Acetaminophen Toxicity

Acetaminophen (N-acetyl-p-aminophenol, APAP, paracetamol, Tylenol®)

Case

An 18 year old female presents to the Emergency Department 2 hours after the ingestion of 75 acetaminophen (APAP) 500 mg tablets

She has mild abdominal cramping

A 4 hour acetaminophen level is 180mcg/mL

Case

A 27 year old male presents to the Emergency Department with emesis, jaundice and altered mental status

He has recently been depressed

Two empty bottles of APAP were found in his bedroom

There is no further history available

Case

A 28 year old male, with a PMH for hepatitis C and alcohol abuse, presents to the ED with RUQ pain and emesis

He has been taking supratherapeutic doses of APAP

His AST and ALT are 360 u/L and 489 u/L respectively

APAP level is 45mcg/mL

Objectives

Understand basic pharmacology, metabolism, and mechanism of acetaminophen toxicity

Describe the clinical features associated with APAP toxicity

Discuss the principles of treatment:

- Rationale
- Indications
- Timing

Pharmacology

Analgesic, antipyretic with weak anti-inflammatory properties

Analgesia at serum APAP concentration of 10mcg/mL

- Central inhibition of COX-2 and prostaglandin synthase

Antipyresis at 4-18mcg/mL

- CNS inhibition of PGE_2

Dosing

Therapeutic:

- Pediatric: 15 mg/kg every 4 hours; no more than 5 doses/day
- Adult: 1 gram every 4 hours, not to exceed 4 grams/day

Toxic:

- Acute: >150mg/kg (pediatric) or >7.5g
- Chronic: less clear
  - >150mg/kg/day or 7.5g/day
  - Febrile children: >75mg/kg/day

Pediatrics

- Children can tolerate a higher level of acetaminophen without becoming toxic
- Misadventures in dosing is more common due to the different liquid pediatric preparations
- Febrile children are at greater risk of acetaminophen toxicity

