Poisoning & Drug Overdose

**Def’n:** overdose: exposure to an amount of a substance likely to produce untoward effects in the individual

1. ~ 20% of overdoses are at any significant risk
2. ≥ 50% of suicidal overdoses are mixed, frequently including ethanol

- **Age Distribution**
  
a. 25% < 5 years → usually accidental
b. 50% ~ 5-30 years → F:M > 2:1
c. 25% > 30 years

**NB:** overall mortality ~ 0.5% 1:200

- **General Principals**
  
**NB:** three basic management principles

1. **resuscitation** - ABC
2. **diagnosis**
   
   i. history and examination
   
   ii. investigation
      
      - E.C&U, FBE, AGA's, osmolality & osmolar gap
      - blood & urine drug screening
      - CXR
   
   iii. gastric lavage *if appropriate
3. **treatment**
   
   i. drug manipulation
      
      - general
         
         - emetics, lavage, cathartics
         - dilution
         - activated charcoal
      
      - specific
         
         - antidotes
         - forced diuresis ± pH modification
         - altered drug metabolism (methanol/ethanol)
         - haemoperfusion, dialysis, plasmapheresis
   
   ii. complications
      
      - airway obstruction, respiratory failure
      - hypoglycaemia, metabolic derangement
      - seizures
      - arrhythmias, hypotension
      - NB: CVS, CNS, RS, temperature
ICU Admission Criteria

1. requirement for intubation
   i. ventilatory failure
   ii. airway protection / maintenance
   iii. therapy → induced hypcapnia/alkalosis

2. CNS
   i. uncontrolled seizures
   ii. coma, GCS < 9

3. CVS
   i. arrhythmias
   ii. AV block, prolonged QRS
   iii. hypotension requiring CVS support

4. large ingested dose
   • ± high blood levels predictive of poor outcome

Serum Levels Predictive of Outcome

<table>
<thead>
<tr>
<th>Essential</th>
<th>Useful</th>
</tr>
</thead>
<tbody>
<tr>
<td>paracetamol</td>
<td>lithium</td>
</tr>
<tr>
<td>theophylline</td>
<td>barbiturates</td>
</tr>
<tr>
<td>salicylates</td>
<td>phenytoin</td>
</tr>
<tr>
<td>alcohols</td>
<td>iron</td>
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</tbody>
</table>
Drug Removal General

- **Emetics**
  - Ipecac syrup 10-30 ml, apomorphine, pharyngeal stimulation
  - must have *awake* patient with gag reflex present
  - use is controversial, there being *no direct evidence* that these agents improve morbidity or mortality associated with drug overdosage
  - **absolute contraindications**
    1. unprotected airway
    2. strong acids / alkalis
    3. petroleum derivatives

  *NB:* generally *not recommended* as impedes the subsequent use of activated charcoal, which has been shown to improve clearance

- **Gastric Lavage**
  - exchange volumes ≤ 1 ml/kg *greater volumes promoting gastric emptying*
  - useful early after ingestion ≤ 1 hr
  - doubtful efficacy after this but may be useful for slow release preparations and slowly absorbed agents, eg. tricyclics
  - **indications** where large dose within 24 hours,
    1. analgesics - paracetamol, aspirin, dextropropoxyphene
    2. antidepressants - tricyclics
    3. alcohols - methanol, ethylene glycol
    4. others - theophylline, digoxin

  - **contraindications**
    1. unprotected airway
    2. strong acids / alkalis → risk of *oesophageal perforation*
    3. petroleum derivatives
      - most of these are relatively *nontoxic* following ingestion
      - aspiration of volumes ~ 1 ml may produce *severe pneumonitis*
- **Activated Charcoal**
  - 50-100g immediately following lavage, then 50g q4h
  - repeated doses effective for,
    1. benzodiazepines, barbiturates, narcotics
    2. tricyclics, phenothiazines
    3. salicylates
    4. theophylline
    5. digoxin, digitoxin
    6. atropine
    7. some heavy metals

  - relatively ineffective for,
    1. most heavy metals - Li⁺, Fe²⁺, boron
    2. pesticides - organophosphonates, DDT, carbamates
    3. alcohols - ethanol, methanol, ethylene glycol, isopropyl alcohol
    4. cyanide
    5. strong acids/alkalis

- **Contraindications**
  1. unprotected airway
  2. strong acids / alkalis
  3. petroleum derivatives

- **Cathartics**
  - sorbitol 70% with charcoal
  - use with first dose, subsequent use doubtful

- **Drug Removal Specific**
  1. forced diuresis - acid or alkaline
  2. altered drug metabolism - N-acetylcysteine, thiosulphate, ethanol
  3. antidotes - chelating agents, antibodies
  4. extracorporeal techniques - haemodyalisis, haemoperfusion
      - plasmapheresis, exchange transfusion
Activated Charcoal

a. non-specific absorbent - drugs, toxins, gases
   - especially alkaloids and other bases
b. fine black powder, odourless, tasteless
c. insoluble in water or lipids
d. large surface area & absorptive capability

- prepared from vegetable matter, eg. sawdust, peat, coconut shells
- treated with "activators", CO\textsubscript{2}, steam, strong acids
- contains 15% H\textsubscript{2}O, therefore stored airtight
- absorptive capacity,
  a. per gram charcoal ~ 100-1000 mg (ie. ~ 10-100% by weight)
  b. optimal charcoal:toxin ratio ~ 8:1 (calculated for salicylates)

- increases systemic clearance of drugs through the GIT,
  1. interrupted enterohepatic circulation
  2. enteric "dialysis"

<table>
<thead>
<tr>
<th>Repeated doses effective</th>
<th>Charcoal is ineffective</th>
</tr>
</thead>
<tbody>
<tr>
<td>• benzodiazepines, barbiturates</td>
<td>• alcohols - ethanol, methanol</td>
</tr>
<tr>
<td>• opioids</td>
<td>• ethylene glycol, isopropyl</td>
</tr>
<tr>
<td>• tricyclics, phenothiazines</td>
<td>• pesticides - organophosphates</td>
</tr>
<tr>
<td>• salicylates</td>
<td>• DDT, carbamates</td>
</tr>
<tr>
<td>• theophylline</td>
<td>• heavy metals - Li, Fe, Hg</td>
</tr>
<tr>
<td>• digoxin, digitoxin</td>
<td>• Cu, Au, Bo</td>
</tr>
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<td>• cyanide</td>
</tr>
<tr>
<td>• some heavy metals</td>
<td>• strong acids &amp; bases</td>
</tr>
<tr>
<td></td>
<td>• paraquat\textsuperscript{1}</td>
</tr>
</tbody>
</table>

