ACETAMINOPHEN TOXICITY

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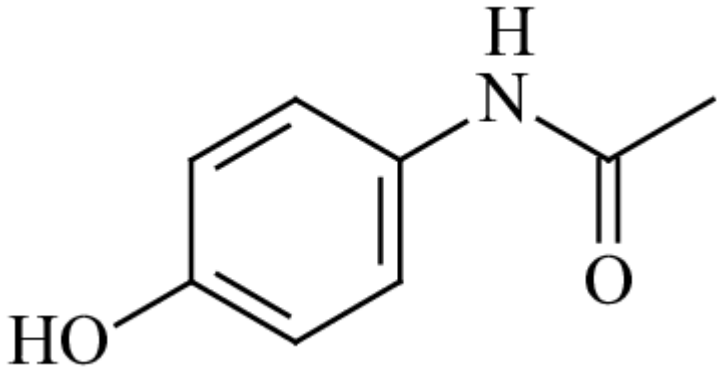
Introduction



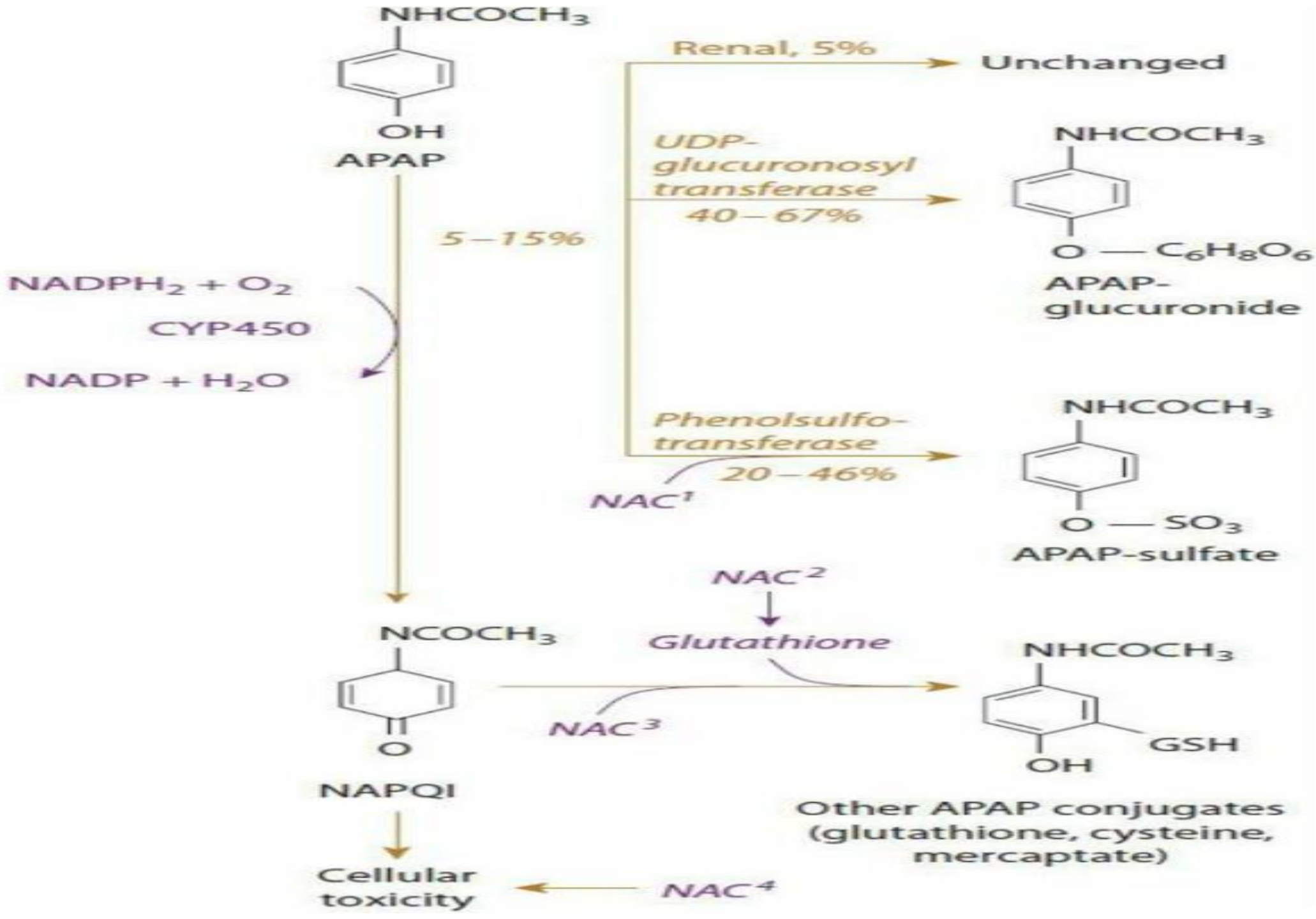
- It is a **para-aminophenol** derivative.
- It has potent **antipyretic** and **analgesic** effects with **poor anti-inflammatory** activity
- It usually does **not produce** gastric irritation
- It has **no antiplatelet** action
- Paracetamol is the **preferred** analgesic and antipyretic in patients with peptic ulcer, bronchial asthma and in children

