SALICYLATE AND PARACETAMOL TOXICITY

SALICYLATE TOXICITY

- Derivatives of salicylic acid and include acetyl salicylic acid, sodium salicylate and methyl salicylate
- widely used for their analgesic and anti-inflammatory properties.
- They are over-the-counter analgesics, cold preparations, and topical keratolytic products (methyl salicylate).
- Two distinct syndromes of intoxication may occur, depending on whether the exposure is acute or chronic.

USES

1. SALICYLATE AND ACETYL SALICYLIC ACID

- Antipyretic
- Analgesic
- Treatment of Rheumatoid arthritis
- Prophylaxis of cerebrovascular ischemic events, angina pectoris and also for the prevention of colon cancer and migraine

2. SODIUM AMINOSALICYLATE

- Used in tuberculosis

3. BISMUTH SUBSALICYLATE

- Used to treat diarrhea and sometimes as a prophylaxis in traveler's diarrhea

4. MESALAMINE –used as a suppositories or rectal suspension enema in IBD

5. DIFLUNISAL, a diflurophenyl derivative of salicylic acid – musculoskeletal sprains and osteoarthritis

6. METHLY SALICYLATE – used for the local treatment of musculoskeletal pain and inflammation, as a flavoring agent

7.HOMOMENTHYL SALICYLATE- is used in sunscreen

8.TROLAMINE SALICYLATE – management of osteoarthritis

MECHANISM OF TOXICITY

- Stimulation of the respiratory center results in hyperventilation, leading to respiratory alkalosis.
- Secondary consequences from hyperventilation include dehydration and compensatory metabolic acidosis.
- Intracellular effects include uncoupling of oxidative phosphorylation and interruption of glucose (Krebs cycle) and fatty acid metabolism, which contribute to ketosis and a wide anion-gap metabolic acidosis

- The mechanism by which cerebral and pulmonary edema occurs is not known but may be related to an alteration in capillary integrity.
- Salicylates alter platelet function and may also prolong the prothrombin time
- Salicylates are extremely irritating to the GI mucosa and overdose often results in hemorrhagic gastritis.

TOXICOKINETICS

- Salicylates are rapidly absorbed from the stomach, and to a slightly lesser extent from the small intestine.
- Salicylic acid and methyl salicylate are readily absorbed through intact skin.
- Therapeutic serum salicylate levels should not exceed 30 mg/100 ml.
- Salicylates distribute well into plasma, saliva, milk and spinal, peritoneal and synovial fluid and into body tissues including kidney, liver, lung and heart.

- Metabolism occurs chiefly in the liver, where salicylates are broken down into salicylic acid, ether glucuronide, ester glucuronide, and gentisic acid
- Excretion is mainly through urine.
- The half-life of salicylates is 2 to 4 hours at therapeutic levels, but may increase to 20 hours at toxic levels.

- Plasma salicylate is 50 to 80% protein bound, especially to albumin.
- As salicylate doses are increased, the proportion bound to plasma protein decreases, and the volume of distribution increases.
- There is also a decrease in protein binding from 90% at therapeutic levels to less than 75% at toxic levels. The apparent volume of distribution increases from 0.2 L/kg to more than 0.3 L/kg.

TOXIC DOSE

- Acute ingestion of 150–200 mg/kg will produce mild intoxication
- Severe intoxication is likely after acute ingestion of 300–500 mg/kg
- Chronic intoxication may occur with ingestion of more than 100 mg/kg/day for 2 or more days.

CLINICAL MANIFESTATIONS

ACUTE POISONING

- **EARLY**—Nausea, vomiting, sweating, tinnitus, vertigo, and hyperventilation due to respiratory alkalosis.
- Irritability, confusion, disorientation, hyperactivity, slurred speech, agitation, combativeness, hallucinations, ataxia, and restlessness may be early findings in patients with severe toxicity.

- **LATE**—Deafness, hyperactivity, agitation, delirium, convulsions, hallucinations, hyperpyrexia. Coma is unusual.
- **COMPLICATIONS**—Metabolic acidosis, pulmonary edema, rhabdomyolysis, cardiac depression, thrombocytopenic purpura.
- **Three main auditory alteration** seen in salicylate poisoning - tinnitus, loss of absolute acoustic sensitivity, and alterations of perceived sound
- Dehydration and hypokalemia are common

- QT prolongation, U waves and flattened T waves have been seen
- **Respiratory alkalosis** is also seen
- Salicylates must **not** be therapeutically administered to children under 15 years of age, especially if they are suffering from chicken pox or influenza.
- there is a serious risk of precipitating Reye's syndrome which can be fatal.

CHRONIC POISONING (SALICYLISM) -

- It occurs as a result of chronic repeated over medication for several days
- This is characterized by slow onset of confusion, agitation, lethargy, disorientation, slurred speech, hallucinations, convulsions and coma.
- There may also be tinnitus, hearing loss, prolongation of PT time, nausea, dyspnea, tachycardia and fever

- Sometimes salicylism presents as pseudo sepsis syndrome characterized by fever, leukocytosis, hypotension and multi-organ system failure.
- Cerebral and pulmonary edema are more common than with acute intoxication
- Chronic maternal ingestion is associated with an increased incidence of stillbirths, antepartum/postpartum bleeding, prolonged pregnancy/labor, and lower birth weight

REYE'S SYNDROME

Stage	*Manifestations*
I	Lethargic
II	Stuporous, sluggish pupillary reaction, conjugate deviation of eyes (oculocephalic reflex)
III	Comatose, decorticate posture, sluggish pupillary reaction, conjugate deviation of eyes (oculocephalic reflex)
IV	Comatose, decerebrate posture, sluggish pupillary reaction, inconsistent response (oculocephalic reflex)
V	Comatose, flaccid posture, no pupillary reaction, no response to painful stimuli, no response to oculocephalic reflex

DIAGNOSIS

- Monitor serum salicylate level, glucose and electrolytes every 2 hours until the salicylate level is consistently falling and acid base abnormalities are improving .Obtain an arterial blood gas in symptomatic patients and follow until acid base abnormalities are improving
- Obtain CBC, renal and hepatic function tests and INR or PT and PTT in patients with clinical evidence of moderate to severe toxicity

- In patients with pyloric stenosis (in whom the serum salicylate levels do not continue to rise or decline), installation of contrast media into the stomach followed by an abdominal x ray can detect enteric coated aspirin that remains in the stomach for prolonged time . The drug appears in radio opaque in plain abdominal radiographs
- **LABORATORY TESTS-**

  - Anion-gap acidosis

  -Hypokalemia (acidosis may mask it)

  -Hypocalcemia

  -Hypoglycemia

BED-SIDE TESTS-

a. **FERRIC CHLORIDE TEST –**

Few drops of 10% ferric chloride + 1ml of urine ⟶ Purple color

It is not conclusive, since positive result is also obtained in phenol, phenothiazine, phenyl-butazone and oxyphenbutazone

b. TRINDERS TEST – (40gms of mercuric chloride + 120ml of aqHCl + 40gms of ferric nitrate)

0.1ml of Trinder's test + 2ml of sample ⟶ strong violet color (keep for 5min)

Urine sample, stomach contents or scene residue can be tested.

If stomach contents or scene residue are tested , first boil 1ml of the sample with 1ml of aqueous HCl for 10 minutes, cool , filter and then neutralize with 1 ml of aqueous sodium hydroxide

c. CONFIRMATORY TEST –

is to estimate the serum salicylate level

But this method has severe limitations to its use and is now not generally considered reliable

It has shown to underestimate or over estimate salicylate poisoning.

TREATMENT

1. Patients with **major signs and symptoms**(metabolic acidosis, dehydration, mental status changes, seizures, pulmonary edema) should be admitted to the ICU regardless of serum salicylate level
2. Patients with minor symptoms only following acute overdose maybe managed with **decontamination and alkaline diuresis** if the salicylate level is shown to decline
3. **Stomach wash** maybe beneficial up to 12 hours after ingestion, since toxic doses of salicylates often cause pylorospasm and delayed gastric emptying.
4. **Whole bowl irrigation** might be useful in patients with bezoars, or patients who have ingested enteric coated or sustained release tablets

5. **Activated charcoal-** it is effective in the treatment of salicylate poisoning, a 10:1 ratio of activated charcoal to salicylate ingested appears to result in maximum efficacy. Some investigators recommend multiple dosing

6.**Urinary Alkalization-** alkalization of blood and urine can be achieved by administration of sodium bicarbonate. Acetazolamide should not be used as it can lead to metabolic acidosis

- For mild poisoning – 1mEq/kg of sodium bicarbonate is added to the first bottle of 5% dextrose. If alkalization (i.e. urinary pH between 7.5 and 8.5)is not achieved in a few hours, it can be repeated
- For severe poisoning- Additional bolus therapy of 50 -100mEq of sodium bicarbonate over 1 to 2 hours maybe necessary

- Monitor serum electrolytes and urine pH every 1-2 hours. Adjust potassium and bicarbonate administration it required. It is important to correct hypokalemia while alkalization of urine. Alkalization should be stopped when the serum salicylate level falls below 35mg/100mL

7.Haemodialysis- It is very effective in salicylate poisoning

- must be considered in presence of cardiac or renal failure, intractable acidosis , convulsions, severe fluid imbalance, or serum salicylate level more than 100mg/100ml.
- Patients with evidence of **cerebral edema** require **immediate dialysis.**
- **Charcoal hemoperfusion** produces **better** salicylate clearance than hemodialysis, but does not correct fluid and electrolyte imbalance

8. SUPPORTIVE MEASURES

- Correct fluid and electrolyte imbalance
- Correct dehydration with 0.9% saline 10-20 ml/kg/hr. over 1-2 hours until a good urine flow is obtained. In patients, in whom urinary alkalization is being considered, initial hydration may be with 10 to 20ml/kg of D5W with 88 to 132 milliequivalents of bicarbonate added. Patients in shock may require rapid fluid administration
- Hypoprothrombinemia can be corrected by 2.5 to 5mg vitamin K IV every day
- Hyperpyrexia must be tackled by cooling measures
- Correction of metabolic acidosis with $NaHCO_3$
- Correction of hypocalcemia with calcium gluconate IV

