Liver

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ABSTRACT. The liver’s unique metabolism and relationship to the gastrointestinal tract make it an important target of the toxicity of drugs and xenobiotics. The developmental changes that occur in the liver’s metabolic activity from birth to adolescence contribute to the varied sensitivity to toxins seen in the pediatric population. Hepatic drug metabolism, often with an imbalance between the generation of toxic metabolites and detoxification processes, can influence the degree of hepatotoxicity. The decreased capacity of the neonatal liver to metabolize, detoxify, and excrete xenobiotics explains the prolonged action of drugs such as phenobarbital, theophylline, and phenytoin. The reduced capacity of glucuronide conjugation in the neonate not only predisposes them to physiologic jaundice but also is probably responsible for the chloramphenicol-induced gray infant syndrome. Age-related sensitivity to drugs is attributable in part to differences in metabolic activity. For example, young children are more resistant to acetaminophen hepatotoxicity when compared with adults, whereas children are more susceptible to valproic acid–induced toxicity. The resistance to acetaminophen toxicity is attributable to biochemical differences in young children. In children, sulfation predominates over glucuronidation, leading to decreased formation of toxic intermediates. In addition, infants have a greater capacity to synthesize glutathione, thereby inactivating toxic metabolites of acetaminophen more effectively. Hepatic toxicity as a result of drugs and environmental toxins presents a wide spectrum of clinical disease. Hepatitis is the most common presentation, but every major type of liver pathology can occur. Most drug reactions are attributable to idiosyncratic hepatotoxins; therefore, liver injury occurs rarely. The diagnosis of toxin-induced liver disease requires a high index of suspicion and often entails the exclusion of other causes of liver disease in children. Drug or environmental xenobiotic-induced hepatotoxicity should be considered in the setting of identified exposure or when other causes of childhood liver disease are excluded. Children who take medications that are known to be hepatotoxic, such as anticonvulsants and antineoplastic drugs, need frequent monitoring for evidence of hepatic toxicity. The treatment is often nonspecific; the most important intervention is the prompt discontinuation of the drug or removal of the environmental toxin. A specific antidote is available only for acetaminophen intoxication. In cases of severe toxicity, the patient may develop liver failure. Liver transplantation may be necessary for patients whose liver failure does not resolve. Pediatrics 2004;113:1097–1106; hepatotoxicity, xenobiotic, drug metabolism.

ABBREVIATIONS. CYP, cytochrome P450; ALT, alanine aminotransferase; AFB, aflatoxin B; ALP, alkaline phosphatase; VOD, veno-occlusive disease; PCP, polychlorinated biphenyl; PCP, pentachlorophenol; TCHQ, tetrachlorohydroquinone.

The liver’s main function is to synthesize an array of body proteins and to act as the detoxifying center for the multiple toxic metabolic byproducts endogenous to the body and the toxins ingested daily by the organism. The liver undergoes dramatic changes in structure and function during development. The developmental changes that occur in the liver determine the rate and metabolic pathways used in the disposition of drugs and other xenobiotics. The resultant metabolic intermediates may in themselves be toxic to the liver but may also cause detrimental effects to other organs of the body. This article discusses some of those xenobiotics that are hepatotoxic, with particular emphasis on substances found to be toxic in the pediatric age group. For understanding the variable effects of environmental xenobiotic exposures in children, a basic review of liver anatomy, physiology, and development is necessary.

MORPHOLOGY AND FUNCTION OF THE LIVER
Microscopic Anatomy and Liver Physiology

The liver performs many essential functions, including the production of bile, regulation of plasma proteins and glucose, and biotransformation of drugs and toxins. The liver is the first organ that comes into contact with enterally absorbed nutrients and xenobiotics via the portal vein. Other products of metabolism—substances that enter the body through other pathways and substances that are not extracted from the portal blood during the first pass—reach the liver by the hepatic artery. The newborn liver manifests many unique physiologic traits that are likely part of the normal developmental process and may predispose the liver in infants and children to the toxic effect of xenobiotics at levels that may be safe for the adult. The neonate has <20% of the hepatocytes that are present in the adult liver, and liver growth continues after birth until it reaches its mature size. The liver consists of 4 main types of cells. The hepatocytes are the biosynthetic engines of the liver. Their prominent Golgi system and rough endoplasmic reticulum enable them to synthesize and secrete a variety of proteins. The en-
dothelial cells line the sinusoids and serve as a barrier (interface) between the blood and hepatocytes. Two other cell types line the sinusoids: the Kupffer cells, which function as macrophages, and the stellate cells, which store fat and vitamin A.1,3

