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, theophyline, 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; PCB, 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.[1] 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.[2] 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.[1,2] 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-

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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 biotransformation 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]

Functional Development of the Liver: Differential Vulnerabilities of the Liver at Different Stages of Development

The functional development of the liver has been studied extensively in the rat, less so in humans.[7] It involves complex changes in liver function in the embryo and the fetus. Some enzyme activity is high in the fetus and falls during postnatal development (thymidine kinase and ornithine decarboxylase), whereas other enzymes are expressed in the fetus and increase postnatally (fructose-1,6-diphosphatase and aspartate aminotransferase). Another group of enzymes is expressed perinatally and continues to increase postnatally (uridine 5′-diphosphate glucuronyl transferase). Finally, some enzymes are expressed at birth and peak at the time of weaning in the rat (alanine aminotransferase [ALT] and alcohol dehydrogenase).[2] The development of physiologic jaundice in the newborn may be caused in part by low glucuronidation activity in the liver (Table 1). These developmental changes most likely place the developing fetus and infant at differential risk from environmental toxins. For example, the reduced capacity of glucuronide conjugation in the neonate is probably responsible for the gray infant syndrome from chloramphenicol.[8] Unfortunately, few studies are available in the literature exploring the effects of environmental toxins on the liver at various stages of development. This is further complicated by the lack of appropriate experimental models available to examine the effect of xenobiotics at different developmental stages.

The structural and functional development of the liver can influence the absorption, excretion, and metabolism of drugs and other xenobiotics. Most of the knowledge regarding the differential hepatic metabolism is based on studies of drugs. Some of these observed differences in drug metabolism highlight potential susceptibilities of the developing human. Hepatic biotransformation is divided into 2 broad categories: phase I, or activation reactions (oxidations-reductions and hydrolysis), and phase II, or detoxification reactions (synthetic conjugations with sulfate, glucuronic acid, glutathione, acetate, and glycine). Many phase I and phase II enzymes that are