PHARMACOLOGY

- The mechanism of analgesic action of acetaminophen is **unclear**.
- The drug is only a **weak COX-1 and COX-2 inhibitor** in peripheral tissues, which accounts for its lack of anti-inflammatory effect.
- Evidence suggests that acetaminophen may inhibit a third enzyme, **COX-3, in the CNS**.
- Acetaminophen is an **analgesic** and **antipyretic** agent; it **lacks** antiinflammatory or antiplatelet effects.

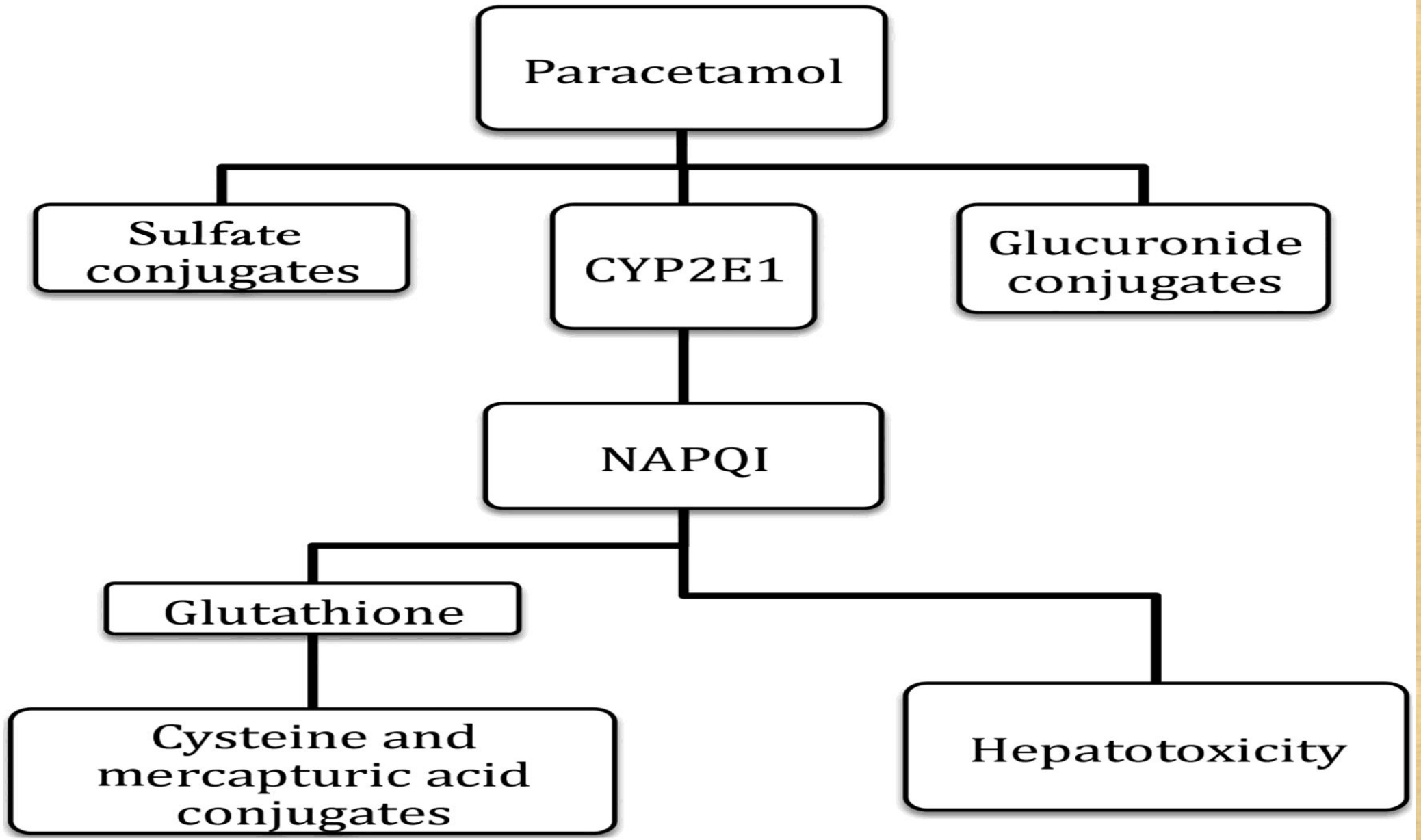
PHARMACOKINETICS

1. It is effective by **oral** and parenteral routes.
2. It is **well absorbed**, The oral **bioavailability** is 60% to 98%,
3. **Widely** distributed all over the body, (Vd) is 1 L/kg
4. Metabolized in **liver** by sulphate and glucuronide conjugation.
5. The **metabolites** are excreted in **urine**


NHCOCH3
OH
APAP
Renal, 5%
Unchanged
UDP-glucuronosyl transferase
40–67%
NHCOCH3
O — C6H8O6
APAP-glucuronide
5–15%
NADPH2 + O2
CYP450
NADP + H2O
Phenolsulfo-transferase
20–46%
NAC1
NHCOCH3
O — SO3
APAP-sulfate
NAC2
Glutathione
NCOCH3
O
NAPQI
NAC3
NHCOCH3
GSH
OH
Other APAP conjugates (glutathione, cysteine, mercaptate)
Cellular toxicity
NAC4

Mechanism of toxicity

- At therapeutic doses, glutathione inactivates **NAPQI by conjugation** and subsequent transformation to acetaminophen-3-mercapturic acid, which is readily excreted.
- When a **massive overdose** is ingested, liver enzymes are **saturated** and the supply of glutathione is inadequate to detoxify NAPQI.