From a functional standpoint, the liver has been described as a collection of acini that are present by the third month of gestation. Each acinus is defined as the tissue supplied by the terminal branches of the portal vein and hepatic artery and drained by the terminal branches of the hepatic vein. The parenchyma is divided into 3 zones according to proximity to the portal triads. The hepatocytes closest to the portal areas (zone 1) receive the richest oxygen and nutrient supply and have a high concentration of enzymes involved in cell respiration; they mostly synthesize glycogen and other proteins. The hepatocytes in zone 3 are closest to the central veins (terminal branches of the hepatic veins). In zone 3, little oxygen is available and the hepatocytes are involved in glycolytic energy production and contain cytochromes P450 (CYP), a class of enzymes responsible for metabolizing many xenobiotics. Therefore, the hepatocytes in zone 3 are more specialized in bio-transformation reactions.4,5 Zone 2 is the intermediate area of hepatocytes between zones 1 and 3. Cells more distant from the portal supply (acinar zones 2 and 3) have a different enzymatic phenotype and respond differently to hypoxia and toxin exposure.

The liver performs multiple functions: bile formation and excretion, synthesis of liver proteins, detoxification of xenobiotic and endogenous compounds, and regulation of blood glucose. Toxicity caused by xenobiotics therefore can cause derangement in any of these functions and can be detected by laboratory tests used to measure these functions. Bilirubin and bile acids are the 2 primary components of bile and the best-known products of liver metabolism. Bile formation is essential for the excretion of endogenous waste products and the glucuronide and glutathione conjugates of many xenobiotics.6 The capacity to synthesize and excrete bile is immature in the neonate, making the neonate susceptible to significant cholestasis from toxic injury (Table 1).2

**TABLE 1.** Developmental Changes in Hepatic Metabolism, Biotransformation, and Enterohepatic Circulation

<table>
<thead>
<tr>
<th>Change</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low rates of gluconeogenesis and glucose use by the fetal liver</td>
<td></td>
</tr>
<tr>
<td>Amino acids are an important energy source for fetal liver (transamination and oxidative degradation)</td>
<td></td>
</tr>
<tr>
<td>Decreased capacity of the neonatal liver to metabolize, detoxify, and excrete xenobiotics</td>
<td></td>
</tr>
<tr>
<td>Decreased levels of many enzymes involved in oxidation, reduction, and conjugation reactions</td>
<td></td>
</tr>
<tr>
<td>Early expression of many CYP enzymes in the embryo and fetus (eg, CYP3A7, involved in steroid metabolism)</td>
<td></td>
</tr>
<tr>
<td>Delayed expression of other CYP enzymes important for xenobiotic metabolism (eg, CYP1A2, important in drug metabolism)</td>
<td></td>
</tr>
<tr>
<td>Reduced activity of phase II enzymes (eg, UGT, NAT2) in the fetus and neonate</td>
<td></td>
</tr>
<tr>
<td>Decreased hepatocyte bile acid uptake, binding, and transport in the fetus and newborn</td>
<td></td>
</tr>
<tr>
<td>Altered conjugation and sulfation of bile acids</td>
<td></td>
</tr>
<tr>
<td>Decreased bile acid pool size (mostly in the premature infant)</td>
<td></td>
</tr>
<tr>
<td>Decreased bile flow rates and intraluminal bile acid concentration</td>
<td></td>
</tr>
</tbody>
</table>

UGT indicates uridine diphosphate glucuronyl transferase; NAT2, N-acetyltransferase 2.
important for drug metabolism are polymorphically expressed and subject to developmental regulation. The balance between activation and detoxification reactions is critical in determining the hepatotoxic risk of drugs and toxins. For example, toxicity of benzene most likely results from oxidative metabolism of benzene to reactive products. A recent study showed that both phase I and phase II pathways influence the relative risk from exposure to benzene, underscoring the importance of considering the balance between activation and detoxification reactions in the elimination of toxicants.\(^9\) This balance is influenced by stage of development, state of nutrition, exposure to multiple drugs or chemicals, and immunomodulators resulting from viral infections. Some enzymatic inducers may affect phase I and phase II reactions disproportionately. In addition, polymorphisms of CYP (the major phase I enzymes) also influence this balance.\(^10\) Finally, drugs and xenobiotics utilize energy-dependent pathways for the excretion of the drug metabolites and their conjugates. These pathways, recently referred to as phase III of hepatic drug metabolism, include the multidrug resistance protein and the multidrug resistance-related proteins that transport drugs and chemicals into bile or into the sinusoidal circulation.\(^{11}\) Depending on the dose and on the metabolic and excretory pathway of xenobiotics, metabolic intermediates that can lead to varied manifestations of hepatic toxicity are formed (Fig 1). Thus, it is clear that multiple and complex interactions can alter the hepatic susceptibility of infants and children to environmental toxins.

