CARDIAC TOXIDROMES

AMIODARONE:

ACUTE INGESTION UNCOMMONLY PRODUCES TOXICITY, REGARDLESS OF DOSE

CHRONIC TOXICITY IS COMMON

RISK ASSESSMENT:

- Delayed cardiac effects, including hypotension, atrial flutter and TWI have been observed following acute toxicity, but the results are usually benign → there are no reported fatalities
- Chronic toxicity is common and manifestations include
    - Pulmonary fibrosis
    - Cardiovascular effects → bradycardia and AV block, torsades, negative inotropy, hypotension
    - Thyroid dysfunction (both over and under-activity reported)
    - Hepatic toxicity
    - Corneal micro-deposits

TOXIC MECHANISM:

- Predominant CLASS III effects (due to blockade of potassium channels)→ prolongation of phase 4 of the action potential in addition to prolonging the refractory period of ventricular and atrial tissue.
- Also has class I, II and IV effects as well

TOXICOKINETICS:

- Oral bioavailability is generally poor
- Large volume of distribution due to almost exclusive protein binding
- Hepatic metabolism to produce active metabolite
- Elimination is mainly biliary and very slow (up to 100 days for chronic ingestion)

MANAGEMENT:

- Management is entirely supportive with resuscitation rarely being required
- Bradycardia may require pacing, or adrenaline/isoprene as it may be resistant to atropine
- Hypotension responds to vasopressors
- CV effects delayed, so admission for monitoring advised → discharge if ECG normal and asymptomatic at the end of that time

ACE-INHIBITORS

OVERDOSE IS RELATIVELY BENIGN, THE MAIN ISSUE BEING HYPOTENSION THAT IS GENERALLY FLUID RESPONSIVE

RISK ASSESSMENT:

- Mild hypotension can occur, usually within 2 hours of ingestion and may last for several hours
- Kids can tolerate up to twice adult daily dose well

TOXIC MECHANISM:

- ACE-I bind to and inactive ACE (reversible) thus preventing formation of AT-II → which is a powerful vasopressor in addition to multiple endocrine functions (↓ aldosterone)

TOXICOKINETICS:

- Rapidly and well absorbed after oral intake, elimination is renal
- Many are pro-drugs requiring hepatic conversion

CLINICAL FEATURES:

- Usually asymptomatic
- If hypotension will occur, it will be within 2 hours of ingestion, lasting many hours
- Check EUC (renal impairment and hyperkalaemia, both mild)

MANAGEMENT:

- Resuscitation rarely required
- Judicious fluid bolus
- Charcoal unlikely to alter course
- If asymptomatic at four hours → discharge, otherwise, non-monitored bed sufficient

BETA BLOCKERS:

PROPRANOLOL AND SOTALOL REPRESENT LIFE-THREATENING TOXIDROMES, BUT OTHERWISE BETA-BLOCKER OVERDOSE IS BENIGN

RISK ASSESSMENT:

- Toxicity DOES NOT correlate with ingested dose
- Risk factors for severe toxicity:
  - Sotalol or propranolol as ingested agent
  - Underlying heart/lung disease
  - Co-ingestion with CCB/digoxin
  - Age
- Threshold dose for toxicity with propranolol is as little as 1g
- Usually manifests within first few hours, unless controlled-release preparation
- PR prolongation (even without bradycardia) is an early manifestation of toxicity
- Kids are at risk after ANY INGESTION OF PROPRANOLOL OR SOTALOL!

TOXIC MECHANISM:

- Competitive antagonism at both beta-1 and beta-2 receptors → ↓ cAMP → hence blunts effects of catecholamines
- Propranolol also has class I activity and being LIPID SOLUBLE it also has a direct toxic effect in the CNS
- Sotalol also blocks K+ channels leading to QT prolongation

TOXICOKINETICS:

- Rapidly absorbed
- Propranolol is distinct as it is EXTREMELY LIPOPHILIC
- Half life is prolonged in overdose due to overwhelmed hepatic metabolism

CLINICAL FEATURES:

- Bradycardia normally manifests within four hours of ingestion
- CARDIOVASCULAR EFFECTS:
  - Hypotension/bradycardia
  - Bradyarrhythmia → sinus brady, 1-3rd degree HB, junctional or ventricular bradycardia
  - QRS widening following propranolol due to Na+ channel blocking effects → magnitude is predictor of ventricular arrhythmia
  - QT ↑ following sotalol
- CNS EFFECTS:
  - Delirium, coma and seizures with propranolol
- OTHER:
  - Bronchospasm
  - APO
  - ↑ K+
  - ↓/↑ BSL

MANAGEMENT:

- Acute resuscitation is likely to be required after propranolol OD:
  - Prompt intubation
  - SODIUM BICARBONATE (to control ventricular arrhythmia, as in TCA overdose)
- TREATMENT OF BRADYCARDIA:
  - Atropine 10-30 microg/kg IV (temporisin)
  - Isoprenaline → 4microg/kg/min IV
  - Adrenaline → peripheral vasodilation a problem
  - HIGH-DOSE INSULIN
- TREATMENT OF WIDE QRS:
  - Sodium bicarbonate 1-2meq/kg boluses
- TORSADES (SOTALOL):
  - ISOPRENALINE
  - OVERDRIVE PACING
  - MAGNESIUM
- INVASIVE MONITORING AND ICU LEVEL CARE PREFERRED (involve early if there are ECG manifestations of toxicity
- DECONTAMINATION AN OPTION WITH CHARCOAL IF PRESENATION IS WITHIN 2 HOURS OF INGESTION:
  - Exert caution following propranolol due to risk of coma and seizures
- No role for enhanced elimination or antidotes
- Discharge possible if patients have normal ECG and remain asymptomatic after 6 hours

CONTROVERSIES IN MANAGEMENT:

- **INTRALIPID** may be considered in life-threatening propranolol overdose, but indications are controversial
- **Precise indications for high-dose insulin are uncertain**

CALCIUM CHANNEL BLOCKERS

VERAPAMIL AND DILTIAZEM ARE VERY DANGEROUS IN OVERDOSE → COMMONLY CAUSE CARDIOVASCULAR COLLAPSE WHICH MAY BE DELAYED BETWEEN 4-16 HOURS DEPENDING ON WHETHER CONTROLLED-RELEASE PREPARATIONS ARE USED

DIHYDROPYRIDINE C.C.B. NOT USUALLY ASSOCIATED WITH SEVERE TOXICITY

RISK ASSESSMENT:

- Ingestion of 2-3x normal therapeutic dose can cause severe toxicity in susceptible individuals
- All deliberate self-poisoning are considered serious
- Ingestion of >10 tablets of XR preparation of verapamil or diltiazem likely to cause life-threatening toxicity
- Co-ingestion with other cardiac-toxic medications significantly increases risk of toxicity
- Advanced age and cardiac co-morbidities detrimental
- Greater than two tablets is potentially lethal in kids

TOXIC MECHANISM:

- CCB prevent opening of L-type calcium channels, resulting in decreased Ca2+ influx → slowing of cardiac contraction and ↓d force of contraction (verapamil/diltiazem) in addition to vascular smooth muscle relaxation (dihydropyridines)
- Hypotension with cardiac-selective CCB due to bradycardia and ↓d contractility → often associated with hyperglycaemia and lactic acidosis

TOXICOKINETICS:

- Peak concentrations at 6-12 hours for controlled release, but this peak is often delayed in overdose
- High first pass metabolism, which is saturated in overdose, leading to higher free levels
- Both form active metabolites

CLINICAL FEATURES:

- Peak effects in standard preparations with in 1-2 hours, up to 24 hours in controlled release
- CARDIOVASCULAR:
    - Bradycardia, first degree HB, hypotension are early signs → progresses to refractory shock and death with consequent myocardial/cerebral/mesenteric ischaemia
- CNS:
    - Seizures and coma are rare → usually means co-ingestant
- METABOLIC:
    - Hyperglycaemia and lactic acidosis
- ECG → varying degrees of heart block
- Serum calcium, lactate and ABG instructive but not diagnostic

MANAGEMENT:

- **TIME-CRITICAL EMERGENCY**
- Hypotension refractory to fluid resuscitation indicates onset of significant toxicity
- Early controlled intubation and ventilation suggested with early invasive blood pressure monitoring
- GRADUATED APPROACH TO HYPOTENSION:
    - Initial fluid bolus
    - CALCIUM GLUCONATE (60mL) OR CALCIUM CHLORIDE (20mL) → provide temporary ↑s in heart rate and BP → can be repeated up to three times
    - Start an infusion to maintain ionized Ca2+ above 2
    - CATECHOLAMINE INFUSION → adrenaline or noradrenaline
    - **HIGH-DOSE INSULIN:**
        - Produces significant inotropic response in severe CCB OD with haemodynamic compromise (can also be used in beta blocker OD)
        - Insulin has a well-established positive inotropic effect in the failing heart → thought to be due to its ability to increase lactate oxidation while at the same time completely eliminating myocardial fatty acid oxidation, hence optimizing cardiac function
        - Glucose is given simultaneously to maintain euglycaemia
        - Careful attention to BSL and potassium levels
        - Give 1 unit per kg bolus after 50ml of 50% bolus of glucose
            - Continue 0.5units/kg/hour with 25g glucose per hour
            - Titrate glucose infusion to BSL
        - Combined infusion should continue for as long as the patient has CV instability
        - START AS SOON AS HAEMODYNAMIC COMPROMISE MANIFESTS RATHER THAN WAITING FOR POOR RESPONSE TO OTHER MEASURES
    - CARDIAC PACING → not above 60 and may not improve perfusion
    - SODIUM BICARB → for acidosis
    - Cardiopulmonary bypass and IABP → heroic measures for severe/refractory cases
    - DECONTAMINATION:
        - Charcoal should be given to all who present within 1 hour (standard) or 4 hours (Controlled release)
        - Whole bowel irrigation to those with deliberate self-poisoning with controlled-release preparations (or those with >10 tablets).
    - USE OF INTRALIPID IS STILL EVOLVING

ACUTE DIGOXIN POISONING

ACUTE TOXICITY MANIFESTS WITH EARLY VOMITING AND ↑K+ BUT CAN PROGRESS TO LIFE-THREATENING CARDIAC DYSRHYTHMIAS AND COLLAPSE

CARDIOVASCULAR COMPLICATIONS ARE REFRACTORY TO STANDARD RESUSCITATION MEASURES, BUT DIGOXIN IMMUNE FAB (DIGIBIND) IS A HIGHLY EFFECTIVE ANTIDOTE

RISK ASSESSMENT:

- Acute intoxication occurs if more than 10x daily dose is ingested
- Potentially lethal intoxication is predicted by:
    - Dose ingested (>10mg for adult, 4mg for kids) → ingestion of up to 75microg/kg is considered safe.
    - Serum digoxin level >15nmol/L
    - Serum potassium >5.5

TOXIC MECHANISM:

- Digoxin inhibits membrane Na/K ATPase pump, leading to a reduced sodium gradient and reduced calcium extrusion from the cell → ↑ intracellular Ca2+ with resultant enhanced automaticity and positive inotropy and ↑extracellular K+
- Digoxin also enhances vagal tone → ↓SA and AV node conduction velocities

TOXICOKINETICS:

- Good oral bioavailability (60-80%), with peak effects after 6 hours
- Eliminated unchanged by the kidneys

CLINICAL FEATURES:

- Early N+V (2-4 hours), peak levels at 6 hours with CV collapse at 8-12 hours.
- GI EFFECTS:
    - Nausea, vomiting, abdominal pain
- CARDIOVASCULAR:
    - Bradycardias (1-3rd HB, AF with slow response)
    - ↑ automaticity (ventricular ectopics/bigeminy, SVT with AV block, VT)
    - Hypotension
- CNS:
    - Lethargy, confusion, delirium

INVESTIGATIONS:

- SERUM DIGOXIN LEVELS (confirms poisoning, indications for antibody treatment)
    - Perform four hours post-ingestion and then every two hours
- EUC (↑ K+ of any magnitude is an important early sign of severe digoxin toxicity)
- ECG:
    - Monitor progression or resolution of toxicity

MANAGEMENT:

- In cardiac arrest, standard resus IS FUTILE → ALS protocol while procuring 20 ampoules of digoxin immune fab → continue resuscitation efforts for at least 30 minutes after administration
- If digoxin immune fab is not immediately available → temporizing measures for ↑K (bicarb, insulin/dextrose NOT CALCIUM), AV block (atropine, pacing) ventricular dysrhythmia (lignocaine 1mg/kg up to 100mg over 2 mins)
- Offer decontamination to those presenting within first hour
- DIGOXIN IMMUNE FAB:
    - Binds directly to the free intravascular and interstitial digoxin with far greater affinity than for the Na/K ATPase receptor → a concentration gradient is thus created and intracellular digoxin dissociates from tissues and moves to the intracellular space where binding continues
    - An extremely safe antidote
    - INDICATIONS:
        - Acute toxicity with cardiac arrest, life threating arrhythmia, ingested dose >10mg, serum level >15nmol/L, K+>5
        - Chronic toxicity with cardiac arrest, life-threatening arrhythmia, dysrhythmia or ↑ automaticity that is likely to be poorly tolerated, moderate-severe GI upset, any symptoms with impaired renal function
    - DOSING:
        - ACUTE POISONING → known dose → Number of ampoules = ingested dose in mg x 0.8 (bioavailability) x 2
            - If dose is UNKNOWN → start with five ampoules if stable and ten if unstable and repeat dosing every 30minutes (5 amp)
        - CHRONIC POISONING → number ampoules = serum level (ng/mL) x body weight/100
    - Be aware that serum digoxin levels post digibind will be very high as most assays measure both free and fab-bound digoxin

CHRONIC DIGOXIN POISONING:

UNDERDIAGNOSED CONDITION THAT CARRIES SIGNIFICANT MORBIDITY AND MORTALITY

INTOXICATION IS COMMON IN ELDERLY PATIENTS WITH MULTIPLE COMORBIDITIES

USE OF DIGOXIN-IMMUNE FAB REDUCES MORTALITY AND MAY REDUCE HOSPITAL LENGTH OF STAY

RISK ASSESSMENT:

- Untreated, the mortality within a week is 15-30%
- Probability of intoxication is predicted by considering digoxin level and clinical features:
    - AUTOMATICITY ALONE WITH LEVEL > 1.5 NG/ML CARRIES RISK OF INTOXICATION OF 70%
    - Other symptoms include bradycardia and GI symptoms

CLINICAL FEATURES:

- Consider in elderly patients with intercurrent illness, particularly in those with altered renal function
- In addition to symptoms of acute toxicity, chronic toxicity can manifest VISUAL PROBLEMS → ↓VA, chromatopsia (aberration of colour vision) and xanthopsia (yellow haloes)
- The diagnosis of chronic digoxin intoxication is based on a steady state level ≥ 6 hours post last dose
- Management in arrest situation identical
- Early treatment with digoxin immune fab is COST-EFFECTIVE as it decreases need for monitoring as well as length of stay in hospital
- Consider the diagnosis in any patient on digoxin who presents with collapse, hypotension, bradycardia, dysrhythmia, GI complaints, altered mental state or general deterioration

CLONIDINE:

PRODUCES VARYING DEGREES OF CNS DEPRESSION AND MILD CARDIOVASCULAR EFFECTS

CLASSICAL TRIAD OF DROWSINESS, MIOSIS AND BRADYCARDIA

TREATMENT IS SUPPORTIVE

RISK ASSESSMENT:

- Clinical effects correlate poorly with ingested dose
- Onset of features is rapid, usually within 2 hours
- In kids, ingestion of two tablets is potentially lethal without supportive care (20microg/kg respiratory depression or apnoea

TOXIC MECHANISM:

- Centrally acting alpha-2 adrenergic agonist, acting as a sympathoplegic agent, decreasing CNS sympathetic outflow

CLINICAL FEATURES:

- Onset of toxicity is rapid
- Lethargy, miosis, slurred speech and ataxia usually occur within 2 hours
- The patient can often be roused with stimulation, only to lapse in to unconsciousness when not disturbed
- Severe intoxication is associated with coma, bradycardia and hypotension
- Hypothermia, respiratory depression and apnoea are uncommon but have been reported
- Symptoms resolve within 24 hours
- CARE IN PAEDIATRIC CASES
- BASIC RESUSCITATIVE MEASURES ENSURE SURVIVAL IN VAST MAJORITY