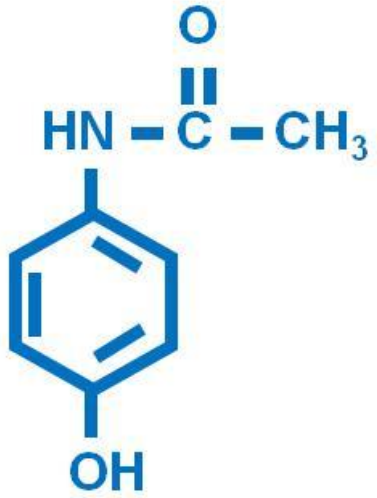
Acetaminophen (paracetamol) Toxicity

Key points

- Suspect paracetamol poisoning in all adolescent deliberate self-poisonings.
- N-acetylcystine (NAC) is a safe and effective antidote. Time to NAC is crucial to protect the liver from significant toxicity.
- Stated timing and dose are often unreliable and this needs to be taken into consideration.

Paracetamol



- N-acetyl-p-aminophenol (APAP)
- Effective analgesic and anti-pyretic
- Its antipyretic action is directly on the hypothalamus
- ……APAP action is mediated by interference with PG synthesis in the CNS
- Very weak activity as inhibitor of the peripheral PG synthetase……weak anti-inflammatory action

Paracetamol

- Generally well tolerated
- Use: analgesic / anti-pyretic (0.5-1 g every 4 to 6 hours, maximum daily dose 4 g) (2000 mg/day for chronic alcoholics)
  - 2014 FDA Alert: discontinue prescribing and dispensing prescription combination drug products containing >325 mg acetaminophen per dosage unit.
- Children (less 12 years) : up to 75mg/kg/day
- Available in tablets regular strength 325mg, 500mg
- Also supplied as suppositories 125, 250mg
- Extended-release preparation

Aspirin vs 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 ….*but,….***

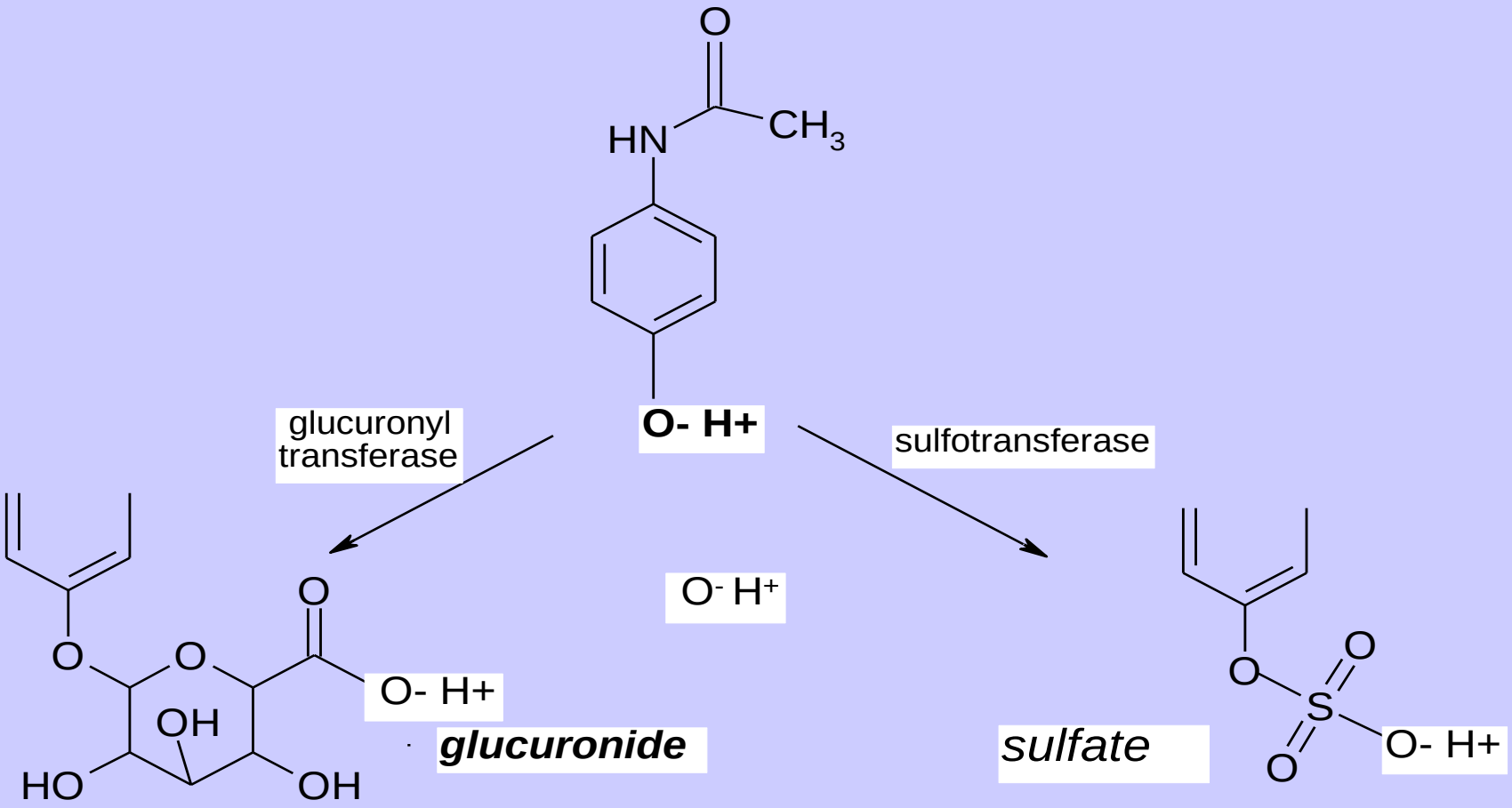
Br Med J 1966 (27 Aug); 2 (5512)

