinuation of penicillamine,<sup>46</sup> fatalities associated with the drug have been reported in which hepatic failure was a prominent feature.<sup>47,48</sup> Features of both cholestatic and hepatocellular injury have been described in hepatotoxicity associated with penicillamine.<sup>47</sup>

Hepatocellular injury has been reported in a patient being treated with penicillamine and an acetylsalicylic acid-acetaminophen ester.<sup>49</sup> Liver biopsy 2 months after the clinical hepatitis demonstrated centrilobular necrosis characteristic of acetaminophen hepatotoxicity. However, as the patient was receiving low doses of acetaminophen and had no known risk factors, the authors suggested that penicillamine had predisposed to acetaminophen toxicity by depleting the glutathione precursor cysteine as the cysteine-penicillamine conjugate.<sup>49</sup> No additional evidence for this potential adverse drug interaction has been published. Animal data are conflicting, as penicillamine administration has been reported to increase<sup>50</sup> or decrease<sup>51</sup> hepatic glutathione content, and protect against acute acetaminophen toxicity.<sup>52</sup> Glutathione conjugate formation does not appear to be important in eliciting an immune response to penicillamine, although it does with other sulfhydryl-containing drugs.<sup>51</sup>

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## SUMMARY

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A number of drugs widely used in the treatment of rheumatic diseases can induce hepatic disease (*Table 2*). The physician's awareness of these potential adverse effects, knowledge of their clinical presentation and host risk factors, and implementation of prudent monitoring protocols will minimize patient morbidity.

TABLE 2  
HEPATOTOXICITY OF ANTIRHEUMATIC DRUGS

Class or drug	Histology	Typical time of presentation	Risk factors	Recommendations
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Varied	First 6 months	Previous history of NSAID hepatotoxicity	Monitor plasma transaminases monthly on initiation of therapy
Methotrexate	Fibrosis	Late	Cumulative dose, ethanol abuse, renal failure	Consider liver biopsy after 2 years of therapy or cumulative dose of 1.5 g
Gold	Cholestasis	First 35 days	Unknown	Monitor plasma bilirubin and alkaline phosphatase
Penicillamine	Mixed	First 6 months	Prior history of penicillamine hypersensitivity	Monitor for evidence of hypersensitivity reaction

ity during use of these efficacious agents. Unfortunately, insufficient data are available to provide definitive recommendations for all clinical situations, such as, for example, the use of liver biopsies during methotrexate therapy in patients with rheumatoid arthritis. In addition, the true incidence of hepatotoxicity is not known for most of the antirheumatic drugs, in part because of the rarity of this adverse effect. Thus, the physician must utilize the available

scientific information, the patient's clinical history, and his or her own preferences and clinical judgment to optimize patient care.

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