NON-STEROIDAL ANTI-INFLAMMATORY DRUGS(NSAID) TOXICITY

INTRODUCTION

- Non-steroidal anti-inflammatory drugs are a group of medicines that relieve pain and fever and reduce inflammation.
- They are readily available and are therefore commonly taken in overdose.

CLASSIFICATION

PYRAZOLONES	Oxyphenbutazones, phenylbutazones
PROPIONIC ACIDS	Benoxaprofen, ibuprofen, carprofen, ketoprofen, naproxen
FENAMIC ACIDS	Flufenamic acid, meclofenamic acid, mefanamic acid
HETEROCYCLIC ACETIC ACIDS	Etodolac, indomethacin, ketorolac, sulindac, tolmetin, zomepirac
ARYL ACETIC ACID	Diclofenac, alclofenac
OXICAMS	Piroxicam, isoxicam, tenoxicam
SULFONANILIDE	Nimesulide

USES

- Antipyretics
- Analgesics
- Inhibitors of thrombocyte aggregation
- Anti-inflammatory

MECHANISM OF ACTION

- NSAIDs produce their pharmacologic and most toxicologic effects by inhibiting the enzyme cyclooxygenase (isoforms COX-1 and COX-2); this results in decreased production of prostaglandins and decreased pain and inflammation. Prostaglandins are also involved in maintaining the integrity of the gastric mucosa and regulating renal blood flow; thus, acute or chronic intoxication may affect these organs.

DIAGNOSIS

- In asymptomatic patients : baseline renal and hepatic function tests.
- In symptomatic patients:
  - Serum electrolytes
  - Renal function studies
  - Liver function tests
  - Coagulation studies (prothrombin time, INR)
  - Complete blood count (CBC)

- Arterial blood gases and plasma lactate in case of anion gap.
- CT scan for patients with seizures, altered mental status or coma.
- ECG for hyperkalemic patients and incase of acute overdose to exclude TCA or cardioactive drug toxicity.
- Lumbar puncture to be done in patients with altered mental status and symptoms suggestive of CNS infection.

TOXICOKINETICS

- ABSORPTION :
  - They are rapidly absorbed following oral ingestion
  - Peak concentration of 2 hours
  - 2-5 hours for immediate and sustained release preparation respectively.
- DISTRIBUTION :
  - NSAIDs are weakly acidic
  - Low volume of distribution(0.1-0.2 L/kg)
  - Highly bound to protein (mostly albumin).

- METABOLISM
  - Metabolism is mostly hepatic
- EXCRETION
  - Renal elimination.
  - The half-life is variable:
    - 2 hours for ibuprofen, diclofenac, mefenamic acid
    - 4 hours for indomethacin
    - Up to 15 hours for naproxen.

GENERAL MANAGEMENT

- Management of acute NSAID poisoning is essentially supportive and symptomatic.
- No specific antidotes for NSAID poisoning exist.
- Initial stabilization consist of securing airway, breathing and circulation (ABCs).
- For GI decontamination,
  - Syrup of ipecac not recommended
  - Activated charcoal can be used (within 1-4hrs of ingestion) after securing airway, to prevent aspiration of charcoal
  - Orogastric lavage can be used in conditions of massive overdose

- Hemodialysis may be considered for
  - correction of severe acidosis in conditions of acute kidney injury
  - correction of acid-base electrolyte abnormalities
  - Management of volume status in critically ill patients
- Sodium bicarbonate can be recommended for treatment of recalcitrant acidosis (pH<7).
- Seizures can be treated with benzodiazepines or GABAergic drugs (barbiturates) or propofol

PYRAZOLONES

INTRODUCTION

- Phenylbutazone and its metabolite oxyphenbutazone are potent anti-inflammatory drugs, but have significant adverse effects, and hence withdrawn from several countries.
- USE :
  - acute gout
  - acute exacerbations of rheumatoid arthritis
  - ankylosing spondylitis.
- Related drugs: aminopyrine, antipyrine, amidopyrine, phenazone, and sulfinpyrazone

MODE OF ACTIONS

- Phenylbutazone interferes with prostaglandin synthesis via inhibition of the COX pathway.
- It is an irritant of the mucosal layer of the GIT.

CLINICLAL FEATURES

- Main features of overdose of phenylbutazone and oxyphenbutazone include
  - GI system : nausea, vomiting, diarrhoea
  - CNS : dizziness, seizures, coma
  - CVS : pulmonary edema, cardiac arrest
  - Metabolic and respiratory acidosis
  - Electrolyte abnormalities

- Salicylate - like symptoms: stimulation of respiratory centre, respiratory alkalosis and metabolic acidosis have been reported.
- Delayed severe toxicity(2-7 days) : renal, hepatic and hematologic dysfunction.
- Renal dysfunction is common including proteinuria, haematuria, anuria, oliguria.
- Urine may be red due to a pyrazolone metabolite.
- Blood dyscrasias are more common with dipyrone, methemoglobinemia has been reported with antipyrine.