8. SUPPORTIVE MEASURES

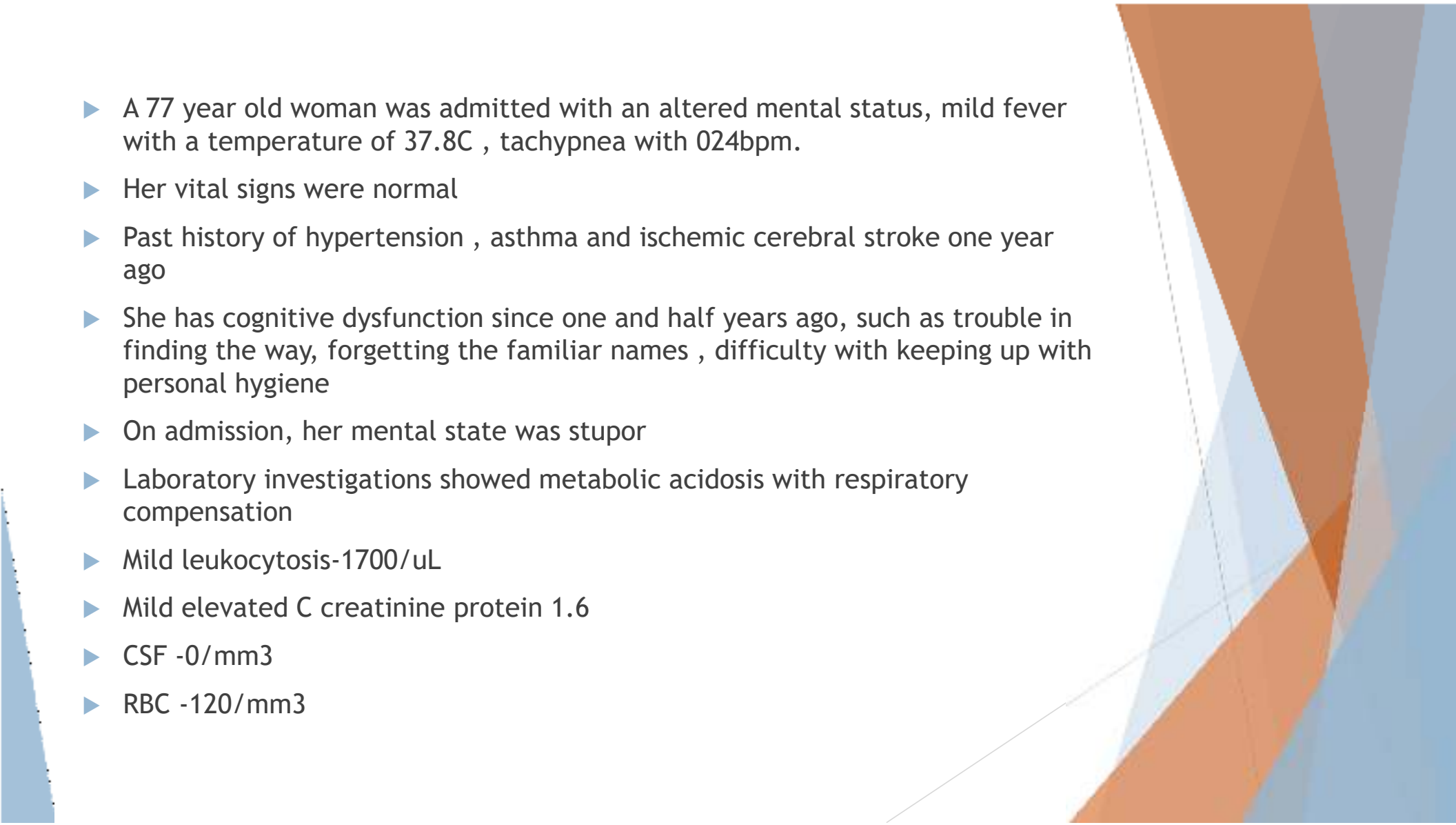
- Correct hypokalemia as needed, cardiac monitoring is required in these patient
- Correction of hypoglycemia with glucose IV
- Treatment of convulsions with benzodiazepines
- Mild cerebral edema and elevated intracranial pressure can be managed by head elevation and administration of mannitol
- Salicylates can interfere with coagulation mechanisms therefore, patients with evidence of active bleeding or coagulation disorders – monitor PT and INR . For prolonged PT and INR administer Vit K

9. TREATMENT OF REYE'S SYNDROME-

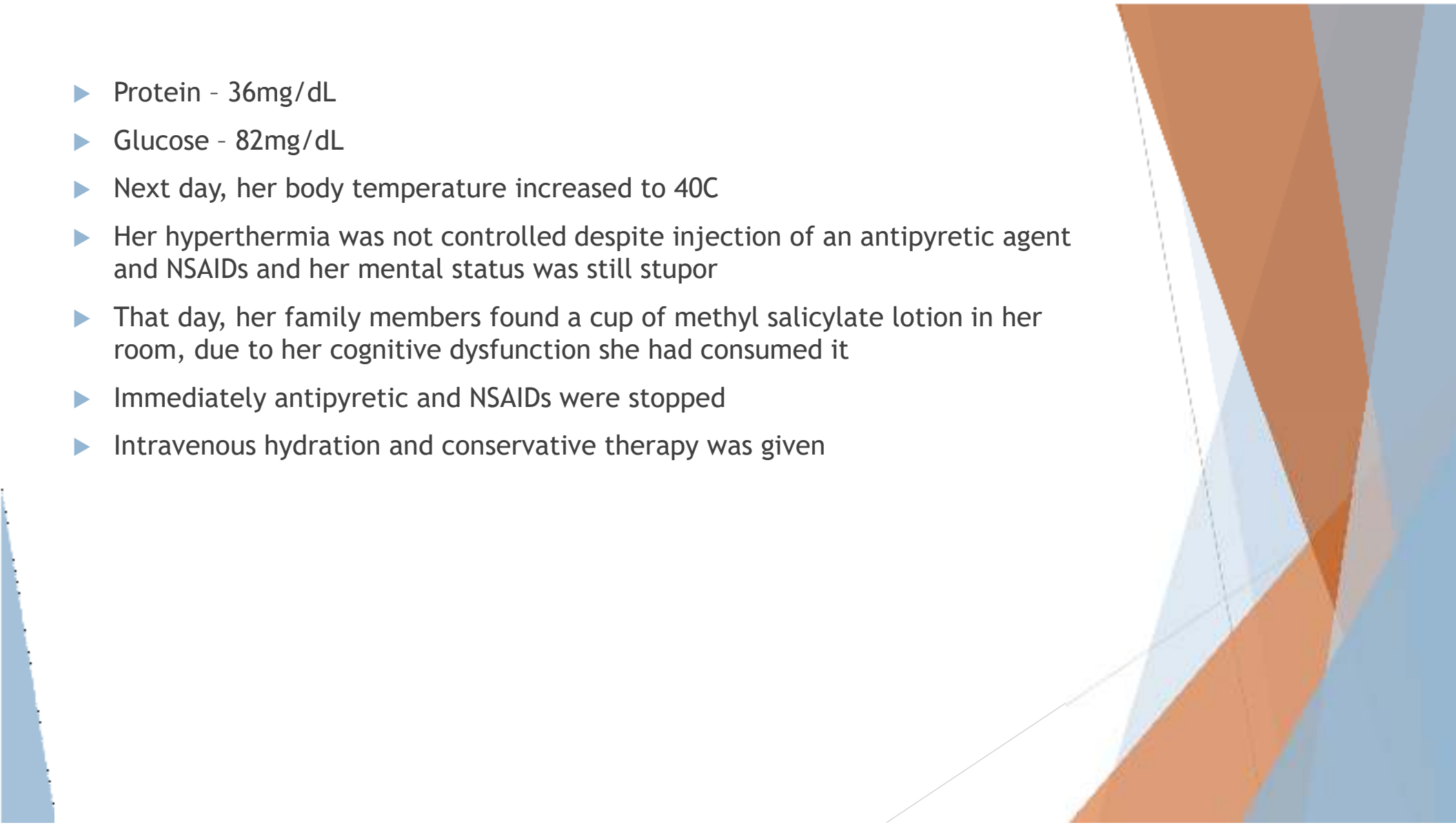
- Admit the patient to an intensive care unit
- Raise the head-end of bed
- Mannitol IV (0.2 to 1.0g/kg)
- Acute hyperventilation may be helpful
- Short acting barbiturates in resistant cases