\textsuperscript{1} one study showing equally efficacious to Fuller's earth

- contraindications include,
  a. inability to protect the airway
  b. strong acids & bases (caustics)
     • risk of oesophageal perforation with passage of the gastric tube
  c. petroleum derivatives
     • risk of aspiration & severe chemical pneumonitis
Fuller's Earth
- specific antidote for paraquat, also used in chemical warfare decontamination
- paraquat neutralised by contact with soil & only 5-10% absorbed in 24 hrs
  1. initial dose ~ 30% solution, 300 g/l
     + 200 ml of 20% mannitol
  2. subsequently q2h ~ 15% solution, 150 g/l
     + mannitol q4h

Enhanced Elimination

Forced Diuresis

- acid diuresis → phencyclidine and amphetamine overdose
- alkaline diuresis → salicylate and barbiturate overdose

- unless managed carefully, potential for fluid overload & electrolyte abnormalities
- sedation is preferred for the former, haemodialysis for salicylates and repeat charcoal for barbiturates

<table>
<thead>
<tr>
<th>pH Dependent Renal Excretion</th>
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<tbody>
<tr>
<td>Weak Bases</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>amphetamine</td>
</tr>
<tr>
<td>ephedrine</td>
</tr>
<tr>
<td>phencyclidine</td>
</tr>
<tr>
<td>quinidine</td>
</tr>
<tr>
<td>tricyclics</td>
</tr>
</tbody>
</table>

optimal urine pH ≤ 5.5
- ascorbic acid 0.5-2.0 g ó/IV
- NH₄Cl 0.1 g ó/IV

optimal urine pH ≥ 7.5
- bicarbonate 1-2 mmol/kg
- acetazolamide 500 mg

Peritoneal Dialysis
- effectively no place in management of drug overdose
Haemodialysis

- indications for use include severe poisoning with,
  1. salicylate
  2. lithium
  3. alcohols - isopropranolol, methanol, ethylene glycol
  4. phenobarbitone

- Charcoal Haemoperfusion

  NB: largely unproven form of therapy, rarely recommended

- filter composed of activated charcoal granules covered with cellulose or cellophane
- large active surface area ~ 1000 m²/g
- effective for lipid soluble molecules, where plasma clearance may approach circuit plasma flow
- duration for drug overdose is ~ 4-8 hrs, or until symptoms are controlled
- for hepatic failure ~ 4-8 hrs/day
- recently developed polystyrene resins (Amberlite XAD-4) also have high affinity for lipid soluble compounds and have a clearance ~ 2x charcoal

- Clinical Uses

  a. hepatic failure, encephalopathy
     - randomised studies from King’s group → no additional benefit in survival
  b. drug overdose
    - often recommended for
      - theophylline
      - methotrexate
      - disopyramide
    - other drugs
      - barbiturates
      - ethanol, methanol
      - lithium
      - paraquat
      - salicylates (dialysis better)
  i. theophylline
    - acute \( \geq 500 \mu mol/l \geq 100 \mu g/ml \)
    - chronic \( \geq 200-300 \mu mol/l \geq 40-60 \mu g/ml \)
    - severe refractory seizures, arrhythmias
    - severe cardiac, respiratory, or hepatic disease \( \geq 40 \mu g/ml \)
  ii. salicylates \( \geq 0.5-1.0 \text{ mg/ml} \)
    - severe intoxication and unable to promote diuresis and alkalisation
Complications

a. those of central line insertion
b. those of anticoagulation
c. thrombocytopenia
d. haemolysis
e. electrolyte disturbances
f. pyrogenic reactions
g. time delay for commencement - severe toxicity of paraquat
h. hyperglycaemia - primed with dextrose

Toxicological Screens

a. spot urine tests
   • colour tests
   • rapid < 2 hrs, cheap
   • qualitative, non-specific
   • not for initial assay
   • use to confirm prior to more sensitive/specific assay
b. thin layer chromatography
   • rapid ~ 2-4 hrs, qualitative
   • interference common
   • urine or plasma
   • not useful for volatiles, alcohols, metals, salicylates, cyanide
c. gas and high pressure chromatography
   • useful for any specimen
   • not useful for initial screen
   • more specific & quantitative
d. enzyme immunoassay
   • measures rate of conversion NAD/NADH with photometry
   • more expensive & specific
   • useful for conformation
e. mass spectometry
   • highly specific/sensitive
   • qualitative & quantitative
   • expensive
**Alcohols**

- the various alcohols are metabolised by *alcohol dehydrogenase* and *aldehyde dehydrogenase*

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Alcoholic Dehydrogenase</th>
<th>Aldehyde Dehydrogenase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>→ Acetaldehyde</td>
<td>→ Acetate</td>
</tr>
<tr>
<td>Methanol</td>
<td>→ Formaldehyde</td>
<td>→ Formate</td>
</tr>
<tr>
<td>Ethylene Glycol</td>
<td>→ Glycoaldehyde</td>
<td>→ Glycolate</td>
</tr>
<tr>
<td>Isopropanolol</td>
<td>→ Acetone</td>
<td>→</td>
</tr>
<tr>
<td>Paraldehyde</td>
<td>→ Acetaldehyde</td>
<td>→ Acetate</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>→ Formate</td>
<td></td>
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</tbody>
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- **Ethanol**
  - hepatocyte alcohol dehydrogenase metabolises ETOH at a constant rate ~ 7-8 g/hr
  - this reduces NAD⁺ → NADH + H⁺ and increases the lactate:pyruvate ratio
  - clinical effects correlate with blood levels,
    - a. 0.5-1.5 g/l → ataxia, slurring of speech, drowsiness
    - b. 1.5-3.0 g/l → stupor
    - c. > 3.0 g/l → coma
    - d. fatal dose ~ 320 g, which may produce blood levels ≤ 7.6 g/l
  - management is largely supportive

- **Methanol**
  - methanol itself is non-toxic, however its metabolite *formic acid* produces,
    1. profound metabolic acidosis
    2. inhibits cytochrome oxidase → lactic acidosis
    3. retinal damage ± blindness
  - as little as 4 ml may lead to blindness, 30-250 ml may be fatal
  - the clinical features of formaldehyde poisoning are essentially identical
  - not reproducible in animal models as most readily metabolise formate to CO₂ & H₂O
  - later discovered this pathway is also present in humans but requires ↑ folinic acid
  - ∴ in suspected methanol O/D → Rx with folinic acid, then folate
• clinical features,
  1. often asymptomatic for 12-24 hrs
  2. nausea, vomiting, abdominal pain
  3. headaches, disorientation, vertigo
  4. blurring of vision, blindness > 24-72 hrs
     - may be permanent
  5. fixed, dilated pupils, coma death