- The concentration of toxic metabolite, therefore, increases and can **bind covalently** to sulfhydryl groups of hepatic cellular proteins, resulting in centrilobular necrosis.
- N-acetyl-p-benzoquinoneimine (NAPQI) binds covalently to hepatocyte proteins causing hepatocellular necrosis.


Paracetamol
Sulfate conjugates
CYP2E1
Glucuronide conjugates
NAPQI
Glutathione
Cysteine and mercapturic acid conjugates
Hepatotoxicity

Dose

- **10-15mg/kg/dose** up to 2.6g/day.
- The **minimal toxic amount** is approximately **3g or 140-200mg/kg** in child and **7.5g** or more in adult.
- Liver toxicity usually follow ingestion of **more** than **15g** in adult.
- Patient who have liver disease or depleted glutathione stores may toxic after taking as small an amount as 7.5g.
- The threshold dose for producing hepatotoxicity is **250 mg/kg.**

CLINICAL MANIFESTATIONS

Stage	Time Post-Ingestion	Characteristics
I	0 – 24 h	Anorexia, nausea, vomiting. Hepatic transaminases may start to rise.
II	24 – 72 h	May see improvement in clinical findings, some patients may report right upper quadrant abdominal pain. Elevated AST, ALT, bilirubin, INR.
III	72 – 96 h	Hepatic failure, acidosis, sometimes renal failure and pancreatitis. Peak AST, ALT, bilirubin, and INR levels.
IV	> 5 days	Progression to multiple organ failure (sometimes fatal) Resolution of hepatotoxicity in survivors

