Drug-Induced Liver Injury (DILI) AASLD Wrap-up 2008

Craig J. McClain, M.D., Professor
Division of Gastroenterology/Hepatology
Departments of Medicine, Pharmacology and Toxicology
Associate Vice President for Translational Research
Louisville VA Medical Center
University of Louisville
Jewish Hospital Louisville

Objectives

- Background on drug metabolism and hepatotoxicity
- Magnitude of and screening for drug induced liver injury (DILI)
- Examples of drug-induced liver disease
- CAM-induced hepatotoxicity

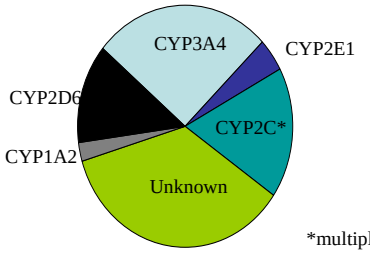
BACKGROUND

- **Most drugs absorbed the GI tract**
- **Drugs eliminated unchanged, metabolized by enzymes or spontaneously transformed**
- **Most drugs lipophilic**
- **Transformed to hydrophilic**
- **Excreted in urine or bile**

PHASE 1 REACTIONS

- **Cytochromes P450**
- **Oxidation or demethylation**
- **Liver, also intestine, kidney, brain**

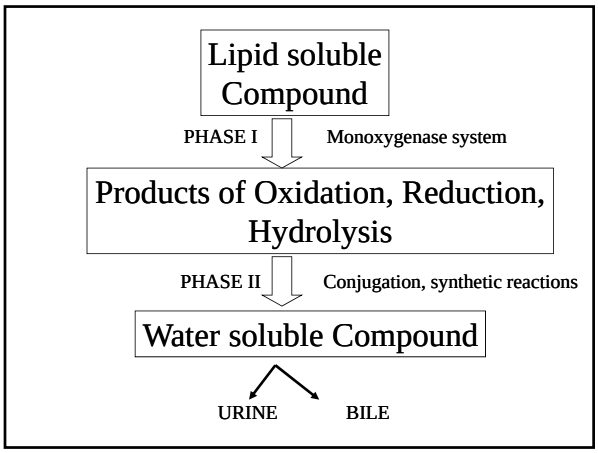
CONTRIBUTIONS OF SPECIFIC P450s TO DRUG METABOLISM



*multiple subfamily members exist

PHASE 2 REACTIONS

- **Water soluble polar groups added**
- **Glucuronidation (e.g. morphine, Lasix)**
- **Sulfation (e.g. steroids, bile acids)**



Magnitude of and screening for drug induced liver injury

RECENT WITHDRAWAL OF MAJOR DRUGS SUCH AS TROGLITAZONE ATTRACT ATTENTION

- Lawsuits 
- Fatalities/transplantation 

- Post-marketing surveillance important
- 5000 people in clinical trial
- Severe adverse drug reactions 1:50,000
- Only 10% serious drug reactions reported to FDA
- Usually take ~3 years to "convict"

DILI – Prevalence

- Community Hospital in Indiana
  - Bili ≥3 mg % - 29/732 = 4% - most AC
- LA AIDS
  - Jaundice 102/1040 – Drugs 39.4%
  - HAART, TB, T-Sulfa, AC
  - Infection 28.4%, EtOH 18.6%, colangiopathy 8.8%

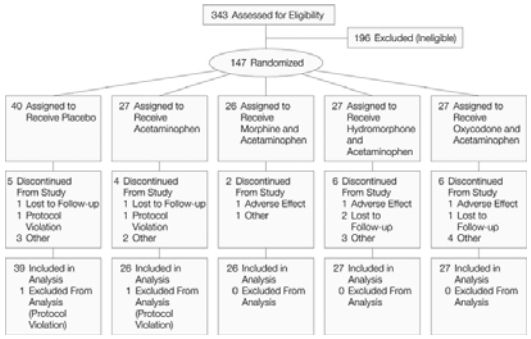
DILI – Other "Causes"

