Paracetamol Poisoning

Fb/Nurse Info

PARACETAMOL POISONING:

- Hepatic damage: more than 150mg per kg

Clinical feature :

- Nausea ,
- vomiting ,
- abdominal discomfort
- In untreated patient`s developing liver damage , vomiting continues beyond 12 hrs and there is tenderness over the liver , jaundice ,hepatic encephalopathy , loin pain , haematuria , proteinuria suggest renal failure.
- Investigation :LFTs, liver enzyme ,INR(international normalised ratio)

What is Paracetamol?

- Also known as N-Acetyl-p-aminophenol (acetaminophen)
- Analgesic- antipyretic with poor anti-inflammatory action
- Weak COX-1 and COX-2 inhibitor in peripheral tissue but more active on COX in brain
- Administered orally
- Peak blood concentration in 30-60 min

Metabolism of PCM

- Therapeutic dose:

➢ metabolised in liver by conjugation with glucuronide and sulphate

➢ Small amount by oxidase enzymes (CYP2E1)

- Overdose:

➢ liver glutathione reserves get exhausted and toxic metabolite accumulate and react with hepatocytes and proteins causing cellular damage

Acetaminophen

- *Acetaminophen is a synthetic nonopiate derivative of p-aminophenol widely used in* humans for its antipyretic and analgesic properties. Its use has largely replaced salicylates due to the reduced risk of gastric ulceration.
- Acetaminophen is rapidly absorbed from the GI tract. Peak plasma concentrations are usually seen within an hour, but can be delayed with extended-release formulations.
- It is uniformly distributed into most body tissues. Protein binding varies from 5-20%.
- The metabolism of acetaminophen involves 2 major conjugation pathways in most species. Both involve cytochrome P-450 metabolism, followed by glucuronidation or sulfation.