• biochemistry,
  1. profound metabolic acidosis
     • often severe for clinical appearance
  2. high osmolar gap
  3. raised serum methanol

• ineffective therapy includes,
  1. gastric lavage - absorption is rapid & usually complete by presentation
  2. activated charcoal

• specific therapy includes,
  1. haemodialysis
     • indicated if > 30 ml ingested
     - serum methanol > 0.3 g/l (0.03%)
     - severe metabolic acidosis
     • high levels may be seen in chronic alcoholics (≥ 1.6 g/l) without signs of intoxication, due to ethanol inhibition of methanol metabolism
     • dialysis should be continued until plasma levels < 0.1 g/l
  2. IV ethanol
     • alcohol dehydrogenase has ~ 20x the affinity for ethanol cf. methanol
     • acts as a competitive substrate at plasma levels ≥ 1.5 g/l
  3. 4-methylpyrazone
     • inhibits action of alcohol dehydrogenase, :: formate production
     • 10 mg/kg / 250 ml N.Saline over 45 mins, q12h
  4. folinic acid
     • theoretically may increase the metabolism of formic acid, however doses required for significant effects are > 2000x normal plasma levels
  5. fluids & electrolytes
     i. acid-base status, osmolar gap
     ii. hyperkalaemia
     • monitor q2h early in treatment & treat in standard manner
Ethylene Glycol

- metabolised to glycolic acid → glyoxylic acid & oxalic acid
- the former is converted to glycine and enters the citric acid cycle, with thiamine as a cofactor
- the later is excreted through the kidney as calcium oxalate
- this may precipitate in the proximal tubules and produce acute renal failure
- clinical features,
  1. often asymptomatic for 8-12 hrs
  2. nausea and vomiting
  3. headache, visual blurring, nystagmus
  4. stupor, seizures & coma
  5. pulmonary oedema
  6. cardiac arrhythmias
  7. acute renal failure > 48 hrs post-ingestion

- biochemical findings,
  1. high anion gap metabolic acidosis
  2. high osmolar gap
  3. hypocalcaemia
  4. hyperoxaluria, calcium oxalate crystals in the urine

- management,
  1. fluids & electrolytes
     i. acid-base status, osmolar gap
     ii. hyperkalaemia
     iii. hyponatraemia
  2. alkaline diuresis
     • theoretically to reduce calcium oxalate precipitation and ARF
     • N.Saline + mannitol ± bicarbonate ± acetazolamide
  3. haemodialysis
  4. IV ethanol
     • effective at levels ~ 1.3-2.0 g/l
     • increases the elimination half-life from 3 hrs to ~ 17 hrs
     • recommended with > 0.5 g/l serum level
     • > 0.25 g/l in symptomatic patients
  5. 4-methylpyrazone
     • 10 mg/kg / 250 ml N.Saline over 45 mins, q12h
     • inhibition of alcohol dehydrogenase
Antihistamines

- produce a mixture of.
  1. CNS excitatory & depressant effects
     - central *anticholinergic* action - see later
  2. myocardial depression
     - *quinidine*-like effects

- clinical features,
  1. nausea, vomiting, dry mouth
  2. headache, drowsiness
  3. agitation, tremors, ataxia, delerium, halucinations
  4. seizures, coma
  5. hyperthermia
  6. tachycardia, hypotension, pulmonary oedema, shock

- management,
  1. ABC
  2. IVT
  3. gastric lavage
  4. repeated oral *charcoal*
  5. physostigmine
     - may reverse CNS effects, however use is controversial
  6. cooling if hyperthermic
Carbamazepine

- structurally related to tricyclics, however toxicity is not similar

.
Carbon Monoxide Poisoning

- **Toxicity**
  
a. avid binding of CO to Hb $\sim 250\times$ that for O$_2$ $\Rightarrow$ L-shift of HbO$_2$ curve
  b. vasodilatation
  c. stimulation of chemoreceptors
  d. cellular hypoxia
    - CO also binds to *cytochrome oxidase*, however affinity of O$_2$ $\sim 8\times$ that of CO
  
  **NB:** complete clinical picture *not* explained by above, effects may result from action as a *cellular messenger* cf. NO

- **Severity**
  
a. *mild* $< 30\%$ COHb
    - symptoms - headache, nausea, vomiting
    - signs - vasodilatation ($>10\%$)
      - no neurologic or CVS dysfunction
    - $R_x$ - admit if COHb $> 20\%$
      - F$_2$O$_2$ = 100% until COHb $< 5\%$
      - symptomatic therapy
      - CVS monitoring if pre-existing disease
  b. *moderate* $\sim 30\text{-}40\%$ COHb
    - symptoms - headache, nausea, vomiting
      - fatigue, drowsiness, weakness
    - signs - vasodilatation
      - *no* neurologic or CVS dysfunction
      - dyspnoea on exertion
    - $R_x$ - admit
      - F$_2$O$_2$ = 100% until COHb $< 5\%$
      - symptomatic therapy
      - CVS & acid-base monitoring
  c. *severe* $> 40\%$ COHb or CVS/CNS dysfunction
    - symptoms - above plus dyspnoea, confusion
    - signs *neurologic ± CVS dysfunction
      - tachycardia, tachypnoea
      - $> 50\%$ respiratory failure, seizures, coma
      - $> 70\%$ rapidly fatal
    - $R_x$ - F$_2$O$_2$ = 100%
      - *hyperbaric* O$_2$ if available
      - CVS & acid-base monitoring
### Blood COHb Clinical Features

<table>
<thead>
<tr>
<th>Blood COHb</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5%</td>
<td>• normal</td>
</tr>
<tr>
<td>5-10%</td>
<td>• smokers</td>
</tr>
<tr>
<td>10-20%</td>
<td>• headache, mild dyspnoea</td>
</tr>
</tbody>
</table>
| **20-30%** | • increasing headache, dyspnoea  
  • **admit** to hospital |
| 30-40%     | • further increasing headache, dyspnoea  
  • irritability, confusion  
  • nausea & vomiting |
| **> 40%**  | • visual disturbance, severe headache  
  • tachycardia, tachypnoea, dyspnoea |
| 40-50%     | • cerebral hypoxia, syncope |
| 50-60%     | • coma, convulsions, respiratory failure |
| 70-80%     | • rapidly fatal |

#### Delayed Complications

1. diffuse cerebral demyelination  
   • gradual neurological deterioration with *polyneuropathy*
2. dementia
3. parkinsonism
4. late coma ~ 1-4 weeks following initial hypoxic insult

**NB:** frequency ~ 2-10% of patients

*N-acetyl-cysteine*, may reduce the frequency of late onset complications

#### Management

- the elimination *half-life* of COHb,
  a. room air $t_{\text{half}} \sim 4$ hrs
  b. $F_1O_2 = 100\%$ $t_{\text{half}} \sim 40-90$ min
  c. hyperbaric $O_2$ $t_{\text{half}} \sim 30$ min (2.0 Atm.)