- Macromolecular AST
- Weight lifting
- Hemolysis

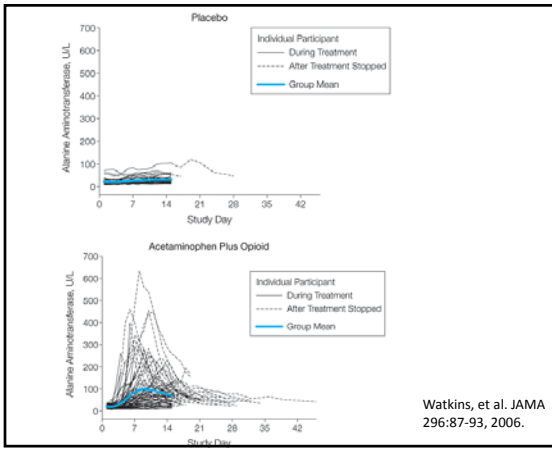
Aminotransferase Elevations in Healthy Adults Receiving 4 Grams of Acetaminophen Daily
A Randomized Controlled Trial

> 20% on 4 g Tylenol/day have LFTs > 5 x ULN

Watkins, et al. JAMA. 2006;296:87-93.



Watkins, et al. JAMA 296:87-93, 2006.



Watkins, et al. JAMA 296:87-93, 2006.

Updated definitions of healthy ranges for serum alanine aminotransferase levels.
Prati, et al. Ann Intern Med. 2002 Jul 2;137(1):1-10.

- Current "normal" AST/ALT too high!
- Recommend ALT:
  - –Men ≤ 30 U/L
  - –Women ≤ 19 U/L

AT: Not specific to liver

AST	ALT
Liver (9000:1)	Liver (7600:1)
Muscle (5200:1)	Muscle (750:1)
Heart	Kidney
Kidney	
Red cells	
Brain	

AT: Properties

- Source of normally circulating AT unclear
- AST and ALT activity in liver is 7000 and 3000 times higher than in serum
- AT are released either due to cell destruction or leaky cell membrane
- ALT is exclusively in cytoplasm whereas AST is both cytoplasm and mitochondrial
- Half life of total AST 17± 5 hours; ALT 47 ± 10 hrs
- AST/ALT ratio depends on gender and age

Clinical Value of Different Patterns

- In almost all liver diseases, ALT is higher than AST except in alcoholic liver disease and in advanced fibrosis
- In alcoholic hepatitis, AST is greater than ALT
  - Alcohol increases mitochondrial AST and decreases cytoplasmic ALT
  - ALT is also low due to pyridoxine deficiency
- AST and ALT are significantly lower in patients with renal failure

Clinical value of different values

- < 8 fold elevations are non-specific
- Fluctuating levels are not uncommon
- Normal AT in patients with HCV and NAFLD may still be associated abnormal hepatic histology
- Levels < 300 IU/L in chronic HCV/HBV, NAFLD, ALD, and hemochromatosis

Clinical value of different values

- Very high values in thousands

Ischemic injury

Drug or toxin injury

Viral Hepatitis

Autoimmune

Budd-Chiari

Stones

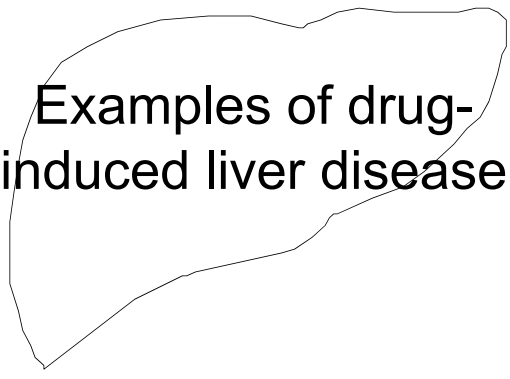
RISK FACTORS FOR DRUG-INDUCED LIVER DISEASE