**Developmental Changes in Bioactivation and Detoxification**

The ontogenic (developmental) changes in metabolism interact with the genetic determinants of drug metabolism (pharmacogenetics) to regulate the biotransformation of xenobiotics. The development of phase I enzymes, specifically the expression of CYP in the fetus, infant, and child, has received considerable attention.\(^{12-14}\) Fourteen CYP families have been described in humans, although mostly members in CYP families 1 to 3 are important with respect to drug and xenobiotic metabolism and toxicity in humans.\(^{10}\) Several examples of developmental changes
in the functional capacity of the liver will be men-
tioned. Although the fetal liver can metabolize many
xenobiotics, the neonate has a prolonged half-life for
most drugs. Significant and rapid maturation occurs
in the first year of life; the most rapid elimination of
drugs is found in school-age children and adoles-
cents, and thereafter plasma clearance slows with
age.14 The total hepatic microsomal CYP content
ranges from 0.3 nmol/mg microsomal protein in the
fetus to 0.5 in the adult. There is a tendency for CYP
content to increase with age, but the specific transi-
tion age is unknown. Numerous xenobiotics are
transformed to toxic intermediates in the liver. The
presence of CYP in the liver and in the placenta may
contribute to the toxic effects of known teratogens
such as thalidomide, phenytoin, and ethanol. Of par-
1100
ricular interest is CYP3A7, the major CYP constituent
in fetal liver that is not present in adult liver.
CYP3A7 metabolizes many foreign compounds and
plays a major role in the fetal metabolism of xenobi-
otics, including potential hepatotoxins such as afla-
toxin, aniline, and diethylnitrosamine.15

Microsomal epoxide hydrolase is a critical bio-
transformation enzyme that catalyzes the hydrolysis
of a wide variety of xenobiotic epoxides, including
hydrocarbons, aromatic amines, benzene, and afla-
toxin B (AFB). Studies of transplacental transfer of
AFB suggest that the developing human fetus may
be a sensitive target for AFB injury. Currently, there
are no data on the function of this enzyme with
increasing age, making it impossible to determine at
which age adult levels are reached or whether the
microsomal epoxide hydrolase activity in infants and
children exceeds that of adults.13 An important
phase II enzyme that undergoes dramatic ontogenic
and polymorphic change is N-acetyltransferase 2.
This enzyme mediates the biotransformation of a
large number of drugs and chemicals, including
many carcinogenic arylamides. Before 15 months of
age, approximately 50% of infants are slow acetyla-
tors. By the age of 3 years, N-acetyltransferase 2
activity is fully expressed, although possible compe-
tence (compared with adult values) is reached by 12
months of age.13 Additional research into the onto-
genic development of metabolizing enzymes is
needed, in particular the changes that occur in in-
fants and children.

ENVIRONMENTAL CHEMICALS, DRUGS, AND
PHYSICAL AGENTS THAT ARE TOXIC
TO THE LIVER

Classification of Toxic Liver Injury

Intrinsic Versus Idiosyncratic

Hepatotoxicity is defined as liver injury caused by
drugs or chemicals. Several classifications of hepato-
toxic agents are used in the medical and toxicologic
literature. Classification may focus on the source and
the chemical class of the toxicant, on the circum-
stances of exposure, on the type of hepatic lesion
produced, on the cell structure damaged, or on the
molecular or cellular mechanisms involved. Liver
toxins are often classified as intrinsic (obligatory) or
facultative (idiosyncratic) toxins. Intrinsic liver tox-
icity is dose dependent, is reproducible in animal
models, and occurs in every person who is exposed
to a sufficient dose. This type of hepatotoxicity is
found in occupational, environmental, or household
chemicals. Only a few drugs in clinical use are in-
trinsically toxic (eg, chemotherapeutic agents, acet-
aminophen); the toxicity often is seen above therape-
uthetic dose levels. Idiosyncratic reactions are
unpredictable and are caused by the inability of sin-
gle individuals to tolerate the compound. They can
be hypersensitivity reactions accompanied by clinici-
symptoms as eosinophilia, fever, and rash. An-
other type of idiosyncratic reaction is attributable to
pharmacogenetic differences between individuals
(genetic polymorphism in the metabolism of com-
pounds). These individuals are not able to detoxify
the parent compound, or there is an accumulation of
toxic metabolites. As these pharmacogenetic mecha-
nisms are elucidated, animal models can be designed
in which the metabolic alterations are mimicked,
therefore allowing prediction of hepatotoxicity for
these susceptible individuals.16