**NB:** if there is no impairment of *consciousness*, then hyperbaric $O_2$ is not indicated
Central Anticholinergic Syndrome

**NB:** toxic dose for *atropine*  
child ~ 10 mg  
adult ~ 100 mg  
* but wide variability

- commonly involved drugs,
  a. atropine  
  b. hyoscine  
  c. propantheline  
  d. methylbromide  
  e. benzhexol  
  f. benztropine - eg. accidental ingestion  
  g. anti-ACh effects of *tricyclics*, or antihistamines

- **Clinical Features**
  a. fixed *dilated pupils* - ↑ IOP  
  b. dry mouth  
  c. flushed, dry skin - unable to sweat  
  d. cardiovascular - tachycardia, tachyarrhythmias  
  - hyper, then *hypotension*  
  e. CNS - agitation, delerium, excitement  
  - disorientation, hallucinations  
  - *hyperpyrexia*, disordered thermoregulation  
  - seizures, coma  
  f. GIT - reflux, vomiting  
  - gastric stasis, ileus  
  g. GUS - urinary retention  
  h. respiratory - tachypnoea, stertorous respiration

**NB:** ΔΔ use of *cholinergic eyedrops* for D\textsubscript{x}  
no miosis \rightarrow anti-ACh  
miosis \rightarrow neurologic

- **Treatment**
  a. ABC - supportive  
  b. physostigmine 1 mg in cases of coma (controversial)
Chloral Hydrate

- drug levels,
  a. therapeutic 20 mg/kg
  b. toxic 100-150 mg/kg
  c. lethal > 10 g

- a halogenated hydrocarbon $\rightarrow$ CCl$_3$ + CH(OH)$_2$
- rapid GIT absorption
- high first pass metabolism, rapidly metabolised to *trichlorethanol*
- enzyme inducer, metabolism increased with ethanol use

**NB:** tolerance, dependence, and withdrawal syndromes are common

### Features

a. cardiovascular - malignant and resistant ventricular arrhythmias, SVT
   - hypotension
   - sensitization of the myocardium to catecholamines
   - ≤ 30% of severe cases have SVT or ventricular tachyarhythmias

b. neurological - profound respiratory depression
   ± coma

c. GIT - irritation
   - *hepatitis*

### Treatment

a. supportive
b. gastric aspiration and lavage
c. repeated charcoal administration ± mannitol NG
   - no data for repeated charcoal
d. $\beta$-adrenergic blockade for arrhythmias
   - propranolol ~ 0.5 mg IV + 1-2 mg/hr
   - esmolol ~ 0.5 mg/kg stat, rpt x1
   - lignocaine
   - amiodarone
e. charcoal haemoperfusion
Colchicine Poisoning

- occurs within 3-6 hrs of toxic ingestion and may be fatal within 24 hrs
  a. toxic dose $\geq$ 6-10 mg
  b. fatal dose $\geq$ 20 mg

- side-effects of normal dosage include,
  a. nausea, vomiting, diarrhoea
  b. agranulocytosis, thrombocytopaenia
  c. impaired $\text{B}_{12}$ metabolism

■ Toxic Features

  a. GIT - mouth pain, sore throat, nausea, vomiting
    - profuse watery diarrhoea, abdominal pain
    - GIT haemorrhage, colic, tenesmus
  b. skin - rashes, toxic epithelial necrolysis
  c. renal - anuria, bladder spasm, ? toxic nephritis
  d. neurological - peripheral neuritis, ascending paralysis
    - convulsions, respiratory arrest
  e. cardiac - hypotension

■ Treatment

  a. respiratory and cardiovascular support - ABC
  b. gastric lavage, repeated activated charcoal, and cathartics
  c. morphine for cramps, diarrhoea etc.
  d. ?? $\text{B}_{12}$ / folinic acid
Cyanide Toxicity

- CN$^-$ combines with cytochrome oxidase Fe$^{+++}$ effectively paralysing cellular respiration
- lethal dose of hydrocyanic acid ~ 50 mg, cf. ingested cyanide salt ~ 250 mg
- poisoning may also occur with amygadaline toxicity, a cyanogenic glycoside found in the kernels of almonds, apricots, peaches & plums
  a. large doses are associated with rapid death, usually within 1-15 mins
  b. moderate doses usually result in death within 4 hrs

Clinical Features

a. tachypnoea, high $V_M$

b. agitation, confusion, convulsions, coma

c. vomiting

d. hypotension, tachycardia

e. breath smells of "bitter almonds"

Metabolism

- CN$^-$ ions have 4 fates,
  1. 60-70% enzymatically converted $\rightarrow$ thiocyanate
     - catalyzed by rhodanese in the liver and kidneys
     - requires thiosulphate and B$_{12}$ as cofactors
     - rate limiting factor is the availability of endogenous thiosulphate
  2. combination with MetHb $\rightarrow$ cyanmethaemoglobin
  3. combination with hydroxocobalamin $\rightarrow$ cyanocobalamin
  4. combination with tissue cytochrome oxidase $\rightarrow$ toxicity
- **Treatment**
  - aimed at the formation of MetHb and detoxification of CN⁻
    1. supportive measures
      i. *oxygen* should be administered
      ii. potentiates the effectiveness of sodium nitrite & thiosulphate (? mechanism)
      iii. removal of contaminated clothing / washing skin
    2. *dicobalt edetate*
      - chelating agent with higher affinity for CN⁻ than cytochrome oxidase
      - give in 2 divided 300 mg doses, with 50 ml 50% dextrose between doses, due to risk of *angioneurotic oedema*
      - only use if *definite* history of cyanide exposure
    3. sodium thiosulphate ~ 150 mg/kg over 15 mins
      → SH⁻ ions necessary for the formation of thiocyanate
    4. sodium nitrite ~ 5 mg/kg over 3-4 mins
      - reduces HbO₂ to *MetHb*
      - competes with cytochrome oxidase for CN⁻ ions
      *aim* ~ 25% [metHb] is optimal for *Rx*
    5. amyl nitrite inhalation - achieves ~ 5% MetHb which is inadequate
      - may however be used as interim measure in emergency
    6. hydroxocobalamin ~ 5-10 mg slowly IV → *cyanocobalamin*
      - LIGW states required dose ~ 50 mg/kg (~ 3000 ampoules)
      - not effective in acute toxicity cf. above agents

