Paracetamol (Acetaminophen)

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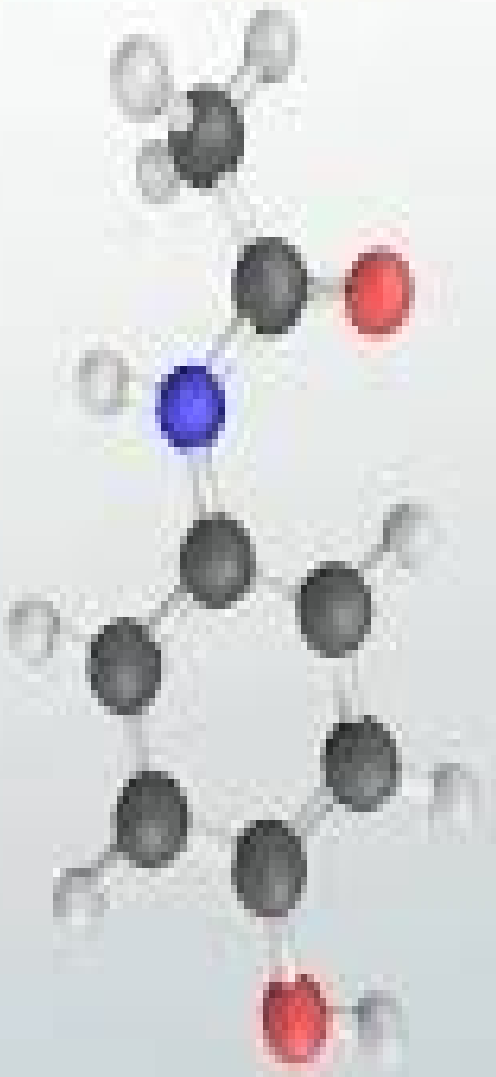
LEARNING OBJECTIVES

- Describe pharmacokinetics of Paracetamol
- Describe mechanism of action of Paracetamol
- Describe the clinical uses of Paracetamol
- Describe the adverse effects of Paracetamol
- Give the therapeutic and fatal doses of Paracetamol
- Describe the drug treatment of Paracetamol poisoning

ACETAMINOPHEN VS. PARACETAMOL

acetaminophen

paracetamol



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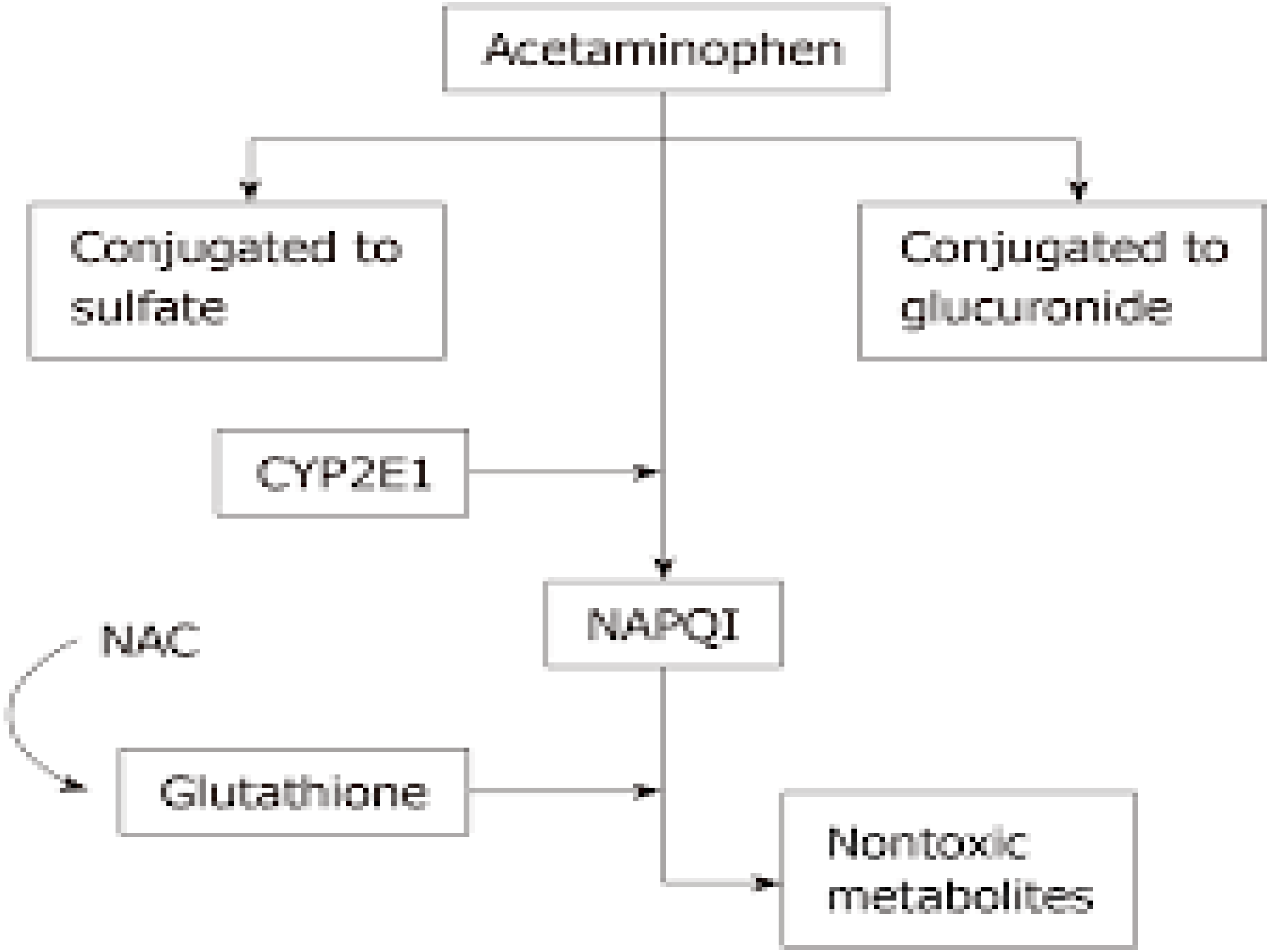
ACETAMINOPHEN