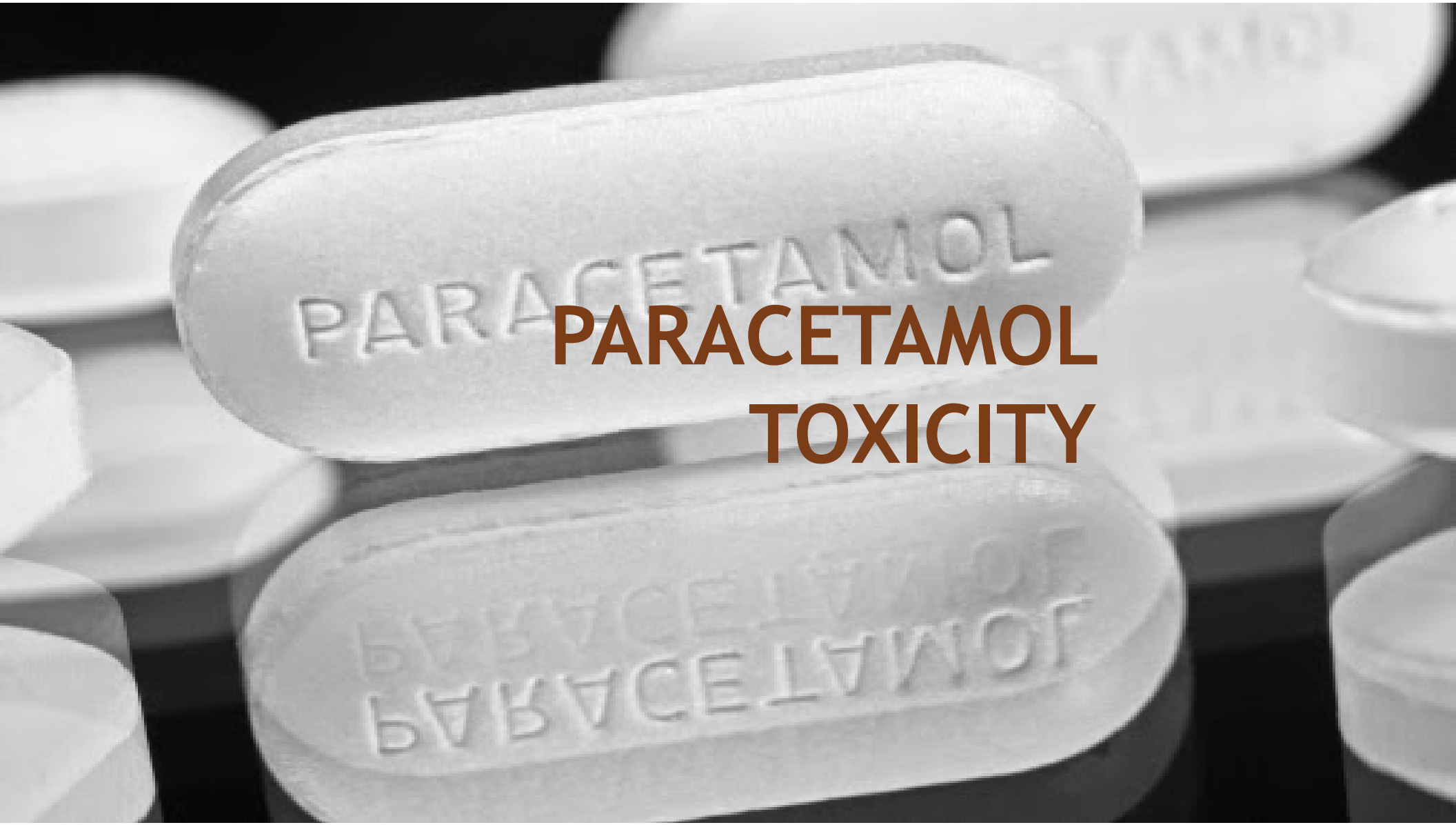
CASE

- A 77 year old woman was admitted with an altered mental status, mild fever with a temperature of 37.8C , tachypnea with 024bpm.
- Her vital signs were normal
- Past history of hypertension , asthma and ischemic cerebral stroke one year ago
- She has cognitive dysfunction since one and half years ago, such as trouble in finding the way, forgetting the familiar names , difficulty with keeping up with personal hygiene
- On admission, her mental state was stupor
- Laboratory investigations showed metabolic acidosis with respiratory compensation
- Mild leukocytosis-1700/uL
- Mild elevated C creatinine protein 1.6
- CSF -0/mm3
- RBC -120/mm3



- Protein – 36mg/dL
- Glucose – 82mg/dL
- Next day, her body temperature increased to 40C
- Her hyperthermia was not controlled despite injection of an antipyretic agent and NSAIDs and her mental status was still stupor
- That day, her family members found a cup of methyl salicylate lotion in her room, due to her cognitive dysfunction she had consumed it
- Immediately antipyretic and NSAIDs were stopped
- Intravenous hydration and conservative therapy was given





PARACETAMOL TOXICITY

Introduction

- **Drug Class :**Nonsteroidal Anti-inflammatory Drugs
- **Synonyms :**Acetaminophen ,Panadol , Paracetamol , Acephen…etc
- **Physical description** : Odourless white crystalline solid. Bitter taste.

- Acetaminophen is a p-aminophenol derivative
- Widely used non-prescription analgesic and antipyretic medication for mild-to-moderate pain and fever.
- **Harmless** at low doses
- Acetaminophen has direct hepatotoxic potential when taken as an **overdose** and can cause **acute liver injury** and death from acute liver failure.
- Even in **therapeutic doses**, acetaminophen can cause transient **serum aminotransferase**

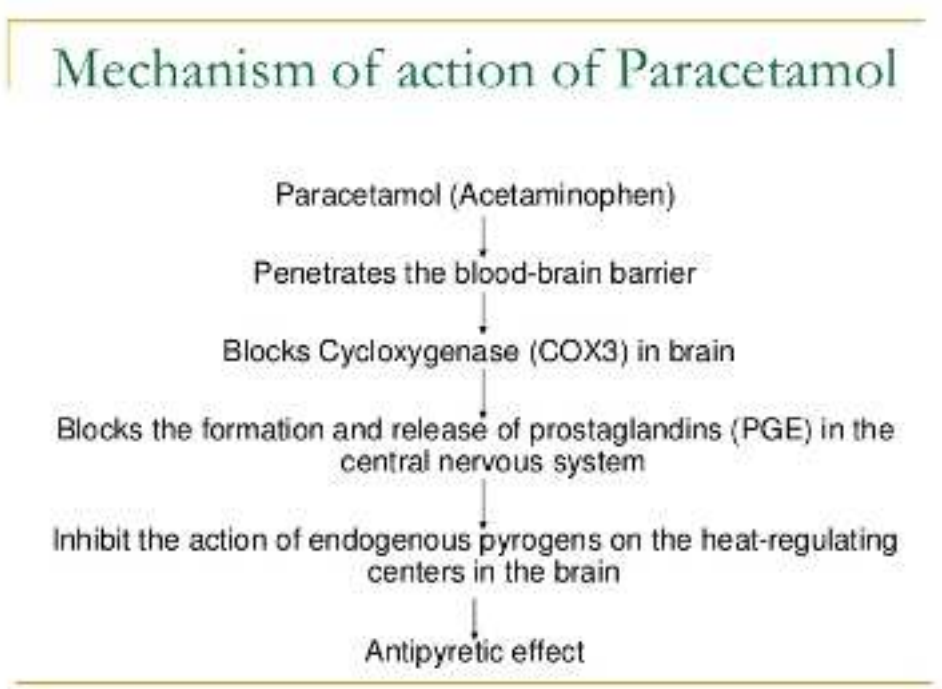
USES

- Analgesic (mild to moderate pain)
- Antipyretic
- For temporary relief of fever, minor aches, and pains.

MECHANISM OF ACTION

- Although the exact mechanism through which acetaminophen exert its effects has yet to be fully determined
- Acetaminophen may inhibit the nitric oxide (NO) pathway mediated by a variety of neurotransmitter receptors including N-methyl-D-aspartate (NMDA) and substance P, resulting in elevation of the pain threshold.
- The antipyretic activity may result from **inhibition of prostaglandin synthesis** and release in the central nervous system (CNS) and prostaglandin-mediated effects on the heat-regulating centre in the anterior hypothalamus.

