Acetaminophen Overdose

Team leaders: khalid alzahrani - abdullah aljunaydil - futoon alsaleh

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

Done by:

- ✓ Atheer Alnashwan

Revised by:

- ✓ Futoon Alsaleh

[Important | Notes | Extra | editing file]

ACETAMINOPHEN = Paracetamol

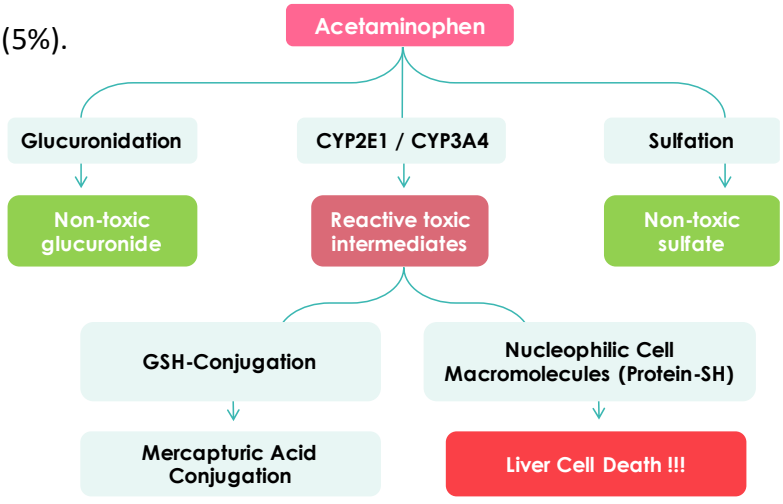
- الاسم العلمي لأسيتامينوفين-**APAP** (acetyl-para-aminophenol) :
  - has been approved for OTC use since 1960
  - 1st cases of hepatic damage after APAP OD 1966 جت حالة التوكسستي بعد فترة قصيرة من بداية استخدام الأسيتامينوفين!
- :dose of acetaminophen Therapeutic
  - Children 10-15 g/kg/dose
  - Adults → 325-1000 mg/dose every 4-6 hours in adults, with a maximum of 4g/day
- Overdose = per 1 single ingestion (1 dose at a time)

dose of APAP Toxic	
Children	**Youth & Adult**
✓ < 12 months → 150 mg/Kg ✓ 1-6 yrs → **200 mg/kg** (liver in child is very healthy bc they didn't expose to toxins) ✓ 1-6 yrs with **risk factors*** → 150 mg/kg (*any condition affect liver function: disease, meds, …) ✓ 7-12 yrs → 150 mg/kg So in general, the toxic dose in child is **150 mg/kg**.	✓ 7.5-10 g/dose cirrhotic patient get toxic with less than this dose

Metabolic Pathways

- Acetaminophen has 3 pathways for metabolism, 2 major & 1 minor:
  a. Major pathways (90%): produce **inactive** (non-toxic) metabolites excreted in the urine.
     1. Hepatic **glucuronide conjugation** → (40-65%)
     2. Hepatic **sulfate conjugation** → (20-45%)
  b. Minor pathway (5-15%):
     1. Oxidation by **P450 cytochromes** (CYP 2E1, 1A2, and 3A4) to **NAPQI** (هنا المصيبة)
        - ✓ GSH combines with NAPQI → GSH will combine with NAPQI, which is good & prevent toxicity!
        - ✓ nontoxic cysteine/mercaptate conjugates
        - ✓ excreted in urine
  c. Excretion of unchanged APAP in the urine (5%).

يعني في الحالة العادية، أي أحد يأخذ أسيتامينوفين بيشتغل عندي الميجور باثواي، وبيطلع لي non-toxic ويطلع في البول. لكن في حالة الoverdose بيصير فيه saturation للميجور باثواي، فهنا بنحوّل على الماينور CypP450 وهو اللي يطلع لي المصيبة! اللي هو NAPQI !
الماينور باثواي زي ما نشوف في الدياقرام مب كله شرير ☺
نلاحظ إن GSH شاد حيله عشان يرتبط بNAPQI ويمنعه إنه يسوي toxic effect .. لكن الGSH مب دايم لي! فمجرد ما يخلص المخزون عندي بروح للباثواي الثاني اللي بيسبب لي Liver cell death ☹



What happens in acetaminophen overdose (OD)?

