L2-Acetaminophen overdose

هذه المذكرة شاملة كل
محتوى سلايدات الدكتور!

By:
Ahmed Elalem

Objectives:
-Know the potential toxic dose of APAP according to age
-Know the symptoms and signs of APAP OD
-Know the indications of NAC therapy

Editing File

Acetaminophen

AKA: N -acetyl-p-aminophenol (APAP), or Paracetamol
Trade name: Tylenol, or Panadol

Therapeutic dose:
Adults: 325-1000 mg/dose
Children: 10-15 mg/kg/dose
(Every 4-6 hours, with a maximum of 4g/day)

Toxic dose:
Adults: >6 g
Children: depends on age per year
- <1: 150mg/kg
- 1-6: 200mg/kg (150mg/kg if he has risk factors)
- 7-12: 150 mg/kg

Metabolism

- **90%** conjugated by the liver
-mostly with glucuronide (60%), or with sulfate (40%)

- **5%** excreted unchanged in urine

- **5-10%** Oxidation by P450 cytochromes (CYP 2E1, 1A2, 3A4) to NAPQI
-NAPQI is toxic, so its combined with GSH (Glutathione) ⟶ cysteine/mercaptate conjugates ⟶ urine (and thiol-containing substances)

In case of OD:
1/ Saturation of glucuronidation and sulfation
2/ increase NAPQI & overwhelming of GSH

NAPQI will bind to cell proteins of sulfhydryl group and cause cells lyses.

Acetaminophen was first used in 1960 and first case of hepatic damage was on 1966

Factors affecting metabolism

- Increase CYP 2E1 enzyme activity
- Decreased glutathione stores (Animal models: hepatotoxicity when GSH stores fall <30% of baseline)
- Frequent dosing interval
- Prolonged duration of excessive dosing
- Others: Smoking, barbituates, rifampin, carbamazepine, phenytoin, INH, and ethanol
- doesn't have a harmful effect on alcoholics livers

OD stages:

1/ Nausea, vomiting, anorexia or asymptomatic

2/ resolution of symptoms → RUQ pain→ elevation of PTT, INR bilirubin, and liver enzymes (at latest by 36h)

3/ Coagulopathy, peaking of enzymes, Acidosis, Hypoglycemia, Bleeding diathesis, Jaundice / anuria / cerebral edema, Coma, ARF (25% of pts with hepatotoxicity) [Fulminant hepatic failure]

4/ resolution and healing

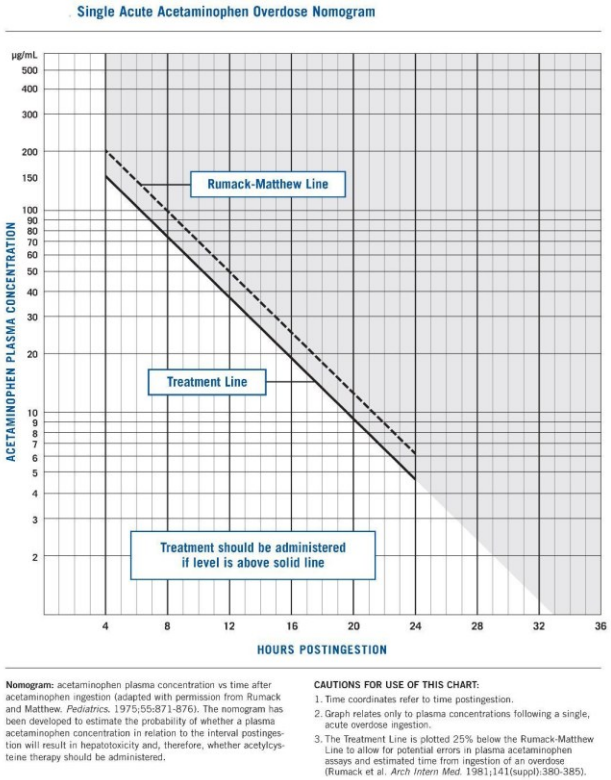
Diagnosis

Measure serum levels 4 and 24 hours after ingestion and use Rumack-Matthew nomogram to determine the need for NAC therapy

- It uses serum APAP levels in different times to predict **AST** elevation (above 1,000 U/L)
- Only used in acute ingestion of immediate released acetaminophen
- Recommended line of treatment has been lowered by 25% to increase its sensitivity and safety.
- 60% of patients who OD are likely to develop hepatotoxicity

History taking

- Often unreliable, **except for pills containers!**
- 5 W's: Who (age, wieght…), What (drug's' and dose), When (time of ingestion's'), Where (geographical location, ingestion rout), Why



Treatment

A: airway

B: Breathing

C: circulation

D: decontamination (Activated Charcoal)

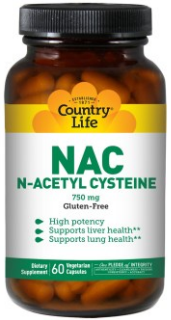
E: end treatment (NAC)