MECHANISM OF ACTION



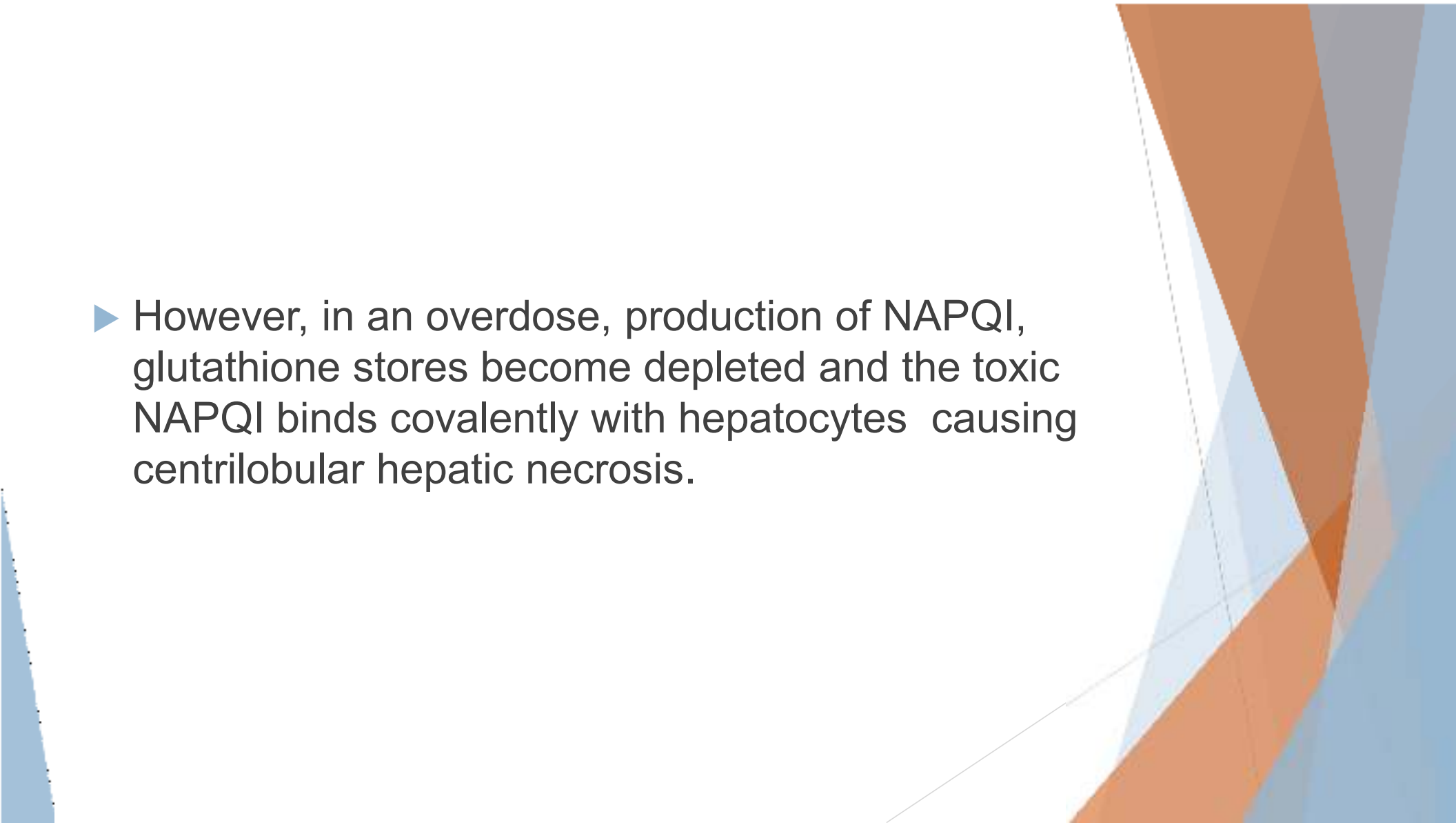
Minimum/Potential Fatal Human Dose

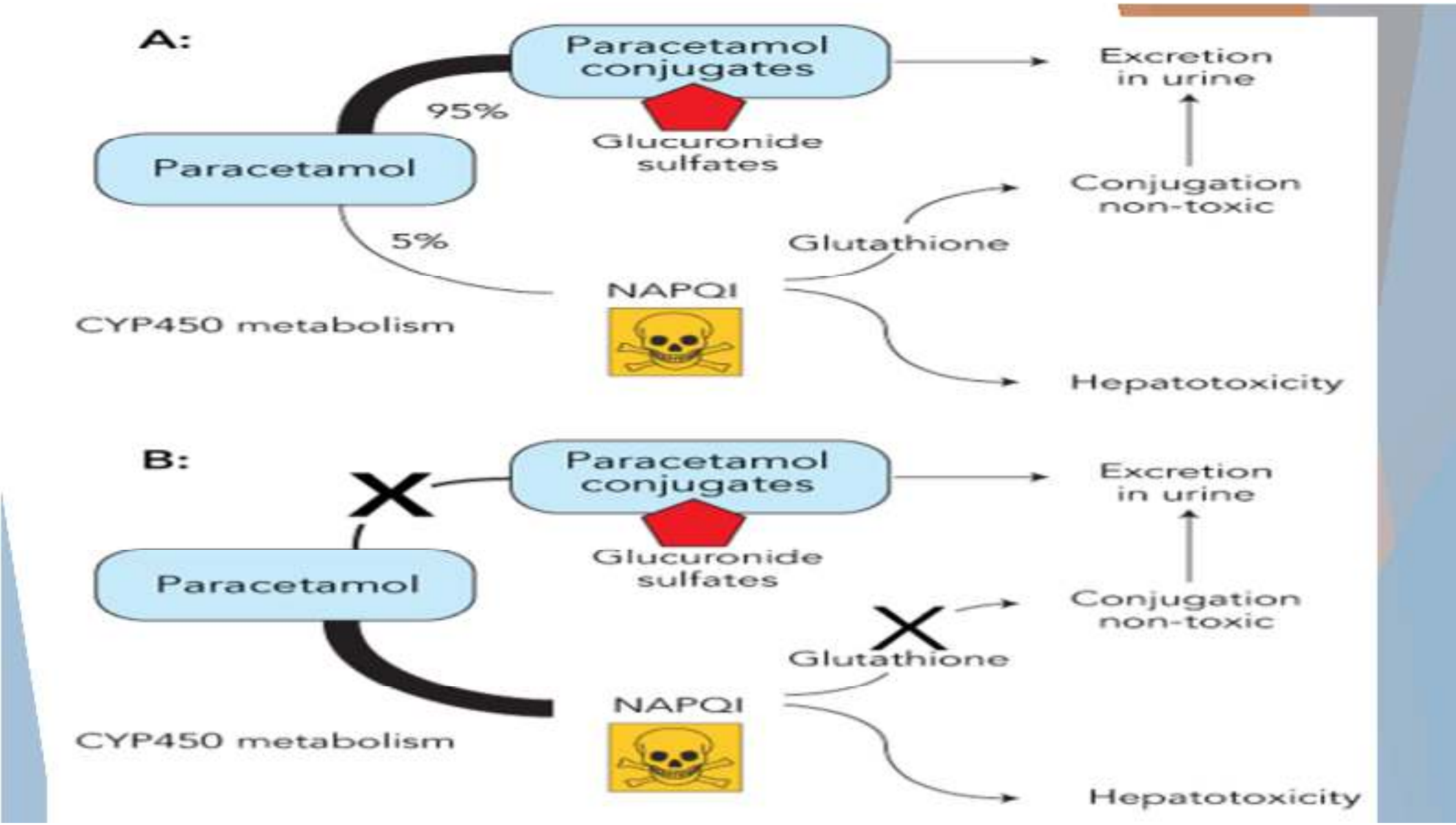
- In **adults**, hepatic toxicity rarely has occurred with acute overdoses of **less than 10 g**
- Hepatotoxicity has been reported in **fasting patients ingesting 4-10 g** of acetaminophen.
- In children : **150 mg/kg ; 200 mg/kg** in **healthy** children (age 1 – 6 yrs.)

MECHANISM OF TOXICITY

- One of the products of normal metabolism of acetaminophen by CYP-450 mixed-function oxidase enzymes is highly toxic.
- Normally this reactive metabolite N-acetyl-p-benzoquinoneimine (NAPQI) is rapidly detoxified by glutathione in liver cells to cysteine and mercapturate conjugates.

- However, in an overdose, production of NAPQI, glutathione stores become depleted and the toxic NAPQI binds covalently with hepatocytes causing centrilobular hepatic necrosis.




A:
Paracetamol conjugates
95%
Glucuronide sulfates
Paracetamol
Excretion in urine
Conjugation non-toxic
5%
Glutathione
NAPQI
CYP450 metabolism
Hepatotoxicity
B:
Paracetamol conjugates
Glucuronide sulfates
Paracetamol
Excretion in urine
Conjugation non-toxic
Glutathione
NAPQI
CYP450 metabolism
Hepatotoxicity

TOXICOKINETICS

ABSORPTION

- After oral administration paracetamol is **rapidly and completely absorbed**
- Virtually **no absorption** occurs from the **stomach.** Absorption from the **small intestine** is rapid
- Plasma t half is 2 hrs

DISTRIBUTION

- Distribution is **rapid and uniform**.
- The apparent volume of distribution is **0.8 to 1 L/kg.**
- Plasma binding is 5-20%
- The elimination half life is **1-3 hours** after a therapeutic dose but may be greater than 12 hours after an overdose.

METABOLISM

Involves three principal separate pathways:

- Conjugation with glucuronide
- Conjugation with sulphate and
- Oxidation

via the **cytochrome P450 enzyme** pathway, primarily CYP2E1, to form a reactive intermediate metabolite (N-acetyl-p-benzoquinone imine or NAPQI).

With therapeutic doses, NAPQI undergoes rapid conjugation with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates.

EXCRETION

- Acetaminophen is excreted in **urine** principally as acetaminophen glucuronide with small amounts of acetaminophen sulphate and mercaptate and unchanged drug.
- Approximately **85%** of a dose of acetaminophen is excreted in urine as free and conjugated acetaminophen within **24 hours** after ingestion.

CLINICAL MANIFESTATIONS

- **Stage I** (0.5-24 hours after ingestion)
  - ✓ Patients may be asymptomatic or report anorexia(loss of appetite), nausea or vomiting, and malaise(feeling of discomfort).
- **Stage II** (24 to 72 hrs.): Relatively symptom-free. There may be right upper quadrant pain. Liver function tests may be abnormal.

- **Stage III** (72-96 hrs.):

- ✓ Hepatic necrosis sets in with coagulation defects, jaundice and encephalopathy
- ✓ Nausea and vomiting reappear
- ✓ Renal failure and myocardial damage are frequently present
- ✓ Death is usually due to hepatic failure and is preceded by coma
- ✓ Elevated blood levels of hepatic enzymes may develop within 24 hours
- ✓ Increased total bilirubin and prolonged PT
- ✓ Decreased serum IL-6

- **Stage IV** (4 days to 2 weeks): If the patient survives the IIIrd stage, complete resolution of hepatic damage is seen and no reported chronic hepatic dysfunction from paracetamol was observed.
- **Additional Manifestations**: Hypotension and shock with hypothermia, Myocardial injury, Coma and metabolic acidosis, Acute pancreatitis, Transient renal damage, hyper phosphotamia

CHRONIC POISONING

- This is **uncommon**, but cases have been reported where-in an individual has consumed large doses of paracetamol over a period of time for relief of chronic pain which resulted in toxic hepatitis.
- This is more common in alcoholics, AIDS patients (in whom there is depletion of glutathione), and patients receiving other medications which are cytochrome P450 inducers, e.g. isoniazid, rifampicin, phenytoin, carbamazepine, and barbiturates.

- Chronic overdose among **children is more common** than in adults mainly because of dose miscalculation by parents.
- Features include anorexia, vomiting, lethargy, low body temperature, hepatomegaly, and oliguria.