PHARMACOKINETICS

- Peak blood level is reached in 30-60 min
- Metabolized by hepatic microsomal enzymes by Conjugation to form acetaminophen sulphate and acetaminophen glucronide
- 5 % = N-acetyl-*p*-benzo-quinoneimine (NAPQI) Toxic to liver and kidneys
- 325 – 1000mg (total dose not > 4000mg)

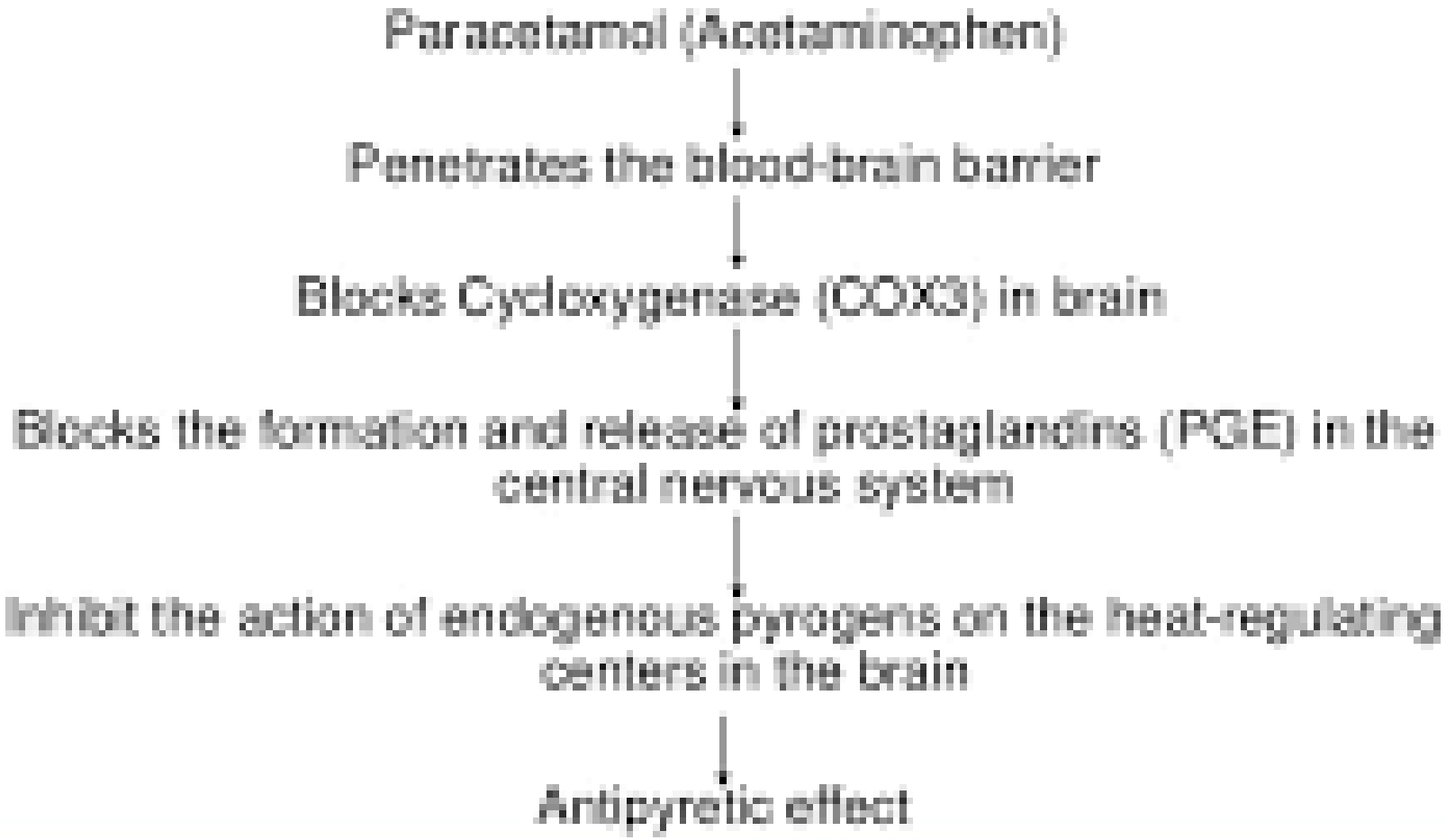
Pharmacokinetics:

- PCM bio availability above 80% .
- Peak plasma concentration occur between 15 mins and 2 hours after ingestion.
- It has few Pharmacokinetics drug interaction.


Acetaminophen
Conjugated to sulfate
Conjugated to glucuronide
CYP2E1
NAPQI
NAC
Glutathione
Nontoxic metabolites

Mechanism of action of Paracetamol

Acetaminophen



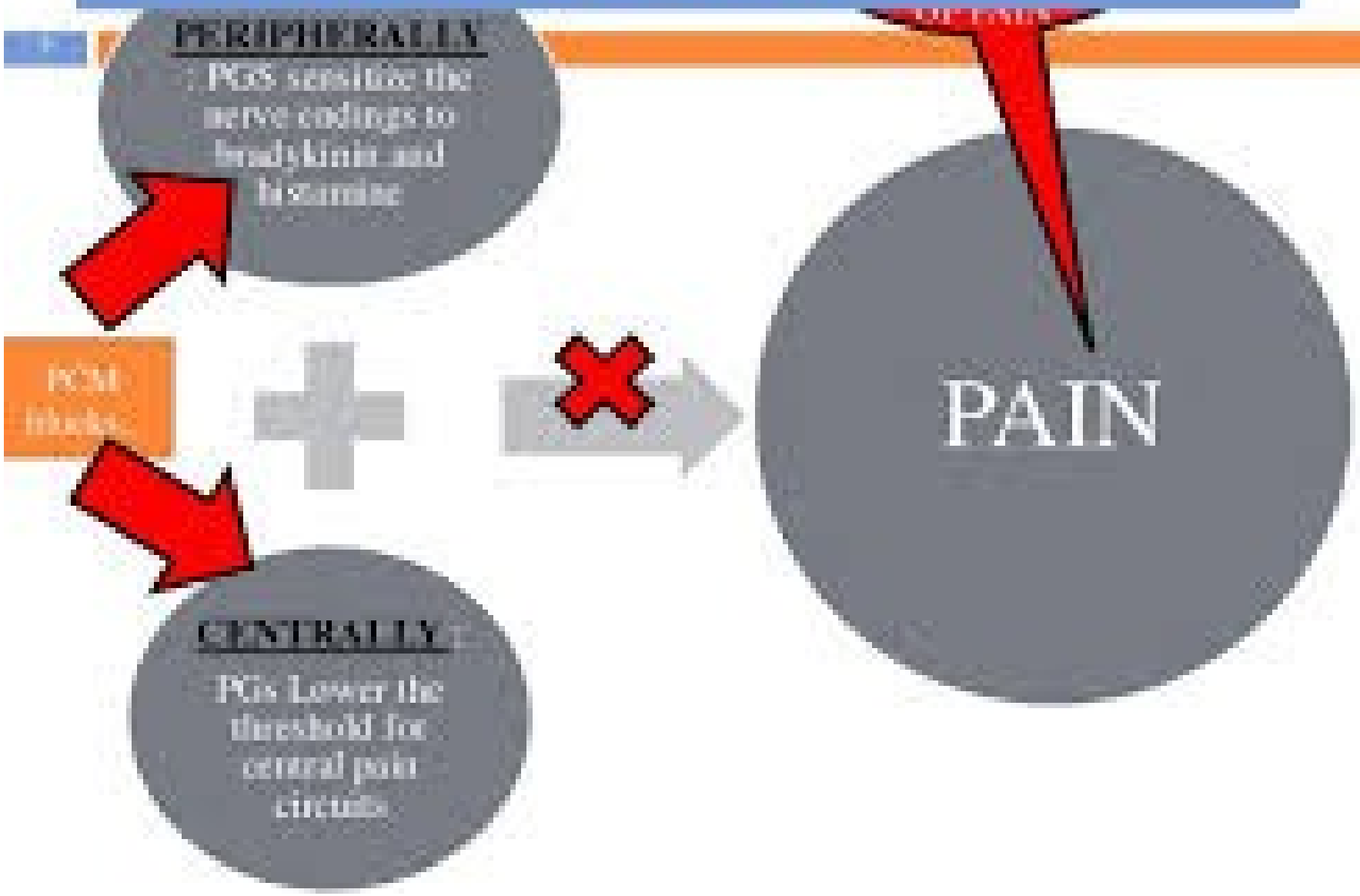
Paracetamol: mechanism of action

- Paracetamol acts as a pro-drug, with the active metabolite (AM404) being formed in the brain through conjugation of the deacetylated derivative of paracetamol (p-aminophenol) with arachidonic acid, by the action of fatty acid amide hydrolase (FAAH).
- At analgesic doses of paracetamol, AM404 which is formed in rat brain regions expressing high levels of FAAH, can indirectly activate CB1 receptors.

PHARMACOLOGICAL ACTIONS

- Active metabolite of phenacetin
- Weak COX-I and COX-2 inhibitor
- Inhibits COX-3 centrally
- No significant anti-inflammatory effects

ANALGESIC ACTIVITY



INDICATIONS

- Anti pyretic
- Headache
- Myalgia and sprains = adjunct with centrally acting muscle relaxants
- Peri menstrual and postpartum pain
- Adjunct with NSAIDs In rheumatoid arthritis

ACETAMINOPHEN…..

ADVANTAGES

Preferable to Aspirin in