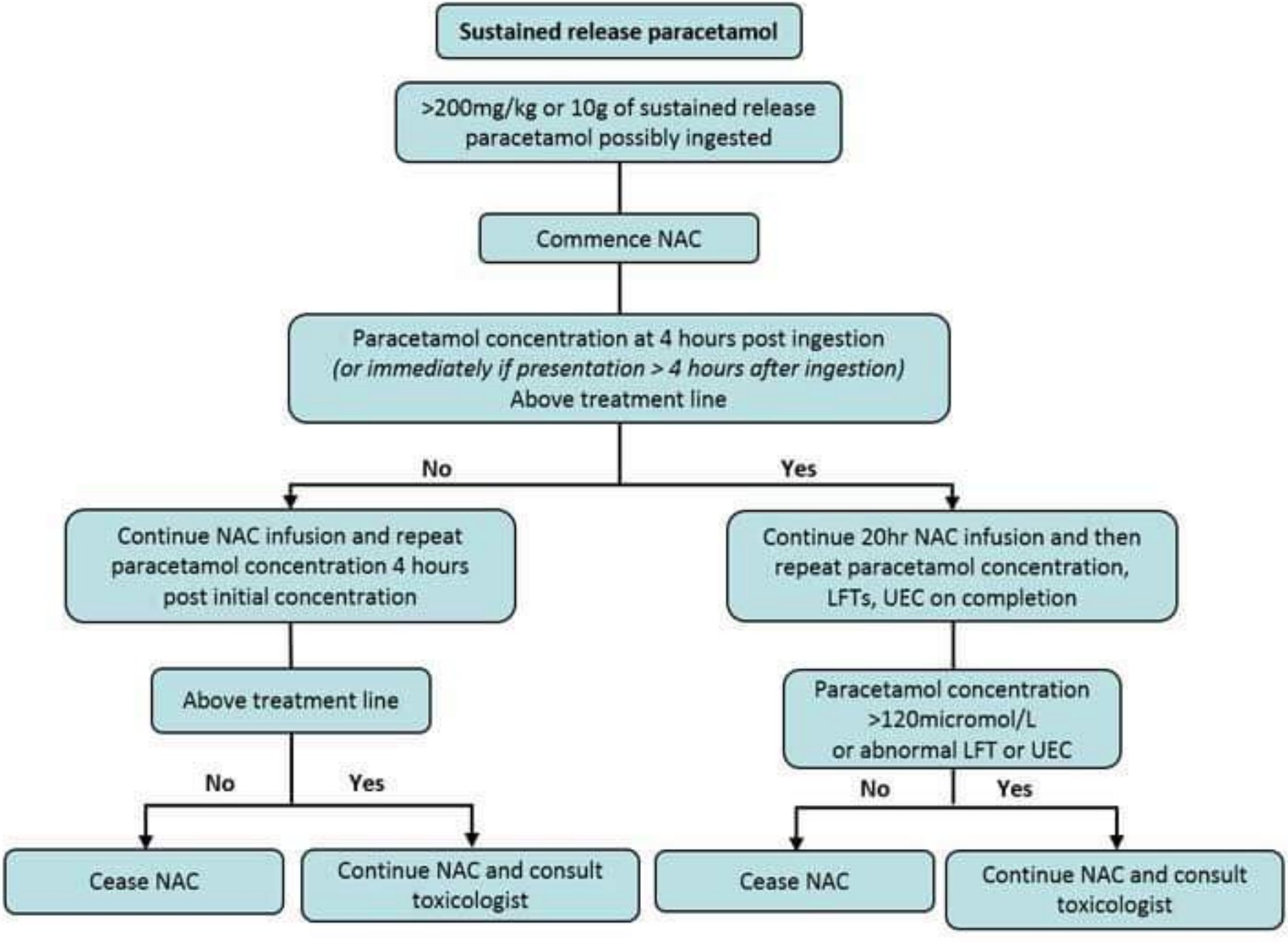
PARACETAMOL:Mechanism of toxicity

- Paracetamol is metabolized to *N*-acetyl-p-benzoquinone imine (NAPQI).NAPQI is extremely toxic to the liver, as a result of covalent binding to proteins and nucleic acids. However, NAPQI is rapidly detoxified by interaction with glutathione . Overdoses of acetaminophen deplete hepatic glutathione stores and allow liver injury to occur.
- **Signs and symptoms**
- PHASE ONE(<24hrs):nausea,vomiting,pallor,sweating
- PHASE TWO(24-72hrs):signs of increasing liver damage(one may experience upper-quadrant pain)In some cases, acute kidney failure maybe the clinical manifestation.
- PHASE THREE(3-5days):complications of massive hepatic necrosis leading to hepatic failure with complications,coagulation defects,hypoglycemia,kidney failure,cerebral edema,sepsi,multiple organ failure and death

ACETAMINOPHEN-Pathophysiology

- 95% of acetaminophen gets metabolised in Liver.
- PCM → Liver → Non Toxic Glucoronide and Sulphate Conjugates.
- PCM → Cytochrome P450 system → NAPQI
- NAPQI+Glutathione → Non Toxic Mercapturates
- In overdose situations, glutathione is depleted, and the excess NAPQI is toxic to hepatocytes, causing centrilobular necrosis.

Stage	Time since ingestion	Presentation
Stage 1	< 24 hrs	Anorexia, nausea, vomiting & diaphoresis Normal lab tests
Stage 2	24-72 hrs	Improved clinically, abnormal laboratory tests (↑serum transaminases, bilirubin, PT
Stage 3 (Hepatic Stage)	72-96 hrs	Signs of hepatotoxicity: AST & ALT level>10,000 IU/L, prolong PT or INR, hypoglycemia, lactic acidosis, total bilirubin>70umol/l (mainly indirect) Death commonly due to multiorgan failure
Stage 4 (Recovery stage)	4days-2wks	Pt. who survive stage 3 Transient Renal Failure after 5-7 days (back pain, proteinuria, haematuria) Complete hepatic recovery: 3-6 months