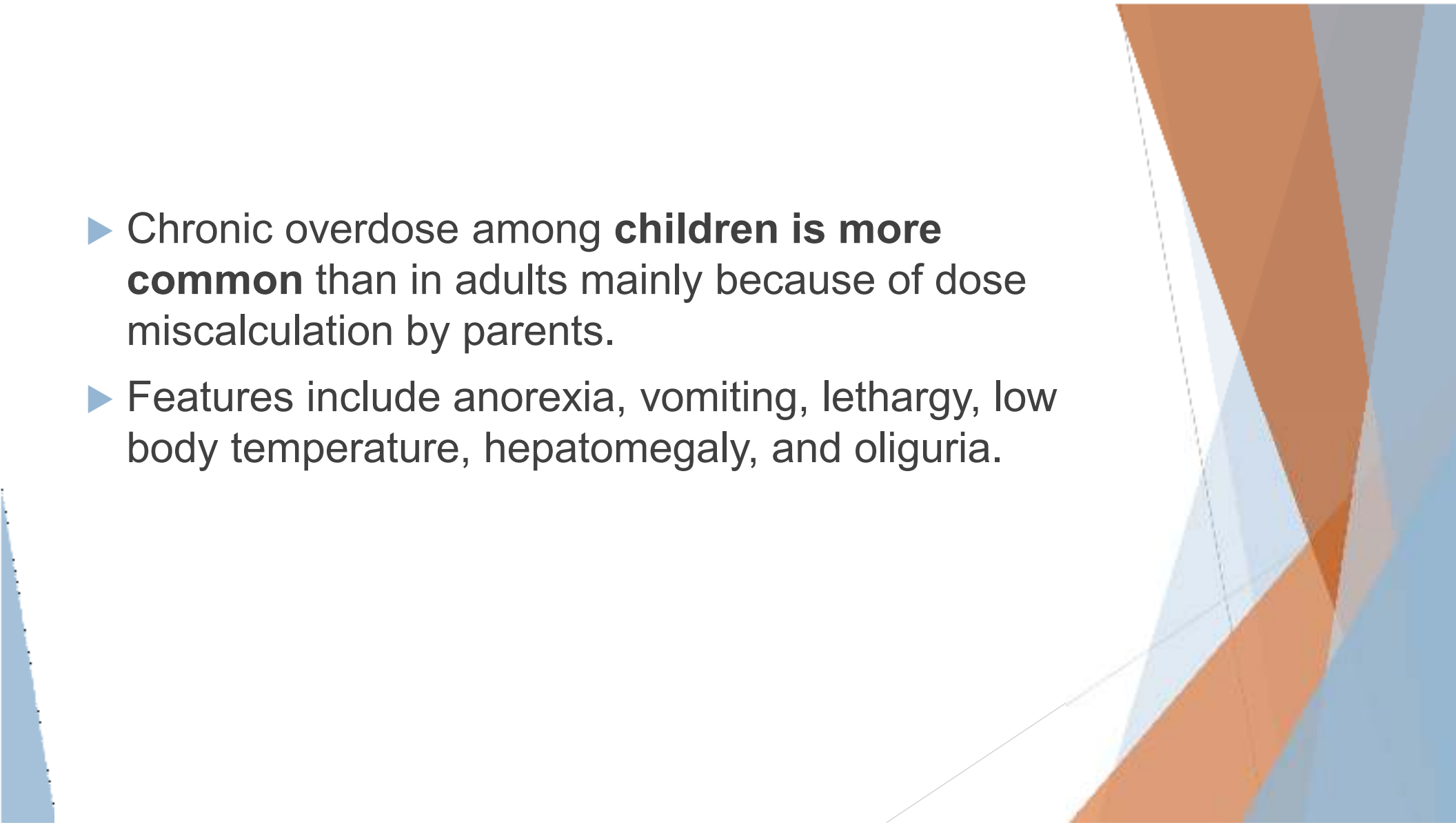


Table 2 — Stages of acetaminophen-induced hepatotoxicity[9,10]

Stage	Postingestion Time	Signs and Symptoms	Laboratory Values	Comments
1	0.5–24 h	• Nausea • Anorexia • Emesis • Diaphoresis • Fatigue • Malaise • Pallor • Compromised hydration	• Subclinically elevated ALT (12 h postingestion) • Subclinically elevated AST (12 h postingestion)	May be asymptomatic; nonspecific symptoms may lead to further inadvertent acetaminophen administration
2	24–72 h	• Right upper quadrant abdominal pain and tenderness • Midline abdominal tenderness • Hepatomegaly • Oliguria • Tachycardia • Hypotension	• Elevated ALT • Elevated AST • Prolonged PT • Elevated bilirubin • Elevated BUN • Elevated creatinine	Stage 1 symptoms may improve or resolve
3	3–5 d	• Stage 1 symptoms • Jaundice • Hypoglycemia • Bleeding (coagulopathy) • Confusion • Lethargy • Coma	• Markedly elevated ALT • Markedly elevated AST • Elevated bilirubin • Elevated BUN • Elevated creatinine • Hyperammonemia • Uremia	Death from multiorgan failure occurs most often in stage 3
4	5–21 d	Eventual resolution	Eventual normalization	Complete hepatic recovery may take months

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; PT, prothrombin time

DIAGNOSIS

1. Evidence of hypoglycemia , metabolic acidosis
2. Evidence of hepatocellular injury

- ✓ Elevated levels of ALT, AST, bilirubin and prothrombin time. ALT and AST levels rise within 24 hours after ingestion. Levels up to 10,000 units/L are common
- ✓ Hypophosphatemia , occurring 48-96 hours after the overdose, it is a poor prognostic indicator
- ✓ Decreased serum interleukin -6 or C reactive protein levels following acute paracetamol overdose. This may serve as a prognostic factors for predicting impeding hepatic injury
- ✓ Fatal cases of paracetamol overdose usually have bilirubin levels greater than 4mg/100ml and a prothrombin time greater than twice the control
- ✓ Serum prealbumin concentration decreases significantly after 36 hours and continue to decrease during liver failure .

3. Evidence of renal damage – proteinuria, phosphaturia
4. Evidence of myocardial damage – ECG changes indicate arrhythmias
5. Serum paracetamol level – The lowest dose of paracetamol capable of toxicity is generally regarded as 7.5 grams in an adult and 150mg/kg in a child, though it is more likely that the actual figures may be 15gms and 250mg/kg respectively

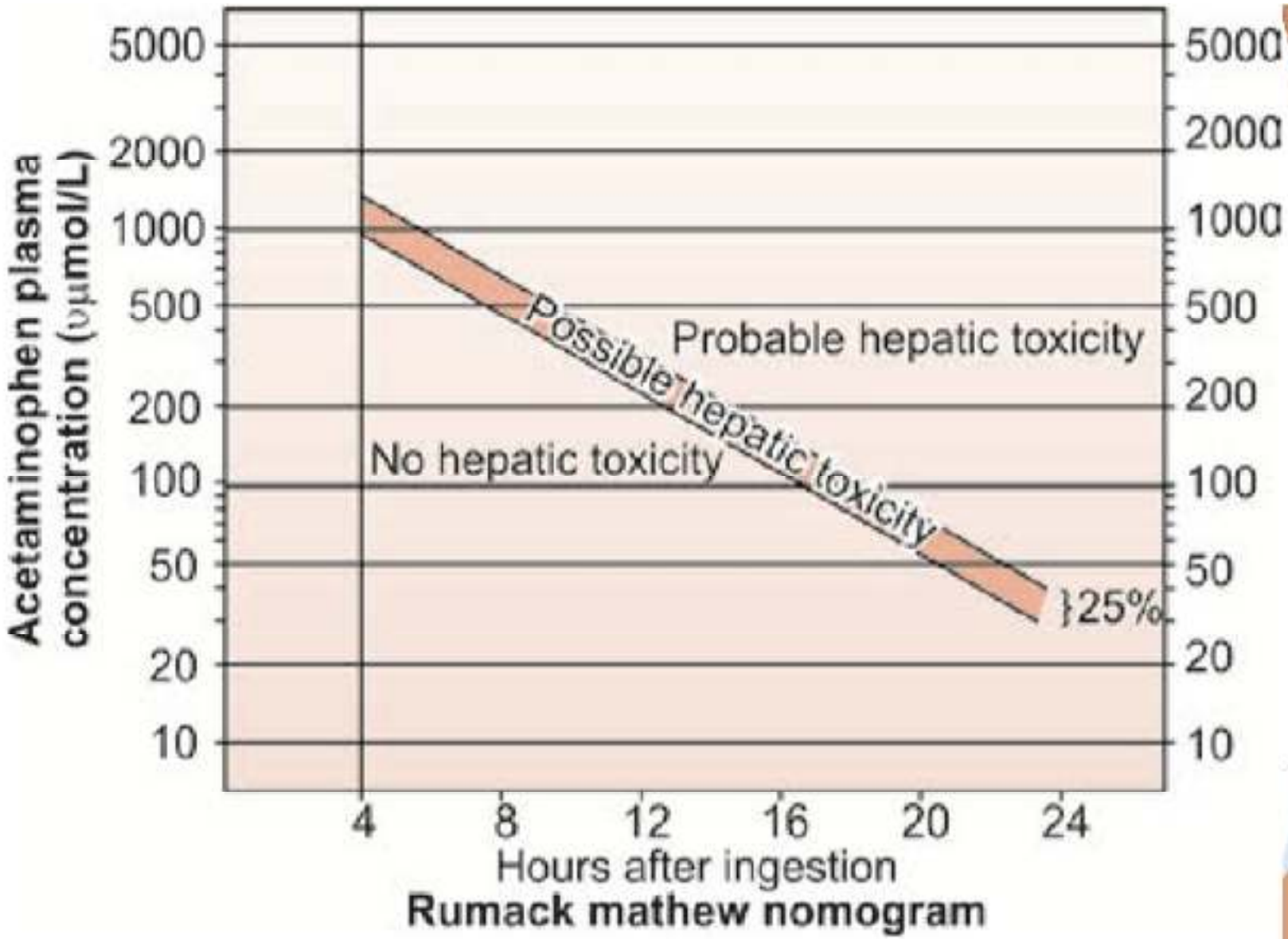
Rumack-Matthew nomogram

- Used to interpret plasma acetaminophen values to assess hepatotoxicity risk after a single, acute ingestion.
- Nomogram tracking begins 4 hours after ingestion (time when acetaminophen absorption is likely to be complete) and ends 24 hours after ingestion.
- The upper line of the nomogram is the “probable” line, also known as the Rumack-Matthew line.
- About 60% of patients with values above this line develop hepatotoxicity.

- The lower line on the nomogram is the “possible” line, which was subsequently added later per request of the U.S. FDA.

- The possible line, also known as the “treatment” line, incorporates a 25% margin of error in measurement variations or uncertainty regarding the time of ingestion.
- The nomogram cannot be used if the patient presents more than 24 hours after ingestion or has a history of multiple acetaminophen ingestions.

- Its reliability decreases for ingestions of extended-release acetaminophen formulations or for co-ingestions of acetaminophen with agents that delay gastric emptying and absorption(e.g. Anticholinergics, opioids etc.).


Acetaminophen plasma concentration (µmol/L)
5000
2000
1000
500
200
100
50
20
10
Probable hepatic toxicity
Possible hepatic toxicity
No hepatic toxicity
25%
4
8
12
16
20
24
Hours after ingestion
Rumack mathew nomogram

TREAMENT

- Children who have an unobtainable history or in whom a large amount of paracetamol is suspected to have ingested (>200mg/kg) should be referred to a health care facility for a 4-hour paracetamol serum level determination and consideration for administration of activated charcoal.