FACTOR	EFFECTS	EXAMPLES
Age	>60 yrs.; greater frequency, severity More common in children	Isoniazid, nitrofurantoin, halothane, Valproic acid, salicylates
Gender	More common in women More common in men	Halothane, methyldopa, nitrofurantoin Azathioprine
Dose	Blood levels related to risk of hepatotoxicity Idiosyncratic rx's, partial dose dependence Total dose, duration exposure	Acetaminophen, aspirin Tetracycline, tacrine, oxypenicillins Methotrexate, vitamin A
Other drugs	Risk and severity of hepatotoxicity Risk of hepatotoxicity	Rifampicin, pyrazinamide & isoniazid Other anti-epileptics and valproic acid
Excessive EtOH	Lowered dose threshold, poorer outcome, Increased risk of liver dz	Acetaminophen hepatotoxicity Isoniazid
Nutrition:		
Obesity	Increased risk of liver injury	Halothane hepatitis
Fasting	Increased risk of hepatotoxicity	Acetaminophen

DRUG-INDUCED ACUTE HEPATITIS: COMPARISON OF IMMUNOALLERGIC AND METABOLIC IDIOSYNCRASY

CHARACTERISTIC	IMMUNOALLERGIC TYPE	METABOLIC IDIOSYNCRASY
Response to rechallenge	Invariable - fever in 12-72 hrs	Usual-abnl liver tests after 3-30 d
Fever	Usual, often first symptom, rigors	Occasional, less striking
Rash, arthralgia, lymphadenopathy	Common	Rare
Eosinophilia-blood -tissue	20-70% of cases Usual, a dominant cell type	< 10% cases Common, relatively minor cell type
Granulomas	Common	Rare
Autoantibodies	Often present	Rare
Latent period onset	2-10 weeks, relatively constant	4-24 weeks, highly variable
Course after d/c drug	Prompt improvement	Slower resp., occ. deterioration
Examples	Nitrofluantoin, methyldopa, phenylbutazone, diclofenac	Isoniazid, niacin, dantrolene, ketoconazole

Examples of drug-induced liver disease

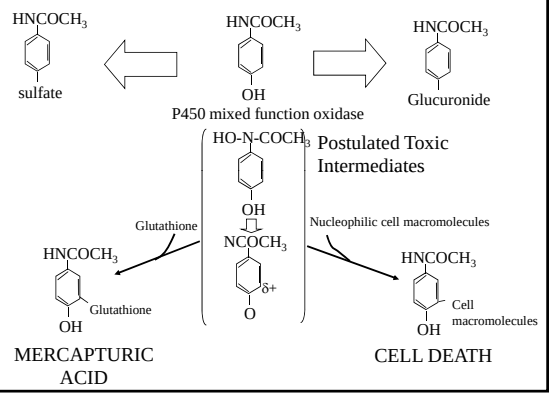


DIRECT TOXIC REACTIONS (ACETAMINOPHEN)

AC TOXICITY

- Purposeful O.D.
- Therapeutic misadventure
- #1 cause of FHF in USA
- EtOH/Fasting ↑ risk

ACETAMINOPHEN



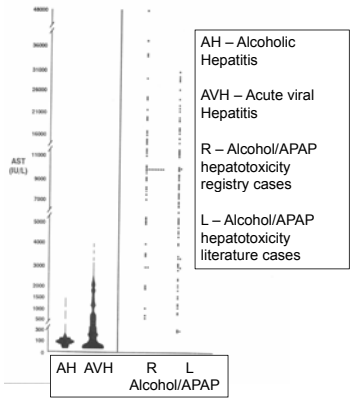
ACETAMINOPHEN TOXICITY PURPOSEFUL OVERDOSE