Lab. analysis

- The **serum** acetaminophen concentration is the basis for diagnosis and treatment. A diagnostic serum concentration is helpful, even in the absence of clinical symptoms, because clinical symptoms are delayed.
- **Liver function** tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST]), bilirubin [total and fractionated], alkaline phosphatase) Prothrombin time (PT).
- Glucose, Renal function studies
- Lipase and amylase.
- Arterial blood gas and ammonia
- Urinalysis (to check for hematuria and proteinuria)
- ECG

Management

- **GASTROINTESTINAL DECONTAMINATION**
- If patients present **within 4 hours** of ingestion:
- 1. **administered activated charcoal**. AC is most effective when given within the first 1 to 2 hours following APAP ingestion,
- 2. **cathartics** (Saline sulfate cathartics are preferred because they may enhance the activity of the sulfate metabolic pathway and provide hepatic protection, but should avoided in the presence of renal failure.

Management

- **3.Emesis** (Ipecac) is best avoided in the emergency department because it may interfere with the retention of activated charcoal and antidote.
- **4.Gastric lavage** has been questioned because it is labor-intestine and delays the administered of activated charcoal.

Management

- **Supportive Care**

➢**General supportive** care consists primarily of controlling nausea and vomiting

➢Monitoring for and treatment of **hypoglycemia** are critical because hypoglycemia is one of the most readily treatable of the life-threatening effects of hepatic failure

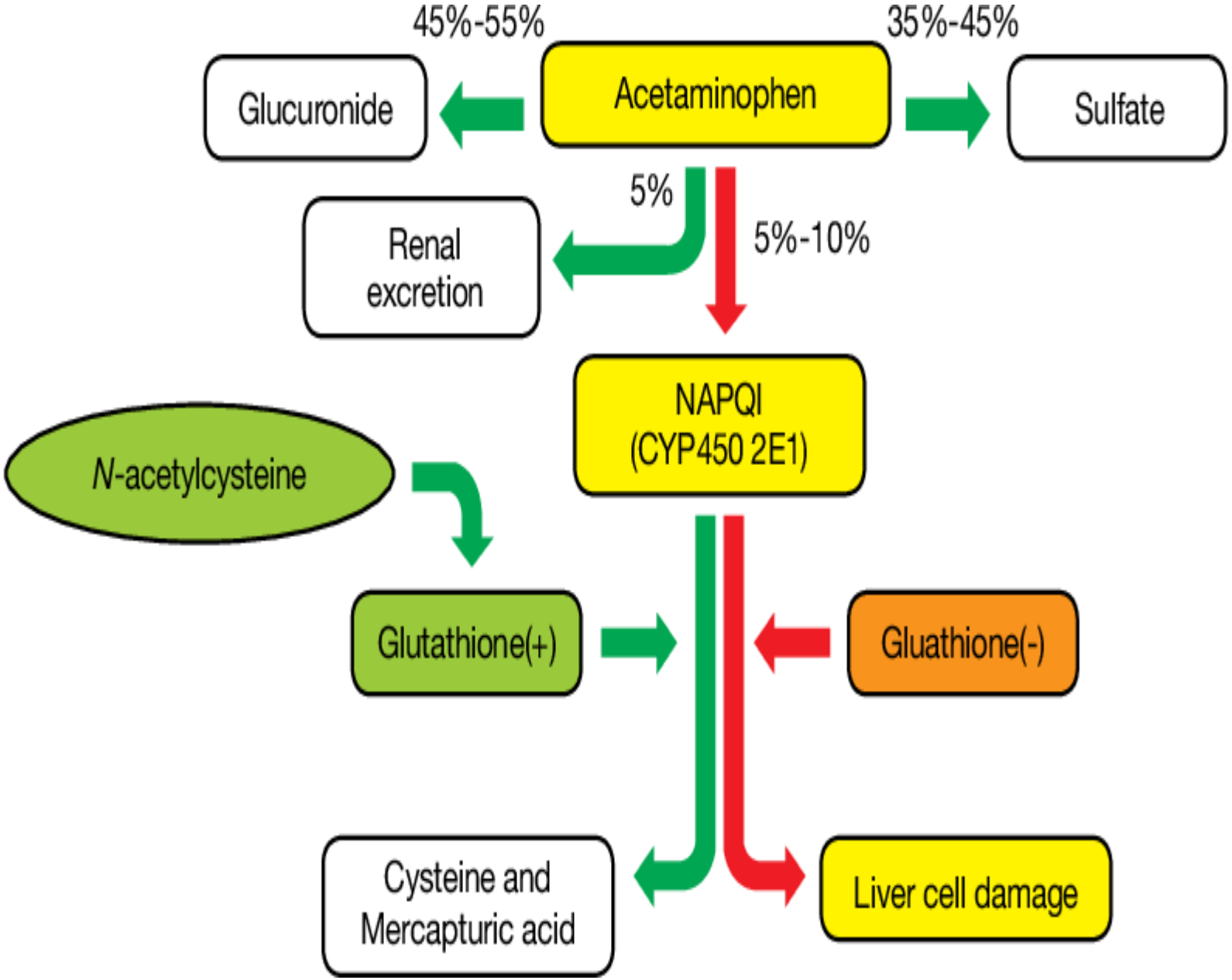
➢**Vitamin K** may produce some improvement in coagulopathy.