1. STOMACH WASH – useful in early presentation (<1 hour) or concomitant administration of other drugs
2. ACTIVATED CHARCOAL- can absorb paracetamol and the antidote , hence must be administered earlier to 4 hours post ingestion. Effective if given within 1 hour
3. ANTI-EMETIC – if the patient is vomiting repeatedly

4. SUPPORTIVE MEASURES –

- ✓ 10 – 20% dextrose for hypoglycemia
- ✓ Vitamin K1 if PT is elevated
- ✓ Fresh frozen plasma if there if over bleeding
- ✓ Mannitol for cerebral edema (0.5g/kg over 10mins)
- ✓ Broad spectrum antibiotics IV if necessary (ceftazidime or fluoxacillin)
- ✓ H2-antagonists to prevent upper GI hemorrhage
- ✓ DO NOT give sedatives, benzodiazepines or NSAIDs

5. ANTIDOTE THERAPY

a) Methionine –

- an oral antidote used in UK and other countries, NOT available in India.
- Glutathione precursor
- Protects against paracetamol induced hepatic and induced renal damage, provided it is administered within 8-10 hours
- DOSE- 2.5grams, 4 doses, at 4 hour interval

b) N-acetylcysteine (NAC)-

- derivative of L-cysteine
- NAC is the choice of antidote for paracetamol poisoning
- Gives maximum protection against hepatotoxicity when administered within 10hours of paracetamol overdose, but can be given with 36 hours (effects will be less)

N-acetylcysteine (NAC)

- INDICATIONS-
- ✓ if PL estimated between 4 – 12 hours post ingestion lies above the nomogram line
- ✓ Paracetamol ingested is more than 100mg/kg
- ✓ Likelihood paracetamol-induced hepatic failure
- DOSE-
- ✓ 5% solution given as loading dose of 140mg/kg
- ✓ This is followed by 17 more doses at 70mg/kg, 4^{th} hourly, totally making up to 1330mg/kg over 72 hours
- ✓ It mixed with water or flavored or carbonated drink.

- For a child – initial – 140mg/kg for one dose, followed by 70mg/kg/dose every 4 hours for 68 hours, beginning within 10 hours of ingestion.
- A shorter duration of oral NAC has been recommended for acute paracetamol overdoses presenting within 24 hours of ingestion –

- loading dose : 140mg/kg followed by 70 mg/kg every 4 hours until serum paracetamol levels is no longer detectable and aminotransferase levels are normal instead of the standard 72 hours treatment protocol.

- investigators found this method safe and effective in patients not demonstrating hepatoxicity within 36 hours of acute overdose

- INTERVENOUS-

a) **20hours regimen (Prescott protocol)**

- 150mg/kg made up in 200ml of 5%dextrose over 4 hours is given IV over 15 minutes

- ✓ 100mg/kg in 1 liter of 5% dextrose over 16 hours . The total dose works out to 300mg/kg given over 20 hours.
- ✓ FOR CHILD – standard intravenous dosing can cause hyponatremia and seizures , to avoid this complication
  - NAC should be diluted to a final concentration of 40mg/ml
  - 150mg/kg infused 15 minutes
  - followed by 50mg/kg infused over 4 hours
  -100 mg/kg infused over 16 hours

b)48 hours regimen

- ✓ useful in delayed admissions and massive ingestion
- ✓ Loading dose of 140mg IV is given over 1 hour
- ✓ 4hours later by the first of 12 maintenance doses of 70mg/kg, each administered over 1 hour .
- ✓ The total dose of NAC works out to 980mg/kg in just 48 hours

- ADVERSE EFFECTS-

- ✓ Oral- induction of vomiting. Ondansetron or metoclopramide can be administered
- ✓ Intravenous – anaphylactoid reactions . It can be managed with antihistamines, epinephrine etc.
- ✓ Isolated effects include pruritis, angioedema, nausea and vomiting, bronchospasm, tachycardia, hypertension and hypotension
- ✓ Facial or chest flushing is common, beginning 15-75 minutes after initiation of infusion
- ✓ A decrease in prothrombin time is seen in patient following the administration of IV NAC for treatment for patients with paracetamol poisoning who did not exhibit signs of hepatotoxicity , this can be misinterpreted as a sign of liver failure

6. LIVER TRANSPLANTATION –

- ✓ Ph<7.3
- ✓ PT >100 seconds
- ✓ Serum Creatinine >3.4mg/100ml in patients with grade III and grade IV encephalopathy

7. FORCED DIURESIS, HEMODIALYSIS AND CHARCOAL HAEMOPERFUSION are of LITTLE value in preventing paracetamol induced hepatotoxicity

8. ALBUMIN DIALYSIS- in this method albumin containing dialysate is used for dialysis, it has been used following massive paracetamol poisoning with hepatic encephalopathy (grade II), sever acidosis, INR of 7 and hepatorenal syndrome . A course of 5 consecutive to 8 hours of treatments was performed

9. CONTINUOUS HEMOFILTRATION – this may be preferable to intermitted hemodialysis in patients with paracetamol- induced hepatic and renal failure . Use of intermitted hemodialysis is associated with increase in intracranial pressure

10. EXTRACORPOREAL SORBENT – BASED DEVICES – Paracetamol –induced hepatitis or hepatic failure have been treated at 16-68 hours after an overdose for 4-6 hours with the Liver dialysis system. During this treatment, paracetamol levels dropped an average of 73%. If paracetamol levels were still measurable in plasma, treatment was repeated24 or 48 hours later.

GUIDELINES FOR TREATMENT OF PARACETAMOL POISONING

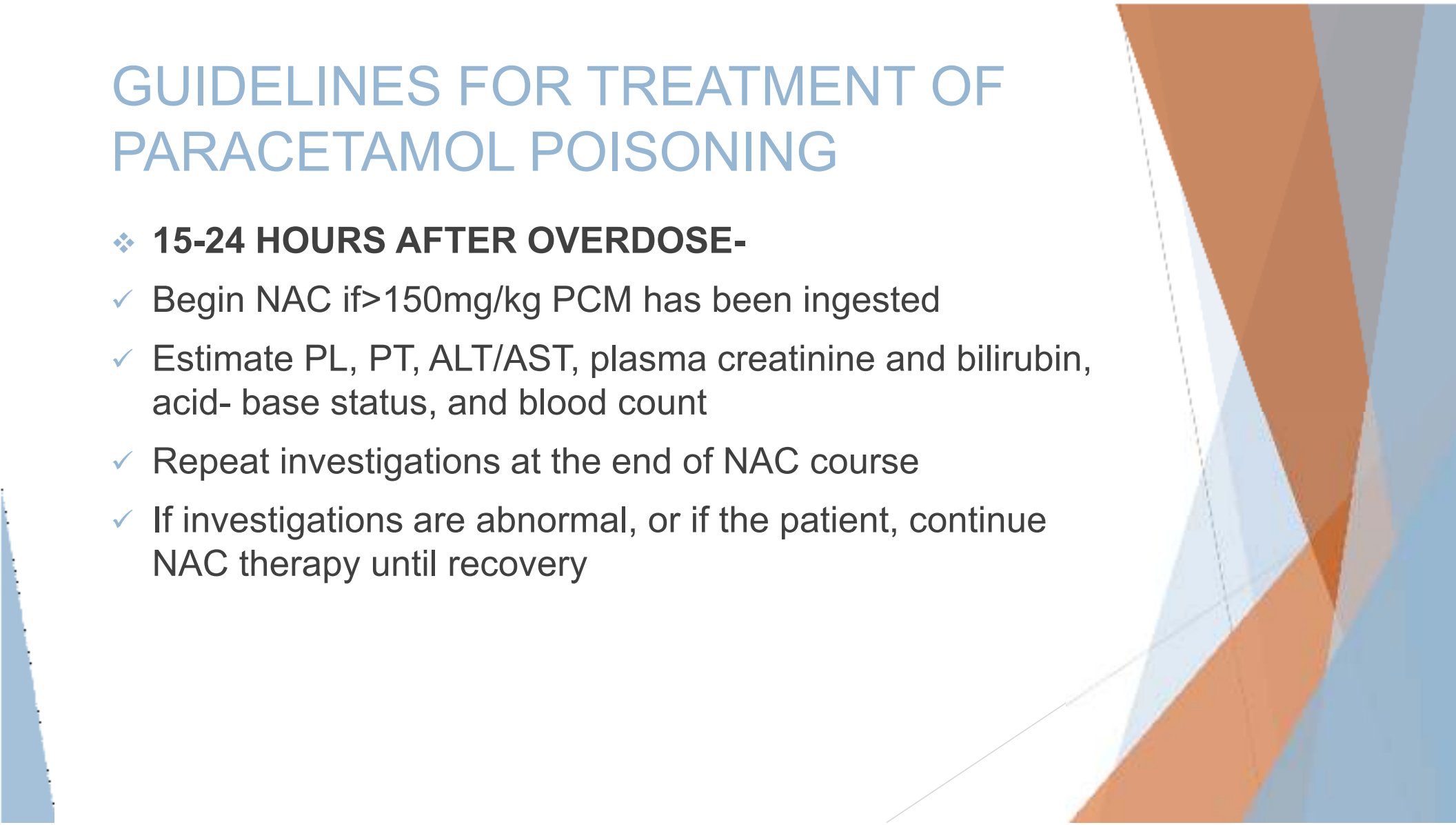
- **< 8 HOURS AFTER OVERDOSE –**
- Estimate PL
- Administer activated charcoal
- Begin IV NAC if PL is above monogram line
- If PL is not available by 8hours, begin NAC if >150mg/kg PCM has been ingested
- Discontinue NAC if PL is below nomogram line
- On completion of NAC therapy, check PT, ALT/AST and PL
- If patient is asymptomatic, and investigations are normal, patient can be discharged

GUIDELINES FOR TREATMENT OF PARACETAMOL POISONING

- **8-15 HOURS AFTER OVERDOSE-**
- Estimate PL, PT, ALT/AST, plasma creatinine and bilirubin, acid – base status, and blood count
- Begin NAC if >150mg/kg PCM has been ingested
- Discontinue NAC if PL is below nomogram line
- On completion of NAC therapy, repeat investigation(except PL)
- If patient is asymptomatic, and investigations are normal, patient can be discharged