Acute Versus Chronic Hepatic Injury

Another classification of hepatic injury is based on
mode of presentation (acute vs chronic) and on the
type of injury caused (Table 2). Acute hepatic injury
may be cytotoxic or cholestatic. Cytotoxic injury re-
sembles acute hepatitis and is characterized by dam-
age to the hepatocytes with prominent elevation of
aminotransferases. Severe cases may result in fulmi-
nant liver failure. Depending on the agent, cell death
of hepatocytes may occur by either necrosis or by
apoptosis (programmed cell death). Apoptosis is a
controlled form of cell death, whereby mitochondrial
function is maintained and it does not induce an
immune response. This lack of inflammatory re-
sponse in apoptosis is advantageous because it al-
ows the tissue to regenerate. Oxidative stress is one
of the important mechanisms that mediate xenobi-
otic-induced cell death. Many chemicals lead to the
production of free radicals that can cause oxidative
stress, leading to apoptosis of hepatocytes.17 In ad-
dition, free radicals can lead to lipid peroxidation of
cellular membranes and cause cell death. Carbon
tetrachloride, a widely known hepatotoxin, causes
lipid peroxidation.18 Inhibition of protein synthesis
can result in hepatocellular necrosis. Mushroom in-
toxication as a result of ingestion of Amanita species
causes severe liver necrosis and is the prototype for
this mechanism of action. Amatoxin in the mush-
room inhibits RNA polymerase and therefore mRNA
synthesis, leading to inhibition of protein synthesis.5
Cholestatic injury resembles obstructive jaundice. Aminotransferase levels are modestly elevated,
whereas the alkaline phosphatase (ALP), γ-glutamyl
transferase, and bilirubin elevations are more prom-
inent. Cholestatic injury has a better prognosis over-
all than cytotoxic injury.

Chronic hepatic injury may also be cytotoxic and
cholestatic; in addition, it may cause vascular lesions
such as hepatic vein thrombosis and veno-occlusive
disease (VOD).19 Another important mechanism of
xenobiotic-induced hepatotoxicity is immunologic
alterations. Immunosuppression is seen with aflatoxins, leading to an increase risk of hepatocellular carcinoma in areas of the world endemic to hepatitis B. Immunoallergic response has been reported with antibiotics such as sulfaonamides, amoxicillin/clavulanic acid, and halothane or with chlorofluorocarbons, still widely available as refrigerants.20

Carcinogens

A variety of xenobiotics can increase the incidence, multiplicity, or type of onset of hepatic cancer. These compounds can either damage the DNA (genotoxic) or produce cancer through nongenotoxic mechanisms. A single exposure to a genotoxic hepatocarcinogen can be sufficient to produce neoplasia. In contrast, a number of drugs and chemicals may induce cancer in laboratory animals when administered at high doses for prolonged periods through nongenotoxic mechanisms.21 In addition, peroxisome proliferation has been implicated to play a role in the induction of liver cancer in rodents. Compounds that have been shown to cause peroxisome proliferation include hypolipidemic drugs (fibrates), phthalate ester plasticizers, and several herbicides (phenoxy acid herbicides, tridiphane, and fomiphthalate ester plasticizers, and several herbicides proliferation include hypolipidemic drugs (fibrates), pounds that have been shown to cause peroxisome in the induction of liver cancer in rodents. Com-
some proliferation has been implicated to play a role recent report23 of mutagenic potential in frogs of

<table>
<thead>
<tr>
<th>Injury</th>
<th>Biochemical Response*</th>
<th>Example of Cause</th>
<th>Susceptible Age Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute syndromes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Necrosis</td>
<td>8–500×</td>
<td>&lt;3×</td>
<td>Ecstasy, CCl₄</td>
</tr>
<tr>
<td>Steatosis</td>
<td>8–20×</td>
<td>&lt;3×</td>
<td>CCl₄</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>&lt;8×</td>
<td>&gt;3×</td>
<td>Anabolic steroids</td>
</tr>
<tr>
<td>Mixed</td>
<td>&gt;8×</td>
<td>&gt;3×</td>
<td>Amanita intoxication</td>
</tr>
<tr>
<td><strong>Chronic syndromes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Necrosis</td>
<td>3–50×</td>
<td>1–3×</td>
<td>Herbal products (eg, Chaparral)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>V×</td>
<td>V×</td>
<td>Arsenic, CCl₄</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>1–5×</td>
<td>3–20×</td>
<td>Methylene dianiline</td>
</tr>
<tr>
<td>Vascular lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peliosis hepatis</td>
<td>&lt;3×</td>
<td>&lt;3×</td>
<td>Vinyl chloride</td>
</tr>
<tr>
<td>VOD</td>
<td>1–3×</td>
<td>V×</td>
<td>Pyrrolizidine alkaloids</td>
</tr>
<tr>
<td>Portal HTN</td>
<td>1–3×</td>
<td>V×</td>
<td>Vinyl chloride, arsenic</td>
</tr>
<tr>
<td>Liver tumors</td>
<td>V×</td>
<td>V×</td>
<td>Hypervitaminosis A</td>
</tr>
<tr>
<td>Adenoma</td>
<td></td>
<td></td>
<td>Anabolic steroids</td>
</tr>
<tr>
<td>HCC</td>
<td></td>
<td></td>
<td>AFB, arsenic</td>
</tr>
<tr>
<td>Hemangiosarcoma</td>
<td></td>
<td></td>
<td>Vinyl chloride</td>
</tr>
</tbody>
</table>