**NB:** normal metabolism will remove ~ 50% of CN⁻ within 1 hour

.: if patient is stable, conscious & oriented, observation for 1-2 hrs is appropriate
Digoxin Toxicity

*Def'n:* toxic level \( \geq 2.6 \text{ nmol/l} \) (> 2.0 µg/l)

- **Predisposing Factors**
  
  a. increased *cardiac sensitivity*
    
    i. acute hypoxia
    
    ii. electrolyte disturbances
      
      - ↓ K⁺, Mg⁺⁺ → altered receptor binding
      
      - severe ↑ K⁺, Ca⁺⁺
    
    iii. respiratory alkalosis
    
    iv. myocardial ischaemia & ? AMI
    
    v. increased sympathetic tone
    
    vi. elderly
    
    vii. DC cardioversion
  
  b. toxic *serum levels*
    
    i. overdose - accidental, iatrogenic
    
    ii. renal failure
    
    iii. drug interactions
      
      - quinidine, quinine
      
      - verapamil
      
      - amiodarone
      
      - diuretics - K⁺-wasting
      
      - spironolactone
      
      - erythromycin, tetracycline - ↓'d bacterial metabolism

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### Clinical Features

<table>
<thead>
<tr>
<th>Acute Toxicity</th>
<th>Chronic Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>• arrhythmias</td>
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</tr>
<tr>
<td>• nausea &amp; vomiting</td>
<td>• anorexia, nausea, vomiting</td>
</tr>
<tr>
<td>• confusion, coma, seizures</td>
<td>• visual disturbance</td>
</tr>
<tr>
<td>• hyperkalaemia</td>
<td>• confusion</td>
</tr>
</tbody>
</table>
the incidence of arrhythmias is dose dependent,

a. 2.2 nmol/l ~ 10%
b. 3.3 nmol/l ~ 50%
c. 4.4 nmol/l ~ 90%

NB: → ventricular ectopy, ventricular bigeminy, ventricular tachycardia, bidirectional ventricular tachycardia, increased atrial rate, conduction blockade, especially AV

- **Mechanism of Toxicity**
  
a. excessive Na\(^+\)/K\(^+\)-ATPase inhibition →
   - hyperkalaemia
   - increased ICF Ca\(^{++}\) → conduction block
   - afterdepolarisations
   - decreased ICF K\(^+\)
  
b. increase in central vagal & sympathetic tone
  
c. stimulation of area postrema → GIT effects

- **Management**
  
a. supportive measures are usually sufficient for - sinus bradycardia
   - PAT
   - junctional tachycardia
  
b. atropine or ventricular pacing for - SA or AV block
   - severe sinus bradycardia
  
c. phenytoin, lignocaine, or Fab fragments for - PVC's, ventricular bigeminy
   - bidirectional VT, VT, VF
  
d. glucose/insulin/HCO\(_3^-\) for - hyperkalaemia
  
e. Fab fragments

  - Fab dose (mg) ~ ingested dose (mg) x 67 *acute
  - Fab dose (mg) ~ serum level (nmol/l) x 3 x wt. *chronic
  - ingested dose ~ level (nmol/l) x wt. x 5.6(l/kg) x 0.0078
  
f. decreased GIT absorption

  i. **activated charcoal** or cholestyramine ↓ enterohepatic circulation
  
  ii. emesis, lavage for acute ingestion ? maybe

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**Digoxin Antibodies**

- purified digoxin specific antibody derived from sheep, cost ~ $110 / 40 mg
- cleaved to leave the F_{ab} fragment \( \rightarrow \) **less immunogenic**
- rapid, extensive distribution into the ECF
- rapid renal elimination of Ab-digoxin complexes
- produces control of,
  a. GIT symptoms \( \sim \) immediate
  b. bradyarrhythmias \( \sim \) 30-60 min
  c. hyperkalaemia \( \sim \) 60 min
  d. tachyarrhythmias \( \sim \) 4 hrs

- criteria for use in digoxin toxicity,
  1. life-threatening toxicity
  2. failed conventional therapy
  3. negative skin test for hypersensitivity to Ab

- complications occur \( \leq 1\% \) and include,
  1. hypersensitivity
  2. skin rash, urticaria
  3. angioneurotic oedema
  4. serum sickness
Heavy Metal Intoxication

**Iron Poisoning**

- elemental iron content of principal preparations are,
  
  a. gluconates ~ 12%
  
  b. sulphates ~ 20%
  
  c. fumarate ~ 33%

- ingestions are described as,
  
  1. nontoxic < 20 mg/kg (≤ 1.5g / 70 kg elemental iron)
  2. mild ~ 20-60 mg/kg
  3. severe > 60 mg/kg

  *NB: serum levels > 60 µmol/l are usually associated with toxicity (N: 13-32 µmol/l)*

- poisoning occurs frequently in paediatric age groups
- clinical features relate to direct *corrosive* properties, and are divided into 4 stages
  
  1. 0-6 hrs post-ingestion
    
    - nausea, vomiting, abdominal pain, diarrhoea
    
    - *haemorrhagic gastritis*, intestinal necrosis, perforation & peritonitis
    
    - hypotension, hypovolaemia & haemoconcentration
  2. 6-12 hrs post-ingestion
    
    - often clinically appear to be improving and severity of overdose underestimated
  3. 12-24 hrs post-ingestion
    
    - *systemic signs* of toxicity appear
    
    - metabolic acidosis, hepatic failure, renal failure, shock
    
    - fever, seizures, coma
    
    - haemorrhagic complications
  4. 1-2 weeks hrs post-ingestion
    
    - intestinal scarring & obstruction

- management,
  
  1. supportive measures
  2. *desferrioxamine*
    
    - iron-specific chelating agent → 1g binds ~ 85 mg elemental iron
    
    - administered both *enterally*, to reduce absorption, and *parenterally* to complex circulating iron, which is then excreted via the kidney
    