- **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*****.**

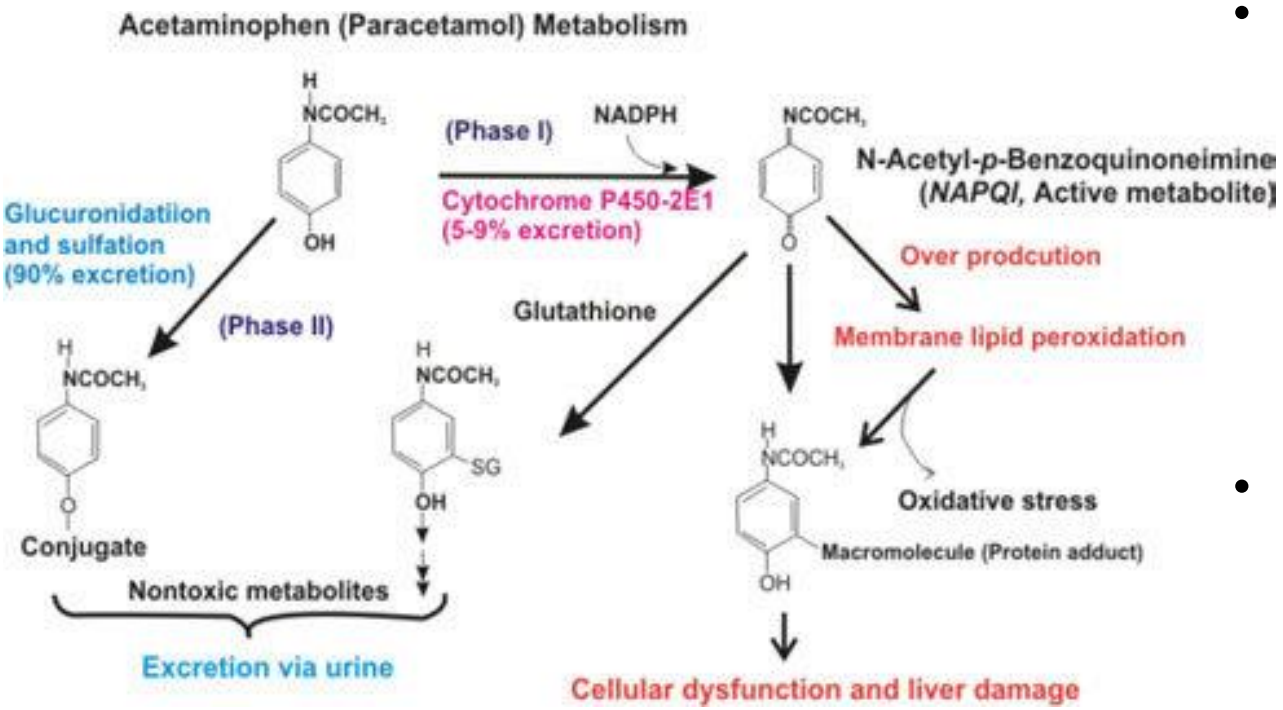
Paracetamol ToxicoKinetics

- Rapidly absorbed from GI tract and reaches a peak plasma level in 30min to 2 hrs; half life is approximately ~3 hrs
- Elimination is by hepatic metabolism (95%):
- Metabolized in liver mainly through glucuronic acid conjugation
- 65% inactive glucuronide conjugation, 30% sulfate conjugate
- A small portion of the ingested dose undergoes metabolism by the cytP450 mixed function oxidase to a reactive, arylating metabolite, **N-acetyl-p-benzoquinoneimine (NAPQI)**

Acetaminophen (APAP) Conjugates



Paracetamol Metabolism



- **<u>At therapeutic doses</u>** acetaminophen is **glucuronidated or sulfated** at its –OH group which can be **<u>excreted</u>**

- When the glucuronidation and sulfation pathways **become saturated**, a **<u>cytochrome p450 pathway</u>** converts the acetaminophen to NAPQI (a reactive compound)

Mechanism of Toxicity

- NAPQI is a strong oxidizing agent, **subsequently reduced by the sulfhydryl groups of glutathione to a nontoxic form**
- This glutathione conjugates is then converted to **cysteine and mercapturic acid conjugate**
- If no sufficient glutathione available…..NAPQI bind covalently to cellular protein…..**hepatocellular and renal toxicity**

HEPATOTOXICITY

- **Hepatotoxicity In adults,** hepatotoxicity may occur after ingestion of a single dose of 10 to 15 g (150 to 250 mg/kg) of acetaminophen
- • Doses of 20 to 25 g or more are potentially fatal High-risk people:

• Conditions of CYP induction (e.g. heavy alcohol consumption, those on anticonvulsant drugs)

• Condition of GSH depletion

• With pre-existing liver disease

Phases of toxicity

- Phase 1 – from to of ingestion to 24 hours

