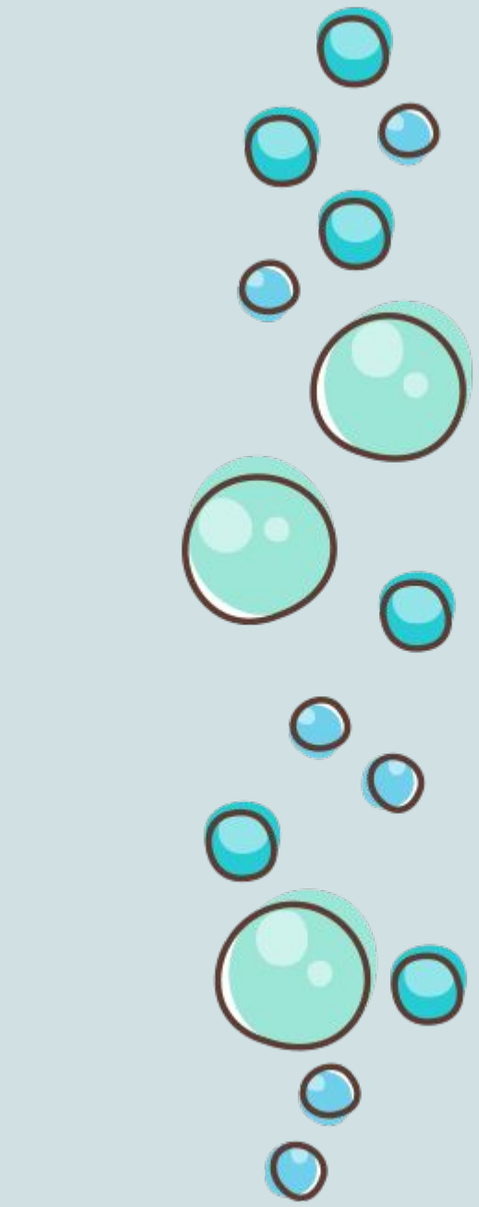
Acetaminophen Overdose



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Objectives

1. Potential toxic dose of APAP according to age
2. Symptoms and signs of APAP OD
3. Indications of NAC therapy

NOTES EXTRA BOOK IMPORTANT GOLDEN NOTES

APAP

- Acetaminophen has been approved for OTC use since 1960
- First case of hepatic damage after APAP OD 1966

In this course we will be taking about single acute overdose ingestion, not about chronic use.

Acetaminophen (N-Acetyl-p-aminophenol)

Therapeutic Dose

- 10-15 mg/kg/dose in children.
- 325-1000 mg/dose every 4-6 hours in adults, with a maximum of 4g/day.

Liver is the major organ affected by toxic dose which can cause fulminant liver failure.

Toxic Dose

- **Children**[1]:
< 12 months: 150 mg/kg
1 – 6 y : 200 mg/kg
1 – 6 y with risk factors : 150 mg/kg
7 – 12 y : 150 mg/kg

Toxic dose depends on:
1- age
2- weight (with children)

-**Youth & Adult:** 7.5 - 10 g

One of the fundamental differences between children and adults in toxicology is:
in children it's an Accidental ingestion, while in adults it's Intentional ingestion. and the Intentional ingestion is more dangerous than the Accidental ingestion.

(1)Children can handle more toxic dose per kg compared to adults because of 1- higher liver mass compared to their bodies and 2- More active enzymes

Metabolic Pathways (image)

1-Hepatic Conjugation of APAP: (90%)[2]
- Hepatic glucuronide conjugation (40-65%)
- Hepatic sulfate conjugation (20-45%)

➔ inactive metabolites excreted in the urine.

(2)The major way in Metabolic Pathways is conjugation.

2 - Excretion of unchanged APAP in the urine (5%).

3 - Oxidation by P450 cytochromes (CYP 2E1, 1A2, and 3A4) to NAPQI (5-15%) and this is a problem since NAPQI is toxic and causes cell lysis!!