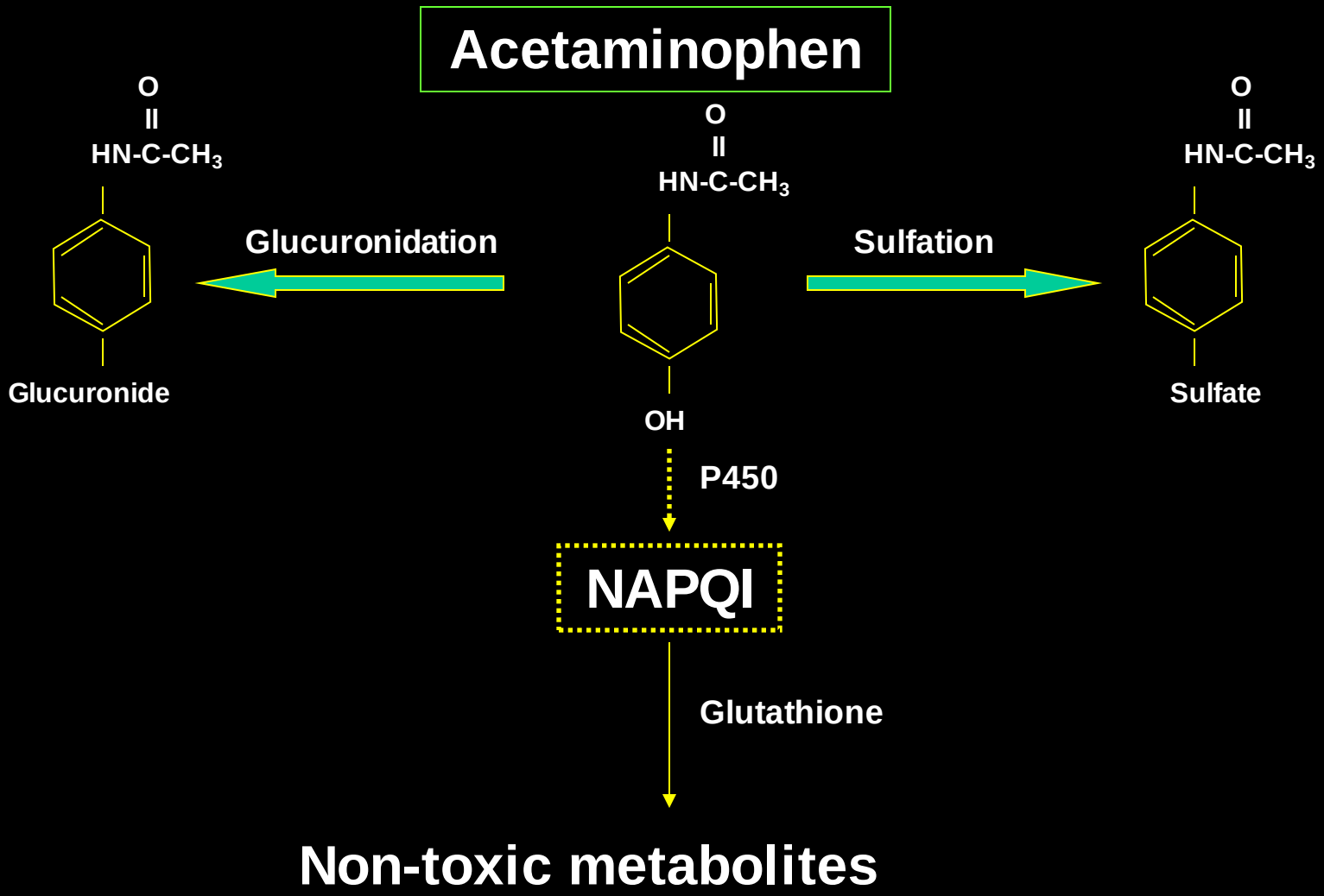
Toxicity

Little to no toxicity in therapeutic dosing

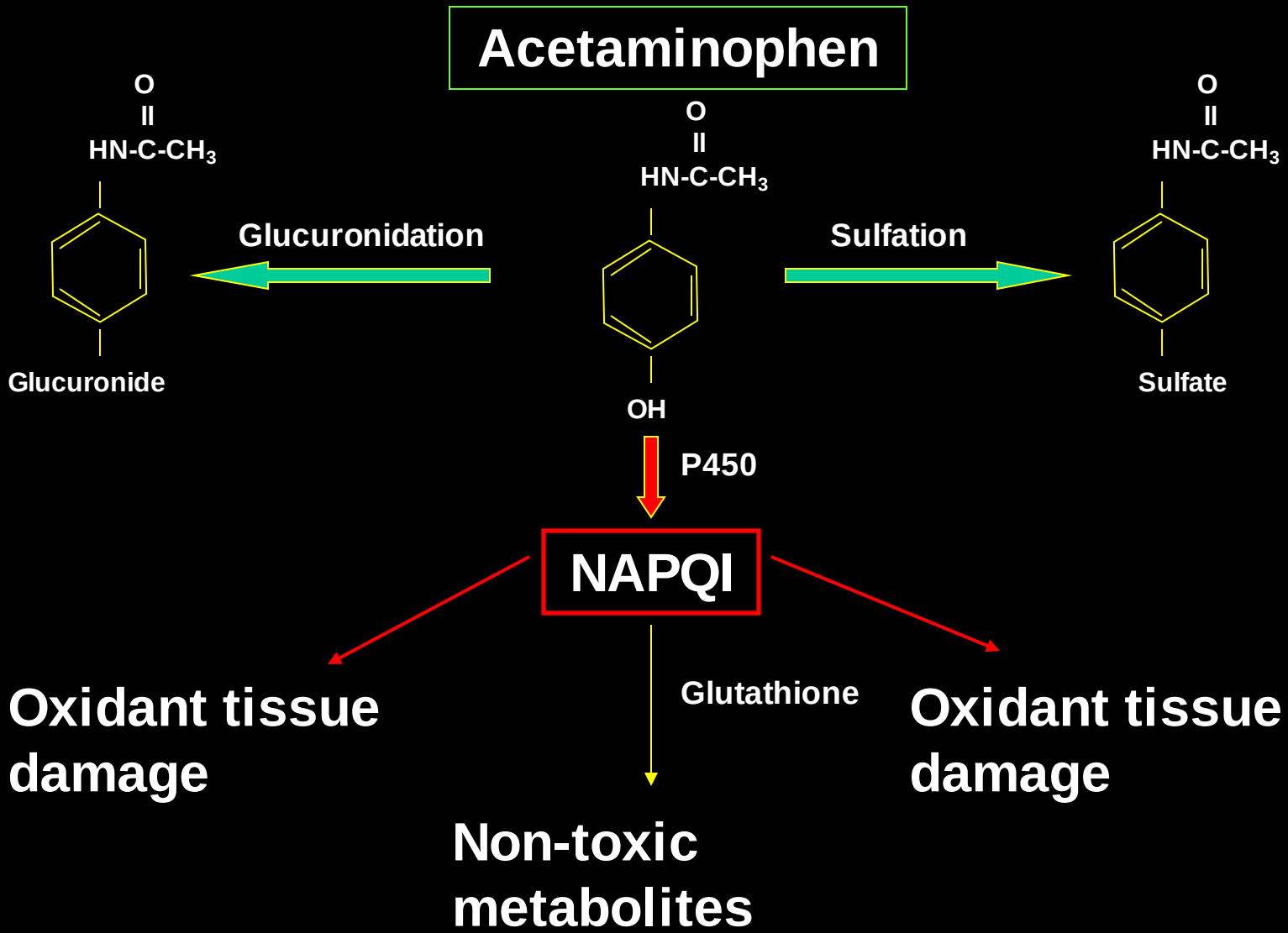
With overdose:

- Hepatic toxicity progressing to fulminant hepatic failure, encephalopathy and death within days

Acetaminophen Metabolism



Acetaminophen Overdose



Overdose

- Normal conjugation metabolism routes are saturated
- More NAPQI is produced
- Glutathione reserves fall below 30%
- Unable to detoxify all NAPQI formed
- Cellular injury results

NAPQI

Covalently binds cellular proteins

Alters cell function

Results in cell injury and death

Detoxified by glutathione

Phases of Toxicity

Phase I

0 to 24 hours

Usually asymptomatic

- “silent overdose”:
  - Importance of obtaining level

Nausea, vomiting, abdominal pain

Phase II

24-72 hours

Resolution of initial physical symptoms

- May develop right upper quadrant pain

Evolving liver injury

- Elevation of LFT, PT, Bilirubin

Phase III

- 3 to 4 days
- Nausea, vomiting, and abdominal pain reoccur
- Maximal manifestation of hepatic injury- AST/ALT in 10,000s
- Coagulopathy, hepatic necrosis, acidosis, encephalopathy
- Coma and anuria precede death

Phase IV

- Beyond 4 days
- Recovery phase
- LFTs will decrease, but bilirubin may remain elevated for some time
- May take several weeks for LFTs to normalize

Other Overdose Sequelae

Renal toxicity

- Occasionally renal failure can occur from massive overdoses
  - Possibly 2° to P450 activity in the kidney