The patient typically has anorexia, nausea, vomiting, and diaphoresis

The results of laboratory tests are usually normal.

- Phase 2 – 24-72 hours

RUQ pain, elevated liver enzymes, prolonged PT.

Phases of toxicity

- Phase 3 – 72-96 hours

Also known as the hepatic stage

Severe signs of hepatotoxicity appear

This includes:

1. Plasma ALT and AST levels often >10,000 IU/L, Increased in PT or INR
2. A total bilirubin concentration above 70umole/l (primarily indirect)
3. Death most commonly occurs in this stage, usually from multiorgan system failure.

Phases of toxicity

- Phase 4 (4 days-2 weeks) :

• Is the recovery stage

• Patients who survive stage III enter a recovery phase that usually begins by day 4 and is complete by 7 days after overdose

• However, transient renal failure may develop 5-7 days after ingestion

• Complete hepatic recovery may take 3-6 months.

Table 1. Phases of Acute Acetaminophen Toxicity

Phase 1
(30 minutes to 24 hours)
Anorexia
Nausea
Vomiting
Pallor
Diaphoresis (excessive sweating)
Patient may also be asymptomatic

Phase 2
(24-72 hours)
Symptomatology from Phase 1 becomes less pronounced
Right upper quadrant pain from liver damage
Liver enzyme abnormalities
PT and creatinine abnormalities

Phase 3
(72-96 hours)
Sequelae of hepatic damage
Jaundice
Coagulopathy
Encephalopathy
Renal failure
Cardiomyopathy
Death

Phase 4
(4 days to 2 weeks)
Resolution of symptoms and lab abnormalities, with complete resolution of liver damage
or
Continued worsening of liver function and death

Complications

- 10% of patients develop renal impairment from **acute tubular necrosis** - occasionally in the absence of hepatic failure
- Very rarely patients with G6PD deficiency develop methemoglobinemia and hemolysis

