Section 19

LECTURE

Alcohol and Drug-Induced Liver Disease

Harvard-MIT Division of Health Sciences and Technology
HST.121: Gastroenterology
Gastroenterology, Intestinal Physiology, Pathology, Pathophysiology,
and Mechanisms of Disease

Alcohol and Drug Induced Liver Disease

I. Alcoholic Liver Disease

Alcohol abuse affects more than 10 million Americans, and is responsible for more than 45 billion dollars in lost productivity and health care costs annually. Most alcoholics develop only modest hepatic injury, such as fatty infiltration, while approximately 1 in 5 alcoholics will develop alcoholic hepatitis and/or cirrhosis. Alcoholism represents the leading cause of cirrhosis in the United States. In recent years, cirrhosis resulting from chronic alcohol abuse has become one of the most common indications for liver transplantation in this country.

There exists significant variability with regard to the dose and duration of alcohol consumption required to produce hepatic injury. Short-term ingestion of up to 80 grams of ethanol a day (3-4 ounces of mixed drink, or 8 12 ounce beers) may lead to mild and reversible hepatic injury (fatty liver). Daily ingestion of >160 grams of ethanol for 10-20 years typically is necessary to develop severe injury (alcoholic hepatitis, cirrhosis or a combination of the two). As a consequence of genetic variability in ethanol metabolizing enzymes, and environmental factors, such as dietary intake, severe liver injury may develop in select individuals who ingest significantly less than 160 grams of alcohol per day.

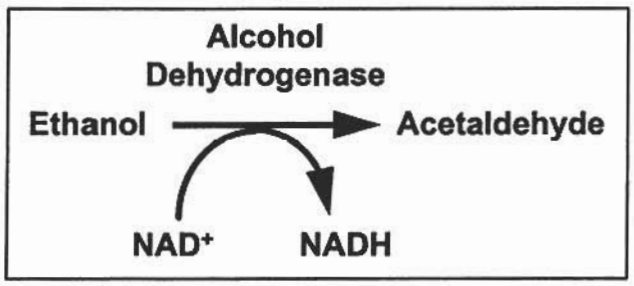
Alcohol induced liver damage

1. *Ethanol metabolism*

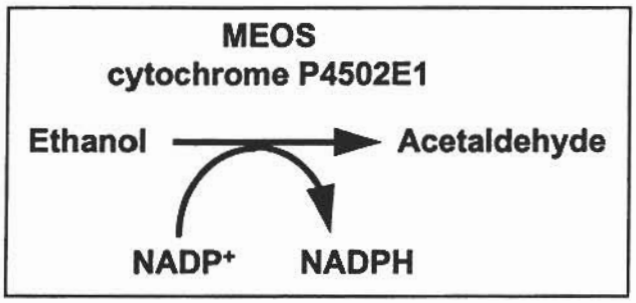
Ethanol is metabolized primarily by means of oxidation within the hepatocyte, with much smaller contributions from the lungs and kidneys at high blood alcohol concentrations. Recent, controversial data has suggested a first pass metabolism in the stomach by gastric alcohol dehydrogenase although the physiologic importance of this metabolic pathway remains to be elucidated. Within the hepatocyte there are three primary pathways of ethanol degradation which include 1) cytosolic alcohol dehydrogenase, 2) microsomal ethanol oxidizing system (MEOS) and 3) catalase. Under normal conditions, the alcohol dehydrogenase system is thought to be responsible for >80% of total ethanol breakdown.

A. Alcohol dehydrogenase

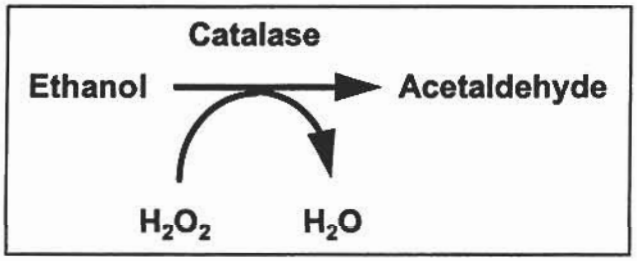
- hepatocellular cytosolic location
- results in excessive production of NADH at expense of NAD
- rate-limiting step in production of acetaldehyde
- enzyme activity varies between individuals and is, in part, genetically determined



B. Microsomal ethanol oxidizing system (MEOS)
- cytochrome P4502E1 is primary enzyme
- enzymes are inducible by phenobarbital, as well as other drugs, and chronic alcohol consumption
- localized to microsome (primarily endoplasmic reticulum)



C. Catalase
- localized to peroxisomes and mitochondria
- role under physiologic conditions controversial and likely minimal