Management

Determine if acetaminophen ingestion occurred

Determine if ingestion requires treatment

Initiate appropriate treatment

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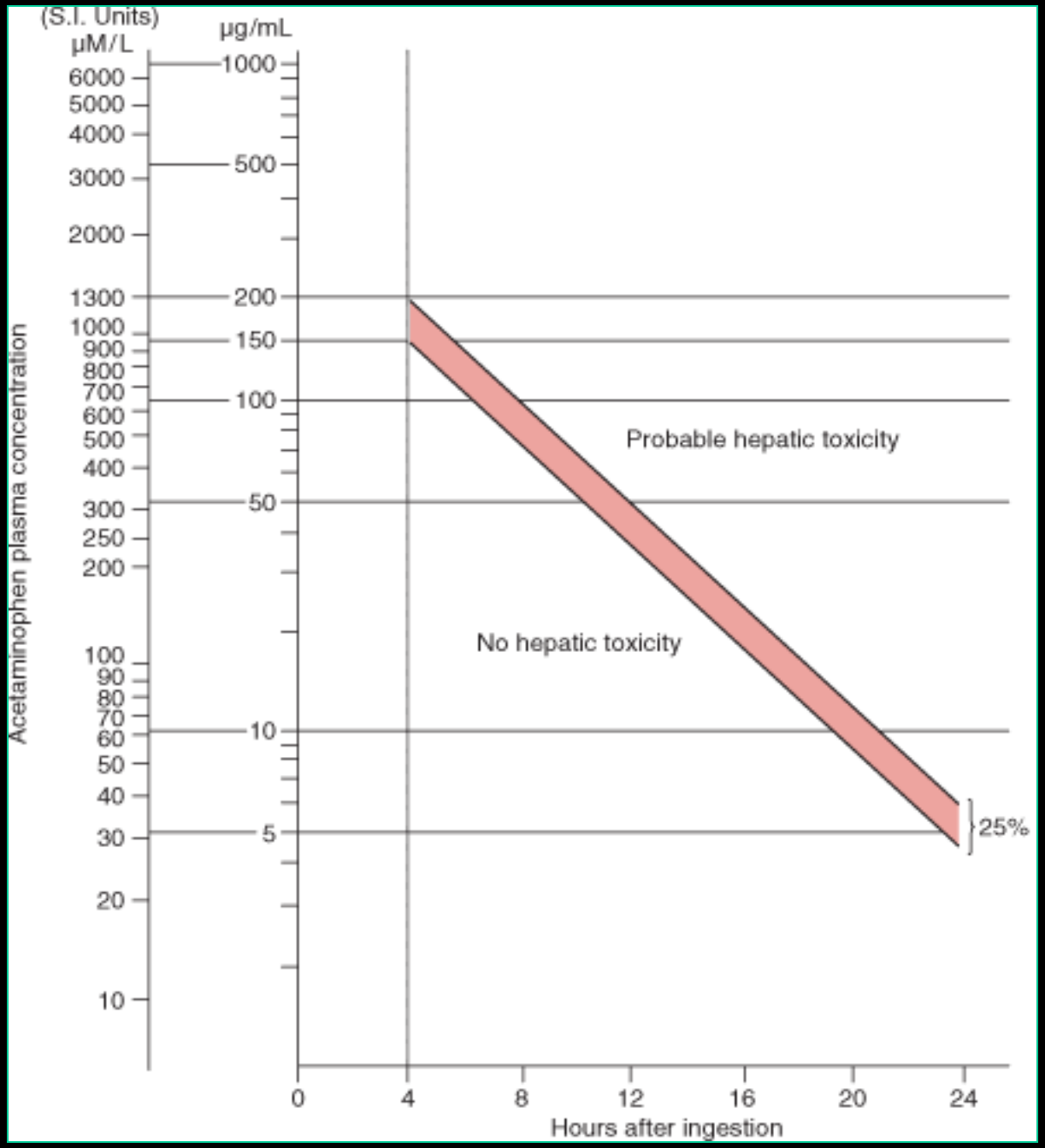
Rumack-Matthew Nomogram for Acute Acetaminophen Toxicity



The Nomogram

Is a guideline for determining who should be treated for a *single acute* ingestion