Modified from Zimmerman.19

HTN indicates hypertension; HCC, hepatocellular carcinoma; AST, aspartate aminotransferase; V×, variable; CCl₄, carbon tetrachloride; Adol, adolescents; OE, occupational exposure.

* Expressed as times (×) upper limit of normal.
accurately the long-term effects of environmental toxins.

Environmental Toxins

There are very few reports of hepatic injury in children caused by environmental toxins. Because most of these hepatotoxins are industrial or agricultural products, adolescent and adults are at higher risk. Few pesticides are reported to cause hepatotoxicity. Among them, chlordane can cause mild hepato cellular injury. Arsenic, used as a pesticide and wood preservative, can cause hepatitis, cirrhosis, and angiosarcoma (see above and Table 2). Carbon tetrachloride, found in many industrial applications, is a cause of hepato cellular necrosis and steatosis (Table 2). Industrial agents that are reported to cause hepatitis include dioxane, picric acid, tetrachloroethane, and tetrachlorethylene. Polychlorinated biphenyls (PCBs), used in electrical equipment and other industrial applications, can cause hepatitis and may cause cirrhosis. Trinitrotoluene and phosphorus, used in explosives, can also cause hepatitis. Vinyl chloride, used in solvents and in the production of polyvinyl chloride, is a potent hepatotoxin that can cause fibrosis, portal hypertension, and hemangiosarcoma (Table 2). Other environmental toxins that are not associated with hepatotoxicity include lead, mercury, and tobacco smoke.11

Several environmental hepatotoxins are ubiquitous in nature and more likely to affect children. Among them, the pyrrolizidine alkaloids found in herbal and bush teas are a recognized cause of VOD in children. This toxic causes sudden onset of portal hypertension, with very prominent hepatomegaly and ascites in a previously healthy infant or child. A recent report documented VOD in a preterm neonate whose mother had been exposed to pyrrolizidine alkaloids. Post mortem examination confirmed the presence of pyrrolizidine alkaloids in the liver.28 Vitamin A is a dose-dependent hepatotoxin. Hypervitaminosis A can cause hepatic fibrosis and portal hypertension. Accidental ingestion of *Amanita phalloides* and other toxic mushrooms can cause fulminant liver failure. Finally, aflatoxin found in contami nated crops is a widely recognized cause of hepato cellular carcinoma.11

Drugs

Many drugs are known to be hepatotoxic, ranging from mild, asymptomatic elevation of aminotrans ferases to fulminant liver failure and death. Most drugs are more commonly toxic to adults, as a result of either a lower risk of toxicity in the younger patient or the increased exposure to drugs in the adult and the elderly population. Most drugs that are known to cause hepatotoxicity in children fall into several categories: analgesics, antibiotics, anticonvulsants, and antineoplastic drugs. These and several other miscellaneous drugs that are known to cause hepatotoxicity in children are listed in Table 3. Toxicity by antineoplastic drugs deserves special consideration. The diagnosis of hepatotoxicity induced by antineoplastic drugs can be complicated by the fact that these patients often are treated with multiple drugs and may also receive irradiation that can enhance the toxicity of the drugs. Nitrosoureas, 6-mercaptopyrurine, cytosine arabinoside, cis-platinum, cyclophosphamide, and dacarbazine (DTIC) may cause mild hepatitis with asymptomatic elevation of serum aminotrans ferases. Adriamycin, dactinomycin, and vinca alkaloids are infrequently associated with hepatotoxicity. L-Asparaginase has been associated with more severe damage characterized by severe steato sis, hepatocellular necrosis, and fibrosis. VOD can be seen in patients who receive thioguanine, cytosine arabinoside, DTIC, busulfan, and carmustine. Most often, VOD presents acutely with a tender, enlarged liver; ascites; and unexplained weight gain. Most cases of VOD are seen in patients after bone marrow transplantation, often in patients who also receive irradiation.