FATAL DOSE

- Highly variable
- Ranges from 4-40 gm

DIAGNOSIS

- Ferric chloride test
- Obtain a baseline CBC, renal and liver function test and urinalysis in symptomatic patients.
- After 24 hrs red discolouration of the urine may be seen, due to rubazonic acid, a pyrazolone metabolite.

TREATMENT

- Stomach wash , activated charcoal.
- Ipecac-induced emesis is not recommended because of the potential for CNS depression and seizures.
- Treat convulsions in usual manner.
- The excretion of phenylbutazone may be enhanced in an alkaline urine(considered in severely intoxicated patients), but alkaline diuresis is of questionable value since pyrazoles are extensively metabolized,
- Hemoperfusion in life threatening cases, haemodialysis is not likely to be effective due to low water solubility and high protein binding.
- Plasmapheresis is beneficial in severe poisoning

PROPIONIC ACIDS

INTRODUCTION

- All propionic acids inhibit PG synthesis as well as platelet aggregation by inhibiting COX isoenzymes.
- USES : relief of musculoskeletal disorders, fractures, sprains, and dysmenorrhoea.
- Examples: ibuprofen, carprofen, fenbufen, ketorolac etc

CLINICAL FEATURES

- Angioedema, hives, itching, rash, swelling, GI distress, nausea, and epigastric pain are the most common side effect with the therapeutic doses.
- Upper GI bleeding, enteropathy may occur acute or chronic ingestion.
- Oesophageal strictures may occur with minimal liquid intake.
- Ibuprofen may cause stomach bleeding.
- Isolated case of thrombocytopenia, agranulocytosis, haemolysis, lymphopenia have been reported with therapeutic use of propionic acids.
- Miosis has been reported in acute overdose.
- Hypokalemia, hypophosphatemia, hyponatremia, and hyperkalemia can occur.

DIAGNOSIS

- Monitor for signs and symptoms of gastrointestinal ulceration and/ or haemorrhage.., i.e stool guaiac test.
- Stool guaiac test : faecal sample placed on guaiac paper and Hydrogen peroxide is applied → blue reaction within seconds in the presence of blood.

FATAL DOSE

- Children ingesting less than 200mg/kg generally are asymptomatic or have mild effects.
- Ingestions of 400mg/kg in children have been associated with severe toxicity.
- Therapeutic plasma levels should be between 20-30 mcg/ml.

TREATMENT

- Gastric lavage, activated charcoal and supportive measures.
- Patients with severe epigastric pain, dysphagia or drooling should be evaluated for possible oesophageal strictures.
- Management of hypotension, acidosis, and gastrointestinal bleeding may be necessary.
- Enhanced elimination using urine alkalinisation or haemodialysis has not been shown to be beneficial.

PREGNANCY

- >30 wks of gestation : premature closure of ductus arteriosus
- Avoid 1st and 3rd trimesters.
- Possible complications of use during pregnancy
  - Delayed labour
  - Complications during delivery
  - Postpartum bleeding
  - Respiratory depression in newborn

FENEMIC ACIDS

INTRODUCTION

- Also referred as anthranilic acids, these compounds are used in mild to moderate pain (e.g. headache, dental pain, dysmenorrhea, musculoskeletal and joint disorders)
- It has been suggested that therapeutic serum levels must not exceed 20mcg/ml.
- The lowest dose to cause coma and seizures in an adult was 3.5 grams
- Safety and effectiveness in paediatric patients under 14 years have not been established.

CLINICAL MANIFESTATIONS

- ADVERSE EFFECTS : GI irritation or ulceration, GI bleeding, headache, dizziness, drowsiness, skin rashes, acute renal failure, elevated liver enzymes, increased bleeding time and tinnitus.
- RARE EFFECTS : anaphylactoid reactions, cardiovascular effects, hyperglycemia, hallucinations, coma, meningitis, seizures, respiratory depression, pneumonia, dermal reactions, haematologic abnormalities (e.g. haemolytic anaemia, agranulocytosis, pancytopenia, thrombocytic purpura, bone marrow aplasia

- OVERDOSE :
  - Muscle twitching and seizures are common
  - Vomiting, diarrhoea, abdominal pain, lethargy, drowsiness and acidaemia can occur
  - Lesser frequent symptoms are respiratory depression, hypertension, coma, dyskinesias, agitation, restlessness, GI bleeding, acute renal failure

MANAGEMENT

- Supportive treatment following GI decontamination (gastric lavage, activated charcoal).
- Monitor renal function and acid base status in symptomatic patients.
- Control of convulsions can be achieved with benzodiazepines or barbiturates.
- Haemodialysis is not effective in treating acute intoxication, but charcoal hemoperfusion might be effective.