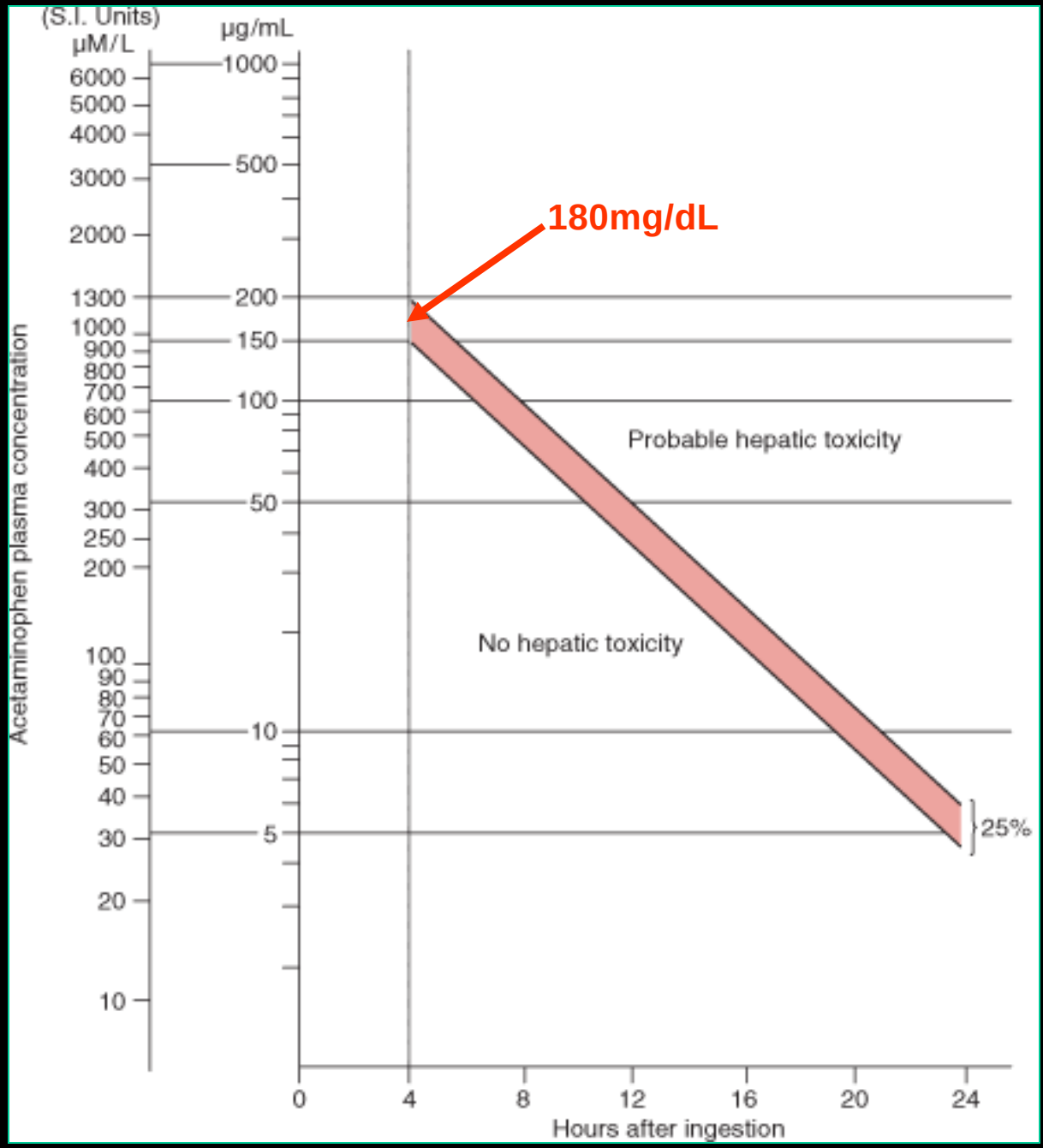
Is not a representation of the elimination kinetics