➢Administration of fresh-frozen plasma **(FFP)**

➢Supportive therapy for **cerebral edema**, including cooling, hypertonic saline, elevation of the head, and support of the cerebral perfusion pressure, are all indicated

Management

- **N-Acetylcysteine**
- It is N- acetyl derivative of the amino acid cysteine.
- NAC is metabolized to a glutathione precursor (cysteine) that provides protective levels of glutathione surrogate to detoxify the hepatotoxicity reactive metabolite of APAP.
- The **dose** of NAC for the treatment of APAP intoxication is a **loading dose 140mg/kg** followed by **70 mg/kg** every **4 hours** for **17** additional doses giving a total by **72 hours** of therapy.
- The **initial** dose of N-acetylcysteine is given within the **first 10 to 16** hrs. after ingestion of acetaminophen


45%-55%
35%-45%
Glucuronide
Acetaminophen
Sulfate
5%
5%-10%
Renal excretion
NAPQI (CYP450 2E1)
N-acetylcysteine
Glutathione(+)
Gluathione(-)
Cysteine and Mercapturic acid
Liver cell damage


4 x 30mL Sterile Vials
NDC 66220-107-30
Acetadote®
(acetylcysteine) Injection
200mg/mL (6g/30mL)
For Intravenous Use
CUMBERLAND
Acetadote
200mg/mL
(6g/30mL)

N-acetylcysteine administration

- NAC may be administered via the **oral** or **intravenous** routes
- **IV route** cause rare but severe **anaphylactoid** reactions
- **Oral route** associated with a greater than 20% risk of **vomiting**
- There are **three** scenarios in which **intravenous NAC** is generally recommended:
- (1) APAP toxicity in pregnant women,
- (2) APAP-induced hepatic failure,
- (3) intractable vomiting preventing oral treatment.

N-acetylcysteine administration

- The **loss** of efficacy **16** hours after ingestion is not complete.
- **After 24** hours NAC may **not** be effective if APAP hepatotoxicity is already present.
- **NAC** should be **stopped** if hepatic encephalopathy develop
- If patient **vomits** the loading dose or any of the maintenance doses within 1 hr of administration, a replacement dose is given immediately and the patient continues on the same schedule.
- When **persistent vomiting** occurs, NAC can be instilled through a **nasogastric tube**. past the stomach into duodenum and administered the antidote by a slow drip over an hour.