HETEROCYCLIC ACETIC ACIDS

CLINICAL FEATURES

- ADVERSE EFFECTS :
  - Frontal headache is the most common
  - Other reported effects include gastritis, epigastric distress, light headedness, vertigo, dizziness, mental confusion and occasionally somnolence, stupor or hallucinations.
  - Neutropenia, thrombocytopenia and rarely aplastic anemia may occur following chronic ingestion of therapeutic doses.

- Intoxication with indomethacin is generally not associated with serious effects, occasionally may cause convulsions.
- Sulindac overdose – renal failure and development of psychosis in elderly.
- Ketorolac has been withdrawn – severe side effects relating to GI tract and kidneys.
- Zomeprine has been withdrawn – induces anaphylaxis.

TREATMENT

- Treatment of overdosage is symptomatic and supportive.
- Patients should be monitored for possible gastrointestinal ulceration and / or haemorrhage.
- Monitor renal function and haematocrit in symptomatic patients.
- Antacids may be of some value for relief of symptoms in patients with gastrointestinal symptoms.

ARYL ACETIC ACIDS

- Diclofenac toxicity is relatively benign resulting in nausea, abdominal pain, drowsiness, headache and tinnitus.
- Treatment is supportive following decontamination.
- Rare instances of anaphylaxis have also been reported.

OXICAMS

- Intoxication with piroxicam or tenoxicam results in dizziness, blurred vision and sometimes coma.
- Most cases of overdose develop no effects or mild effects consisting of lethargy and gastrointestinal upset.
- Severe overdose may cause hypotension, coma, respiratory depression, gastrointestinal bleeding or acute renal insufficiency.
- Seizures can occur.
- Treatment is on symptomatic and supportive lines.

NIMESULIDE

- Belongs to the sulphonamide class of NSAIDs.
- Has anti-inflammatory action and analgesic-antipyretic properties
- Has a good safety profile, and overdose is rarely been reported.
- Few rare cases - fulminant hepatic failure in patients who were taking nimesulide regularly.
- These patients had increasing jaundice over a 7-10 day period, in addition to confusion, nausea and vomiting. Despite liver transplantation some patients died due to multi-organ failure.

COX – 2 INHIBITORS

INTRODUCTION

- Has anti-inflammatory and analgesic properties.
- Examples: Celecoxib, parecoxib, rofecoxib, valdecoxib, and etoricoxib.
- USES :
  - Treatment of osteoarthritis and rheumatoid arthritis
  - management of acute pain in adults
  - treatment of primary dysmenorrhoea

MODE OF ACTION

The Cyclo-oxygenase enzymes consists of 2 isoforms, COX-1 and COX-2,

- The COX-2 inhibitors decrease the synthesis of prostaglandins H2 through the selective inhibition of COX-2 with a little or no inhibition of COX-1,resulting in anti-inflammatory and analgesic properties.

CLINICAL FEATURES

- Several authors have reported cases of acute renal failure with therapeutic dosing of cox-2 inhibitors, COX-2 inhibitors are said to be nephrotoxic.
- Celecoxib is contraindicated in patients with hypersensitivity to sulfonamides.
- Overdose information with COX-2 inhibitors is limited. Symptoms are similar to those observed in typical NSAIDs, such as GI upset and lethargy.
- Rare side effects include hypertension, acute renal failure, respiratory depression and coma.

- Patients receiving rofecoxib have a risk of developing serious, thrombotic, cardiovascular adverse effects (MI, ischemic stroke, unstable angina, cardiac thrombus, sudden or unexplained death, transient ischaemic attack, resuscitated cardiac arrest) compared with those treated with naproxen.
- The results may be due to prothrombotic effects of rofecoxib or the antithrombotic effects of naproxen.

TREATMENT

- Monitor the serum electrolytes, renal functions and urinalysis after significant overdose.
- Management consists of controlling possible gastrointestinal bleeding and providing supportive care.
- No data available regarding the utility of extracorporeal elimination techniques. However based upon the high degree of protein binding and volume of distribution it is highly unlikely to be clinically useful.

CASE PRESENTATION

- A 26-year old woman with no significant past medical history presented after ingestion of up to 132 tablets of 800mg sustained release ibuprofen, equivalent to approximately 105g. This estimate of the amount ingested was based on empty ibuprofen packets found near her.
- The patient was brought into the Emergency Department having been found collapsed and unconscious at home by her family, who had last seen her well approximately 5hrs previously.
- There was no history of vomiting, GI haemorrhage or seizures prior to presentation at the hospital.