- Serial levels not useful

In US, line positioned 25% lower

- ↑ sensitivity – no missed cases
- ↓ specificity

Important to use a 4-hour level whenever possible

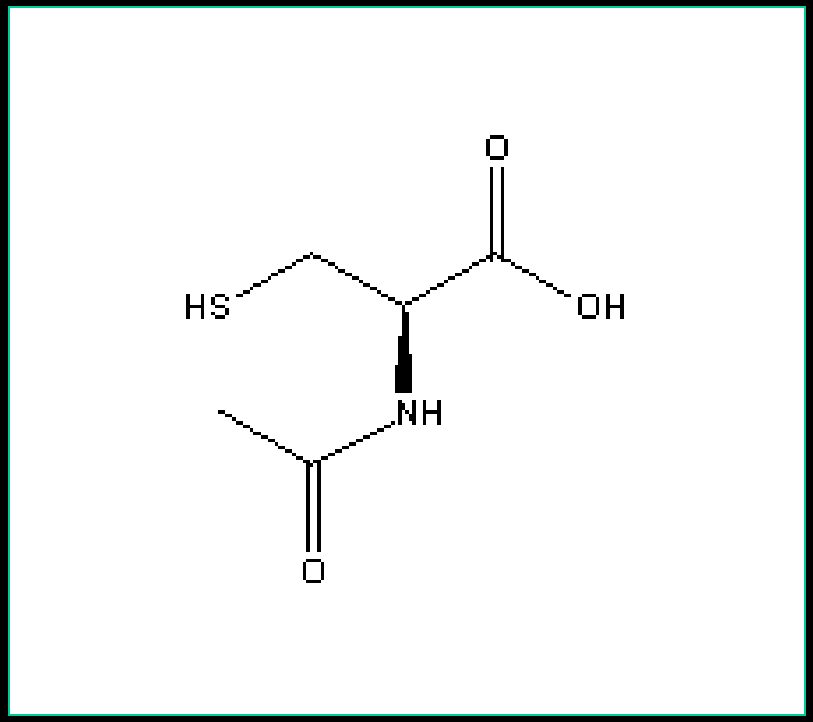

(S.I. Units)
μM/L
μg/mL
Acetaminophen plasma concentration
6000
5000
4000
3000
2000
1300
1000
900
800
700
600
500
400
300
250
200
100
90
80
70
60
50
40
30
20
10
1000
500
200
150
100
50
10
5
180mg/dL
Probable hepatic toxicity
No hepatic toxicity
25%
0
4
8
12
16
20
24
Hours after ingestion