➔ GSH combines with NAPQI this combination will neutralize NAPQI which is good and prevents toxicity "how our body gets rid of it"

➔ Nontoxic cysteine/mercaptate conjugates

➔ Excreted in urine.

Factors that adversely affect APAP metabolism:

1. **Up regulation** (i.e. induction) of CYP2E1 enzyme activity[3]

(3)E.g. smoking, barbiturates, rifampin, carbamazepine, phenytoin, INH (isoniazid), + ethanol (alcohol) in these cases, decrease acetaminophen dose

2. **Frequent** dosing interval of APAP[5]

(5)No time to regenerate GSH

3. **Decreased Glutathione stores:**
- Eating[4]
- NAC

(4) Malnutrition or poor diet leading to deficiency of precursors

4. **Prolonged** duration of excessive dosing

APAP Overdose

OD causes the following to the metabolic pathway: (image)

Why there is a toxicity in paracetamol OD? Because there will be a Saturation in the major pathway which make the liver depending on the minor pathway, which in turn will deplete GSH and that will produce a large amount of NAPQI molecules!

- Saturation of Glucuronidation and Sulfation pathways
- Amount of APAP metabolized by p450 cytochromes to NAPQI increases;
  - Normally **NAPQI** is detoxified by reduced GSH (Glutathione) and thiol-containing substances
  - In OD: rate and quantity of **NAPQI** formation overwhelms the GSH supply and regeneration, leading to:
    -Prolonged elimination of **NAPQI**
    -Free NAPQI binds to critical cell proteins with Sulfhydryl groups causing cellular dysfunction and cell death
- Animal models: Hepatotoxicity when GSH stores fall <30% of baseline

(NAPQI = N-acetyl-p-benzoquinoneimine)

Clinical manifestation of APAP OD:

The importance of the stages is to predict the time of ingestion and to plan the treatment.

Why they have RUQ pain although they take a sedative drug? Because these patients have a vascular pain and APAP doesn't work on this type of pain

Hepatic phase

I	N/v, anorexia, asymptomatic A child accidentally ingested a toxic dose at 12 A.M, his parents brought him to the ER at 12:30 A.M, what symptoms do you expect the child come with? nausea and vomiting or maybe asymptomatic.	0.5-24h
II	Resolution of stage I sxs RUQ pain, elevation of PTT, INR,bilirubin + enzymes (at the latest by 36h) Think they are fine now and don't go hospital.	24-48h
III	Coagulopathy, peaking of enzymes, acidosis, hypoglycemia, bleeding diathesis, jaundice, anuria, cerebral edema, coma. ARF in 25% of pts with hepatotoxicity. Fulminant hepatic failure and they will need liver transplant	48-96h
IV	Resolution If there is no improvement >2 weeks, there's no chance for resolution ,and this is an indication for liver transplant!	4-14d

Assessment and Management

Diagnosis:

The most important step is serum level since it matters in management when to ask for serum APAP level?
if you suspect that the patient took a potential toxic dose.
for example: if it was child this will depend on his weight and the dose, if it was above 200 mg/kg then you have to take serum level test.

- In patient with a history of APAP overdose, a serum APAP level should be measured between 4 and 24 hours after ingestion Taking it before 4h is useless
- The value obtained should be evaluated according to the **Rumack-Matthew Nomogram** for determining:

Risk of Hepatotoxicity

Need for NAC Therapy

Rumack-Matthew Nomogram

Click on me to reveal me! (:

- ❏ APAP level to predict which patients 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
- ❏ Recommended line of treatment has been lowered by 25% to increase its sensitivity

60% of patients whose APAP level falls above the upper line of the Rumack-Matthew nomogram will develop hepatotoxicity

"Defined as elevation of the plasma transaminases above 1000 U/L"

Toxicological History:

- Often incomplete, unreliable or unobtainable
- Sources: Patients, friends, family, EMS or pill containers
- PMHx, Liver/renal diseases we asses the liver injury through the AST level. , concurrent medications, previous overdoses, PΨHx, substance abuse

"AST" is the most sensitive lab test for early detection of hepatotoxicity

Assessment and Management

The 5W's of toxicology:

1 Who

Age, weight, relation to others

2 What

Name and dose of medication, coingestants and amount ingested

3 When

Time of ingestion, single vs. multiple ingestions

4 Where

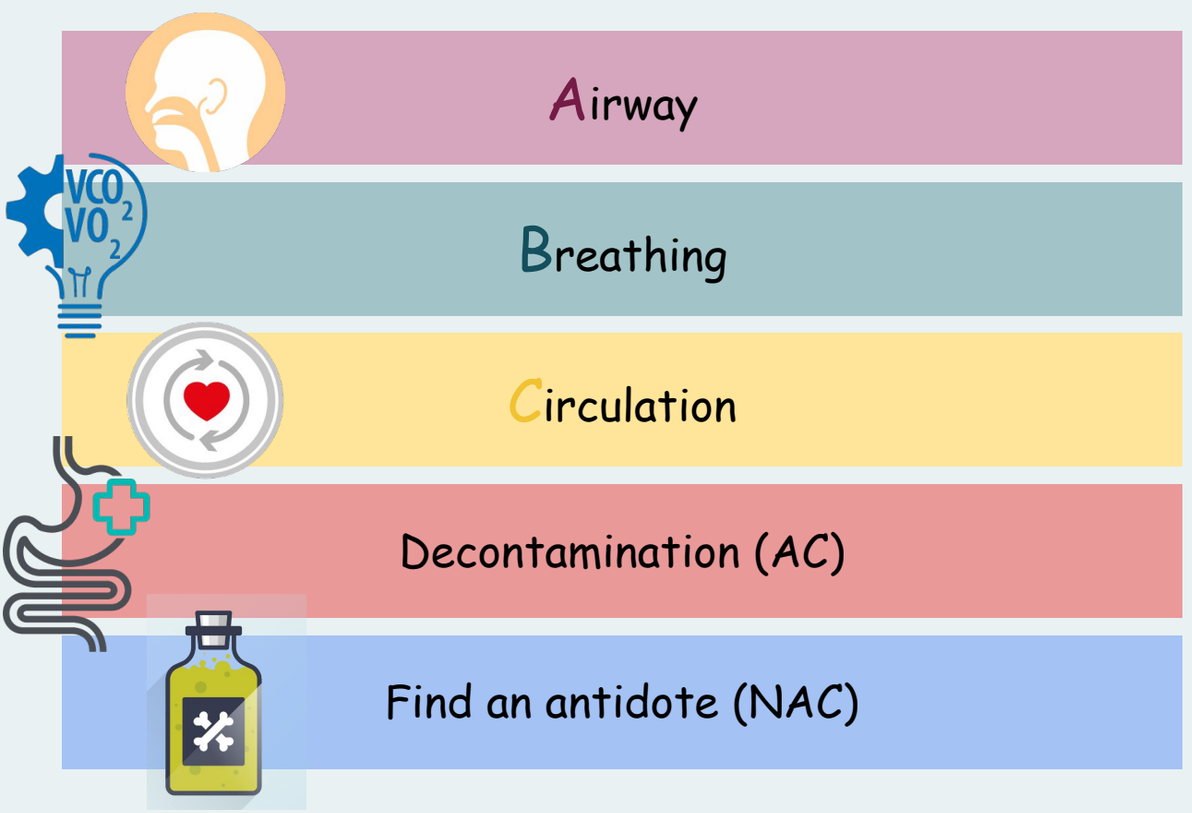
Route of ingestion, geographical location

5 Why

Intentional vs. Unintentional

Management Guidelines:

What's your name? ABC (;



NAC

N-Acetylcysteine (NAC)

(image)

