MISCELLANEOUS BENIGN TOXIDROMES

ANTIHISTAMINES (NON-SEDATING):

MILD CNS DEPRESSION IN OVERDOSE

NOTABLE FOR THEIR ASSOCIATION WITH QT PROLONGATION, LESS MARKED WITH NEWER AGENTS

RISK ASSESSMENT:

- Mild sedation or anticholinergic effects anticipated
- QT prolongation following overdose is reported but rare

TOXIC MECHANISM:

- Mildly lipophilic and are less able to cross BBB than sedating agents
- Selective competitive reversible H1 antagonists
- Compared to sedating antihistamines, they have lower affinity for central H1, M1, alpha-1 and serotonergic receptors
- In overdose, selectivity may be lost and some sedation, anticholinergic effects and hypotension may be seen
- QT prolongation is due to cardiac potassium channel blockade

TOXICOKINETICS:

- Well absorbed, with peak effects in 1-3 hours

CLINICAL FEATURES:

- Minor sedation, nausea and ataxia
- Mild anticholinergic symptoms
- Symptoms develop within 4-6 hours and resolve within 12-24 hours

MANAGEMENT:

- Resuscitation is rarely required
- Manage anticholinergic delirium as previously outlined
- Severe QT prolongation with torsades is largely a theoretical risk
    - If it does occur → correct hypoxia, hypokalaemia
    - Administer magnesium and if the heart beat is less than 100/min → isoprenaline or overdrive pacing to maintain HR (QT is relatively shorter when rate is faster)

SEDATING ANTI-HISTAMINES:

OVERDOSE CHARACTERISED BY DOSE-DEPENDENT SEDATION AND ANTICHOLINERGIC EFFECTS

CARDIOVASCULAR TOXICITY IS ASSOCIATED WITH MASSIVE OVERDOSE

RISK ASSESSMENT:

- Dose-dependent sedation, anticholinergic effects and orthostatic hypotension
- All agents lower seizure threshold, but seizures are infrequent
- Massive overdose may result in cardiac conduction anomalies (↑d QT/QRS) and perhaps hypotension requiring inotropes

TOXIC MECHANISM:

- Act by competitive inhibition of H1 receptors
- Side effects and toxicity are due to inhibition at M1, α-1 and 5HT receptors
- Cardiac sodium and potassium channel blockade in massive overdose

CLINICAL FEATURES:

- CNS depression
- Anticholinergic syndrome including delirium
- Significant hypotension requiring inotropes occur after massive overdose (especially with diphenhydramine), due to sodium channel blockade

MANAGEMENT:

- Resuscitation rarely required, but monitoring is advised for up to 6 hours if symptomatic
- Manage seizures and anticholinergic delirium along standard lines
- Hypotension usually responds to fluid resuscitation → if not an α-1 agonist like noradrenaline is used
- In rare event of ventricular arrhythmia → intubate/hyperventilate and administer sodium bicarbonate
- Beware urinary retention

BENZTROPINE:

FREQUENTLY ADMINISTERED TO AMELIORATE DYSKINESIA TO THOSE ON ANTIPSYCHOTICS

POTENT ANTICHOLINERGIC AGENT IN OVERDOSE

RISK ASSESSMENT:

- Any overdose likely to precipitate anticholinergic syndrome

TOXIC MECHANISM:

- Acts as an anticholinergic/antihistamine/dopamine reuptake inhibitor

CLINICAL FEATURES:

- Features are those of anticholinergic syndrome → delirium, mydriasis, blurred vision, sinus tachycardia, warm flushed/dry skin, urinary retention, ileus → lasts 12 hours to five days

MANAGEMENT:

- Supportive → benzodiazepines, fluids, IDC insertion
- Control of delirium can be challenging and may require physical restraints
- Consider physostigmine if delirium not controlled with benzos

DIPHENOXYLATE-ATROPINE:

CAUSES DELAYED ONSET OF OPIOID AND ANTICHOLINERGIC EFFECTS WHEN INGESTED BY CHILDREN, EVEN IN SMALL AMOUNTS

RISK ASSESSMENT:

- Adults much less susceptible
- Fatalities are reported in kids after repetitive or incorrect dosing
    - Acute ingestion of six or more tablets is associated with potentially lethal opioid poisoning

TOXIC MECHANISM:

- Diphenoxylate is an opioid, and atropine has anticholinergic properties
- Used as an adjunct in acute/chronic diarrhoea

TOXICOKINETICS:

- Diphenoxylate is rapidly and well absorbed following PO administration
    - Metabolized to difenoxine, which is 5 times more active than parent compound and undergoes enterohepatic circulation

CLINICAL FEATURES:

- Combined features of opioid and anticholinergic toxidromes
- OPIOID FEATURES:
    - ↓ LOC
    - Respiratory depression
    - Miosis
    - Opioid features manifest early and may recur after apparent improvement
- ANTICHOLINERGIC:
    - Delirium/agitation
    - Tachycardia, dry skin
    - Urinary retention

MANAGEMENT:

- Basic resuscitative measures ensures the survival of most
- Naloxone is indicated to reverse opioid toxicity
- Children who have ingested ≥2 tablets should be observed for 12 hours

METHOTREXATE:

THE TOXIC EFFECTS ARE EMPLOYED IN THERAPEUTIC CIRCUMSTANCES

TOXICITY NOT DESCRIBED FOLLOWING ACUTE OVERDOSE

SEVERE TOXICITY OCCURS FOLLOWING REPEATED SUPRATHERAPEUTIC DOSING

FOLINIC ACID IS USED AS AN ANTIDOTE IN SELECTED CASES

RISK ASSESSMENT:

- ACUTE OVERDOSE:
  - Toxicity not described following single acute deliberate self-ingestion
- REPEATED SUPRATHERAPEUTIC INGESTION:
  - Potentially lethal bone marrow suppression if weekly therapeutic oral dose taken on as few as THREE CONSECUTIVE DAYS
  - Patients with renal impairment/malnutrition are more susceptible to methotrexate-induced bone marrow suppression
- INTRATHECAL → potentially lethal in overdose

TOXIC MECHANISM:

- Analogue of folate → acts by competitive inhibition of dihydrofolate reductase and thymidylate synthetase, resulting in ↓d DNA/RNA synthesis, hence ↓d cell replication
- Toxicity related to inhibition of dividing cells → GIT, bone marrow, hair
- Renal and hepatic injuries are also reported

TOXICOKINETICS:

- Intestinal absorption is saturable
- Hepatic metabolism creates nephrotoxic metabolite, which accumulates at high doses
- Eliminate half life increases with dose

CLINICAL FEATURES:

- GIT, bone marrow, hepatic and renal injury
- Stomatitis is an early sign
- N+V+D common
- Pallor and fatigue indicate anaemia, which reaches a nadir at 7-14 days

INVESTIGATIONS:

- Methotrexate level and renal function
- Following acute single overdose a timed methotrexate level and renal function determines need for folinic acid
  - If folinic acid indicated, follow up methotrexate levels determine duration of therapy

MANAGEMENT:

- Resuscitation along standard lines
- Supportive care includes meticulous fluid resuscitation, management of sepsis and administration of GCSF
- In those presenting following acute overdose (<500mg or <5mg/kg in kids) → check renal function and methotrexate at ≥6hours
    - If higher ingestion → charcoal, commence folinic acid, ensure hydration, check renal function/methotrexate level
    - If renal function is normal and serum methotrexate level is below toxic threshold → no folinic acid. Follow up FBC at 7 days
    - Folinic acid indicate if methotrexate level cannot be obtained within 24 hours, the patient is symptomatic, renal function is abnormal or if methotrexate level is above toxic threshold
- FOLINIC ACID:
    - Reduced biologically active form of folic acid and is essential for DNA/RNA synthesis, when administered it bypasses methotrexate-induced inhibition of dihydrofolate reductase → restoring DNA/RNA synthesis
    - It also enhances elimination of FORMATE in methanol toxicity
    - Give 15mg orally, IM or IV every 6 hours
    - May be ceased following single acute overdose if methotrexate is below toxic threshold