1. Saturation of glucuronidation and sulfation pathways
2. Amount of APAP metabolized by **p450 cytochromes** to NAPQI increases
3. Normally NAPQI is detoxified by reduced GSH (glutathione) and thiol-containing substances
4. In OD: rate and quantity of NAPQI formation overwhelms GSH supply and regeneration:
   - ✓ elimination of NAPQI prolonged → free NAPQI binds critical cell proteins with sulfhydryl groups → **cellular dysfunction and cell death**.
5. Animal models: hepatotoxicity when GSH stores fall <30% of baseline.

❖ Factors Adversely Affect APAP metabolism:

1. Up-regulation (i.e. induction) of CYP 2E1 enzyme activity. E.g. smoking, barbituates, **rifampin**, carbamazepine, phenytoin, **INH** (isoniazid), + ethanol (alcohol) → in these cases, decrease acetaminophen dose.
2. **Change in glutathione stores**:
   a. Eating (e.g. malnutrition) glutathione is not formed by the body, so we get it from external source.
   b. NAC (will be explained later)
3. Frequent dosing interval of APAP → this might put u at higher risk for toxicity compared to smbdy took 1 single dose.(if someone takes 2 gm per dose instead of 1gm , so his baseline drug levels are higher and more susceptible to toxicity)
4. Prolonged duration of excessive dosing

❖ Clinical manifestation:

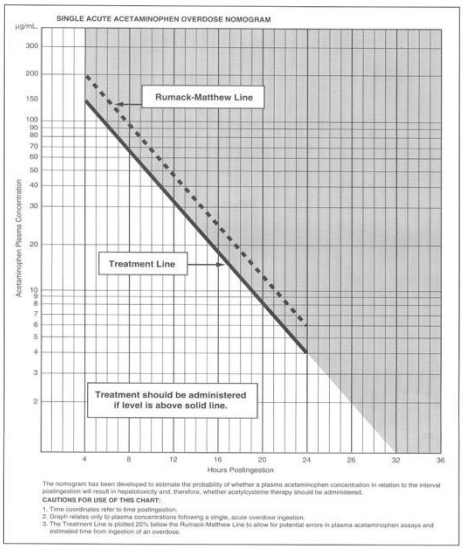
Stage	Time	Clinical manifestation
I	0.5 – 24 hs	✓ n/v, anorexia or asymptomatic. لما يجونك الأهل بطفلهم وقالوا لك إنه أكل العلبة كاملة وتسألهم متى يقولون مدري، وأنت شايف الطفل مافيه إلا العافية، فهنا تتوقع إنه في الستيج ١ لأن ما ظهرت الأعراض عليه.
II	24 – 48 hs	✓ Resolution of stage I signs and symptoms. ✓ RUQ pain, elevation of: PTT, INR, bili & liver enzymes (at the latest 36hs) Case: If a teenager presents with attempt of suicide , comes with RUQ pain , jaundiced , increased liver enzymes ,high PTT and INR
III	48 – 96 hs	✓ Hepatic fulminant: coagulopathy, peaking of enzymes, **acidosis**, **hypoglycemia**, bleeding diathesis, jaundice, anuria, cerebral edema, coma. ARF in 25% of pts with hepatotoxicity.
IV	4-14 dys	✓ Resolution. • If there is no improvement >2 weeks, there no chance for resolution ,and this is an indication for liver transplant!

❖ Diagnosis:{ the drug levels is an Important dx tool for acetenomphen, this is not true for most drugs except; Panadol and aspirin }.

