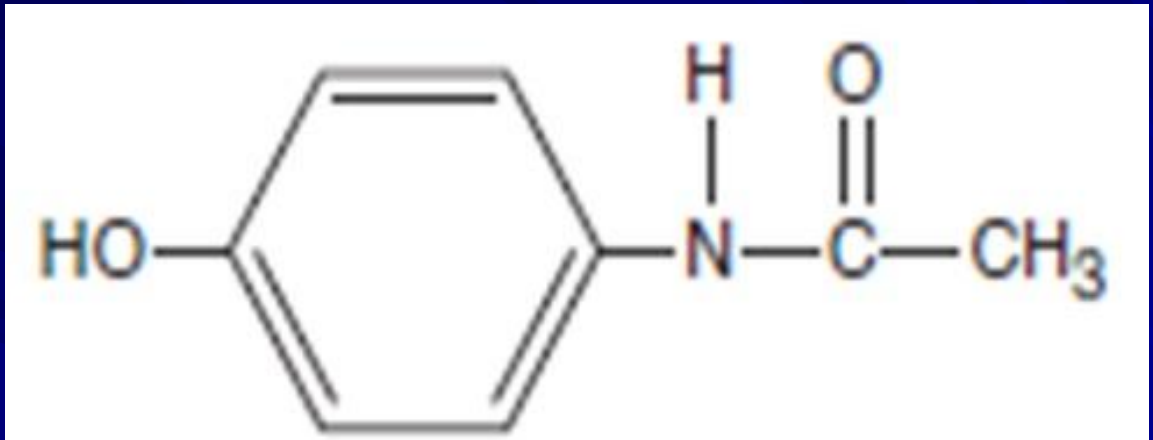
Acetaminophen

Assistant Prof. Dr. Najlaa Saadi
PhD Pharmacology
Faculty of Pharmacy
University of Philadelphia



***N*-Acetyl-*p*-aminophenol**
(acetaminophen)

- Acetaminophen Is used in the treatment of mild to moderate pain when an anti-inflammatory effect is not necessary.
- Phenacetin, a prodrug that is metabolized to acetaminophen, is more toxic than its active metabolite and has no rational indications.

Acetaminophen

- Inhibits prostaglandin synthesis in the CNS. (antipyretic and analgesic properties)
- Has less effect on cyclooxygenase in peripheral tissues, (no significant or weak anti-inflammatory activity)
- Not affect platelet function or increase blood clotting time.

Therapeutic Uses of Acetaminophen

Mild to moderate pain such as headache, myalgia, postpartum pain, it is a substitute for the analgesic and antipyretic effects of aspirin for those patients with:

1. Allergyic reaction to aspirin (bronchospasm)
2. Poorly tolerated to Salicylates
3. Hemophilic patient
4. Who have history of peptic ulcer
5. Concomitantly with probenecid in the treatment of gout (It does not antagonize the effects of uricosuric agents)
6. Children with viral infections

Dosage

- Acute pain and fever may be effectively treated with 325-500 mg four times daily and proportionately less for children.
- Dosing in adults is now recommended not to exceed 4 g/d, in most cases.

Note: 15 g of acetaminophen may be fatal, death being caused by severe hepatotoxicity with centrilobular necrosis, sometimes associated with acute renal tubular necrosis