Early effect <8h It gives both effects of early and late	Late effect 12-24h The patient already in stage 3 or 4 it's never late to give NAC
Prevents binding of NAPQI to hepatocytes	Modulates the Inflammatory Response Since most of the damage is secondary to inflammation
GSH precursor : increases GSH stores	Antioxidant, free radical scavenger
Increases sulfation metabolism of APAP : less NAPQI formed Promotes the 1st pathway	Reservoir for thiol groups (i.e. GSH)
Reduces NAPQI back to APAP (at least in animal models)	Impairs WBC migration and function : anti-inflammatory
Sulfur group of NAC binds and detoxifies NAPQI to cysteine and mercaptate conjugate (= GSH substitute) New pathway	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

Indication for NAC:

Let's say a patient overdosed what should you do? Ask the time and the dose. If the dose is below the threshold then he can go home if it is above the threshold then we measure the APAP level 4 hrs after ingestion if it is below rumacks line then he can go home if it is not then start NAC and admit.

APAP level above the treatment line

Hx of significant APAP ingestion presenting close to 8h (give while waiting for level)

Hx of exposure and FHF

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

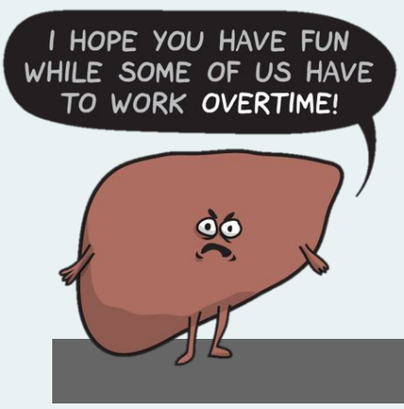
You should remember...!

- NAC should optimally be given within 8 to 10 hours after ingestion
- More delayed therapy is associated with a progressive increase in hepatic toxicity
- some benefit may still be seen 24 hours or later after ingestion. Only stop NAC when APAP level is 0 and liver enzymes are normal

Outcome

Poor prognostic indicators:

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



XR 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 nomogram line as late as 11-14 hours post ingestion of the extended-release preparation

Studies

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

No deaths in 169 patients with a treatment delay below 10 hours. In contrast, 200 patients treated at 10 to 24 hours had a 2.0 to 7.4 percent mortality, which was still lower than the 5.3 to 10.7 mortality in 85 patients who received only supportive care. There was a 1.6 to 10 percent incidence of liver damage (defined as a plasma ALT or AST level above 1000 IU/L) when the treatment delay was less than 10 hours. Comparable values were 27 to 63 percent in patients treated at 10 to 24 hours and 58 to 89 percent in those receiving supportive care

Improved outcome of Paracetamol-induced FHF by late administration of NAC *"Lancet 1990 Jun 30;335 (8705) : 1572-3"*

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%)

Summary

Therapeutic Dose	Toxic Dose	Metabolic Pathways
In children: 10-15 mg/kg/dose Adults: 325-1000 mg/dose every 4-6 hours	Children: < 12 months: 150 mg/kg 1 – 6 y (no risk factors) : 200 mg/kg 1 – 6 y with risk factors : 150 mg/kg 7 – 12 y : 150 mg/kg Youth & Adult: 7.5 - 10 g	1- **Hepatic Conjugation (90%)** 2-Excretion of unchanged APAP in the urine (5%). 3- Oxidation by P450 →NAPQI → GSH combines with NAPQI → cysteine → Excreted in urine