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

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

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

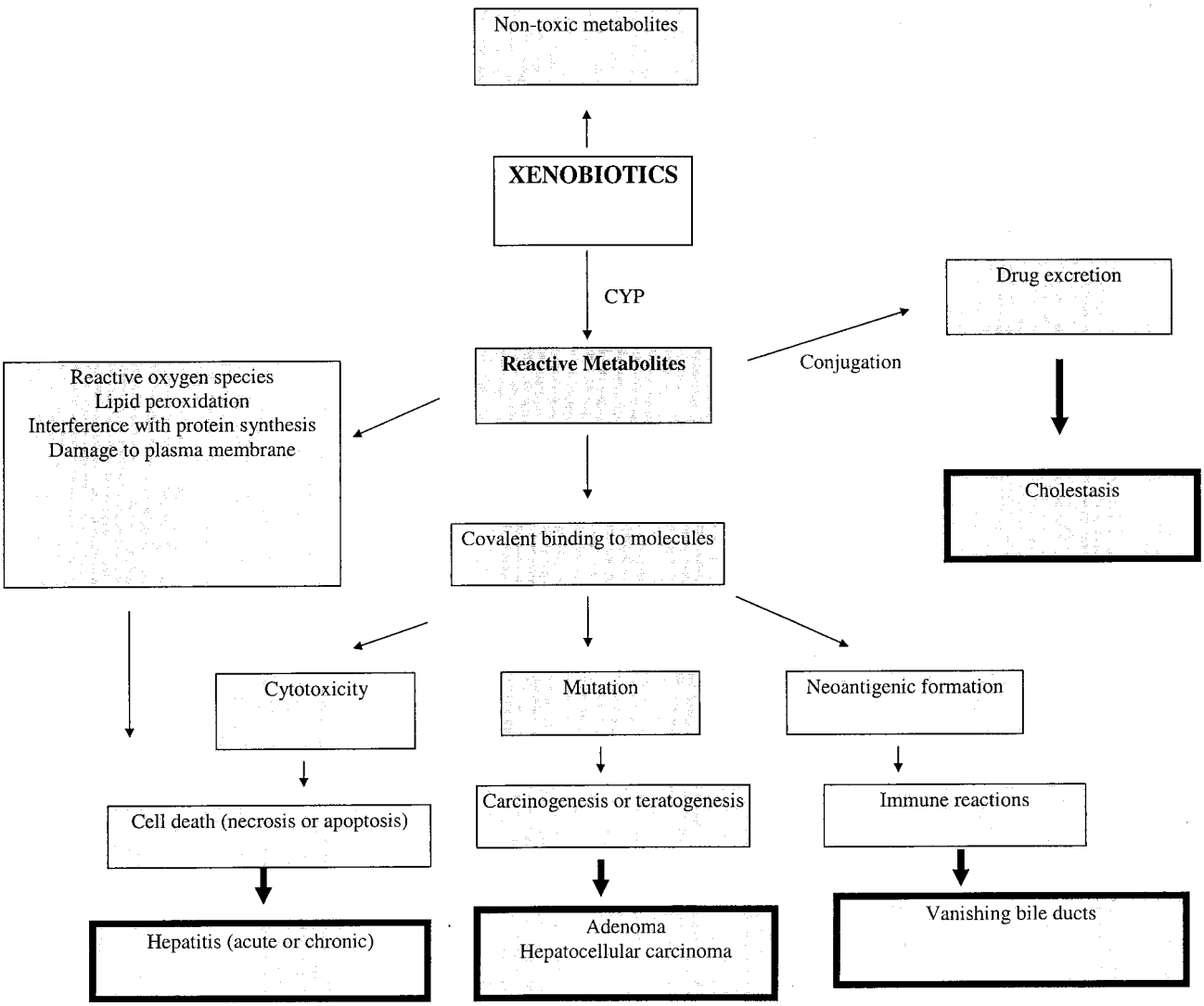

Fig 1. Toxic mechanisms of liver injury.

in the functional capacity of the liver will be mentioned. 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 adolescents, 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 transition 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 particular 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 xenobiotics, including potential hepatotoxins such as aflatoxin, aniline, and diethylnitrosamine.[15]

Microsomal epoxide hydrolase is a critical biotransformation enzyme that catalyzes the hydrolysis of a wide variety of xenobiotic epoxides, including hydrocarbons, aromatic amines, benzene, and aflatoxin 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 acetylators. By the age of 3 years, N-acetyltransferase 2 activity is fully expressed, although possible competence (compared with adult values) is reached by 12 months of age.[13] Additional research into the ontogenic development of metabolizing enzymes is needed, in particular the changes that occur in infants 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 hepatotoxic agents are used in the medical and toxicologic literature. Classification may focus on the source and the chemical class of the toxicant, on the circumstances 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 toxicity 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 intrinsically toxic (eg, chemotherapeutic agents, acetaminophen); the toxicity often is seen above therapeutic dose levels. Idiosyncratic reactions are unpredictable and are caused by the inability of single individuals to tolerate the compound. They can be hypersensitivity reactions accompanied by clinical symptoms as eosinophilia, fever, and rash. Another type of idiosyncratic reaction is attributable to pharmacogenetic differences between individuals (genetic polymorphism in the metabolism of compounds). These individuals are not able to detoxify the parent compound, or there is an accumulation of toxic metabolites. As these pharmacogenetic mechanisms 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 resembles acute hepatitis and is characterized by damage to the hepatocytes with prominent elevation of aminotransferases. Severe cases may result in fulminant 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 response in apoptosis is advantageous because it allows the tissue to regenerate. Oxidative stress is one of the important mechanisms that mediate xenobiotic-induced cell death. Many chemicals lead to the production of free radicals that can cause oxidative stress, leading to apoptosis of hepatocytes.[17] In addition, 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 intoxication as a result of ingestion of *Amanita* species causes severe liver necrosis and is the prototype for this mechanism of action. Amatoxin in the mushroom 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 prominent. Cholestatic injury has a better prognosis overall 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

TABLE 2. Pathologic and Biochemical Changes in Environmental Toxin–Induced Injury

