MISCELLANEOUS SERIOUS TOXIDROMES

BACLOFEN:

LARGE OVERDOSES ARE CHARACTERISED BY RAPID ONSET OF DELIRIUM, RESPIRATORY DEPRESSION, COMA AND SEIZURES → POTENTIALLY LETHAL WITHOUT PROMPT SUPPORTIVE CARE

RISK ASSESSMENT:

- Ingestions >200mg in adults → causes significant CNS effects (see above)

TOXIC MECHANISM:

- Synthetic derivative of GABA → at therapeutic doses, it acts principally on spinal GABA-B receptors
- It also mediates pre and post-synaptic inhibition → paradoxical seizures in overdose

CLINICAL FEATURES:

- Clinical features of intoxication develop within 2 hours:
  - CNS → delirium, respiratory depression, profound/prolonged coma, seizures
  - CV → sinus bradycardia, hypertension, first degree AV block/QT prolongation
- Following large ingestions, coma may be profound → MIMICS BRAIN DEATH →fixed/dilated pupils, absent brainstem reflexes, profound hypotonia
  - Duration of coma 24-48 hours

MANAGEMENT:

- Respiratory depression and coma → intubate early
- Treat seizures with diazepam
- Fluid boluses for hypotension
- Not detected on routine drug screens
- It is often delivered by continuous intrathecal infusion → pump malfunctions resulting in even small IT boluses can produce profound coma
- Baclofen WITHDRAWAL syndrome occurs between 24-48 hours → seizures, hallucinations, dyskinesia and visual disturbance

CHLOROQUINE AND HYDROXYCHLOROQUINE:

QUINOLONE-RELATED DRUGS → MOST TOXIC OF ALL THE ANTI-MALARIAL AGENTS

HYDROXYCHLOROQUINE ALSO USED IN TREATMENT OF LUPUS AND RHEUMATOID ARTHRITIS

OVERDOSE PRODUCES RAPID-ONSET HYPOTENSION, CNS DEPRESSION, CARDIAC CONDUCTION DEFECTS AND HYPOKALAEMIA

MANAGEMENT IS SUPPORTIVE

RISK ASSESSMENT:

- Ingestion of 10mg/kg of chloroquine potentially toxic, but serious toxicity and increasing mortality over 30mg/kg
    - Ingestion of 5g in adults is usually fatal without intervention
    - Ingestion of even one tablet in a child is considered potentially lethal

TOXIC MECHANISM:

- Direct toxic effect on CNS via voltage-dependent sodium channels, which is compounded by cerebral hypoperfusion
- Hypotension and cardiogenic shock are due to a direct cardiodepressant effects
- Hypokalaemia believed to be due to transport-dependent mechanism

CLINICAL FEATURES:

- Onset of symptoms within 2 hours
- CARDIOVASCULAR:
    - Rapid onset hypotension
    - QRS widening, QT prolongation
    - Cardiac arrest
- CNS:
    - Depressed consciousness, seizures
- METABOLIC:
    - Hypokalaemia due to intracellular shift of potassium

MANAGEMENT:

- EVENTS THAT MAY REQUIRE IMMEDIATE INTERVENTION:
    - Coma → intubate early
    - Broad complex tachycardia → sodium bicarbonate for serum alkalinisation → aim pH 7.5-7.55
    - Hypotension → fluid bolus, then IV adrenaline if BP does not respond
- Ensure NORMOKALAEMIA → avoid aggressive replacement as total body potassium is NOT DEPLETED
- Anticipate catastrophic deterioration in any patient presenting following chloroquine overdose

COLCHICINE:

UNCOMMON BUT POTENTIALLY LETHAL

TOXICITY CHARACTERISED BY SEVERE GASTROENTERITIS FOLLOWED BY MULTI-SYSTEM ORGAN FAILURE

AGGRESSIVE DECONTAMINATION AND SUPPORTIVE CARE CORNERSTONES OF MANAGEMENT

RISK ASSESSMENT:

- **<0.5MG/KG** → GI symptoms
- **0.5-0.8mg/kg** → SYSTEMIC TOXICITY INCLUDING BONE MARROW SUPPRESSION, 10% MORTALITY
- **>0.8mg/kg** → Severe poisoning involving CV collapse, coagulopathy, acute renal failure. Mortality approaches 100%
- **BE AWARE THAT DEATHS HAVE OCCURRED WITH DOSES AS LITTLE AS 0.2MG/KG**

