ACETAMINOPHEN OVERVIEW

acetyl-para-aminophenol (APAP)

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Flight from Pain

salicin
(willow bark)
prehistoric; Leroux 1829

salicylic acid
Na-salicylate: 1875

acetylsalicylic acid (ASA)
Gerhardt 1853; Bayer 1879
Dreser "aspirin" 1899
Coal-tar Analgesics

- Acetanilide, "afebrin" 1886
- Phenacetin 1887
- N-acetyl-p-aminophenol, acetaminophen; paracetamol; APAP
- Von Mering, 1893
Aspirin to Acetaminophen (APAP)

- Aspirin considered a wonder drug for >50 years (1899-1950). but found to cause gastrointestinal ulcers and bleeding, to cause CNS “salicylism,” altered acid-base balance (respiratory alkalosis), inhibit cyclooxygenase, Reye’s syndrome in children with viral infections.

- Acetaminophen approved 1950 and for OTC use about 1959 (proof of efficacy not required). did not cause bleeding or GI ulcers, did not cause Reye’s syndrome (noted in 1963, associated with aspirin 1980s) but, . .
Davidson DGD, Eastham WN. (Edinburgh) pp 497-9
Acute liver necrosis following overdose of paracetamol.

Thompson JS, Prescott LF. (Aberdeen) pp 506-7
Liver damage and impaired glucose tolerance after paracetamol overdosage.

Editorial pp 485-6
Liver necrosis from paracetamol.
An Insidious Agent

- After acute ingestion of a large amount (8-20 g in adult) *may (or may not)* experience nausea, sweating, vomiting, drowsiness - - - subsides -
- “latent period” of no symptoms for 24-72 hours *(but a lot of metabolic changes going on)* - - -

- nausea, anorexia, vomiting, tender-swollen liver, with ALT and AST in -000s, PT (INR) elevated
- liver failure: encephalopathy, acidosis, jaundice, 2° renal failure, hypoglycemia, bleeding, . . . death.
Acetaminophen (APAP) Conjugates

glucuronyl transferase → glucuronide

O- H+

sulfotransferase → sulfate

O- H+

O- H+

O- H+
Acetaminophen-induced hepatic necrosis

- **I. Role of drug metabolism** pp 185-194
  Mitchell JR, Jollow DJ, Potter WZ, Davis DC, Gillette JR, Brodie BB

- **II. Role of covalent binding in vivo** pp 195-202
  Jollow DJ, Mitchell JR, Potter WZ, Davis DC, Gillette JR, Brodie BB

- **III. Cytochrome P-450-mediated covalent binding in vitro** pp 203-210
  Potter WZ, Davis DC, Mitchell JR, Jollow DJ, Gillette JR, Brodie BB

- **IV. Protective role of glutathione** pp 211-217
  Mitchell JR, Jollow DJ, Potter WZ, Gillette JR, Brodie BB
APAP-induced hepatic necrosis

- Centrilobular liver necrosis in mice and rats related to drug metabolism rate, not to plasma levels of drug;

- Liver damage severity in mice related to covalent binding in vivo of metabolite to hepatocyte microsomal protein;

- Cytochrome P-450-mediated covalent binding of acetaminophen metabolites to cell microsomal protein;

- Glutathione depletion worsens, and glutathione addition prevents damage, without affecting metabolism
Acetaminophen Oxidation

NH\_CH\_3

O

O

N\_CH\_3

144x666 OH

S

OH

S

O

O

N-acetyl-benzoquinone imine

CYP 2E1

NAPQI

G

GSH

glutathione transferase

GSH

harmless mercapturide

CYP 3A4

CYP 1A2

CYP 2E1

N-acetyl-benzoquinone imine

cell necrosis!

cell protein
NAPQI Detoxification

NAPQI

*OXO

N-acetylcysteine

HS

COOH

H₃C

N-acetylcysteine

glutathione
Four Lines of Defense

- excretion of unchanged APAP - < 5%
- glucuronide conjugation - about 55 - 60%
- conjugation with sulfate - about 30 - 35%
- mercaptide formation with GSH - about 5%
- N-acetylcysteine conjugation - last chance
Moderate, Chronic Overdose

- about 30-50% of hep-toxic cases unintentional
- may have no prodromal symptoms
- doses of 4-8 g/day, after “inducers” dangerous?
- may develop tolerance (M. Black’s case)

- acetaminophen (APAP) plasma levels not always helpful, and may be too late for effective
treatment with Mucomyst (N-acetylcysteine), and no time for a liver transplant...
Factors Affecting Absorption and Metabolism

- dissolution
- gastric emptying
- absorption fraction
- glucuronidation
- sulfation
- renal function
- liver function
- mercaptides
- NAPQI formation

- solution, capsule, tablet
- varies up to 9-fold, (-) meals
- 1-3x in uptake, $C_{\text{max}}, AUC, T_{1/2}$
- (-) Gilbert’s, ranitidine
- (+) acetaminophen, estrogens
- (++) glucuronides, sulfates
- (++) $T_{1/2}$ with toxic overdose
- (++) GSH, N-Acys; (-) depletion
- (-) cimetidine, chronic APAP
- 60-fold inter-individual variation
- “overdose” for given person
- reperfusion, ischemia
Cytochrome P-450 2E1 Inducers

- alcohol (ethanol)
- isoniazid
- acetaminophen
- aspirin
- chlorzoxazone
- other alcohols, acetone
- retinol (vitamin A)
- obesity; cigarette smoke
- clofibrate, ciprofibrate
- trichlorethylene, pyrazole

Also, CYP 1A2 and 3A4 inducers, such as:

rifampacin, omeprazole, broiled beef; phenobarbital, phenytoin, lovastatin, prednisone, erythromycin, omeprazole.
foods, nutrients, AAs, gluc, FAs

proteins

dietary supplements, food additives, herbal products

alcohol

drugs

OTC remedies

environmental chemicals

hormones, cytokines

bilirubin
Variability of Absorption and Metabolism Among Individuals

- considerable variation at each step
  - absorption, glucuronidation, sulfation, oxidation, GSH conjugation
  - result is 60-fold variation in toxic NAPQI formation among individuals

- many drug-drug and drug-compound interactions