Injury	Biochemical Response*		Example of Cause	Susceptible Age Group
	AST-ALT	ALP		
Acute syndromes				
Hepatocellular				
Necrosis	8–500×	<3×	Ecstasy, CCl_4	Adol
Steatosis	8–20×	<3×	CCl_4	Adol
Cholestasis	<8×	>3×	Anabolic steroids	Adol
Mixed	>8×	>3×	Amanita intoxication	All
Chronic syndromes				
Hepatocellular				
Necrosis	3–50×	1–3×	Herbal products (eg, Chaparral)	Infants
Cirrhosis	V×	V×	Arsenic, CCl_4	Adol (OE?)
Cholestasis	1–5×	3–20×	Methylene dianiline	Adol (OE?)
Vascular lesions				
Peliosis hepatis	<3×	<3×	Vinyl chloride	Adol?
VOD	1–3×	V×	Pyrrolizidine alkaloids	Infants
Portal HTN	1–3×	V×	Vinyl chloride, arsenic	All
			Hypervitaminosis A	Adol
Liver tumors	V×	V×		
Adenoma			Anabolic steroids	Adol
HCC			AFB, arsenic	All?
Hemangiosarcoma			Vinyl chloride	All?

Modified from Zimmerman.[19]
HTN indicates hypertension; HCC, hepatocellular carcinoma; AST, aspartate aminotransferase; V×, variable; CCl_4, carbon tetrachloride; Adol, adolescents; OE, occupational exposure.
* Expressed as times (×) upper limit of normal.

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 sulfonamides, 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 fomesan).[22] Many herbicides and pesticides are found at low levels in the water supply. Despite the contaminant exposure levels used (drinking water standards established by the Environmental Protection Agency), these exposure levels are often not tested for their long-term effect in infants and children. The recent report[23] of mutagenic potential in frogs of another commonly used herbicide, atrazine, and its synergistic interaction with a trematode infection raises the possibility that yet-to-be-determined interactions could predispose susceptible individuals to genotoxic or mutagenic effects even at levels that are now deemed to be safe. Indeed, in vitro coexposure to atrazine potentiates arsenic trioxide–induced cytotoxicity and transcriptional activation of stress genes in transformed human hepatocytes.[24] The enhanced toxicity of arsenic when coexposed to widely used herbicides is especially concerning, given the wide distribution of arsenic in treated wood.

Most available studies report the carcinogenic potential of chemicals in laboratory animals. The risk for humans, specifically for children, is not well known. Most information on cancer risk is based on epidemiologic studies. Several epidemiologic studies of cancer in young children have implicated a number of environmental factors, but most studies have shown negative findings, thereby excluding potential risk factors in a healthy population. The inability to identify environmental causes could mean either that the environment does not substantially affect cancer incidence in young children or that other risk factors, such as chronic hepatitis and genetic liver diseases, are not being considered.[25] The synergistic effect of coexposures to AFB_1 and hepatitis B infection have recently been documented. Individuals who have chronic hepatitis B infection and are exposed to AFB_1 have a 3-fold increased risk for hepatocellular carcinoma.[26] In addition, the role of genetic polymorphism of detoxifying enzymes in liver cancer has only recently been documented. A recent study showed a significant association of hepatocellular carcinoma with the uridine 5′-diphosphate-glucuronosyltransferase UGT1A7*3 allele encoding a low detoxification activity protein.[27] The increased risk of malignancy after chronic xenobiotic exposure may not be apparent for decades. For example, the carcinogenic potential of vinyl chloride was noted after 30 years of extensive polyvinyl chloride production. Careful epidemiologic studies in addition to appropriate laboratory data are needed to determine

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, chlordecone can cause mild hepatocellular 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 hepatocellular necrosis and steatosis (Table 2). Industrial agents that are reported to cause hepatitis include dioxane, picric acid, tetrachloroethane, and tetrachloroethylene. 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 toxin 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 contaminated crops is a widely recognized cause of hepatocellular carcinoma.[11]

Drugs

Many drugs are known to be hepatotoxic, ranging from mild, asymptomatic elevation of aminotransferases 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-mercaptopurine, cytosine arabinoside, cis-platinum, cyclophosphamide, and dacarbazine (DTIC) may cause mild hepatitis with asymptomatic elevation of serum aminotransferases. Adriamycin, dactinomycin, and vinca alkaloids are infrequently associated with hepatotoxicity. L-Asparaginase has been associated with more severe damage characterized by severe steatosis, 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 detoxification 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 3. Clinical and Pathologic Findings in Drug-Induced Liver Disease in Children