Acetaminophen is 1 of the most common causes of drug-induced hepatic toxicity in children. It is a dose-dependent toxin involving the formation of a toxic metabolite. There are 2 main clinical syndromes: acute overdose, either accidental in a toddler or intentional in adolescents, and a subacute form seen in a child who receives moderately large doses administered at regular intervals. Young children are more resistant to acetaminophen hepatotoxicity. The incidence of hepatotoxicity was 5.5% in a study of 417 children younger than 5 years, compared with 29% in adolescents and adults at comparable toxic levels.29 Several studies have demonstrated that these age differences are attributable to biochemical differences in young children. The metabolic profile differs greatly in early childhood. For the phase II detoxication reactions, sulfation predominates over glucuronidation, probably contributing to less formation of toxic intermediates. The switch to the adult pattern occurs at approximately 12 years of age. In addition, infants have a greater capacity to synthesize glutathione, thereby inactivating toxic metabolites of acetaminophen more effectively.10 Conversely, fasting, which enhances hepatotoxicity to many chemicals, is known to deplete glutathione stores.17 Other hepatotoxins, such as bromobenzene, can also lead to glutathione depletion.18 These developmental differences lead to a decreased susceptibility to acetaminophen toxicity in young children. Other drugs that frequently are reported to cause hepatotoxicity in children are listed in Table 3. For a detailed discussion of drug-induced liver disease, the reader is referred to recent reviews.10,11

VULNERABILITY OF CHILDREN TO HEPATOTOXICANTS

Very few studies document the specific vulnerability of children to environmental hepatic toxicants. It is widely known that age plays an important factor in affecting susceptibility to drug-induced hepatic injury. Most hepatic drug reactions are more common in adults. Some examples include isoniazid, acetaminophen, erythromycin, ketoconazole, and halothane. Conversely, children are more susceptible to valproic acid, which is most common in children younger than 3 years, and to aspirin, as evidenced by the occurrence of Reye syndrome in children.
<table>
<thead>
<tr>
<th>Drug*</th>
<th>Biochemical Response†</th>
<th>Pathologic Finding</th>
<th>Risk Factors</th>
<th>Clinical Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AST-ALT</td>
<td>ALP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>8–500×</td>
<td>&lt;3×</td>
<td>Zone 3 necrosis</td>
<td>Dose, ↑ age, fasting</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>1–5×</td>
<td>V×</td>
<td>Steatohepatitis, phospholipidosis</td>
<td>Dose, duration of therapy</td>
</tr>
<tr>
<td>Amoxicillin/ clavulanic acid</td>
<td>&gt;3×</td>
<td>&gt;3×</td>
<td>Cholestasis, hepatitis</td>
<td>↑ age, duration of therapy</td>
</tr>
<tr>
<td>Aspirin</td>
<td>3–20×</td>
<td>&lt;3×</td>
<td>Nonzonal necrosis, steatosis (Reye)</td>
<td>Dose, rheumatoid disease</td>
</tr>
<tr>
<td>Azathioprine/6-MP</td>
<td>&gt;3×</td>
<td>&gt;3×</td>
<td>Cholestasis, hepatitis</td>
<td>Transplantation</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>&gt;3×</td>
<td>V×</td>
<td>Hepatitis (children), granulomatosis</td>
<td>Metabolic idiosyncrasy</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>&lt;3×</td>
<td>&gt;3×</td>
<td>Cholestasis</td>
<td>CYP interactions, dose</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>&lt;3×</td>
<td>&gt;3×</td>
<td>Hepatitis/cholestasis</td>
<td>↑ age</td>
</tr>
<tr>
<td>Estrogens</td>
<td>&lt;5×</td>
<td>&lt;3×</td>
<td>Cholestasis</td>
<td>Dose</td>
</tr>
<tr>
<td>Halothane</td>
<td>8–500×</td>
<td>&lt;3×</td>
<td>Acute hepatitis (zone 3 necrosis)</td>
<td>↑ age, female gender, repeated exposure</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>8–500×</td>
<td>&lt;3×</td>
<td>Acute hepatitis</td>
<td>↑ age, dose?</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>&gt;3×</td>
<td>V×</td>
<td>Zone 3 necrosis</td>
<td>↑ age, female gender</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>1–3×</td>
<td>1–3×</td>
<td>Steatosis and fibrosis</td>
<td>Obesity, ↑ dose, type 2 diabetes</td>
</tr>
<tr>
<td>Minocycline</td>
<td>&gt;3×</td>
<td>&lt;3×</td>
<td>Hepatocellular necrosis</td>
<td>Use &gt;6 mo, female gender</td>
</tr>
<tr>
<td>Pemoline</td>
<td>&gt;3×</td>
<td>V×</td>
<td>Hepatocellular</td>
<td>Immunoallergic idiosyncrasy</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>&gt;3×</td>
<td>V×</td>
<td>Acute hepatitis</td>
<td>Immunoallergic idiosyncrasy</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>&gt;3–8×</td>
<td>&lt;3×</td>
<td>Focal necrosis, granulomas</td>
<td>Pharmacogenetic idiosyncrasy Female gender</td>
</tr>
<tr>
<td>Propylthiouracil</td>
<td>&gt;3×</td>
<td>V×</td>
<td>Hepatocellular</td>
<td>Female gender</td>
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<tr>
<td>Sulfinpyrazone</td>
<td>&gt;3×</td>
<td>V×</td>
<td>Hepatocellular, granulomas, cholestasis</td>
<td>Immunoallergic idiosyncrasy</td>
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<tr>
<td>Valproic acid</td>
<td>8–20×</td>
<td>&lt;3×</td>
<td>Steatosis, hepatocellular</td>
<td>↓ age, multiple anticonvulsants</td>
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6-MP indicates 6-mercaptopurine; SLE, systemic lupus erythematosus; TMT-SMX, trimethoprim-sulfamethoxazole.* Drugs most commonly reported to cause hepatotoxicity in children.† Expressed as times (×) upper limit of normal.
who receive aspirin for symptomatic treatment of a viral infection (mostly influenza and varicella; Table 3). Both valproic acid and salicylates may cause mitochondrial toxicity. The specific reasons for this lower risk to drug hepatotoxicity in children is probably multifactorial and depends on the specific mechanisms of drug toxicity. The overall increased frequency of adverse drug reactions in adults is probably the result of increased exposure, drug interactions, and altered drug disposition. The lower incidence of documented hepatic toxicity from xenobiotics in children is attributable not only to less exposure to environmental toxicants but also to their relative resistance to hepatic toxicity.