- Her initial Glasgow Coma Scale was 3/15 and the patient was therefore intubated and ventilated to provide a protected airway.
- On presentation she was haemodynamically compromised with a systemic BP of 80mmHg.
- The patients initial ECG showed sinus rhythm, normal QRS duration and normal QT duration, but widespread myocardial ischemia was noted.

- Initial biochemistry blood test results were:
  - Sodium – 132 mmol/L
  - Potassium – 4.7 mmol/L
  - Urea – 4.8 mmol/L
  - Creatinine – 159 µmol/L
  - Venous blood glucose – 4.7 mmol/L
- Paracetamol and salicylate concentrations were not detected on her admission blood samples.
- Arterial blood gases showed a severe metabolic acidosis with pH 6.99, base excess of -21 and lactate of 17 mmol/L

- The patient was commenced on epinephrine and norepinephrine for inotropic support in view of the significant hypotension, and the Guy' s and St Thomas' Poisons Unit was contacted for further advice on management.
- Since this was potentially a life-threatening ingestion of a sustained-release preparation of ibuprofen, it was recommended that multidose activated charcoal (50g activated charcoal every 3-4 hrs) should be given via a nasogastric tube to try and reduce absorption of ibuprofen from the GIT.

- The patient's severe metabolic acidosis should be corrected with repeated doses of IV boluses of 8.4% sodium bicarbonate, and haemofiltration with a bicarbonate buffer if the metabolic acidosis did not respond to IV sodium bicarbonate.
- It should be ensured that the patient is adequately administered with IV fluids to sustain blood pressure prior to the commencement of any additional inotropic support.
- Despite fluid resuscitation and maximal infusion doses of epinephrine and norepinephrine, the patient remained hypotensive with a systolic BP of 80 mmHg.

- Additionally her metabolic acidosis remained resistant to IV sodium bicarbonate and haemofiltration with a bicarbonate buffer, with only minor improvement to pH 7.
- Her clinical condition continued to deteriorate and approximately 5hrs post presentation to the Emergency Department the patient suffered a ventricular tachycardia / ventricular fibrillation cardiac arrest, as she did not respond to standard Advanced Life Support protocol for cardiopulmonary resuscitation.

POST DEATH

- Post mortem serum samples in peripheral whole blood, urine, gastric contents and liver extract were analysed and ibuprofen concentrations were found to be:
  - Peripheral whole blood – 518 mg/L
  - Urine – 264 mg/L
  - Gastric contents – 116 mg/L
  - Liver extract – 74 mg/kg
- Ante mortem serum ibuprofen concentrations were 760 mg/L on presentation, rising to a peak concentration of 1050 mg/L 90 minutes after presentation.

MCQs

1. Which mediators of inflammation are aced on by NSAID's?
   A) Eicosanoids – prostaglandins, thromboxanes, leukotrienes
   B) Degradative enzymes – proteases, hyaluronidases
   C) Vasoactive amines – histamine, serotonin
   D) Biologically derived oxidants – hydrogen peroxide, superoxide anion
2. Antidote of nimesulide poisoning
   A) Protamine
   B) Sodium nitroprusside
   C) Oxygen
   D) None of the above

3. The suggested therapeutic serum levels of mefenemic acid should not exceed

A) 20 mcg/ml

B) 200 mcg/l

C) 10 mcg/l

D) 50 mcg/l

4. The red discolouration of urine seen due to rubazonic acid is a metabolite of which drug

A) Pyrazolone

B) Propionic acids

C) Pyrazolidines

D) Heterocyclic acetic acids

5. Frontal headache is the most common adverse effect of which of the following drugs

A) Diclofenac
B) Indomethacin
C) Flufenamic acid
D) Piroxicam

6. Fatal dose of pyrazolones

A) 4 to 40 gm
B) 4 to 40 mg
C) 50 to 100 mg
D) 200 to 800 mg

7. Ingestion of what dose of propionic acid in children result in severe toxicity

A) 50 to 100 mg/kg

B) 100 to 150 mg/kg

C) 150 to 250 mg/kg

D) 400 mg/kg

8. Minimum dose of fenamic acid to cause coma and seizure in an adult

A) 3.5 mg

B) 35 mg

C) 3.5 g

D) 35 g

9. In patients taking nimesulide on a regular basis, which of the following conditions can be expected

A) Gynaecomastia
B) Jaundice
C) Meningitis
D) Hepatitis

10. Ipecac induced emesis in not recommended in NSAID toxicity due to risk of

A) Hepatoxity
B) Ulceration
C) CNS depression and seizures
D) Rhabdomyolysis

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