Drug*	Biochemical Response†		Pathologic Finding	Risk Factors	Clinical Characteristics
	AST-ALT	ALP			
Acetaminophen	8–500×	<3×	Zone 3 necrosis	Dose, ↑ age, fasting	Dose-dependent injury, initial nausea and vomiting; jaundice and coagulopathy if liver failure
Amiodarone	1–5×	V×	Steatohepatitis, phospholipidosis	Dose, duration of therapy	Asymptomatic elevation of ALT and AST common; cirrhosis and liver failure rare
Amoxicillin/ clavulanic acid	>3×	>3×	Cholestasis, hepatitis	↑ age, duration of therapy	Clavulanic acid is likely cause of toxicity; most cases recover fully but rare cases of progressive ductopenia with cirrhosis reported in children
Aspirin	3–20×	<3×	Nonzonal necrosis, steatosis (Reye)	Dose, rheumatoid disease	Dose dependent, rapid recovery if drug discontinued; ↑ risk of Reye syndrome in febrile children
Azathioprine/6-MP	>3×	>3×	Cholestasis, hepatitis	Transplantation	Cholestasis more common with azathioprine; portal HTN and vascular injury also reported
Carbamazepine	>3×	V×	Hepatitis (children), granulomatosis	Metabolic idiosyncrasy	Hepatitis associated with drug hypersensitivity syndrome
Cyclosporine	<3×	>3×	Cholestasis	CYP interactions, dose	Direct hyperbilirubinemia more common, mixed hepatitis/cholestasis at higher doses
Erythromycin	<3×	>3×	Hepatitis/cholestasis	↑ age	Anorexia, nausea, jaundice, and abdominal pain; all forms of erythromycin reported but erythromycin estolate more common in adults (1%–2% develop jaundice)
Estrogens	<5×	<3×	Cholestasis	Dose	Insidious onset of mild jaundice and pruritus; hepatic vein thrombosis, hepatic adenoma with prolonged use
Halothane	8–500×	<3×	Acute hepatitis (zone 3 necrosis)	↑ age, female gender, repeated exposure	Rae in children; mild ↑ ALT in 10%–20% of adults; severe hepatitis and liver failure (fatal in 14%–71%)
Isoniazid	8–500×	<3×	Acute hepatitis	↑ age, dose?	More common in adults; mild ↑ ALT in 7%–17% of children; use of CYP inducers may increase toxicity risk
Ketoconazole	>3×	V×	Zone 3 necrosis	↑ age, female gender	Symptoms of hepatitis and jaundice after 6–8 wk of therapy; caused by metabolic idiosyncrasy
Methotrexate	1–3×	1–3×	Steatosis and fibrosis	Obesity, ↑ dose, type 2 diabetes	Risk of fibrosis with normal ALT; surveillance liver biopsy after high cumulative dose
Minocycline	>3×	<3×	Hepatocellular necrosis	Use >6 mo, female gender	SLE-like syndrome or chronic hepatitis with autoimmune features; monitoring of liver function needed
Pemoline	>3×	V×	Hepatocellular	Immunoallergic idiosyncrasy	Asymptomatic elevation of serum aminotransferases to acute liver failure; several children have required liver transplantation
Phenobarbital	>3×	V×	Acute hepatitis	Immunoallergic idiosyncrasy	Hepatitis rare, usually part of a multisystem drug hypersensitivity; also at risk of hepatitis from phenytoin and carbamazepine
Phenytoin	>3–8×	<3×	Focal necrosis, granulomas	Pharmacogenetic idiosyncrasy	Hepatitis associated with drug hypersensitivity syndrome
Propylthiouracil	>3×	V×	Hepatocellular	Female gender	Symptoms of hepatitis and moderate elevation of ALT/AST within 2–3 mo of starting treatment
Sulfonamides	>3×	V×	Hepatocellular, granulomas, cholestasis	Immunoallergic idiosyncrasy	Hepatotoxicity associated with a systemic drug hypersensitivity reaction; TMT-SMX in children and sulfasalazine in adolescents
Valproic acid	8–20×	<3×	Steatosis, hepatocellular	↓ age, multiple anticonvulsants	Dose-dependent asymptomatic ↑ ALT in 11% of patients; rare severe toxicity resembles Reye syndrome and is frequently fatal in children

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 phenolic 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 hepatotoxicants 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 paotal 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,

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 hepatotoxin is suspected (aspirin and acetaminophen), 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 acetaminophen 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 hepatotoxins; 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.

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