Prognostic features

- A prothrombin time of 20s at 24 hrs indicates significant hepatocellular damage; the more rapid the rise in PT, the poorer the prognosis

- In patients developing hepatic failure, a poor prognosis is suggested by:
  1. Blood pH <7.3;
  2. Prothrombin time >100s;
  3. Serum Creatinine >300 mol/l

  They should be considered for early liver transplantation

Prognostic features

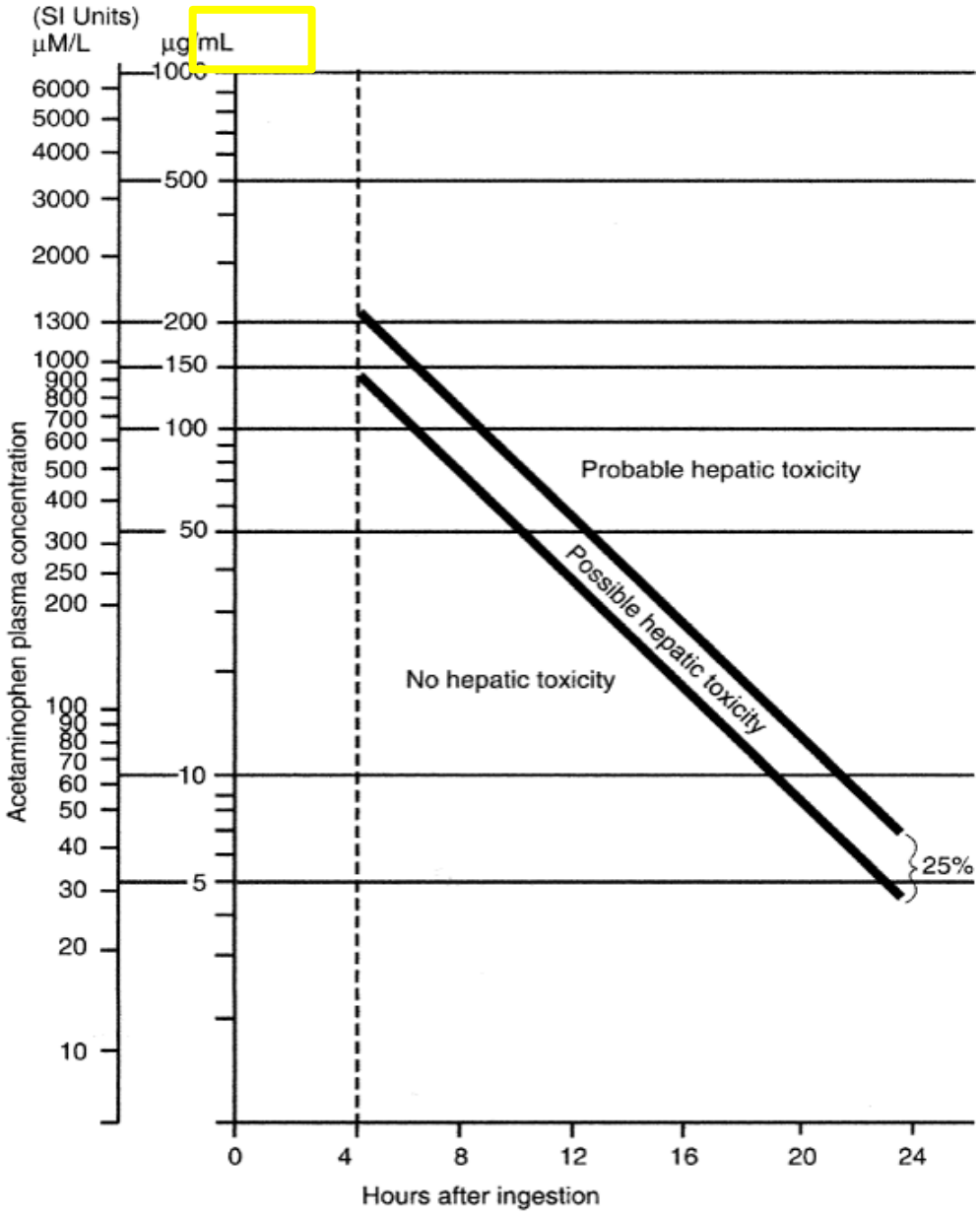
- **Laboratory analysis:**

- paracetamol levels must be determined not sooner than 4 hours after ingestion??.....After the distribution phase