    - gastric lavage ~ 2g/l water
      
      + 5g / 50 ml post-lavage
    
    - IV dose for severe toxicity ~ 5 mg/kg/hr (350 mg/70 kg/hr)
      
      ≤ 80 mg/kg/day maximum
**Barium**

- **severe rapid hypokalaemia ± hypomagnesaemia**
  - reduced membrane K-permeability by direct **channel blockade**
- **GIT** - nausea, vomiting & diarrhoea
- **NMJ / CNS** - muscle **fasciculations**
  - seizures, tremor, paralysis, coma
  - can initiate or potentiate synaptic transmission
- **CVS** - arrhythmias, bradycardia, CCF

**NB:** Rx  
Gastric aspiration and lavage  
Dimercaprol  
Acid diuresis  
Haemodialysis for severe intoxication

**Copper**

- **GIT** - profuse vomiting, diarrhoea  
  - oesophagitis, gastritis, mucosal haemorrhage  
  - hepatic necrosis, haemolysis
- **CNS** - convulsions, coma

**NB:** Rx  
Gastric aspiration and lavage  
Demulcent (milk, paraffin)  
Analgesics  
Penicillamine 2g/day or Na+/Ca++-EDTA

**Gold**

- **skin** - pruritis, rashes, contact dermatitis, photosensitivity, purpura
- **GIT** - stomatitis, colitis, toxic hepatitis
- **Haem** - thrombocytopenia, aplastic anaemia, agranulocytosis
- **GUS** - haematuria, proteinuria, nephrotic syndrome
- **CNS** - peripheral neuritis, encephalitis

**NB:** Rx  
Gastric aspiration and lavage  
Dimercaprol 3-5mg/kg q4h IM  
N-acetylcysteine IV (proven *in vitro* chelator)
**Lead**

a. **GIT** - thirst, metallic taste  
   - burning abdominal pain, V&D, melaena

b. **CVS** - hypotension, oliguria, shock

c. **chronic** - anaemia, *basophilic stipling of RBCs*  
   - abdominal pain, constipation  
   - *blue gum line, lead-line on X Rays*  
   - convulsions, encephalopathy, dementia, neuropathy

*NB:* $R_x$ gastric aspiration and lavage  
$NaHSO_4$ 30g, both cathartic and inactivator  
chelators Dimercaprol 3-5mg/kg q4h IM  
Penicillamine or $Na^+/Ca^{++}$-EDTA

**Arsenic**

a. **GIT** - severe gastroenteritis, NV&D which may be bloody  
   - severe abdominal pain  
   - hepatic failure at 1-3 days

b. **CVS**  
   i. **acute** - hypotension from hypovolaemia, fluid loss  
      - haemolysis
   ii. **chronic** - CCF and arrhythmias

c. **CNS**  
   i. **acute** - seizures & coma
   ii. **chronic** *predominant form in chronic toxicity*  
      - headache, dizziness, cramps, paralysis

d. **GUS** - renal failure at 1-3 days

e. **MSS** - Mees' lines in nails, hyperpigmentation  
   - palmar/plantar hyperkeratosis, superficial BCC's

*NB:* $R_x$ cf. lead intoxication

**Manganese**

a. lethargy

b. Parkinsonian features, coma

*NB:* $R_x$ gastric aspiration and lavage  
?? EDTA ?? Levodopa
## Mercury

a. rapidly absorbed through the skin and mucosa  
b. GIT  
   - thirst, metallic taste  
   - severe abdominal pain, vomiting, bloody diarrhoea, colitis  
   - ashen discoulouration of the mouth, stomatitis  
c. CVS  
   - hypovolaemic shock  
d. chronic  
   - GIT above & loose teeth, salivation, blue gums  
   - tremor, weakness, mental change  
   - dermatitis, acrodynia  
   - anaemia  
   - nephritis

**NB:**  
RX  
Gastric aspiration and lavage  
Dimercaprol 5mg/kg in first 2 hrs, then 2.5mg/kg/d for 10/7  
Acetylsalicylic acid 250 mg qid

## Silver

a. GIT  
   - mouth pain, salivation, diarrhoea, vomiting  
b. CNS  
   - convulsions, coma  
c. blue-black skin discoulouration  
d. methaemoglobinemia

**NB:**  
RX  
Gastric aspiration and lavage  
NaHSO₄ 30g, both cathartic and inactivator

### Antidotes to Heavy Metals

<table>
<thead>
<tr>
<th>Antidote</th>
<th>Metals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimercaprol</td>
<td>bismuth, gold, mercury, lead</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>copper</td>
</tr>
<tr>
<td>NaHSO₄</td>
<td>barium, silver</td>
</tr>
<tr>
<td>Na⁺/Ca²⁺-EDTA</td>
<td>copper, lead</td>
</tr>
</tbody>
</table>
Heroin Overdose

1. CNS depression
2. respiratory depression
3. pulmonary oedema
   i. neurogenic
   ii. secondary to sepsis
   iii. quinine & other "cutting" substances
4. aspiration pneumonitis
5. acute cor pulmonale - talc pneumonitis
6. hypotension
7. ECG changes - ST/T wave changes
   - 1° HB
   - long QT syndrome
   - VT (?quinine)
8. acute cardiomyopathy
9. SBE
10. rhabdomyolysis
    i. pressure necrosis | compartment syndrome
    ii. direct drug | impurity toxicity
11. hyperkalaemia
12. acute renal failure - ATN
    - myoglobinuria
13. hepatitis B, C, D, HIV, CMV
14. opportunistic infections - CMV pneumonia, PCP, fungi, etc.
Lithium Toxicity

- peak serum concentrations occur ~ **2-4 hrs** post-ingestion
- long $t_{1/2}$ ~ 8 hrs, with predominantly **renal excretion** →
  1. ~ 30-60% is excreted after 12 hrs
  2. oliguria & dehydration potentiate toxicity

- therapeutic plasma levels ~ 0.6 - 1.2 mmol/l
  a. side-effects $\geq 1.5$ mmol/l *ie. narrow safety margin
     i. nausea, malaise, fine tremor, weakness
     ii. polyuria, thirst - also with chronic toxicity
        - **nephrogenic DI**, polyuria
     iii. **hypothyroidism**, goitre
  b. minor toxicity $< 2.0$ mmol/l
     i. vomiting, diarrhoea
     ii. slurred speech, blurred vision, ataxia
     iii. coarse tremor, confusion & fasciculations
  c. severe toxicity $\geq 2.0$ mmol/l
     i. nausea, vomiting, diarrhoea
     ii. ataxia, tremor, hyperreflexia, extensor spasms, confusion, seizures, coma
     iii. potentiation of sedatives and muscle relaxants
        - **flaccid paralysis**, coma and cerebral oedema occur $> 3.0$ mmol/l
     iv. hypotension, syncope, cardiac failure, arrhythmias (? hypokalaemia)
        - refractory ventricular tachycardia, bradycardia or asystole
     v. nephrogenic DI, polyuric renal failure