- Peptic ulcer
- Hemophilia
- Bronchial asthma
- Reye ‘s syndrome

Can be given with probenecid

ADVERSE EFFECTS

- Mild increase in hepatic enzymes
- Dizziness
- Excitement and disorientation at larger doses
- **LIVER DAMAGE**

  In dose greater than 4-6 g/d

  15-20gm potentially fatal (30tablets)

PARACETAMOL INDUCED LIVER FAILURE

- **Mechanism**

N-acetyl-*p*-benzo-quinoneimine (NAPQI)

Normally Reacts with sulfhydryl group in GSH

Then excreted as mercapturic acid in urine

In toxic dose GSH is depleted

Toxic metabolite accumulates

Toxicity = centrilobular necrosis, methemoglobinemia,hemolytic anemia

PARACETAMOL INDUCED LIVER FAILURE

Treatment

- Supportive therapy
- *N*-Acetylcysteine

Side effects of Antipyretic

Adverse effect	PCM	NSAID
GI side effect	Rare	++
Skin Rash	Rare	++
RO bleeding	Nil	++
Bronchial hyper-reactivity	Nil	+
Hepato-toxicity	++ (overdose)	++ (Overdose)
Nephrotoxicity	+	++
National Kidney foundation USA, PCM – Safe.		
Seizure	Nil	+
Hypothermia	Nil	+
Pregnancy	Safe	unsafe
< 6 month	Recommended	Not recommended

REFERENCES

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Katzung & Trevor's Pharmacolog: Examination & Board Review, 12th Edition

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