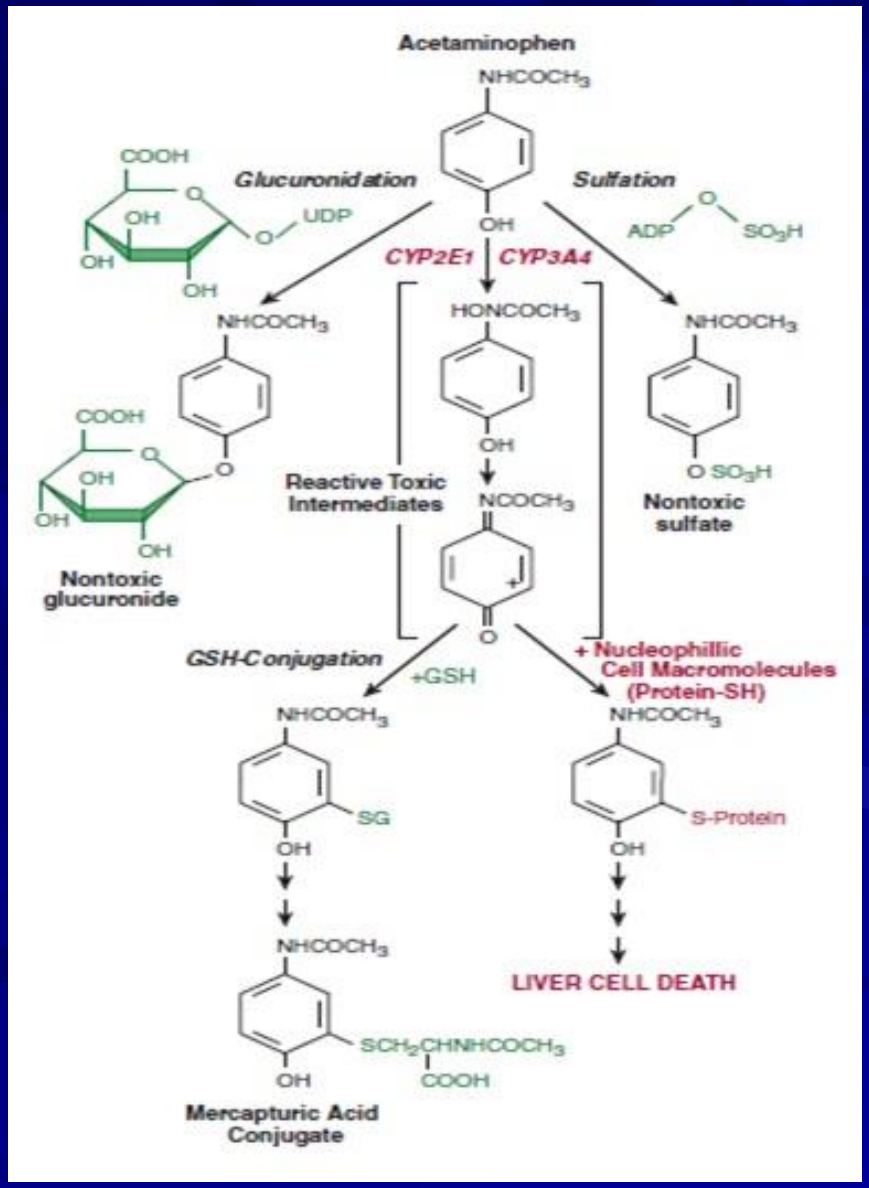
Pharmacokinetics of Acetaminophen

- Rapidly absorbed from the GI tract.
- Peak blood concentrations are usually reached in 30-60 minutes
- A significant first-pass metabolism
- The half-life is 2-3 hours
- Slightly bound to plasma proteins
- Converted to acetaminophen sulfate and glucuronide, which are pharmacologically inactive
- CYP 450 cause production of the minor but highly reactive metabolite (N-acetyl-p-benzoquinone), it is important in large doses because it is toxic to both liver and kidney
- Less than 5% is excreted unchanged.

- At normal doses, the N-acetyl-p-benzoquinone reacts with the sulfhydryl group of glutathione, forming a nontoxic substance
- At large doses of acetaminophen, the available glutathione in the liver becomes depleted and N-acetyl-p-benzoquinone reacts with the sulfhydryl groups of hepatic proteins, forming covalent bonds (Hepatic necrosis occur, Renal tubular necrosis may also occur).

Note: Administration of N-acetylcysteine, which contains sulfhydryl groups to which the toxic metabolite can bind, can be lifesaving if administered within 10 hours of the overdose. This agent should be avoided in patients with severe hepatic impairment

Metabolism of Acetaminophen



Adverse Effects of Acetaminophen

- In therapeutic doses, a mild increase in hepatic enzymes (reversible)
- Dizziness, excitement and disorientation may occur with larger doses,
- Hemolytic anemia and methemoglobinemia are very rare adverse
- Toxic dose cause severe hepatotoxicity with centrilobular necrosis, sometimes associated with acute renal tubular necrosis