Ingestion of single dose

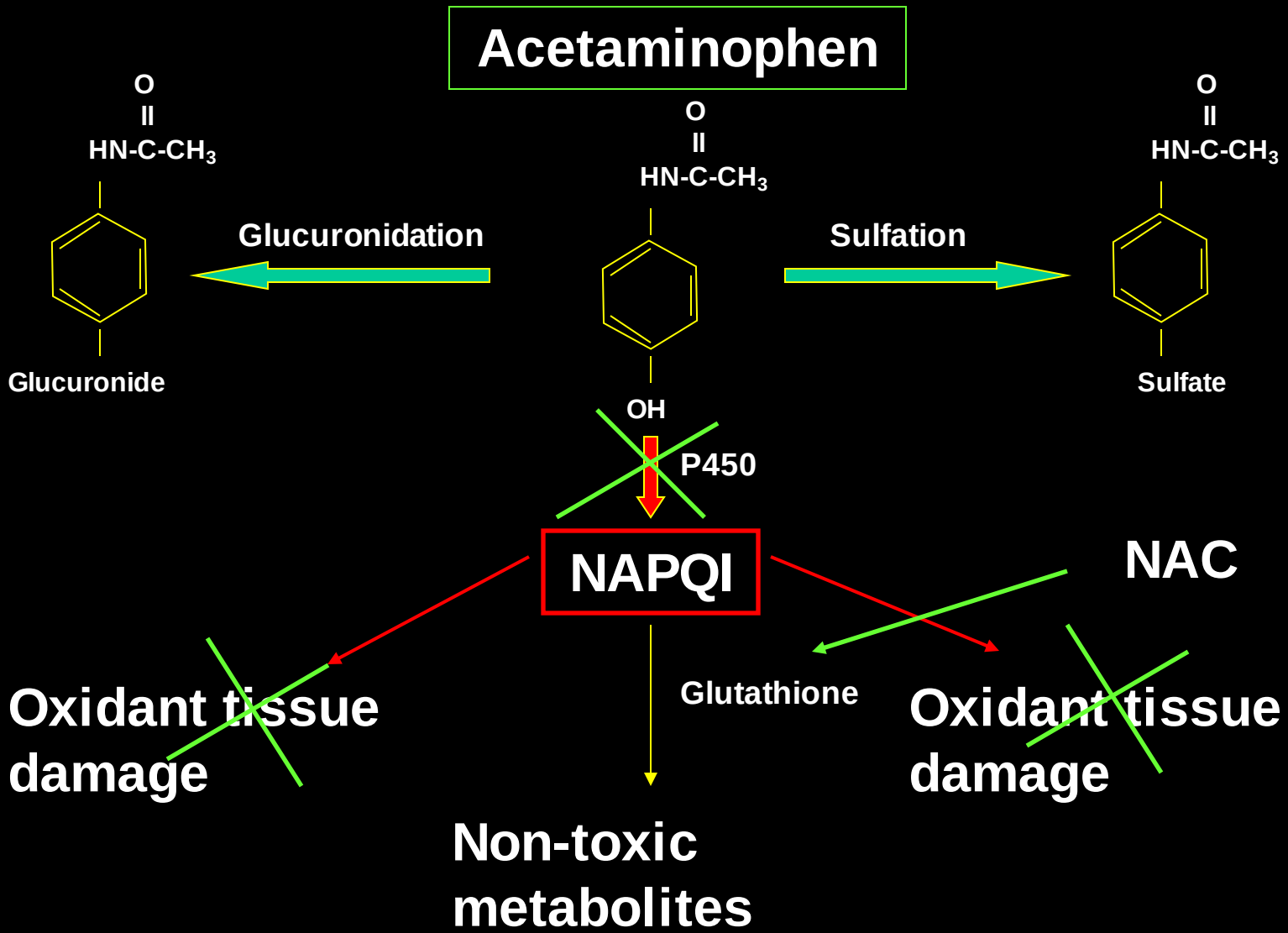
Treatment indicated if:

- Level above 150mg/dL at 4 hours
- Ingestion of 150 mg/kg in children
- Ingestion of 7.5 g in adults
- Patient is unreliable or unconscious

N-acetylcysteine



Acetaminophen Overdose



Mechanism of N-acetylcysteine

Restores glutathione:

- Allows NAPQI detoxification

Augments sulfation reaction

Direct anti-oxidant:

- Directly detoxifies NAPQI
- Improves organ function and limits hepatocyte injury

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He has recently been depressed

Two empty bottles of APAP were found in his bedroom

There is no further history available

Unknown ingestion time

Treat if any sign of liver injury even without history of APAP ingestion

Detectable APAP level in altered patient

If AST/ALT are normal

- And APAP is less than 10 μg/ml
  - Do not treat
  - Narrow window of risk

Laboratory Assessment

If patient is sick, one should obtain LFTs, PT, electrolytes, BUN/Cr, amylase, lipase and glucose

- Late presenting sick patients will not have detectable acetaminophen levels
- Diagnosis can be more difficult
- They will require treatment

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A 28 year old male, with a PMH for hepatitis C and alcohol abuse, presents to the ED with RUQ pain and emesis

He has been taking supratherapeutic doses of APAP

His AST and ALT are 360 u/L and 489 u/L respectively

APAP level is 45mcg/mL

Repeat or Chronic ingestion

Nomogram does not apply

Suggested threshold:

- 150 mg/kg per 24 hours in children
- 7.5 g per 24 hour period in adults

Obtain acetaminophen level, AST, ALT, PT, BUN/Cr and electrolytes

Repeat or chronic ingestion

Patients who should be treated (similar to unknown ingestion time):

- Signs of hepatotoxicity (elevated AST)
- APAP level of ≈25 mcg/ml or greater
- Symptomatic

"Gray area": APAP 11-25 mcg/ml and normal AST in asymptomatic patient

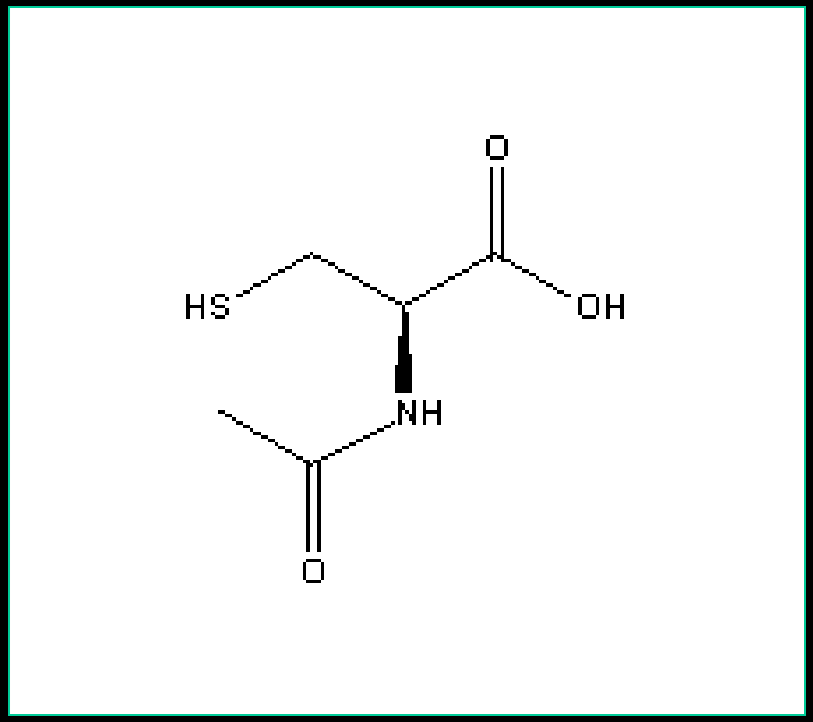
Ethanol And Acetaminophen

Ethanol is metabolized to some extent by P450 system

Chronic ethanol ingestion causes increase in 2E1 P450 activity

- Acute acetaminophen ingestion is treated the same in patients who consume alcohol chronically

N-acetylcysteine



N-acetylcysteine

Greatest benefit if administered within 8 hours:

- No clinical difference within the first 8 hours
- All patients that have a normal AST at time of NAC initiation survive
- Treatment within 8 hours of single ingestion completely prevents liver failure

“Too Late” does not exist

- Improved mortality even in patients with hepatic failure when initiated 2-3 days after ingestion

Oral N-acetylcysteine

Oral loading dose is 140 mg/kg

- Dilute 4:1 with palatable liquid
- Repeat doses are 70mg/kg every 4 hours
- Total of 17 doses for total of 72 hours

Antiemetic treatment may be required

- NAC is very foul “rotten egg” liquid

IV N-acetylcysteine

Can cause anaphylactoid reaction

- Rash, hypotension, bronchospasm and death
- Rate related; rare when given slowly

Higher, continuous blood levels obtained then oral NAC

Bolus administered first, then constant infusion rate may be given

IV vs. Oral

- Both have their advantages and disadvantages
- Each may be more appropriate in certain settings
- No side by side studies to date
- Conclusions of relative benefits are speculative

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Take-Home Points

"Rule of 150's"

- >150mg/kg = toxic dose
  - 7.5g in adults
- >150mg/dL at 4 hours

NAPQI and NAC: what they do

Nomogram for single acute ingestions

- Very conservative but safe

Treatment: indications, timing