Sustained release paracetamol
>200mg/kg or 10g of sustained release paracetamol possibly ingested
Commence NAC
Paracetamol concentration at 4 hours post ingestion
(or immediately if presentation > 4 hours after ingestion)
Above treatment line
No
Yes
Continue NAC infusion and repeat paracetamol concentration 4 hours post initial concentration
Continue 20hr NAC infusion and then repeat paracetamol concentration, LFTs, UEC on completion
Above treatment line
Paracetamol concentration >120micromol/L or abnormal LFT or UEC
No
Yes
No
Yes
Cease NAC
Continue NAC and consult toxicologist
Cease NAC
Continue NAC and consult toxicologist

King's College criteria

- Are used to determine which patients should be referred for consideration of liver transplant.
- These criteria include :
  1. Acidosis (pH <7.3) after adequate fluid resuscitation,
  2. Coagulopathy (prothrombin time [PT] >100 sec),
  3. Renal dysfunction (creatinine >3.4 mg/dL),
  4. Hepatic encephalopathy grade III or IV

Therapeutic and Toxic Dose

- Therapeutic dose: 10-15 mg/kg
- Toxic dose:
  - More than 7.5 gm(around 15 tablets)- minimal toxicity
  - If >15 gm (30 tablets)- severe toxicity
  - In adult- toxic dose is 150 mg/kg
  - In children, toxic dose is 200 mg/kg
  - In presence of chronic disease or malnutrition, even 2gm of paracetamol can be a toxic dose

PCM Poisoning

- Most common form of poisoning
- Severity- dose related
- High-risk patients
  - Existing liver disease
  - Chronic alcohol users
  - Acute or chronic starvation
  - Receiving enzyme-inducing drugs
  - HIV infection

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Approach

- Begin with Primary Survey (ABCDE)
- History
- Examination
- Investigations
  - Initial baseline investigations
    - LFT, PT/INR, Blood glucose, CBC, Platelet count, Electrolyte, Urine routine
  - Plasma paracetamol level
    - as soon as 4 hrs or more have elapsed since ingestion