- The values are plotted on the **modified Rumack-Matthew nomogram** to assess potential toxicity

PARACETAMOL TOXICITY MANAGEMENT

- Paracetamol levels checked at 4hrs & compared to treatment curve (200mg/l or 1.32mmol/l at 4h joined to 6mg/l or 0.04mmol/l at 24h). 60% of patients above the line develop severe liver damage defined as AST >1000
- Patients on or above the line should be given IV N-acetylcysteine*
- up to 10% have a rash, bronchospasm or hypotension during the Tx (acts as a mast cell releaser). Stopping and giving diphenhydramine IV usually allows the IV to be safely restarted al slow infusion rate



PARACETAMOL TOXICITY MANAGEMENT

Cautions for use of this chart:

(1) Must be used only in relation to a **single acute ingestion**, and when the approximate **time of ingestion is known**

(2) Concomitantly ingested drugs (opioids and anticholinergics) or carbohydrate-rich foods may change the gastric emptying time and the peak time

(3) May underestimate the peak concentration of APAP extended-release tablet coz of a possible delayed peak

PARACETAMOL TOXICITY MANAGEMENT

If time of ingestion is not known?

- One way to overcome this obstacle…..determine the patient's plasma **half-life of acetaminophen**
- Determination of at least 3 plasma levels and plotting them to obtain a half-life value
- The approximate **normal half life** of acetaminophen is 1 to 3hrs…..is prolonged following overdose…..use this indicator for potential liver toxicity:
- If plasma **half-life >4hrs**, **liver damage is likely to occur**
- **If >12hrs**, **hepatic coma** will probably ensue

Treatment of Acute Acetaminophen Ingestion

1. **Gastrointestinal Decontamination**

- Is largely determined by the approximate timing and estimated amount of acetaminophen ingested, any suspected co-ingestions, and the patient's mental status
- Administer **activated charcoal** orally. **Gastric lavage is not necessary** after small to moderate ingestions if activated charcoal can be given promptly
- **Spontaneous vomiting** may delay the oral administration of antidote or charcoal and can be treated with **metoclopramide**

Other Therapies for Acetaminophen Toxicity

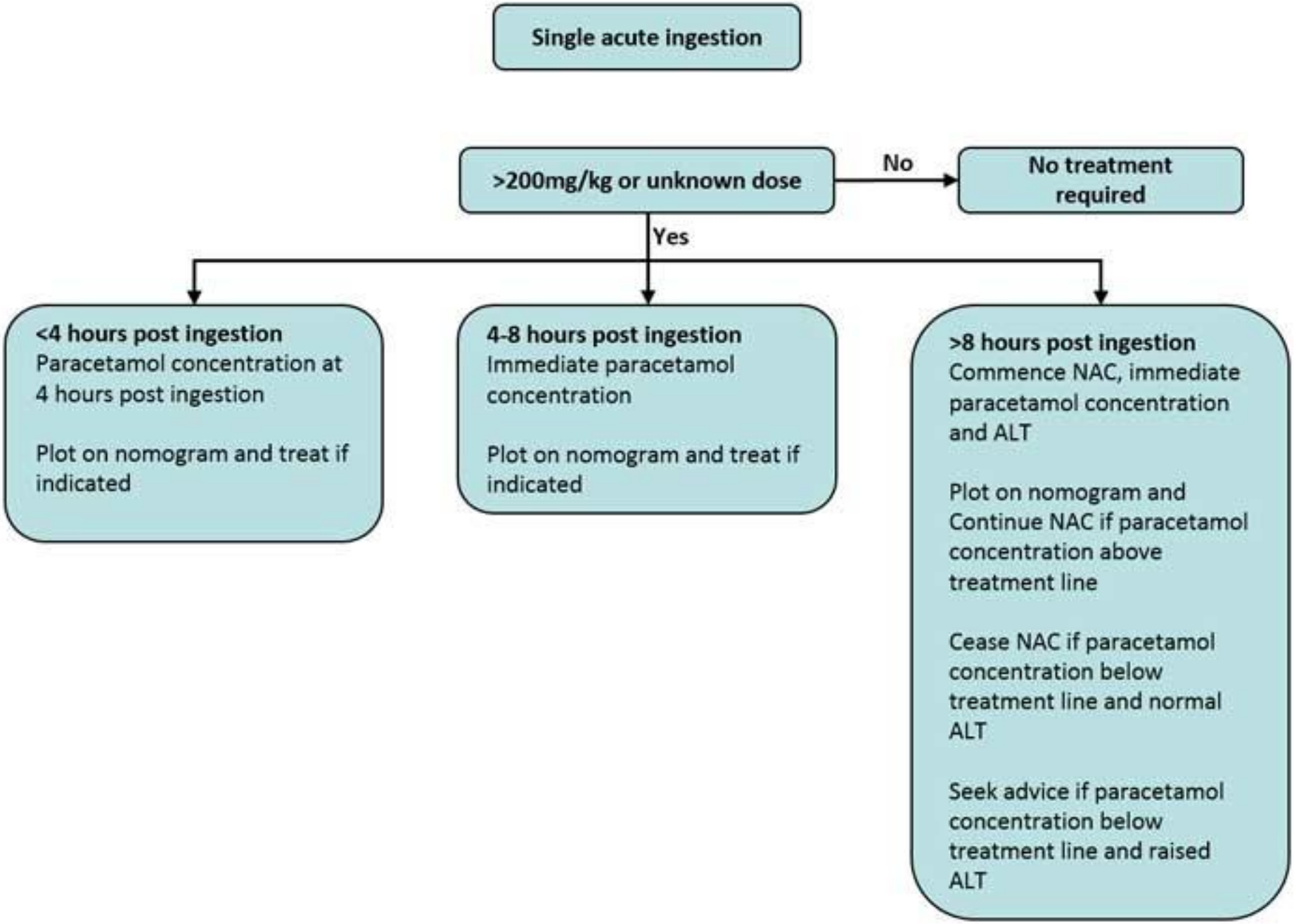
Extracorporeal methods:

- **Hemodialysis** effective but is not generally indicated because **antidotal therapy** is so effective
- **Dialysis s**hould be considered for **massive ingestions** with very high levels (eg, >1000 mg/L) complicated by coma or renal failure that persists more than 48hrs
- **Charcoal hemoperfusion** does not remove any toxic intermediates formed in the liver or the kidney and currently has **no role** in the management of acetaminophen toxicity

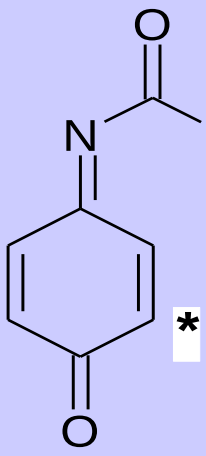
Treatment of Acute Acetaminophen Ingestion

3. **Antidote Therapy for Acetaminophen Toxicity**

- Different amino acids containing sulfhydryl groups were tested as potential antidotes
- **Glutathione** was an immediate choice but was **expensive** and had **poor penetration into cells**
- Although **cysteamine** and **methionine** were found to be effective antidotes, **N-acetylcysteine (NAC)** was **more effective and had fewer adverse effects**

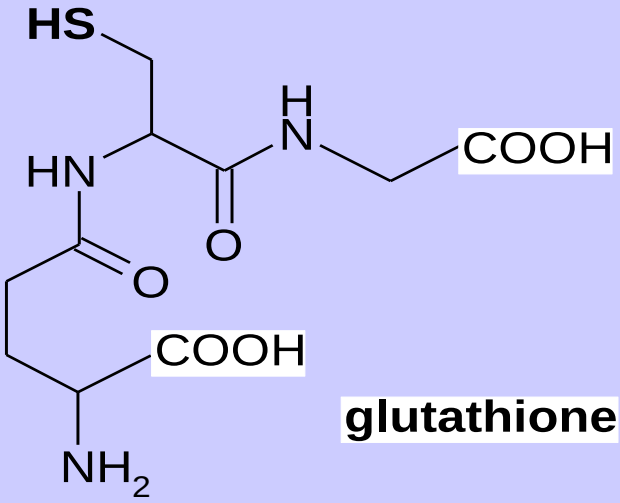

Single acute ingestion
>200mg/kg or unknown dose
No
No treatment required
Yes
<4 hours post ingestion
Paracetamol concentration at 4 hours post ingestion
Plot on nomogram and treat if indicated
4-8 hours post ingestion
Immediate paracetamol concentration
Plot on nomogram and treat if indicated
>8 hours post ingestion
Commence NAC, immediate paracetamol concentration and ALT
Plot on nomogram and Continue NAC if paracetamol concentration above treatment line
Cease NAC if paracetamol concentration below treatment line and normal ALT
Seek advice if paracetamol concentration below treatment line and raised ALT