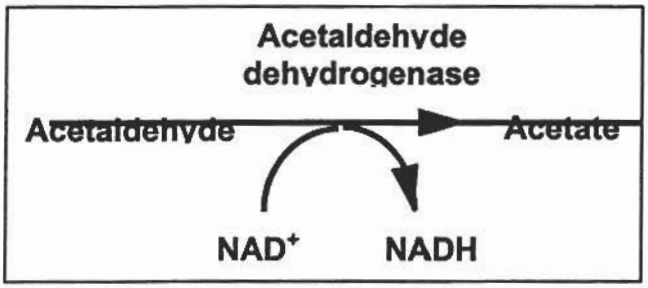


2. *Toxic effects of ethanol metabolism*

A. Increased cellular NADH/decreased NAD^+
- Increased lactate/pyruvate ratio
- Decreased gluconeogenesis from amino acids
- Increased a-glycerophosphate levels leading to increased fatty acid synthesis and hepatocellular accumulation of triglycerides
- Decreased mitochondrial oxidation of fatty acids leading to further intrahepatocyte accumulation of fatty acids

B. Toxic effects of acetaldehyde

- chronic alchohol ingestion results in decreased acetaldehyde oxidization due to reduction in acetaldehyde dehydrogenase and increased NADH levels



- results in microtubular alterations which disrupt protein secretion as well as water and electrolyte export and thus leads to hepatocyte "ballooning degeneration", hepatomegaly and cellular necrosis. Acetaldehyde binds to cysteine and glutathione, thus depleting the concentration of these free radical scavengers and thereby increasing lipid peroxidation as well as diminishing ability to scavange electrophilic drug metabolites (see next section)
- impairs cellular enzyme function (e.g. reduced ability to repair alkylated nucleoproteins)

C. Centrilobular pattern of injury
- decreased centrilobular oxygen tension promotes increase in NADH levels which in turn lead to increased free radical formation in these cells
- increased alcohol dehydrogenase found within centrilobular hepatocytes leads to increased acetaldehyde production in these cells

3. *Clinical manifestations of alcoholic liver disease*

A. Fatty liver
- most common hepatic abnormality in alcoholics
- reversible with cessation of alcohol consumption
- clinical manifestation is hepatomegaly
- liver function tests usually normal, or minimal elevation in alkaline phosphatase and bilirubin
- liver biopsy (not usually indicated) but demonstrates centrilobular steatosis if performed
- therapy is abstinence and provision of adequate dietary intake

B. Alcoholic hepatitis

- occurs in 25% of alcoholics with variable severity
- symptoms include anorexia, weight loss, fever, fatigue, abdominal pain and nausea
- physical findings include hepatomegaly, jaundice, ascites, peripheral edema, encephalopathy
- laboratory findings include increased SGOT and SGPT (usually <300 IU/l), elevated bilirubin and alkaline phosphatase, and leukocytosis
- liver biopsy reveals hepatocellular necrosis, polymorphonuclear cell infiltration of the hepatic parenchyma, pericentral fibrosis, and alcoholic hyaline deposition (Mallory bodies)
- may take weeks to months for signs, symptoms and laboratory abnormalities to correct with abstinence
- corticosteroids will improve short-term outcome in those individuals predicted to have high mortality

C. Alcoholic cirrhosis
- develops in 10-25% of alcoholics
- symptoms may include malaise, fatigue, or more specific symptoms related hepatic synthetic dysfunction: encephalopathy, fluid retention, coagulopathy, portal hypertension
- physical findings include jaundice, ascites, splenomegaly, asterixis, spider angiomata, palmar erythema, Dupuytren's contractures, gynecomastia, and testicular atrophy
- histology demonstrates regenerative nodules entrapped by fibrous septae +/- active hepatic inflammation (dependent on presence of ongoing alcohol consumption)
- therapy centers on abstinence, management of complications (infectious, portal hypertension, encephalopathy)
- in select, compliant, abstinent individuals with irreversible dysfunction, may consider liver transplantation