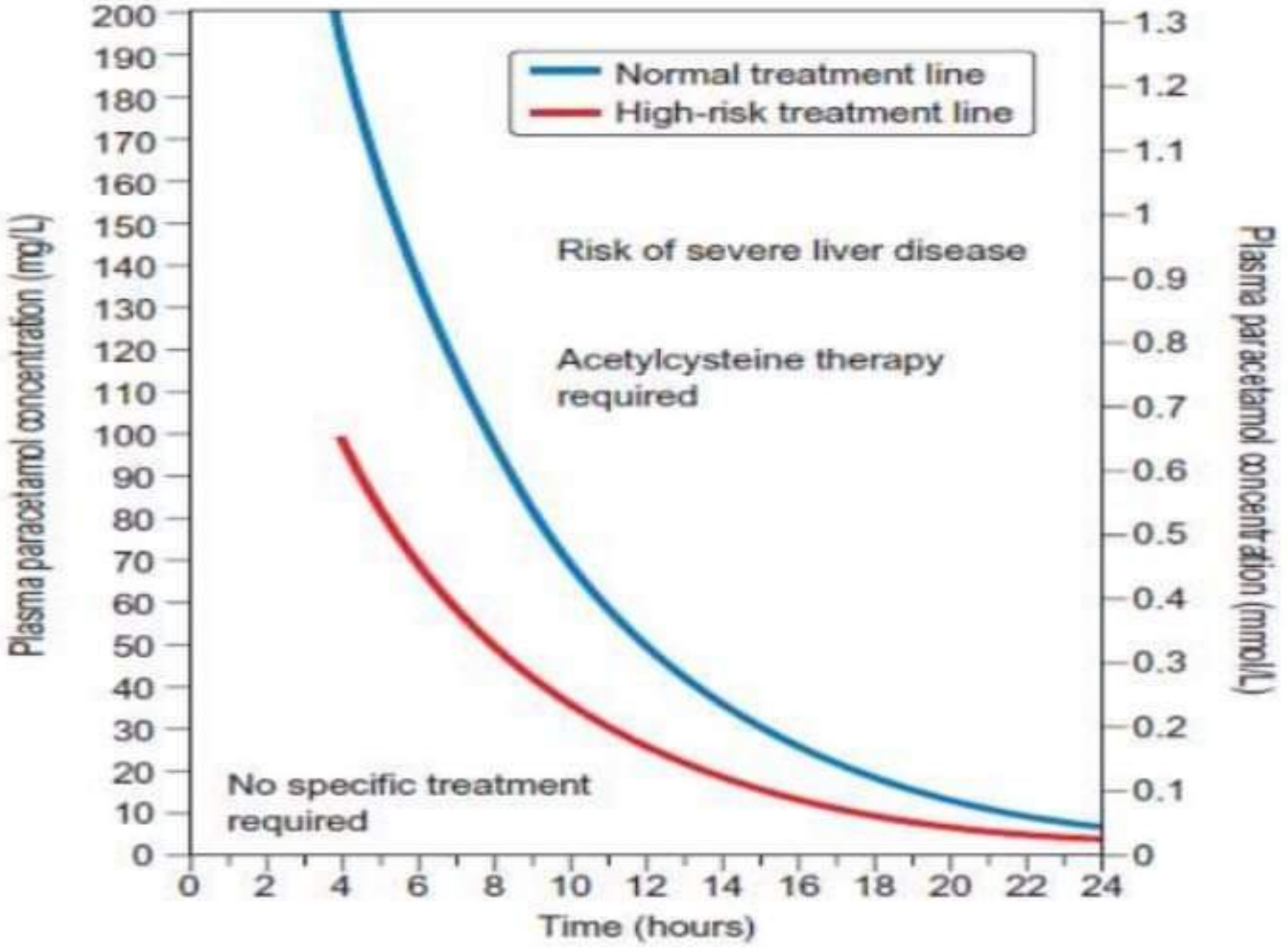

Fig. Normogram of Paracetamol

< 8 hours after ingestion

- If the plasma PCM concentration not available within 8 hours of the overdose and, if 10-15 g (20-30 tablets) or > 150 mg/kg PCM ingested, treat with acetylcysteine at once

- Check INR, plasma creatinine and ALT on the completion of treatment and before discharge

- < 1 hr : Activated charcoal may be used

8-15 hours after ingestion

- Urgent action required
- If > 150 mg/kg paracetamol ingested, start treatment with acetylecysteine immediately
- Discontinue it only if plasma PCM concentration is below relevant treatment line and there is no abnormality of INR, plasma creatinine or ALT and the patient is asymptomatic
- At the end of treatment, measure INR, plasma creatinine and ALT. If any test is abnormal or the patient is symptomatic, further monitoring is required and expert advice should be sought

15-24 hours after ingestion

- Start treatment immediately if > 150 mg/kg PCM ingested
- Prognostic accuracy of the '200 mg/L line' after 15 hours is uncertain
- But plasma PCM concentration above the extended treatment line should be regarded as carrying serious risk of severe liver damage
- At the end of treatment, check INR, plasma creatinine and ALT
- If any test is abnormal or the patient is symptomatic, further monitoring is required and expert advice should be sought

Regimen for Acetylcysteine

- 150mg/kg in 200 ml 5% dextrose over 15 min
- 50mg/kg in 500 ml 5% dextrose over next 4 hours
- 100mg/kg in 1 L 5% dextrose over ensuing 16 hours

Total dose → 300mg/kg over 20.25 hrs

Adverse effects of acetylcysteine

- Itching
- Urticaria
- Angio-edema
- Hypotension
- Bronchospasm

➢ Most can be managed by discontinuation or antihistamine administration

Management Contd...

- Alternative antidote: Methionine 2.5 gram orally 4 hourly to a total of 4 doses (less effective)
- If patient presents after 15 hours of ingestion
  - ➢ LFTs, PT, RFT should be measured and antidote should be started
- Arterial blood gas sample taken in pt. with severe liver function abnormality
- Metabolic acidosis indicates severe poisoning
- Liver transplantation should be considered- if life threatening liver failure