**NB:** **chronic toxicity** usually presents as **thyroid** or **renal** dysfunction, **acute toxicity** usually presents as **neurologic** or **cardiac** dysfunction

**Investigations**

- **serum lithium level**
  0.5-1.0 mmol/l therapeutic
  1.3-2.0 mmol/l toxic
  2.0-3.0 mmol/l severe toxicity
- **hyponatraemia**
- **hypokalaemia** - may be "normokalaemic" with total body deficit
- **ECG** - T wave depression/inversion
  - VE's, sinus bradycardia

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**Treatment**

a. gastric lavage

b. maintain **euvolaemia**
   - saline loading & enhanced diuresis *per se* is of **no value**
   - alkalisation of urine - NaHCO₃, acetazolamide

c. indications for **dialysis**
   i. plasma level > 4.0 mmol/l
   ii. plasma level ~ 2-4 mmol/l + deteriorating clinical status
      ~ 2-4 mmol/l + acute renal failure
   iii. extrapolated time to level < 0.6 mmol/l > 36 hrs
      - CVVHD effective but slow 2° to large $V_{ass}$

d. β-adrenergic blockers for severe tremors

e. **no** useful effect from
   i. diuretics - frusemide (may worsen toxicity)
      - spironolactone
   ii. KCl
   iii. activated charcoal
Monoamine Oxidase Inhibitors

- *tranylcypromine* and *phenylzene* are the commonly used agents
- *moclobamide* is a more recently introduced agent
- selective for MAO_A and therefore has minimal pressor effect in conjunction with *tyramine*

### Clinical Features

- a. fixed, widely *dilated pupils*
- b. excitement, agitation, delerium, ataxia, seizures
- c. pyrexia, tachycardia, hypotension, diaphoresis
- d. muscle rigidity, opisthotonus, trismus
- e. metabolic acidosis, rhabdomyolysis

**NB:** these may be *exacerbated* by,

  i. sympathomimetic amines
  ii. pethidine *not other opioids*
  iii. theophylline
  iv. tyramine containing foods/drugs

### Management

1. supportive
2. gastric lavage
3. activated charcoal
4. β-blockade - providing hypovolaemia is not present
   - may require close monitoring
5. dantrolene ~ 2.5 mg/kg q6h for 24 hrs
   - has been used for muscle rigidity & hyperthermia
Mushroom Poisoning

- only ~ 50 of 2000 species are poisonous to man, 90% of these from the genus *Amanita*
- milder poisoning occurs with varieties which contain either,
  a. atropine → narcosis, seizures, hallucinations
  b. muscarine alkaloids → excess secretions
- severe poisonings occur with,
  1. *Gryomitrin esculenta*
  2. *Amanita phalloides*

**Gryomitrin Esculenta**

- N,V&D, often bloody diarrhoea, severe abdominal pain
- liver failure
- seizures, coma & death in 15-40% of severe cases
- due to *monomethylhydrazine*
- management
  i. supportive
  ii. IV pyridoxine hydrochloride ~ 25 mg/kg

**Amanita Phalloides**

- GIT irritability due to toxin *phalloidin*
  - occurs 6-12 hrs post-ingestion
  - abdominal pain, N, V and watery diarrhoea
- hepatic, renal and cerebral damage due to *alpha-amanitin*
  - occurs 24-48 hrs post-ingestion, often after resolution of GIT symptoms
  - grossly elevated LFT's, prolonged INR
  - elevated creatinine / urea
  - *encephalopathy* follows progressive hepatic and renal failure
- fatal in ~ 50% of cases with ingestion of 50 g (≥ 3 mushrooms)
- management
  i. gastric lavage & repeated activated charcoal
  ii. *penicillin G* ≤ 10⁶U/kg/d
    - specific antitoxin effect and enhances urinary excretion
  iii. *plasmapheresis* → ↓ mortality from 80% to 12%
    - α-amanatin is highly bound to plasma proteins
  iv. liver transplantation
Organophosphate Overdosage

- OGP s phosphorylate the esteratic site of the enzyme
- aging occurs over next 12 hrs & inactivation becomes irreversible
- new enzyme synthesis requires 1-3 weeks
- carbamates combine reversibly at the anionic site, lasting up to 12 hrs for the insecticides

### Clinical Features

1. **muscarinic**
   - i. miosis, lacrimation
   - ii. bradycardia, junctional rhythm, peripheral vasodilatation, sweating
   - iii. bronchorrhoea, bronchospasm, pulmonary oedema
   - iv. salivation, colicky abdominal pains, diarrhoea
   - v. urinary incontinence

2. **nicotinic**
   - i. muscle fasciculation, followed by paralysis
   - ii. sympathetic ganglia stimulation
     - initially $\rightarrow$ ↑ HR/BP
     - later $\rightarrow$ ganglionic paralysis, exacerbating bradycardia/hypotension

3. **mixed- CNS effects**, anxiety, tremor, convulsions, coma

**NB:** $\equiv$ cholinergic over-stimulation $^\S$ most characteristic signs

### Delayed Peripheral Polyneuropathy

- due to CNS tissue esterase phosphorylation
- rapid onset of distal, symmetrical sensorimotor polyneuropathy
- onset ~ 2-5 weeks post-exposure
- early onset motor paralysis developing 1-4 days post-exposure has also been described
- may require up to 18 days mechanical ventilation

### Monitoring

- a. erythrocyte "true" cholinesterase - more sensitive for chronic OGP exposure
- b. plasma "pseudo" cholinesterase - acute OGP or carbamate poisoning

- levels reduced markedly & usually < 30-50% with onset of symptoms
- during recovery phase, may have return of muscle power with ≥ 20% enzyme activity
- RBC esterase levels return after 5-7 weeks & pseudocholinesterase after 4-6 weeks
**Treatment**