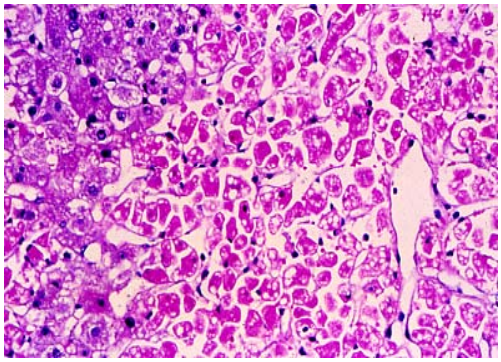
- Most important means of suicide in UK
- Approximately 10% of suicides in USA
- Usual dose > 15 g; range 7-75 g
- Adolescents or adults
- Females in 60% of cases

ACETAMINOPHEN TOXICITY PURPOSEFUL OVERDOSE

- Clinical features-3 phases
  - Phase 1 - 1-12 hrs. Nausea, vomiting collapse
  - Phase 2 - 12-48 hrs. Few or no symptoms
  - Phase 3 - 2-10 days, hepatic failure ± renal failure. Recovery, transplant or death
- Biochemical features
  - AST, ALT levels towering (1000-50,000 IU)
  - LDH very high
  - Acidosis, hypoglycemia
- Histology
  - Zone 3 necrosis

Peak AST values in patients with alcohol-associated acetaminophen hepatic injury compared with a range of values in acute viral hepatitis and alcoholic hepatitis





IDIOSYNCRATIC REACTIONS (ISONIAZID)

INH – Reversible injury; protective proteins

COMBINED TOXIC AND ALLERGIC REACTIONS (HALOTHANE)

- 44 year old white female
- Obese
- S/P heart transplant
- 10 days S/P cholecystectomy
- Presents with fever, myalgias

- AST 861
- Bilirubin 3.1
- Albumin 3.2
- PT 14.8

ALLERGIC/IMMUNOLOGIC HEPATITIS

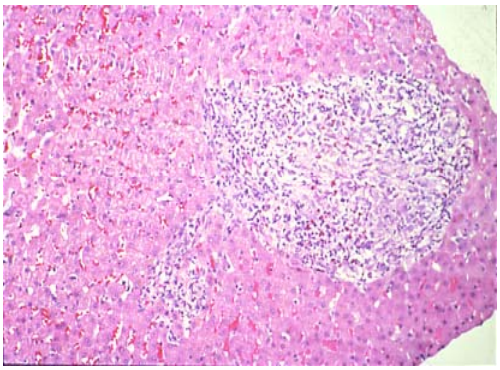
- Phenytoin
- Sulfonamides
- Dihydralazine

DRUG-INDUCED CHRONIC HEPATITIS

- Methyldopa
- Minocycline
- Nitrofurantoin

DRUGS ASSOCIATED WITH GRANULOMATOUS LIVER DISEASE

Allopurinol	Methyldopa	Quindine
Aspirin	Metolazone	Sulfonamides
Carbamazepine	Nitrofurantoin	Sulfonylureas
Cephalexin	Oxyphenbutazone	
Trichlormethiazide		
Diazepam	Penicillin	
Diltiazem	Phenytoin	
Halothane	Procainamide	
Isoniazid	Procarbazine	



MITOCHONDRIAL DYSFUNCTION FATTY LIVER AND ALCOHOLIC HEPATITIS-LIKE REACTIONS

- Amiodarone
- TCN
- Aspirin
- Valproic acid
- Antiiviral nucleoside analogues

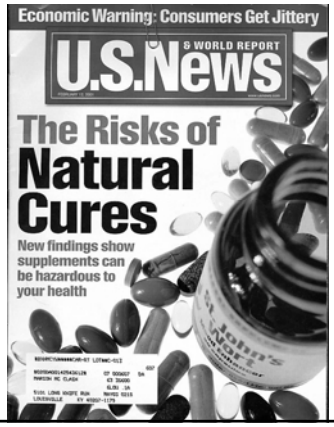
SINUSOIDAL CELL INJURY

- Veno-occlusive disease
  - –Cyclophosphamide
  - –Busulfan
- Monitor hyaluronic acid

INDOLENT CIRRHOSIS (METHOTREXATE)

CHOLESTATIC REACTIONS (ESTRADIOL)