- ✓ Start with history (see below)
- ✓ **Serum APAP level** should be measured between **4 and 24 hours after ingestion**. Very imp parameter to manage your patient!! Take the level, then go for Rumack-Matthew nomogram (see below).
- ✓ The value obtained should be evaluated according-to the **Rumack-Matthew nomogram** for determining the risk of hepatotoxicity and the need for NAC therapy. (hepatotoxicity = defined as elevation of the plasma transaminases above 1,000 U/L)

❖ **Toxicology history:**

- Often incomplete, unreliable or unobtainable
- Sources – Patient, friends, family, EMS, or **pill containers** مهم نحرصهم يجيبون العلبة معهم!
- PMHx, liver/renal disease, concurrent medications, previous overdoses, PΨHx (psychiatric), substance abuse
- Location may be important for environmental or occupational exposures
- The **5W's** of toxicology:
  1. **Who** – pt's age, weight, relation to others.
  2. **What** – name & dose of medication, co-ingestants and amount ingested.
  3. **When** – time of ingestion, single vs. multiple ingestion.
  4. **Where** – rout of ingestion, geographic location.
  5. **Why** – intentional vs. unintentional (intentional is more dangerous!)



❖ **What is the Rumack-Matthew nomogram?**

★ Time against conc. graph.

★ Any level <u>below</u> the solid line → pt is unlikely to develop hepatic toxicity → u can discharge him. If <u>above</u> the solid line → treat him!

- APAP level to predict <u>which patients</u> will develop an **AST elevation >1000** IU/L without antidotal treatment.
- Derived from acute ingestion of immediate release acetaminophen.
- **Begins at 4 h** post ingestion. (don't measure the level before 4 hs! Also s&s wont be visible before 4 hrs and there wont be any harmful effect before 4 hours)
- Recommended line of treatment has been lowered by 25% to increase its sensitivity.

★ What percent of pts whose APAP level falls above the upper line of the Rumack-Matthew normogram will develop hepatotoxicity? = 60% -without treatment-.
→ good #! Means not everyone above Tx line would have hepatotoxicity.

❖ **Which lab test is the most sensitive for early detection of hepatotoxicity? AST**

❖ **Management Guidelines: ABCD**

- Airway, Breathing, Circulation, Decontamination* (→ AC), Find antidote (→ NAC).
  - * you consider to give the pt AC if he came within 1 hr of APAP ingestion of toxic amount.
  - * AC is difficult to be given for child, so they put in it in a Pepsi can ☺. Sometimes they may use NGT, but!!! Make 100% sure that it is not inserted in the lung! U may kill him by charcoal not by his toxicity.

NAC (N- acetylcysteine, anti-dote of acetaminophen)

- Trade name: Mucomyst. | NAC should optimally be given **within 8-10 hs** after ingestion.
- More delayed therapy is associated with a progressive increase in hepatic toxicity.
- Some benefit may still be seen **24 hs** or later after ingestion.

Early Effects (before 24 h.)	Late Effects (after 24 h.)
▪ Prevents binding of NAPQI to hepatocytes. ▪ GSH precursor → increases GSH stores. ▪ Increases sulfation metabolism of APAP → less NAPQI formed ▪ Reduces NAPQI back to APAP (at least in animal models) ▪ Sulfur group of NAC binds and detoxifies NAPQI to cysteine and mercaptate conjugate (= GSH substitute).	▪ .Modulates the inflammatory response ▪ .Antioxidant, free radical scavenger ▪ Reservoir for thiol groups (i.e. GSH). ▪ Impairs WBC migration and function anti-inflammatory. ▪ 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.

Indications of NAC

- Any type of hepatic failure, we start them immediately on a NAC.
- APAP level above the treatment line
- Hx of significant APAP ingestion presenting close to 8h (give while waiting for level)
- All APAP ingestions who present late>24h with either detectable APAP or elevated transaminases
- Chronic ingestions (frequent, not single) (>4g/day in adult, >120mg/d in child) with elevated transaminases (Do not forget to check enzymes if u suspect acetaminophen toxicity)
- Hx of exposure and Fulminant Hepatic Failure (FHF) → irrespective of the APAP level, start treatment!!