QUININE:

TOXICITY CHARACTERISED BY "CINCHRONISM" → NAUSEA, VOMITING, TINNITUS, VERTIGO AND DEAFNESS

LARGER OVERDOSE MAY RESULT IN LIFE-THREATENING CARDIOTOXICITY WITH SEVERE/PERMANENT VISUAL DISTURBANCE

RISK ASSESSMENT:

- Ingestion of ≥1g usually produces some degree of cinchronism
- Cardiotoxicity and CNS disturbances predicted if ≥5g and universal if ≥10g

TOXIC MECHANISM:

- Class 1A antiarrhythmic with sodium channel and potassium rectifier channel blocking functions
- Results in prolongation of both QRS and QT intervals
- In overdose, quinine is directly toxic to the retina
- Also stimulate pancreatic insulin release similar to sulfonylureas

CLINICAL FEATURES:

- CINCHRONISM:
  - Tinnitus, vertigo, N+V, hearing disturbance
- CARDIOVASCULAR:
  - Hypotension, sinus tachycardia, QRS widening and prolongation of QT/PR intervals
  - Wide-complex tachycardia and torsades are reported
    - Occur within 8 hours and resolve as blood levels fall
- CNS:
  - Drowsiness and confusion
  - Coma/seizures rare
- EYES:
  - Not apparent to 6-8 hours
  - Blurring, colour disturbance, pupillary dilation
  - Complete blindness in severe cases
  - Permanent residual deficits

INVESTIGATIONS:

- Blood quinine levels correlate well with toxicity (>10mg/L at six hours associated with CVS toxicity)

MANAGEMENT:

- COMA → Intubation and ventilation
- WIDE-COMPLEX ARRHYTHMIA:
  - Immediate intubation/hyperventilation
  - Serum alkalinisation
- TORSADES:
  - Correct hypoxia/hypokalaemia
  - Magnesium sulphate 10mmol or 0.05mmol/kg

    - Overdrive pacing if HR ≤100
- SEIZURES → benzodiazepines
- Administer charcoal to all those awake and able to drink it
    - MDAC to all those who have ingested ≥5g

THYROXINE:

OVERDOSE IS RARELY SUFFICIENT TO PRODUCE SIGNIFICANT SYMPTOMS OF HYPERTHYROIDISM → IF THEY DO OCCUR THEY ARE MILD, DELAYED AND MAY LAST 2 WEEKS

RISK ASSESSMENT:

- Majority are asymptomatic or experience mild-moderate symptoms of hyperthyroidism 2-7 days later → not expected unless ≥10mg of thyroxine ingested
- The elderly and patients with CVS comorbidities are at increased risk of complications
- Severe toxicity more likely following chronic abuse of thyroid hormones

TOXIC MECHANISM:

- T4 converted to T3 → binds to nucleus and influences multiple metabolic processes

TOXICOKINETICS:

- Oral bioavailability is high
- Maximal effects are not attained until 1-3 weeks
- Thyroxine is extensively distributed and BOUND COMPLETELY TO PROTEINS
- Elimination half-life is 6-7 days

CLINICAL FEATURES:

- When symptoms do occur, they do not occur until at least 24 hours but may last for up to 2 weeks
- Signs and symptoms are those of ADRENERGIC STIMULATION:
    - Fever, agitation, sweating
    - Tachycardia, ↑BP, diarrhoea and vomiting
    - Chronic ingestion → causes severe illness characterised by angina, MI, myocarditis, ventricular and atrial dysrhythmia, LVH, thyrotoxicosis and thyroid storm

MANAGEMENT:

- Beta blockers rapidly control the sympathomimetic symptoms of thyroid excess → PROPRANOLOL 10-40MG EVERY 6 HOURS
    - Calcium channel blockers if beta blockers contraindicated (diltiazem 60-180mg Q8H.
- Consider charcoal to those ingesting ≥10mg
- Thyroxine may be restarted after a week if indicated