ANALGESIC TOXIDROMES

NSAIDS:

UNLESS THE INGESTION IS MASSIVE, OVERDOSE WITH ANY OF THE NSAIDS IS BENIGN!

MANAGEMENT IS SYMPTATIC AND SUPPORTIVE

RISK ASSESSMENT:

- Dose related risk assessment is best defined for ibuprofen, as 2/3 of cases are with this agent
- 100-300mg/kg are associated with mild GI and CNS symptoms while >300mg/kg is associated with severe multi-system organ dysfunction including shock, coma, seizure, ARF and metabolic acidosis → some fatalities reported
- OD with mefenamic acid is commonly associated with self-limiting seizures

TOXIC MECHANISM:

- Exert their pharmacological effects through the competitive inhibition of cyclooxygenase-1 and 2 and thus blockade of prostaglandin synthesis
- They are directly irritant to the GIT
- Prostaglandin inhibition leads to renal glomerular vasoconstriction and mild reversible renal dysfunction
- Bleeding time is prolonged due to inhibition of thromboxane A2 production

TOXICOKINETICS:

- Most agents have half lives of under four hours (other than naproxen and piroxicam, 12 and 45 hours respectively)

CLINICAL FEATURES:

- Most are asympotomatic or experience mild GI upset
- Massive overdose → shock, coma, ARF, seizures and metabolic acidosis → acidosis should resolves within 24-48 hours

MANAGEMENT → SUPPORTIVE CARE IS PARAMOUNT, WITH NO ROLE FOR DECONTAMINATION, ENHANCED ELIMINATION OR ANTIDOTES

PARACETAMOL – ACUTE OVERDOSE:

PROVIDED THAT THE TIME OF INGESTION IS WELL-DEFINED, RISK ASSESSMENTA ND THE DECISION TO TREAT (OR NOT) IS STRAIGHT-FORWARD

TREATMENT WITH N-ACETYLCYSTEINE IS GUIDED BY A SERUM PARACETAMOL LEVEL PLOTTED ON A NOMOGRAM

RISK ASSESSMENT:

- Life-threatening hepatotoxicity is uncommon and fatalities are rare
- Threshold dose for toxicity is highly variable but most often considered to be **150mg/kg or above**
- Risk of hepatic injury following a single acute ingestion without NAC predicted by plotting serum paracetamol ON NOMOGRAM (RUMACK-MATTHEW MOST COMMONLY USED, hepatotoxicity defined as AST/ALT >1000 unit/ml
    - 1-2% if 4 hour level <1320 micromol/L → 200mg/L
    - 30% if >1320-1980 micromol/L (200-300mg/L
    - 90% if >1980micromol/L → >300mg/L
- Risk of hepatic injury WITH NAC IS DETERMINED MOSTLY BY TIME TO COMMENCEMENT
    - 100% SURVIVAL IF STARTED WITHION 8 HOURS
    - Benefit is not established if started beyond 24 hours (except in fulminant hepatic failure where NAC is thought to decrease cerebral oedema, inotropic requirements and mortality)
- If time of ingestion is not known, this complicates risk assessment
    - If transaminases are deranged after 8 hours → assume toxicity and treat
    - If >24 hours and normal LFT, non-detectable level → little risk of developing significant toxicity
- No reported deaths of kids under 8 with non-intentional OD

TOXIC MECHANISM:

- Elevated levels of NAPQI (don't bother learning the real name!) → depletion of hepatic glutathione stores → once glutathione levels reach a critical point → NAPQI binds to other proteins causing hepatocyte injury

TOXICOKINETICS:

- Peak levels within 1-2 hours for tablets, 30mins for liquids
- 90% metabolised by glucuronidation/sulfation → remainder oxidised to NAPQI, which is normally immediately bound by intracellular glutathione and eliminated

CLINICAL FEATURES:

- **PHASES OF ACUTE PARACETAMOL OVERDOSE:**
    - < 24 hours → may have N+V, but otherwise asymptomatic

- 1-3 days → RUQ tenderness, transaminases peak (sometimes up to 20, 000). INR at peak coincident with peak transaminases. ↑bili, ARF may also occur
- 3-4 days → very severe cases → progression to fulminant hepatic failure with coagulopathy, jaundice, encephalopathy and MOF →death may occur and often ppreceded by recalcitrant lactic acidosis (despite resus), renal failure, worsening coagulopathy and encephalopathy
- 4days- 2 weeks → RECOVERY

INVESTIGATIONS:

- **Serum paracetamol taken at 4 or more hours from ingestion** to establish risk of hepatotoxicity and need for treatment
  - **If NAC** is started within 8 hours, the first level is all that is required
- **LFT** → if NAC is commenced later than 8 hours → baseline and serial LFT to monitor hepatic injury
- Coagulation profile → important marker of hepatic injury (take as routine if >24 hours)
- Platelet count, EUC, ABG → monitor status and prognostic indicators in those with established toxicity

MANAGEMENT:

- Resus only required in rare instance of coma at presentation with massive overdose or delayed presentation with established hepatic failure
- Activated charcoal is NOT life-saving, but may be offered to the cooperative patient who presents within the first hour
- ANTIDOTE → IV N-ACETYLCYSTEINE:
  - Indicated in all patients in whom the risk assessment suggests potential for poor outcome and in patients who present late with clinical or biochemical evidence of hepatic injury
  - If <8 hours → defer until 4 hour level plotted on nomogram
  - If 8-24 hours → start immediately and cease once level is available
  - Unknown time → if paracetamol is detectable, start NAC and cease later when history is available or if LFT normal after end of 20 hour infusion
  - If >24 hours → only indicated if paracetamol is detectable or if transaminases are elevated
  - NAC prevents NAPQI induced hepatotoxicity when given within 8 hours by ↑g glutathione availability, direct binding of NAPQI, provision of inorganic sulphate and reduction of NAPQI back to paracetamol
  - Give 150mg/kg over 15 minutes followed by 50mg/kg over 4 hours followed by 100mg/kg over 16 hours
    - Infusion can be stopped if risk of toxicity is excluded
    - May be continued with late presentation, repeated supratherapeutic ingestion or biochemical evidence of toxicity
  - Beware anaphylactoid reaction → need only be ceased if the reaction is severe and may be re-started as soon as reaction is settling

- In uncommon cases, rising INR and transaminases herald fulminant hepatic failure and the need to transfer to a liver transplant service →HIGH RISK CRITERIA:
    - INR>3 at 48 hours or 4.5 at any time
    - Oliguria or creatinine >200
    - Acidosis with pH <7.3 at any time
    - Systolic hypotension with BP <80
    - Hypoglycaemia
    - Severe thrombocytopaenia
    - Encephalopathy of any degree

PARACETAMOL – REPEATED SUPRATHERAPEUTIC INGESTION:

REFERS TO STAGGERED DOSING WITH THERAPUTIC INTENT (>4G/DAY IN ADULTS AND >60MG/KG IN KIDS) → ACCOUNTS FOR ALL PARACETAMOL RELATED DEATHS IN KIDS LESS THAN 6 AND UP TO 15% OF ADULT DEATHS

DECISION TO TREAT IS BASED ON AN ESTIMATION OF DOSE IN CONJUNCTION WITH BIOCHEMICAL TESTING

RISK ASSESSMENT:

- **STANDARD NOMOGRAMS DO NOT APPLY**
- High risk cases:
    - 10g or 200mg/kg (whichever is less) over a single 24 hour period
    - 6g or 150mg/kg per 24 hours for preceding 48 hours or longer
    - Patients who may be more susceptible → alcoholics, isoniazid, prolonged fasting → lower threshold than above
- If ALT/AST <50 units and level <120 micromol (20mg/L) → good prognosis and no further treatment required
- AST/ALT >50 or level <10mg/L → higher risk, commence NAC
- NAC is indicated immediately if there are clinical features of hepatitis and a history of repeated supratherapeutic ingestion → continue for at least eight hours

TRAMADOL:

CENTRALLY ACTING SYNTHETIC ANALGESIC

IN OVERDOSE IT CAUSES DELAYED ONSET SEIZURES, MILD SEDATION AND RESPIRATORY DEPRESSION

RISK ASSESSMENT:

- Opioid effects are usually mild and rarely require intervention
- Major potential risk is seizures → delayed >6 hours, anticipated if ingestion >1.5g
- Serotonin syndrome may develop if co-ingested with other serotonergic agents

TOXIC MECHANISM:

- Weak partial agonist at mu-opioid receptors
- Also inhibits serotonin and noradrenaline reuptake in the CNS → major mediators of toxicity in overdose

CLINICAL FEATURES:

- Opioid agonist effects NOT PROMINENT
- Coma requiring intubation unusual unless co-ingested with other CNS depressants
- Serotonergic/noradrenergic effects → tachycardia, agitation, mydriasis, seizures → usually short duration and easily controlled with benzodiazepines
- Serotonin syndrome if other serotonergically active agents are ingested

MANAGEMENT:

- Seizures are treated with titrated benzos
- ↑g agitation, tachycardia, tremor and myoclonic jerks herald seizures → prophylactic diazepam
- Consider early charcoal if patient cooperative and alert