Poor prognostic indicators

- pH <7.3 (2 days after OD, after fluids)
- Hepatic encephalopathy
- PT >1.8 times normal
- Serum creatinine >300mmol/L
- Coagulation factor VIII/V ratio of >30

→ don't worry about these prognostic factors at ur level, but take in consideration in the west, one of the **commonest indications of liver transplant** is acetaminophen overdose, not like us, we have more congenital diseases needs liver transplant.

XR (extended release) **tablets**

- Several studies show that elimination of extended and immediate-release acetaminophen are nearly identical after 4 hours.
- Some case reports APAP levels falling above the treatment normogram line as late as 11-14 hours post ingestion of the extended-release preparation.
- In extended release we take the first drug level after 4 hours .. then another blood level after 8 hours .. if after 8 hours the drug level is not detectable we discharge …
- If a question came by default it's normal not extended release , if its XR we will say in the question

MCQs

- **15 months 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?**
  A. Give Ipecac STAT
  B. Give 1g/kg activated charcoal
  C. Insert OGT and perform gastric lavage
  D. Should be observed for 4h then to do drug level
  E. None of the above

Ans: E. [(60*120/5) / 10] = 144 mg. The toxic dose for his age group is 200mg.

- **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?**
  A. Obtain CBG, LFT, PT, PTT, INR, drug level if abnormal start NAC
  B. Give activated charcoal immediately
  C. Admit for observation
  D. D/C home, most likely it is related to current URTI

Ans: A..

- **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?**
  A. 1g/kg activated charcoal STAT
  B. Orotracheal intubation
  C. Observation for 4 h
  D. Do CBC, CBG, PT, PTT, INR, Drug level
  E. NAC loading dose followed by infusion over 24 h

Ans: B.

- **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?**
  A. D/C NAC if drug level undetectable
  B. D/C NAC and repeat LFT, INR, drug level after 4h
  C. Continue on NAC until all his labs become normal
  D. D/C NAC, most likely it is secondary to concurrent viral illness

Ans: C.

- **20 yr old pregnant girl ingested 20g of Tylenol in a suicidal gesture 36h ago because she found out it is too late for her to have an abortion. Her APAP is <10 and her AST is 90**
  - **How will you manage her medically?** We treat her as non-pregnant woman (In this case she meets the criteria for treatment)
  - **She asks you whether her baby will have any defects?** No, the child won't have any defect, NAC is not teratogenic.

- **3 years old child present half an hour after an overdose ingestion of acetaminophen syrup . The child was asymptomatic at presentation, you administer him activated charcoal. further management with specific antidote will depend on serum level of acetaminophen .The blood for measuring acetaminophen level should be taken after how many hours of ingestion ?**

A- Immediately at presentation to the ER
B- 1 hour from the time of ingestion
C- 4 hours from the time of ingestion
D- 3 hours from the time of ingestion

Ans: C

- **When acetaminophen overdose occurs, which of the following subjects are at higher risk of acetaminophen toxicity?**

A. A 4-year child who accidently took 1400 mg at once
B. A 19-year-old malnourished girl who took 10 grams for suicide
C. A 90-year-old man who took 1 gram every 4 hours for headache
D. A 25-year-old woman who took 2 grams at once for sever dysmenorrhea

AnsB :

- **Which of the following adversely affect acetaminophen metabolism and increase risk of toxicity?**

A. Amoxicillin
B. Nefazdone
C. Azithromycin
D. Carbamazepine

Ans: D

- Which one of the following adds to the toxicity of Acetaminophen?

a. Bisoprolol
b. Ehtambutol
c. Baclofen
d. Rifampin

Ans: D

- Which one of the following is the antidote for Paracetamol poisoning?

A. Methadone
B. N-acetylcycteine
C. Charcoal
D. Digiband

Ans: B