The syndrome known as Yusho disease exemplifies the risk to the fetus. Infants who are born to mothers who were poisoned with PCB developed a congenital syndrome that included dysmorphism, skin changes, and hepatic dysfunction.\(^{30}\) Hepatotoxicity from low-level fetal exposure to PCBs has not been demonstrated. The risk for liver injury as a result of placental transfer of xenobiotics is also exemplified by a report of neonatal hepatitis in a newborn whose mother was taking propylthiouracil during pregnancy.\(^ {31}\) The risk of toxicity from contaminated breast milk has received considerable attention. Specific guidelines are available regarding use of medications by lactating mothers. There are few cases of hepatic toxicity to breastfed infants caused by xenobiotics. The most important characteristics that determine the rate of transfer of chemicals to breast milk are lipid solubility, ionization, and molecular weight. Chemicals that are most likely to be present in breast milk are neutral, are lipophilic, and have low molecular weight. Breastfed infants from mothers who were exposed to organic solvents are at potential risk. There is 1 report of obstructive jaundice and hepatomegaly in a 6-week-old infant who was exposed to breast milk that was contaminated with tetrachloroethylene, a dry-cleaning solvent. Rapid clinical and biochemical improvement followed breastfeeding discontinuation.\(^ {32}\) Breast milk contains other environmental pollutants, such as PCBs, dioxin, and lead. Although a Canadian study found that only PCBs and dioxins are present at higher-than-acceptable levels in breast milk, low-level exposure and the risk for cancer are ill defined.\(^ {33}\) There are several reported epidemics of percutaneous absorption of xenobiotics, including cases of neonatal jaundice as a result of the use of a phe- nolic disinfectant detergent.\(^ {34}\)

The preschool- and school-aged child begins to explore the neighborhood beyond the immediate confines of the home. Exposures in the school setting and play areas are the most likely sources of toxicants. Significant exposure to hepatotoxins may occur in the playground areas, including exposure to organic pesticides and playground equipment treated with preservatives, such as arsenic, pentachlorophenol, or chromium that may be toxic if ingested. Pentachlorophenol (PCP) is a pesticide used worldwide in industrial and domestic applications as a wood preservative. Recent metabolic studies conducted in rodents and human liver homogenates have indicated that PCP undergoes oxidative dechlorination to form tetrachlorohydroquinone (TCHQ). The results indicated that more toxic effects could be observed in both rats and human hepatoma cell line treated with TCHQ than its parent compound, PCP. Reactive oxygen species may be involved in the mechanism of TCHQ intoxication, suggesting that the risk of intoxication will depend on the metabolic rate of the exposed individual and on their endogenous antioxidant protective capacity.\(^ {35}\)

Adolescents often engage in risky behaviors such as solvent sniffing or the use of illicit drugs that can be hepatotoxic, such as ecstasy.\(^ {36}\) In addition, adolescents may have jobs that may expose them to pesticides (farm workers and lawn care) or to organic solvents (most commonly in food service and automotive services). They are often not properly trained or may not receive adequate protective clothing or gear, which increases their risk. Changes in CYP expression, which may occur in response to growth hormone, may lead to decreased metabolic capacity for some xenobiotics.\(^ {37,38}\)