NAC indications

- APAP level above the treatment line
- History of significant APAP ingestion presenting close to 8h (give NAC while waiting for labs)
- All APAP ingestions who present late >24h with either detectable APAP or elevated transaminases
- Chronic ingestions (>4g/day in adult, >120mg/d in child) with elevated transaminases
- History of exposure and Fulminant Hepatic Failure

●optimum time for NAC is 8-10 h. post ingestion

(More delayed therapy is associated with a progressive increase in hepatic toxicity)



XR tablets

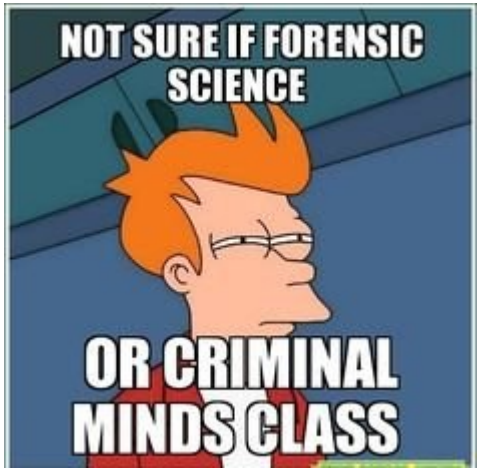
- elimination of extended and immediate-release acetaminophen are nearly identical after 4 hours.
- APAP levels falling above the treatment normogram line as late as 11-14 hours post ingestion of the extended-release preparation

Poor prognostic factors

- pH <7.3 (2 days after OD, after fluids)
- Hepatic encephalopathy
- PT >1.8 times normal.
- Serum creatinine >300mmol/L

(because of renal damage)

- Coagulation factor VIII/V ratio of >30



Antidote: **NAC (N-Acetylcysteine)**

Early effect

- Prevents binding of NAPQI to hepatocytes
- GSH precursor (increases GSH stores)
- Increases sulfation metabolism of APAP (less NAPQI formation)
- Reduces NAPQI back to APAP
- Sulfur group of NAC binds and detoxifies NAPQI to cysteine and mercaptate conjugate (= GSH substitute)

Late effect

- Modulates the inflammatory response
- Antioxidant (free radical scavenger)
- Reservoir for thiol groups (i.e. GSH)
- Impairs WBC migration and function (anti-infl)
- Positive inotropic and vasodilating effects “NO” (improves microcirculatory blood flow and O2 delivery to tissues)
- Decreases cerebral edema formation, prevents progression of hepatic encephalopathy and improves survival

Improved outcome of Paracetamol-induced fulminant hepatic failure by late administration of NAC

The influence of NAC, administered at presentation to hospital, on the subsequent clinical course of 100 patients who developed APAP-induced fulminant hepatic failure was analyzed retrospectively

- Mortality was 37% in patients who received NAC 10-36 h after the overdose, compared with 58% in patients not given the antidote
- In patients given NAC, progression to grade III/IV coma was significantly less common than in those who did not receive the antidote (51% vs 75%)

Paracetamol (acetaminophen) poisoning Vale, JA, Proudfoot, AT. *Lancet 1995; 346:547*

	Treatment delay below 10 hours	Treatment at 10 to 24 hours
Mortality	✓ No deaths	✓ 200 patients had a 2.0 to 7.4 percent mortality, ✓ 5.3 to 10.7 mortality in 85 patients who received only supportive care.
liver damage (defined as a plasma ALT or AST level above 1000 IU/L)	✓ 1.6 to 10 percent incidence	✓ 27 to 63 per cent in patients treated at 10 to 24 hours ✓ 58 to 89 percent in those receiving supportive care

This table is from 433 TeamWork ↑

MCQs & short cases

Q/Which lab test is the most sensitive for early detection of hepatotoxicity.?
AST

Q/ 15 month old child (wt. 10 kg) accidentally took full bottle of Tylenol 60cc(120mg/5cc) 30 mint ago. Clinically looked well. What will be your treatment plan:
Do nothing

Q/ A mother brought her 4 M (5 kg) old son who was febrile for the last 3 days . She was giving him Tylenol (120mg/5 ml) 7ml every 4 h for the last 3 days, she found him today more lethargic, vomiting occasionally, clinically, ill looking slightly jaundiced, afebrile, no meningeal signs, mild injected throat, CSF was obtained & was not suggestive of meningitis. What will be your next step:
Obtain CBG, LFT, PT, PTT, INR, drug level if abnormal start NAC

Q/ 19 y old girl brought to ED with GCS 8 following drug ingestion (empty bottle of Tylenol was found in her room). What will be your first response
Orotracheal intubation

3 y old boy with accidental Tylenol ingestion on NAC for high drug level, after 48 h course LFT ,INR are high. What will be your recommendation:
Continue on NAC until all his labs become normal