GUIDELINES FOR TREATMENT OF PARACETAMOL POISONING

- **15-24 HOURS AFTER OVERDOSE-**
- ✓ Begin NAC if>150mg/kg PCM has been ingested
- ✓ Estimate PL, PT, ALT/AST, plasma creatinine and bilirubin, acid- base status, and blood count
- ✓ Repeat investigations at the end of NAC course
- ✓ If investigations are abnormal, or if the patient, continue NAC therapy until recovery

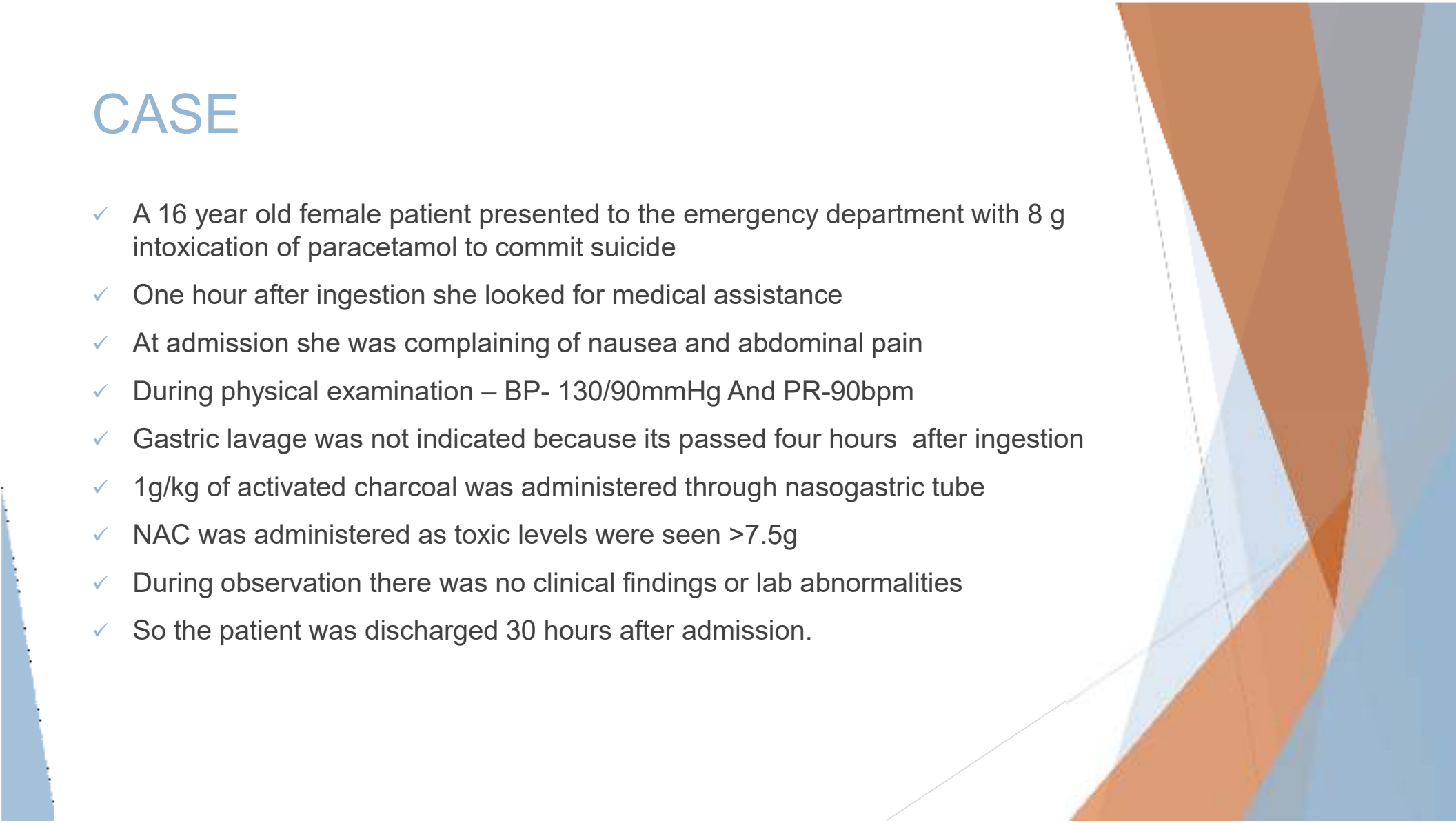


GUIDELINES FOR TREATMENT OF PARACETAMOL POISONING

- **>24HOURS AFTER OVERDOSE –**
- ✓ Estimate PL, PT, ALT/AST, plasma creatinine and bilirubin, acid-base status and blood count
- ✓ If the patient has ingested>150mg/kg PCM, or symptomatic, or has abnormal investigations, begin NAC therapy
- ✓ Repeat investigations at the end of NAC course, and consider continuing the course if the patient has or is at risk of developing hepatic failure

CASE

- A 16 year old female patient presented to the emergency department with 8 g intoxication of paracetamol to commit suicide
- One hour after ingestion she looked for medical assistance
- At admission she was complaining of nausea and abdominal pain
- During physical examination – BP- 130/90mmHg And PR-90bpm
- Gastric lavage was not indicated because its passed four hours after ingestion
- 1g/kg of activated charcoal was administered through nasogastric tube
- NAC was administered as toxic levels were seen >7.5g
- During observation there was no clinical findings or lab abnormalities
- So the patient was discharged 30 hours after admission.



MCQS

1)What type of acid base disorder is common in the terminal stage of salicylate poisoning ?

a)Metabolic acidosis

b)Metabolic alkalosis

c)Mixed acidosis

d)Respiratory alkalosis

2)Which clinical feature is not a sign of salicylate toxicity ?

a)Hyperthermia

b)Hyperventilation

c)Metabolic alkalosis

d)Renal failure

3)Salicylate toxicity can cause

a)Decreased ESR

b)Decreased BUN

c)Increased potassium level

d)Decreased glucose levels

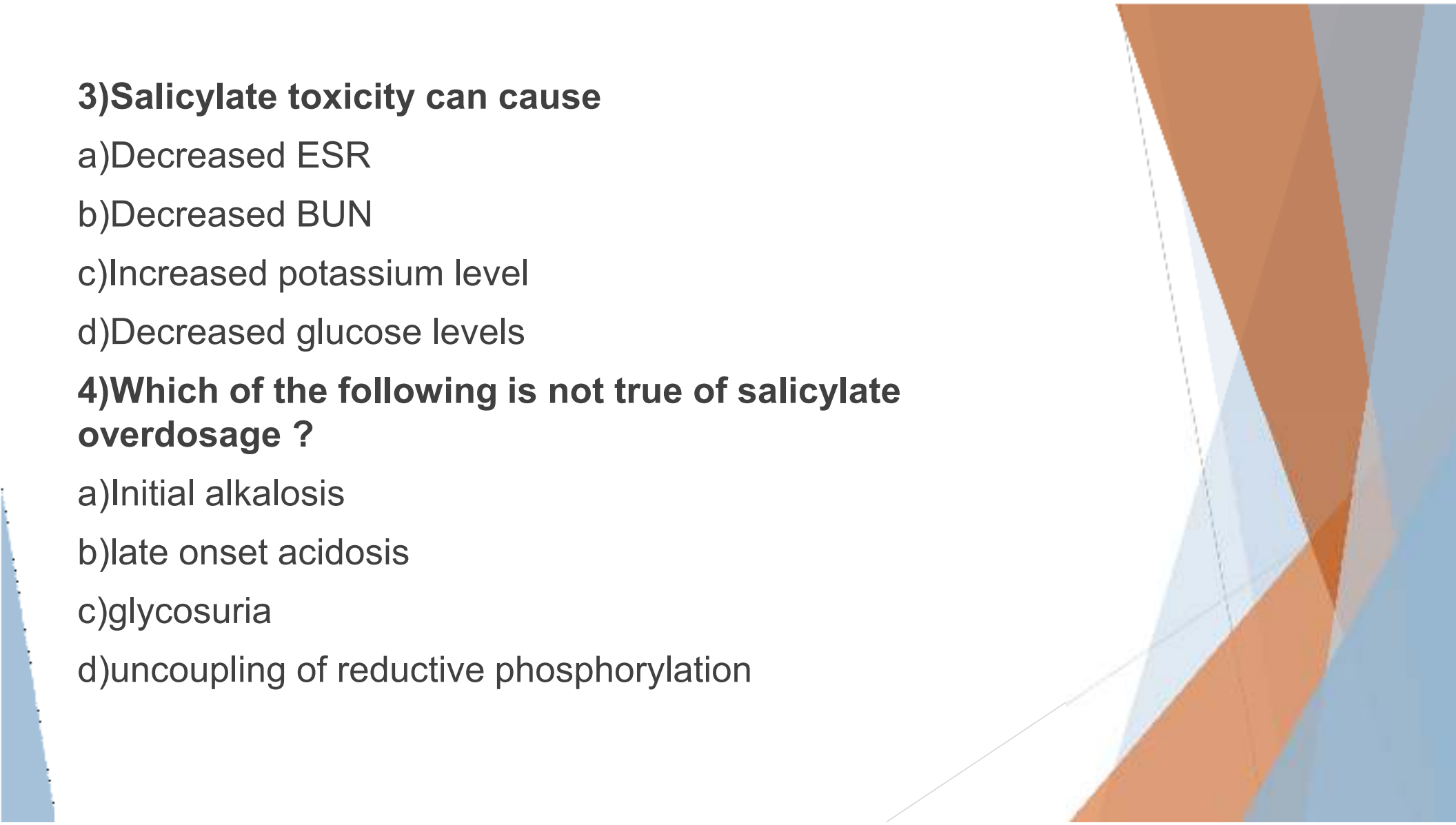
4)Which of the following is not true of salicylate overdosage ?

a)Initial alkalosis

b)late onset acidosis

c)glycosuria

d)uncoupling of reductive phosphorylation



5)Which of the following is not an indication for hemodialysis in acute salicylate toxicity ?