TOXIC MECHANISM:

- Binds tubulin and prevents microtubule formation, thus inbiting mitosis
- Following overdose, tissues with high turnover (GIT, bone marrow) are preferentially affected

TOXICOKINETICS:

- Extensive first pass metabolism
- Highly tissue bound
- Half life over 30 hours in overdose

CLINICAL FEATURES:

- Usually presents with severe gastroenteritis in the first 24 hours, followed by multi-organ toxicity in the second 24 hours
- First 24 hours → GI fluid losses can result in haemodynamic instability
- 2-7 days → bone marrow suppression and PANCYTOPAENIA, rhabdomyolysis, renal failure, worsening metabolic acidosis, respiratory insufficiency/ARDS, cardiac arrhythmia/sudden cardiac death
- >7 days → complete recovery expected in those who survive to this stage

MANAGEMENT:

- Patients may present in hypovolaemic shock due to massive fluid losses from GIT
- Aggressive supportive care in ICU environment offers best chance of survival → meticulous fluid balance, acid-base management and management of infective complications
- ADMINISTER CHARCOAL TO ANYONE WHO HAS INGESTED OVER 0.5MG/KG → even if small amount prevented from being absorbed, this could be life-saving
- Colchicine-specific antibodies were used in one case, but are not currently available

- G-CSF is an option in severe leucopenia, but its use is not widespread

ISONIAZID:

RARE, BUT POTENTIALLY FATAL

SEVERE POISONING PRESENTS WITH RAPID ONSET OF SEIZURES, COMA AND SEVERE METBAOLIC ACIDOSIS

PYRIDOXINE IS THE SPECIFIC ANTIDOTE

RISK ASSESSMENT:

- Doses over 3g (40mg/kg) at risk of seizures, metabolic acidodis and coma
- Doses over 10g (130mg/kg) universally fatal without intervention

TOXIC MECHANISM:

- Toxicity results from deficiency of the active form of pyridoxine as isoniazid interfere with the enzyme responsible for the conversion of pyridoxine to P5P
    - P5P is an essential cofactor for the conversion of glutamic acid to GABA in the CNS → hence a GABA deficiency develops manifesting as status epilepticus
    - The severe lactic acidosis is a dual effect of prolonged seizures and direct inhibition of conversion of lactate to pyruvate

CLINICAL FEATURES:

- Initial symptoms are non-specific
- Physical exam → ↑ HR, mydriasis, slurred speech, ataxia, hyperreflexia
- If sufficient dose ingested → rapid confusion, depressed consciousness, coma, status seizures, severe lactic acidosis and death
- Complications of seizures may develop → aspiration, rhabdomyolysis, hyperpyrexia
- Severe anion gap metabolic acidosis with high serum lactate is a major feature of isoniazid overdose

MANAGEMENT:

- Aggressive management of airway until seizures controlled
- Seizures are controlled with high-dose IV diazepam while sourcing pyridoxine
- ANTIDOTE:
    - Give 1g of pyridoxine for each gram of isoniazid ingested
    - If the ingested dose is not known → 5g and reassess
    - Pyridoxine overcomes P5P-induced GABA deficiency and resultant CNS excitation, thus restoring normal GABA levels and activity
    - Maximum dose 5g (70mg/kg)
    - Give dose as slow IV infusion at 0.5g/minute until seizures stop or infusion is complete
    - Chronic high oral pyridoxine dosing is associated with peripheral neuropathy, but this does not occur with acute dosing for isoniazid overdose
    - Pyridoxine is only available in 50mg vials → large numbers will thus need to be procured

POTASSIUM CHLORIDE:

RARE, BUT DELIBERATE SELF-INGESTION CAN RESULT IN LIFE-THREATENING HYPERKALAEMIA AND CARDIAC ARREST → MAIN CONCERN IS CONTROLLED-RELEASE, WHICH IS AVAILABLE 100 TABLETS WITHOUT PRESCRIPTION

GOOD OUTCOME DEPENDS ON EARLY RISK ASSESSMENT, GIT DECONTAMINATION AND HAEMODIALYSIS WHERE INDICATED

RISK ASSESSMENT:

- Small ingestions usually benign if renal function normal
- Ingestion of >2.5mmol/kg K may theoretically temporarily overwhelm the capacity of the kidneys to excrete potassium
- Lethal dose not well defined
- Massive ingestion (>40 x 600mg) prompts early planning for haemodialysis
- Patients with pre-existing renal impairment and CV disease may be at higher risk

TOXIC MECHANISM:

- Potassium is the principal intracellular cation
- Hyperkalaemia interferes with electrical condiuction in both nerve, muscle and (if severe) → causes cardiac arrest
- Direct GI irritant when ingested

TOXICOKINETICS:

- Rapidly absorbed
- Hyperkalaemia when rate of absorption from gut exceeds combined rate of redistribution to intracellular compartment and urinary excretion

CLINICAL FEATURES:

- Ileus and mucosal perforation may occur
- As hyperkalaemia progresses → worsening lethargy, confusion, weakness, paraesthesiae and hyporeflexia
- Paralysis and bradycardia herald cardiac arrest

INVESTIGATIONS:

- **ECG** →demonstrate a progression of anomalies with rising potassium levels:
    - Peaked TW →PR prolongation→ loss of P waves with atrial paralysis → widening of QRS → QT prolongation → sine wave appearance → ASYSTOLE
- EUC → SERIAL POTASSIUM
- AXR → useful to confirm number of slow-release tablets and in monitoring success of decontamination

MANAGEMENT:

- Initial efforts directed at detected rising potassium while initiating temporizing measures to act as a bridge to urgent dialysis
- Temporizing measures include:

    - Calcium chloride (10mL 10%, 0.15mL/kg in children)
    - Nebulised salbutamol
    - Dextrose/insulin 10 units (0.1 units/kg in kids)
    - Sodium bicarbonate 50-100mmol (1mmol/kg in kids)
- DECONTAMINATION:
    - Activated charcoal DOES NOT BIND POTASSIUM
    - Slow-release KCl tablets are amenable to WBI → main value is in completing decontamination once dialysis is started
- ENHANCED ELIMINATION:
    - HAEMODIALYSIS IS THE DEFINITIVE TREATMENT OF HYPERKALAEMIA FOLLOWING OVERDOSE
    - Plan for dialysis during risk assessment, indicated if:
        - Ingested dose >40 x 600mg tablets confirmed on AXR
        - Renal impairment
        - CV instability
        - Serum potassium > 8.0
        - Rapidly rising serum potassium
    - Dialysis continues until decontamination of GIT with WBI is confirmed on AXR
- Remember that RESONIUM only binds 1mmol potassium per gram!

SALICYLATES:

ACUTE INTOXICATION PRESENTS WITH CLASSICAL SYMPTOMS OF VOMITING, TINNITUS, HYPERVENTILATION, RESPIRATORY ALKALOSIS FOLLOWED BY SEVERE METABOLIC ACIDOSIS → SEVERE TOXICITY MAY RESULT IN COMA AND SEIZURES

CHRONIC INTOXICATION PRESENTS WITH NON-SPECIFIC CLINICAL FEATURES → FREQUENTLY MISSED AND MORBIDITY AND MORTALITY ARE GREATER

URINARY ALKALINISATION AND HAEMODIALYSIS ARE HIGHLY EFFECTIVE METHODS OF ENHANCING ELIMINATION

RISK ASSESSMENT:

- Dose-related toxicity and progresses over hours
- METHYL-SALICYLATE (oil of wintergreen) is the major problem, 1mL containing equivalent to 7.5g of acetylsalicylate, being equivalent to 1400mg of aspirin
- 150-300mg/kg → mild to moderate intoxication → salicylism with hyperpnoea, tinnitus and vomiting
- >300mg/kg → severe intoxication with metabolic acidosis, altered mental state and seizure
- >500mg/kg → POTENTIALLY LETHAL

TOXIC MECHANISM:

- Salicylates cause irreversible inhibition of cyclooxygenase resulting in decreased prostaglandin synthesis
- Stimulation of the respiratory centre causes hyperventilation and respiratory alkalosis
- UNCOUPLING OF OXIDATIVE PHOSPHORYLATION → accumulation of lactic acid
    - In combination with promotion of fatty acid metabolism → ketone body accumulation → profound metabolic acidosis
- Death is associated with very high salicylate levels in the CNS

TOXICOKINETICS:

- Rapidly absorbed and highly protein bound, with small VD
- Absorption may be delayed with enteric-coated formulation or if BEZOAR (tablet masses) form within the GIT
- In overdose, protein binding is saturated and free levels increase
- In acidaemia, more salicylate is in the UN-IONISED state, favouring movement into the extravascular space (including the CNS)
- Kinetics change from first order to zero order in overdose, as metabolic pathways are saturated
- Urinary pH affects renal elimination → high urinary pH promotes urinary salicylate excretion, as a greater proportion of salicylate is ionized and unable to be reabsorbed

CLINICAL FEATURES:

- ACUTE INTOXICATION:
  - Onset at 6-12 hours, but then deterioration may be very rapid
  - GIT → N+V
  - CNS → tinnitus, ↓hearing, vertigo, agitation/seizures
    - May progress to cerebral oedema and death
  - Acid-base disturbance → respiratory alkalosis initially → anion gap acidosis
    - Actual acidaemia occurs late and indicates imminent demise without intervention
- CHRONIC:
  - Difficult to diagnose and often missed
  - Most common in elderly
  - Confusion, delirium, dehydration, fever and unexplained acidosis
  - Cerebral and pulmonary oedema are more common than in acute intoxication

INVESTIGATIONS:

- SALICYLATE LEVEL → poor correlation with toxicity
  - Serial levels to detect ongoing absorption
- ABG

MANAGEMENT:

- Controlled hyperventilation is implemented to maintain respiratory alkalosis after intubation for coma/respiratory insufficiency
- Benzodiazepines for seizures
- DECONTAMINATION:
  - Give charcoal up to 8 hours following acute overdose of >150mg/kg
    - Second dose indicated if levels continue to rise after four hours
- ENHANCED ELIMINATION:
  - URINARY ALKALINISATION → indicated in symptomatic salicylate poisoning. Use sodium bicarbonate
  - HAEMODIALYSIS → rarely required if early decontamination and urinary alkalinisation are implemented. Consider if:
    - Urinary alkalinisation is not feasible
    - Serum salicylate levels rise to >4.4mmol/L (>60mg/dL) despite decontamination and urinary alkalinisation
    - Severe toxicity as evidenced by altered mental state, acidaemia, renal failure
    - Very high serum salicylate levels
    - Threshold to dialyse is lower in the elderly

STRYCHNINE:

ERGOT USED AS A RODENTICIDE

LEADS TO GENERALISED MUSCLE SPASM WITHIN 30 MINUTES

DEATH FROM RESPIRATORY FAILURE MAY FOLLOW PROMPTLY

PARALYSIS, INTUBATION AND VENTILATION ARE LIFE-SAVING IF INSTITUTED EARLY BEFORE HYPOXIC NEUROLOGICAL INJURYA ND MULTIPLE ORGAN FAILURE OCCURS

RISK ASSESSMENT:

- Ingestion of as little as 30-100mg by an adult is potentially lethal and death can occur within 30 minutes
- Any deliberate ingestion is likely to be rapidly lethal without intervention
- In kids, an accidental taste is potentially lethal

TOXIC MECHANISM:

- A competitive glycine antagonist at brainstem and spinal cord post-synaptic receptors → loss of normal descending inhibitory motor tone and the onset of skeletal muscle spasm → respiratory/ventilatory failure

TOXICOKINETICS:

- Not absorbed through intact skin

CLINICAL FEATURES:

- Generalised painful muscle spasms of all voluntary muscles precipitated by any external sensory stimulus rapidly progress, in severe cases, to hyperthermia, rhabdomyolysis, lactic acidosis and respiratory paralysis
- Death is from ventilatory failure
- Loss of consciousness does not develop until secondary hypoxia develops
- If the acute phase is survived, then recovery may be complicated by hypoxic brain injury, myoglobinuria and renal failure

MANAGEMENT:

- TIME-CRITICAL, LIFE-THREATENING EMERGENCY
- Potential early threats → generalised muscle rigidity and respiratory paralysis
- Early neuromuscular paralysis, intubation and ventilation are life-saving
- Mild intoxication with minor twitching without generalised muscle spasm or respiratory compromise is managed with IV diazepam
- If a patients is well without twitching or spasm at four hours →cleared for discharge
- Muscle spasm heralds imminent onset of lethal muscle rigidity