NABQI Detoxification

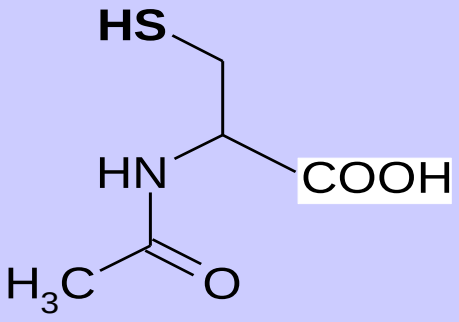


NABQI

*



glutathione



N-acetylcysteine

Mechanism of Action

- **N-acetylcysteine** is the **antidote of choice** for acetaminophen toxicity
- Several different mechanisms of action have been postulated for the antidotal effect of NAC, including:
  1) **NAC is a glutathione precursor** that replace glutathione storage;
  2) **NAC reacts directly with NABQI** and prevents cellular damage;
  3) **NAC acts as a sulfur donor** to enhance the non-toxic sulfation elimination of acetaminophen;
  4) **NAC has some non-specific cellular protective effects**, which may be related to anti-oxidizing effects in the microcirculatory system

Administration…p.o

- In the **United States, the oral form** of NAC is used
- The **loading dose** of NAC **is 140 mg/kg**; the **maintenance dose is 70 mg/kg every four hours** for an additional **17 doses (72 hours total)**
- i.v route avoids the risk of Tx failure by vomiting (available in Canada & EU)

Preparation of Antidote Solution

- The duration of **i.v** regime is 20 hours
- loading dose of 140 mg/kg, 5 maintenance dose of 70 mg/kg every four hours
- If evidence of liver injury develops, continue NAC until liver function tests are improving
- The mixture should be **consumed within one hour** of preparation

Side Effects of Oral NAC

- **Nausea and vomiting**, which are due to the hyperosmolarity and disagreeable "**rotten egg**" odor of NAC
- To minimize these gastrointestinal symptoms, NAC should **be diluted to a 5% solution with a sweet beverage** (juice or soda) to make it more palatable
- **Alternatively, NAC may be administered through a nasogastric tube**
- Anaphylactic reactions are **rare with oral** NAC, although rash, angioedema, and bronchospasm have been reported with intravenous NAC

Tx of Chronic Acetaminophen Poisoning

- Repeated chronic overdose can produce toxic levels of hepatotoxicity
- **NAC is administered no matter what the time since the last dose in case**:
  - History of more than the recommended dose for several days (more than 200 mg/kg within a 24-hour period, 150 mg/kg/d for 2 days, or 100 mg/kg/d for 3 days or more)
  - Elevated liver function tests
  - Detectable acetaminophen in the serum
  - Persistent vomiting

Tx of Acetaminophen Poisoning

- **PREGNANCY:**
- Overdose during **pregnancy** has been associated with **fetal death and spontaneous abortion**
- The available data appear to indicate **no teratogenicity for APAP and NAC (category C)**
- Currently, there are **no recommendations** for the early **termination or delivery** of a fetus in setting of APAP toxicity
- It is recommended that pregnant patients with a toxic blood concentration of APAP be treated with NAC to prevent hepatotoxicity in both fetus and mother

NAC and Activated Charcoal

- Binding of NAC to activated charcoal has been demonstrated both in *in-vitro* and *in-vivo* studies
- Administration of 60 gm of activated charcoal with NAC decreases the bioavailability of NAC by approximately 20%
- The current evidence suggests that a small decrease in NAC does not alter its efficacy
- If multiple doses of activated charcoal are required because of co-ingestions, it would be prudent to separate NAC and activated charcoal dosing by 1-2 hours