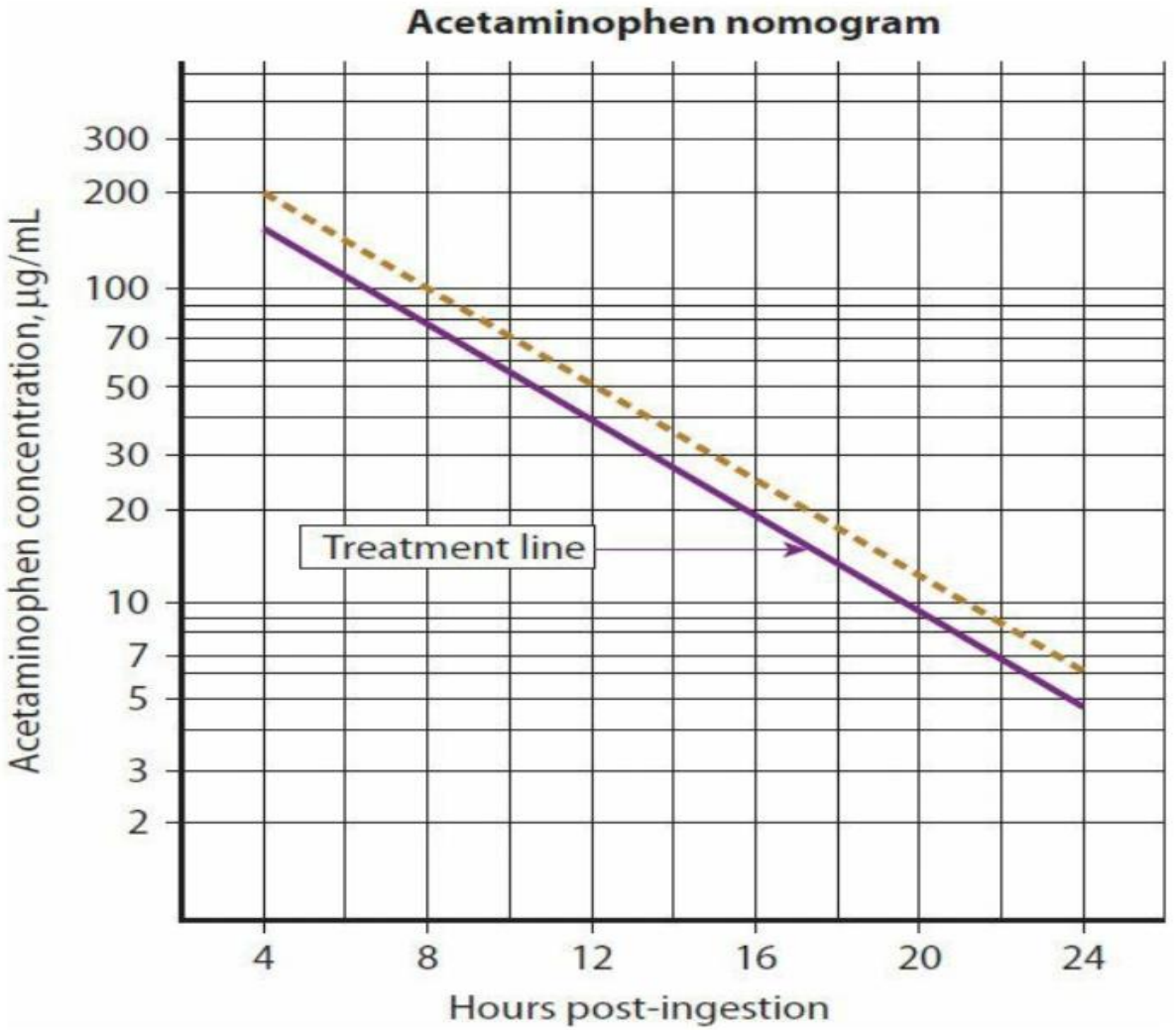


FIGURE 35–2. Rumack-Matthew nomogram (reconstructed) for determining the risk of APAP induced hepatoxicity after a single acute ingestion. Serum concentrations above the treatment line on the nomogram indicate the need for N-acetylcysteine therapy.

Management

- **Hepatic Transplantation.**

➢Hepatic transplantation may increase survival for a select group of severely ill patients who have APAP-induced fulminant hepatic failure

- **Hemodialysis**:

➢Both intermittent hemodialysis (HD) and continuous venovenous hemodialysis (CVVHD) increase elimination of APAP.

➢**Other antidote**: cimetidine, a cytochrome P450 enzyme antagonist has been suggested as an antidote.


Thank You!
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