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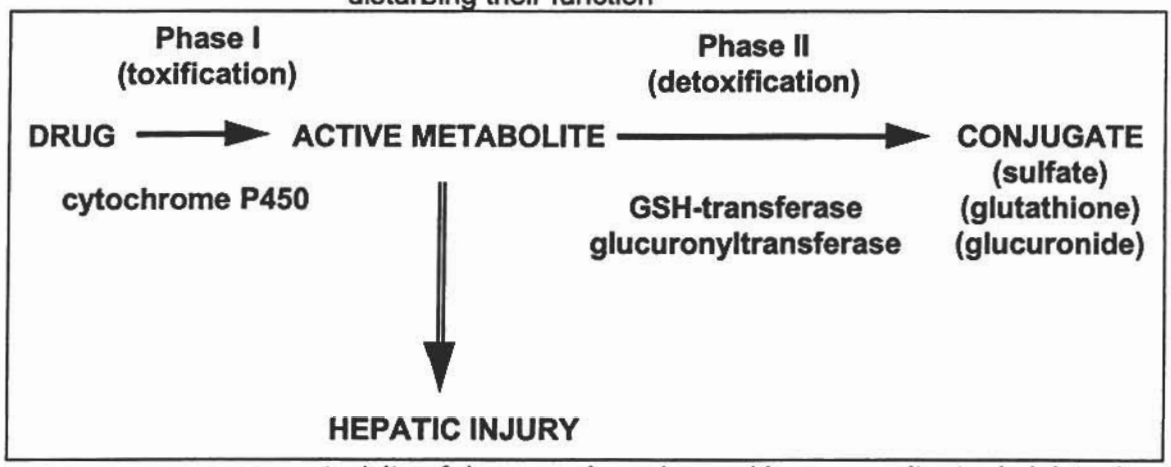
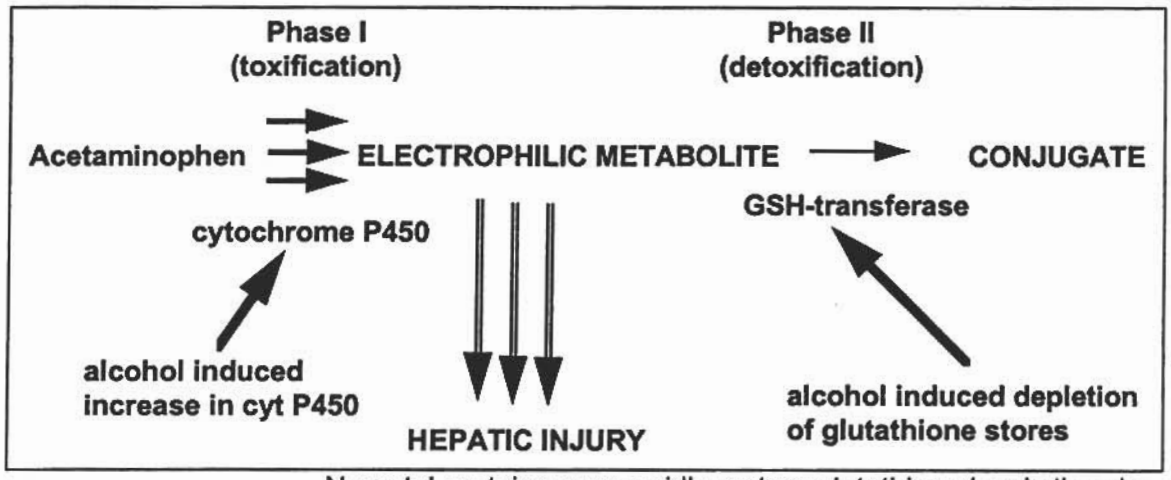
II. Mechanisms of Drug Induced Liver Injury

The liver is the first organ encountered by many drugs after their absorption from the gut, and contains much of the enzymatic machinery essential for the metabolism of a diverse array of compounds. Thus, it is not surprising that the liver is a principal site for adverse drug reactions. Drugs may damage the liver by a variety of mechanisms and produce a broad spectrum of histologic lesions on liver biopsy. As over 600 drugs are believed to be potentially hepatotoxic, it would be impossible to memorize the histologic pattern and mechanism of injury associated with each and every clinically important compound. The following sections will thus focus on the primary mechanisms involved in liver injury resulting from common or prototypical compounds. Tables following this section are provided simply to remind the reader of the spectrum of histologic patterns and drugs considered to be the cause of liver disease.

1. *Electrophilic radical production*
   - electrophilic (toxic) metabolite of offending drug is produced by P450 system (and others) which subsequently escapes detoxification and covalently binds to cellular constituents thereby disturbing their function



   - toxicity of drug may be enhanced by concomitant administration of another drug (e.g. rifampin induced isoniazid toxicity or alcohol accentuated acetaminophen toxicity)



- N-acetyl cysteine may rapidly restore glutathione levels thereby promoting Phase II clearance of active metabolite of acetaminophen

2. *Free-radical mediated injury*
   - production of free radicals leads to lipid peroxidation and cell death (e.g. CCl_4 induced hepatotoxicity). Analagous to acetaminophen story, Phase I reactions lead to production of CCl_3. At low oxygen levels (centrilobular hepatocytes), lipid peroxidation caused by this free radical leads to cell death. N-aceytl cysteine administration may enhance Phase II detoxification. Hyperbaric oxygen may actually promote covalent linkage of CCl_3 to cytochrome P450's and thus shut off further production of toxic free radical leading to improved cell survival.