Metabolic changes in overdose	Saturation of Glucuronidation → Amount of APAP metabolized by p450 cytochromes to NAPQI increases.			
Clinical manifestation of APAP OD	Stage1: N/v, anorexia, asymptomatic **(0.5-24h)**	Stage2:RUQ pain, elevation of PTT, INR, bilirubin + enzymes **(24-48h)**	Stage3: Coagulopathy, peaking of enzymes, acidosis, hypoglycemia, bleeding diathesis, jaundice, anuria, cerebral edema, coma. ARF in 25% of pts with hepatotoxicity **(48-96h)**	Stage4:Resolution **(4-14d)**
Diagnosis	•By serum APAP level which should be measured between 4 and 24 hours after ingestion •**"AST"** is the most sensitive lab test for early detection of hepatotoxicity			
Antidote	**N-Acetylcysteine (NAC)** •Early effect <8h: Prevents binding of NAPQI to hepatocytes,increases GSH stores Late effect 12-24h: Modulates the inflammatory Response,Antioxidant •NAC should optimally be given within 8 to 10 hours after ingestion •More delayed therapy is associated with a progressive increase in hepatic toxicity •some benefit may still be seen 24 hours or later after ingestion.			
Indication for N-Acetylcysteine (NAC)	•APAP level above the treatment line •Hx of significant APAP ingestion presenting close to 8h (give while waiting for level) •Hx of exposure and FHF •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			
Poor prognostic indicators	•pH <7.3 (2 days after OD, after fluids) •Hepatic encephalopathy •PT >1.8 times normal •Serum creatinine >300 mmol/L •Coagulation factor VIII / V ratio of >30			

{ How toxic is your knowledge! }

"From Doctor's slides"

1-15 month old child (wt. 10 kg) accidentally took full bottle of Tylenol 60cc (120mg/5cc) , 30 min 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

First we should ask ourselves, is it a toxic dose or not? This is 15 month old baby so they are one year without risk factors, hence the toxic dose is 200mg/kg. Now, we'll calculate the dose they took: 60/5 = 12cc. 12cc x 120mg= 1440 mg. Since they are pediatric age group then we should consider their weight: toxic dose is 200mg x 10kg = 2000, so they are fine (:

"From Doctor's slides"

2-19 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

This is very simple, your patient has 8 GCS! So there is no protection for their airway; remember ABC rule! After you ensure your pt safety, start them on NAC.

"From Doctor's slides"

3- 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

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

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

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

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

1-E
2-B
3-C
4-D
5-B

{ How toxic is your knowledge! }

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

A) Bisoprolol
B) Ethambutol
C) Baclofen
D) Rifampin

7-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 severe dysmenorrhea

8-which one of the following is the major pathway for Acetaminophen metabolism:

A) Hepatic Conjugation of APAP
B) Excretion of unchanged APAP in the urine (5%).
C) Oxidation by P450 cytochromes
D) Reduction by AST

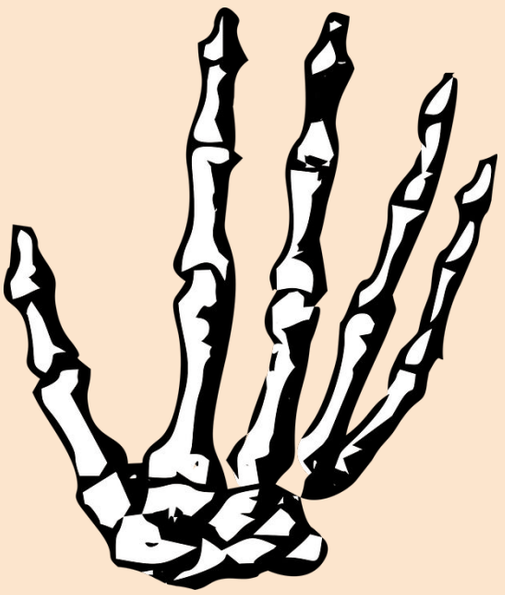
"A-20 yr old pregnant girl ingested 20g of Tylenol in a suicidal gesture 36h ago. Her APAP is <10 and her AST is 90"

-How will you manage her medically?
Same as non pregnant; NAC administration.

-She asks you whether her baby will have any defects?
Acetaminophen and its antidote are both safe during pregnancy and cause no teratogenicity.

6-D
7-B
8-A

Thank you and good luck!



Very Toxic but you are gonna do it!

A+ is yours (:

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