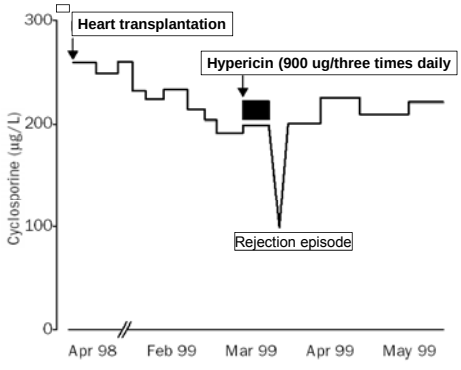
CAM-induced hepatotoxicity



CAM Safety Issues

- The labeling of CAM products is not necessarily correct
- Products may not be pure
- The advertised dose may not be correct.

- Drug Interactions frequent and often unrecognized problem (e.g., P450 system)
- Hepatotoxicity is one of the most frequently reported side effects of CAM products



Ruschitzka, et al. Lancet 355, pg. 548, 2000

Selected CAM agents and related hepatotoxicity

Herb/supplement	Action
Aristolochia	Hepatitis
Bajiaolian	Hepatitis
Black cohosh	Hepatotoxicity, fulminant hepatic failure
Cascara sagrado	Cholestatic hepatitis
Celandine	Acute hepatitis
Chaparral	Liver damage
Eternal Life	Hepatotoxicity

Hanje, et al. Nutr Clin Pract 21:255,2006

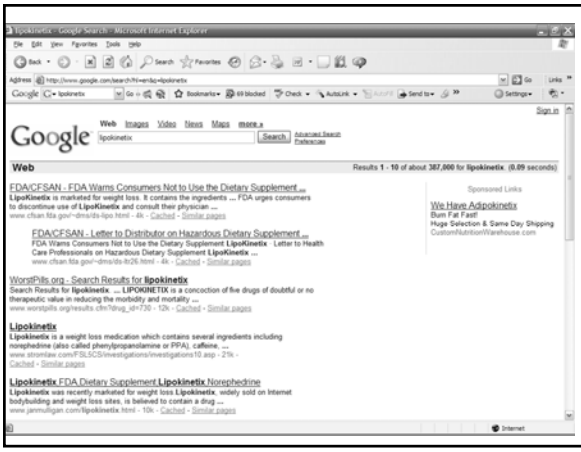
Selected CAM agents and related hepatotoxicity (contd.)

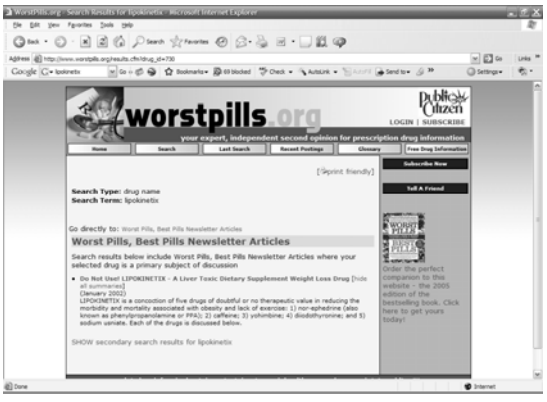
Herb/supplement	Action
Germander	Acute hepatitis
Kava kava	hundreds of cases of hepatic damage worldwide
LipoKinetix	Acute hepatitis, fulminant hepatic failure
Ma huang	Acute hepatitis
Pennyroyal	Hepatotoxicity
Pyrrolizidine alkaloids	veno-occlusive disease
Senna	toxic hepatitis
Skullcap	veno-occlusive disease

Hanje, et al. Nutr Clin Pract 21:255,2006

Diagnose that Liver Disease

- 21 year old obese AA female
- Speaks limited English
- Denies any drugs or hepatitis exposures
- ALT 1920
- Bili 3.9
- Albumin 2.8





CONCLUSIONS

- Drug induced liver disease is the major cause of fulminant liver disease in the USA, and an important cause of "hepatitis"
- High index of suspicion must be maintained