3. *Immunologic mediated injury*
   - protoypical compound=halothane
   - halothane hepatitis occurs in 1:35000 exposures, and is associated with fever, rash and eosinophilia. Incidence increases with repeated exposures
   - trifluoroacetyl (TFA) metabolite (P450 product) reacts with hepatocellular proteins, affected patients develop serum antibodies to these proteins (neoantigens)

III. Histopathological patterns of drug-induced liver injury

A. *Zonal necrosis* (portal or central zones or non-specific)
Usually predictable, dose-related direct hepatotoxins; e.g., CCl_4, acetaminophen (tylenol), and phosphorus cause centrizonal necrosis.

B. *Viral hepatitis-like reactions*
Usually sporadic; variable evidence for toxic metabolite; ? host idio syncracy; e.g., isoniazid, halothane, methylodopa, sulfonamides, phenytoin.

C. *Cholestasis*

- Non-inflammatory - Probable direct effect on canalicular membranes; dose-dependent but with marked difference in individual susceptibility, e.g., natural and synthetic estrogens (oral contraceptives), 17a-substituted steroids (anabolic steroids). May unmask previously unapparent Dubin-Johnson syndrome.

- Inflammatory, with variable necrosis. Probable direct effect of parent drug or metabolite at multiple sites (e.g., inhibition of Na^+/K^+ ATPase, microfilament damage). For example, chlorpromazine, erythromycin estolate, antithyroid agents, oral hypoglycemics.

D. *Chronic hepatitis*

Usually depends on continuing administration of agent, but may be irreversible if advanced; e.g., INH, methyldopa, nitrofurantoin, sulfonamides, dantrolene, propylthiouracil. Association with acetaminophen, aspirin and ethanol is less certain.

E. *Fatty liver*

- Large droplet (nucleus displaced) Usually benign, per se, with hepatomegaly and abnormal liver function tests. Due to relative imbalance of triglyceride synthesis vs. VLDL secretion, e.g., ethanol, corticosteroids.
- Fine droplet (microvesicular with central nucleus) Usually severe metabolic derangement, often with liver failure, e.g., tetracycline (high dose, intravenous), valproic acid

F. *Granulomas*

Mechanism unknown; may be associated with extrahepatic granulomas, e.g., allopurinol, phenylbutazone, quinidine, phenytoin, hydralazine, halothane, proacinamide.

G. *Tumors*

Adenoma, focal nodular hyperplasia, hepatocellular carcinoma, e.g., oral contraceptives, anabolic steroids.

H. *Vascular reaction*

- Budd-Chiari Syndrome - oral contraceptives
- Veno-occlusive disease - antimetabolites
- Peliosis hepatitis - androgenic steroids
- Angiosarcoma - vinylchloride monomer (tire industry), arsenic.

IV. Selected Examples of Drug Hepatotoxicity

A. *Acetaminophen*

- Acute toxic dose > 10 g; chronic toxic dose > 3 g/day

- Most excreted in urine after glucuronidation or sulfation. Some is metabolized by cytochrome P-450 to toxic intermediates which are (1) conjugated with glutathione or (2) bound covalently with cell macromolecules (particularly when cell glutathione stores are depleted) causing cell injury.

- Toxicity is enhanced by chronic alcohol ingestion.

- Treatment: N-acetylcysteine

B. *Isoniazid*

1. Incidence of subclinical abnormalities 10-20% (elevated SGOT).

- Focal necrosis on biopsy
- Apparently self-limited despite continued treatment
- No correlation with INH blood levels or acetylator status

2. Incidence of clinical hepatitis 1%

- Rare in age < 20 yrs; ~2% age > 50 yrs
- Acute viral hepatitis-like lesions
- Onset within 12 months of starting treatment (50% <2 months)
- Relationship to acetylator status unclear
- Rifampin may predispose to INH toxicity
- 10-20% mortality (highest in black females)

3. Management of patients receiving INH prophylaxis

- Use only when clearly indicated, especially inpatients 35 years
- Advise patients; monitor for symptoms and signs of liver disease
- Routine liver function tests in patients >35 years of age

C. *Halothane*

Incidence approximately 1:10,000 patients who receive halothane anesthetics; increased incidence with multiple exposures. Most often obese females, over age 40 y. Onset is similar to viral hepatitis, fever 8-14 days after exposure (2-10 days after multiple exposures). Mortality 15-50% (prothrombin time > 20 seconds and serum bilirubin >10 mg% indicate grave prognosis).

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