**DIAGNOSIS AND TREATMENT**

**Detection of Liver Injury**

Because there are no specific diagnostic tests or pathologic findings, the diagnosis requires a high index of suspicion and a careful drug and environmental exposure history, including over-the-counter and herbal preparations. Always consider the possibility of a child’s taking the parent’s or grandparent’s medication. The most important clue is the temporal pattern of disease evolution in relation to exposure to toxins or drugs. A brief environmental history taken at every patient encounter should document the occupations of the patient and the parents and some information about the community where they live.\(^ {38}\) Often the patient has nonspecific symptoms of general malaise, anorexia, nausea, and vomiting. The patient may have systemic features of drug hypersensitivity, such as fever, rash, lymphadenopathy, or mucositis. The patient with VOD may present with features of portal hypertension in the absence of signs of chronic liver disease. Tender hepatomegaly, ascites, jaundice, and mild elevation of aminotransferases is characteristic. Occasionally, the only evidence of liver disease is a finding of elevated aminotransferases, ALP, or bilirubin in an asymptomatic patient. The detection of liver injury in the clinical setting is often accomplished by the use of a battery of tests for liver function. Although most of these are not specific to the liver, if several of these are abnormal, then a hepatic cause is likely. These tests include serum aspartate aminotransferase and ALT, which measure the integrity of the hepatocyte and the sinusoidal plasma membrane; serum albumin and hepatic clotting factors measure the biosynthetic capacity; and serum bilirubin, ALP, and γ-glutamyl transferase as a measure of biliary excretion. When liver disease is identified on biochemical testing, viral, autoimmune, and metabolic disorders must be considered. Serology for common infectious agents (hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis D virus...
cytomegalovirus, and Epstein-Barr virus) should be done and as well as serologic testing for autoimmune hepatitis (antinuclear antibody and anti–smooth muscle antibody). Metabolic diseases to be considered include Wilson’s disease and α1-antitrypsin deficiency. If a dose-dependent hepatotoxicity is suspected (aspirin and acetylsalicylic acid), then blood levels should be obtained. Additional evaluation should include a liver ultrasound to evaluate for cholelithiasis, cholecystitis, and evidence of cirrhosis or a liver mass. In cases of poorly explained liver disease, possible drug or xenobiotic toxicity should be considered. Most often, an environmental toxin will be difficult to identify. Referral to a pediatric gastroenterologist may be necessary if no cause for the liver disease is identified. In some cases, a liver biopsy may be indicated to exclude other diseases and to help make a specific diagnosis.10,11

Treatment

With the exception of acetaminophen hepatotoxicity, there is little effective treatment for most cases of toxin- or drug-induced liver disease. Most often, the liver disease resolves once the offending agent is stopped. Early detection is important to ensure prompt withdrawal of the offending agent. A specific antidote is available only for acetaminophen. N-acetylcysteine is most effective when given within 10 hours of acetaminophen ingestion. The decision to use it is based on plotting the blood level on a widely available toxicity nomogram. The risk of hepatotoxicity correlates with the plasma acetylsalicylic acid level and the time after ingestion. In cases of a recognized acute overdose, a poison center should be contacted for other specific guidelines (eg, gastric lavage, charcoal use). The use of corticosteroids in drug-induced liver disease is controversial. They are often used when severe acute hepatitis is part of a multisystem hypersensitivity reaction, as with phenytoin, phenobarbital, carbamazepine, or sulfa. The treatment of fulminant liver failure as a result of drug hepatotoxicity is similar to failure caused by viral hepatitis. Deterioration of mental status and sustained impairment of clotting studies in conjunction with a falling ALT indicate poor outcome and require prompt referral to a liver transplant center. Liver transplantation may be necessary and has been reported for acetaminophen and mushroom intoxication, among others.

CONCLUSION

Hepatic toxicity as a result of drugs and environmental toxins presents a wide spectrum of clinical disease. Hepatitis is the most common presentation, but every major type of liver pathology can occur. Developmental changes in xenobiotic metabolism add to the complexity of hepatotoxicity as a result of drugs and environmental toxins in children. Hepatic drug metabolism, often with an imbalance between the generation of toxic metabolites and detoxification processes, can influence the degree of hepatotoxicity. Most drug reactions are attributable to idiosyncratic hepatotoxicity; therefore, liver injury occurs rarely. Making the diagnosis of xenobiotic-induced hepatotoxicity in children requires a high index of suspicion. Drug or environmental xenobiotic-induced hepatotoxicity should be considered in the setting of identified exposure or when other causes of childhood liver disease are excluded. Children who take medications that are known to be hepatotoxic, such as anticonvulsants and antineoplastic drugs, need frequent monitoring for evidence of hepatic toxicity.

REFERENCES


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