a)Salicylate level >100mg/dl

b)cerebral edema

c)respiratory alkalosis

d)ingestion of over 500mg/kg of aspirin

6) Which regimen is useful for the treatment of paracetamol poisoning in case of delayed administration and massive intoxication

a)24 hour regimen

b)20 hour regimen

c)48 hour regimen

d)3 hour regimen

7) Paracetamol toxicity occurs because of which metabolite

a)NAPQI

b)Glutathione

c)Cysteine

d)Non of the above

8) Which stage of paracetamol poisoning is relative free of symptoms

a)Stage 1

b)Stage 2

c)Stage 3

d)Stage 4

9) When should activated charcoal be administered

a)Earlier to 4 hour post ingestion

b)Earlier to 10 hour post ingestion

c)Both a and b

d)Non of the above

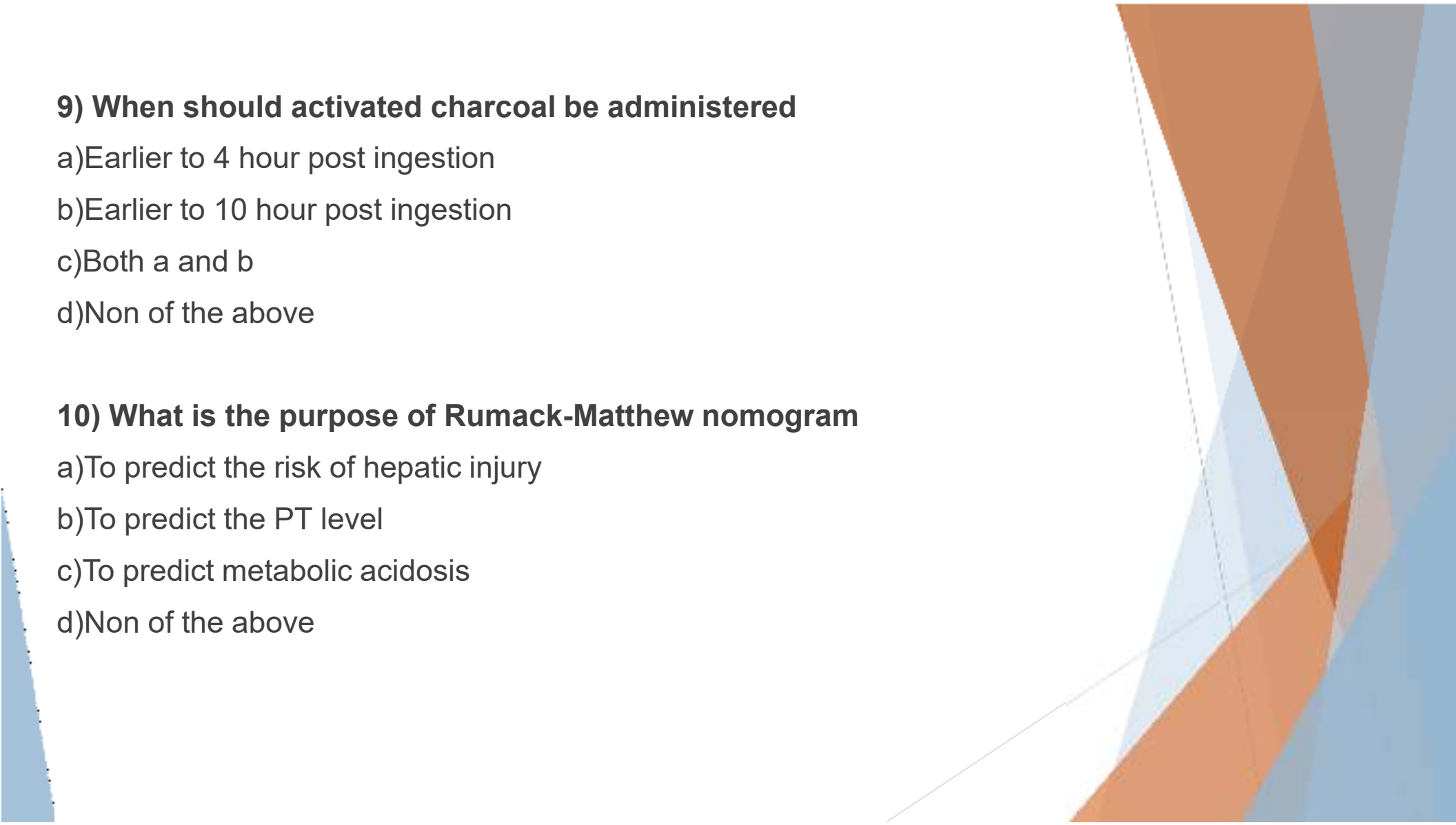
10) What is the purpose of Rumack-Matthew nomogram

a)To predict the risk of hepatic injury

b)To predict the PT level

c)To predict metabolic acidosis

d)Non of the above

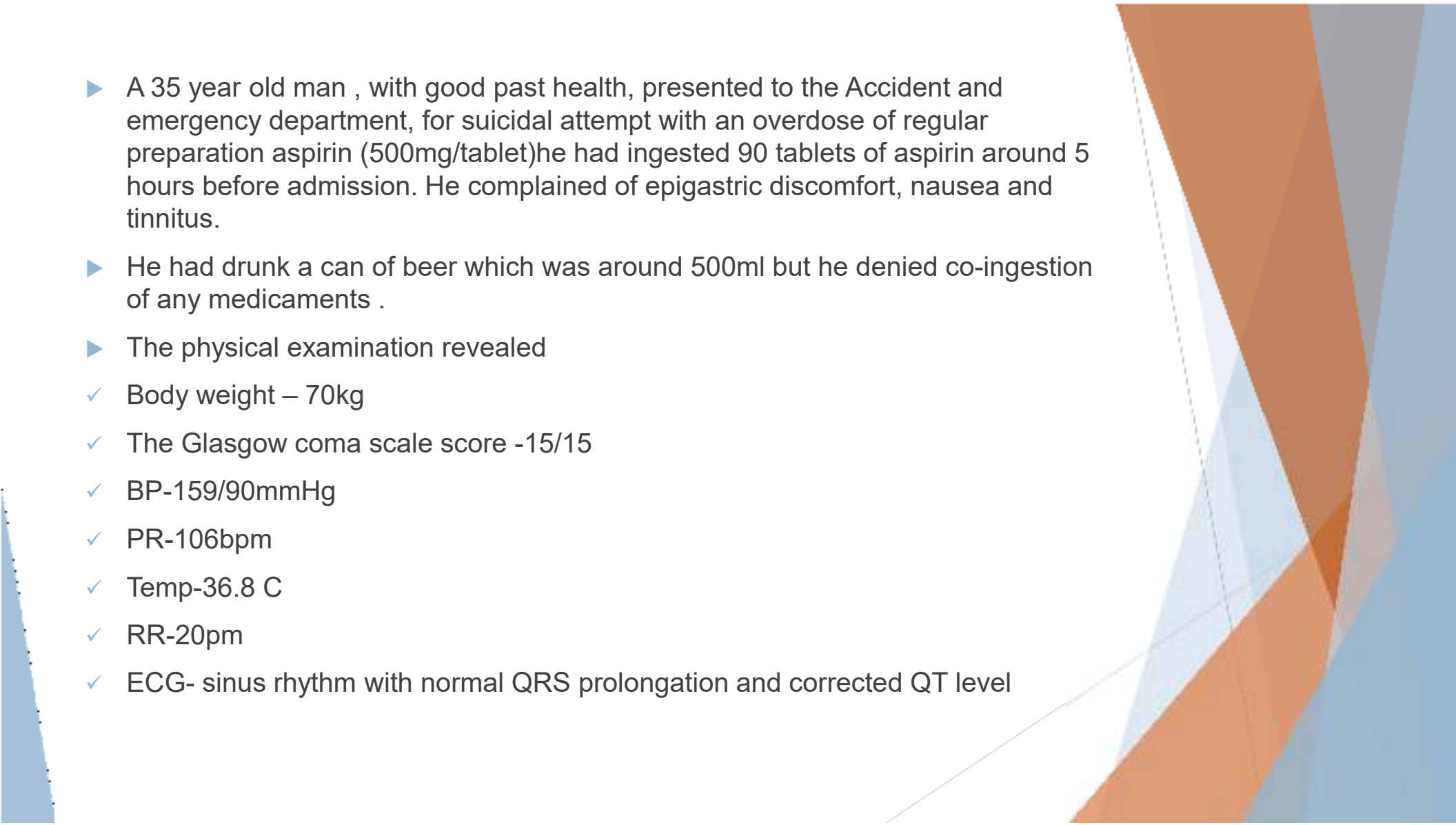


REFERENCE

- VVPILLAY, Modern medical toxicology, fourth edition, JAYPEE publishers. Pg411-421

- A 35 year old man , with good past health, presented to the Accident and emergency department, for suicidal attempt with an overdose of regular preparation aspirin (500mg/tablet)he had ingested 90 tablets of aspirin around 5 hours before admission. He complained of epigastric discomfort, nausea and tinnitus.
- He had drunk a can of beer which was around 500ml but he denied co-ingestion of any medicaments .
- The physical examination revealed

- ✓ Body weight – 70kg
- ✓ The Glasgow coma scale score -15/15
- ✓ BP-159/90mmHg
- ✓ PR-106bpm
- ✓ Temp-36.8 C
- ✓ RR-20pm
- ✓ ECG- sinus rhythm with normal QRS prolongation and corrected QT level



- Blood glucose levels were normal
- X-rays – clear lung fields
- Elevated salicylate levels-3.52mmol/L (reference range <2.17mmol/L)
- Normal renal function
- INR -1.1
- No evidence of metabolic acidosis
- MDAC was given with the regimen of an initial dose of 50g and then 25g every 2 hours for 3 doses
- Urinary alkalization was initiated, An initial bolus of 100mg of 8.4% sodium bicarbonate solution was given IV followed by infusion of sodium bicarbonate solution and 5% dextrose water
- The blood salicylate levels dropped to 2.60mmo;/L around 6 hours after the initiation of MDAC therapy
- There was rebound of the blood salicylate level up to 4.74mmol/L around 5 hours after the last dose of MDAC

- Repeated dose of activated charcoal were given and the blood salicylate levels dropped progressively without further rebound
- There was no evidence of bleeding
- The patient had stable vital signs all along during his stay in hospital and was discharged day 2