1. **decontamination**
   - treating staff must wear gloves ± respirators
   - discard clothing, wash skin with soap & water
   - gastric aspiration & lavage
2. supportive R – O₂, IPPV, IV fluids, etc.
3. **atropine** – 1-5 mg every 5 mins until control PNS → HR > 60 bpm
   - *failure to produce anti-ACh effects is diagnostic of poisoning
   - **ineffective** against neuromuscular paralysis
4. **pralidoxime** – 1-2 g slowly IV, within 24 hrs of poisoning ± infusion 0.5 g/hr (or 1-2 g q4h)
   - plasma levels better maintained by infusion, t½β ~ 1-2 hrs
   - more effective against **nicotinic** symptoms, not useful for **carbamate** poisoning
   - may actually **worsen carbamate** poisoning, due to weak anticholinesterase activity
   - does not cross the BBB, ∴ no use in CNS symptoms
   - one large comparative study showing **no improvement** in outcome

**Classification**

a. latent poisoning - plasma cholinesterase activity ≥ 50%
   - no clinical manifestations
b. mild poisoning - fatigue, headache, dizziness
   - N,V&D, abdominal cramps
   - sweating, salivation, chest tightness
   - plasma cholinesterase activity ~ 20-50%
   - PAM 1g IV, Atropine 1mg s/c
   - good prognosis
c. moderate poisoning - miosis, fasciculations
   - generalized weakness, unable to walk, difficulty speaking
   - plasma cholinesterase activity ~ 20-50%
   - PAM 1g IV
   - atropine 1-5mg IV q5m

d. severe poisoning - miosis, fasciculations, coma, flaccid paralysis, no light reflex
   - profuse sweating, salivation and bronchorrhoea
   - plasma cholinesterase activity ≤ 10%
   - PAM 1-2g IV ± infusion 0.5g/hr
   - atropine 1-5mg IV q5m
   - IPPV & CVS support
   - fatal if untreated

**NB:** § atropine until control of salivation / sweating, or, flushing & mydriasis occur, aim for HR > 60 bpm
Paracetamol Poisoning

**Pathogenesis**

- principal route of metabolism in the liver \( \sim 85\% \)
  
  a. glucuronidation \( \sim 55\% \)
  
  b. sulphation \( \sim 30\% \) → both excreted by the kidney
  
  c. P-450 MFO \( \sim 5-8\% \) → *N-acetyl-p-benzoquinoneimine*
    - normally conjugated with *glutathione* and then excreted by the kidney
    - toxic intermediate, binds to sulphhydryl containing proteins resulting in acute hepatic *centrilobular necrosis*

- increased susceptibility to toxicity with,
  
  1. overdose & saturation of normal conjugation
    - \( \geq 140 \text{ mg/kg} \) → *zero order kinetics* \( (\geq 10 \text{ g/70 kg}) \)
    - \( \geq 25g/70kg \) → usually fatal
  
  2. hepatic glutathione depletion\(^\text{§}\)
  
  3. induction of P-450 MFO system\(^\text{§}\)

*NB: \(^\text{§}\)both of the latter occur in *chronic alcoholism* → these patients may develop toxicity with chronic "normal" usage

**Clinical Features**

- nausea & vomiting
- abdominal pain & tenderness
- pallor
- coma - unusual, unless other drugs or late presentation
- liver dysfunction *late, usually \( \geq 24 \text{ hours} \)
  - \( \sim 60\% \) of non-treated above "treatment line" show severe liver damage at 3-5 days
  - \( \sim 5\% \) progress to hepatic failure, encephalopathy, coma & death
- uncommon complications
  - i. renal failure - ATN ± papillary necrosis
  - ii. cardiac failure
  - iii. pancreatitis
Treatment

a. gastric lavage
b. activated charcoal (100g) & mannitol (500 ml 20%)
c. \textit{N-acetyl-cysteine}
   - dosage $\rightarrow$ 150 mg/kg/200 ml D$_5$W over 15 min, then
     50 mg/kg/500 ml D$_5$W over 4 hrs
     100 mg/kg/1000 ml D$_5$W over 16 hrs
   - total dose $\rightarrow$ ~ 300 mg/kg/24 hrs
   - actions $\rightarrow$ - increases \textit{glutathione} levels
     - increases detoxification, "glutathione substitute"
     - antioxidant
   - in fulminant hepatic failure, dose ~ 150 mg/kg/24 hrs until encephalopathy resolves
   - this equates to 1 x 10g ampoule / day / 70kg patient
d. other therapies
   i. supportive therapy
   ii. l-methionine - substitute for NAC
     - 2.5g q6h for 4 doses
   iii. haemoperfusion
   iv. liver transplantation

\textbf{N-Acetyl-Cysteine Indications}

a. paracetamol ingestion $\geq$ 150 mg/kg (10.5g/70kg)
b. plasma level $>$ 1300 $\mu$mol/l (200 $\mu$g/ml) at 4 hrs
   $>$ 800 $\mu$mol/l (120 $\mu$g/ml) at 10 hrs
   $>$ 300 $\mu$mol/l (50 $\mu$g/ml) at 12 hrs
   $>$ 200 $\mu$mol/l (30 $\mu$g/ml) at 15 hrs
c. within \textbf{36 hrs} of ingestion
   - most effective within 8-10 hrs of ingestion
   - even if given after onset of encephalopathy, still lowers mortality

\textbf{Side Effects NAC}

- ADRAC records show 9 reactions over 30 yrs
- none of these had high risk blood levels $\rightarrow$ \textit{anaphylactic response}
  1. rash, pruritis occur most commonly
  2. angio-oedema, bronchospasm, hypotension, N & V (occur less commonly)

\textit{NB:} 2° \textit{histamine} release $\sim$ 9%
**Prognosis With NAC**

a. none  
   ~ 75% severe liver damage  
   ~ 60% mortality

b. within 10 hrs  
   - low incidence of liver failure  
   ~ 1% mortality

c. between 10-36 hrs  
   - 50% liver damage  
   - 40% mortality

**NB:** the degree of encephalopathy and coagulopathy show *no correlation* with the timing of the overdose and subsequent treatment

**Poor Prognosis**

1. drug levels in the high toxic range
2. late presentation
3. plasma bilirubin > 120 µmol/l at day 3-5
4. INR > 2.2
Paraquat Poisoning

- **Clinical Features**
  - organs affected early include,
    1. lung
    2. liver also affected late
    3. kidney
    4. adrenals
    5. brain
  - nausea, vomiting & abdominal pain occur early
  - signs of renal & hepatic dysfunction develop within 1-3 days & are usually reversible
  - pulmonary oedema occurs within 24 hrs of ingestion
  - followed after 1-2 weeks by progressive pulmonary fibrosis
  - pulmonary effects are similar to those of O₂ toxicity → *fibrosing alveolitis*
  - this is non-reversible and is the common cause of death
  - severe toxicity presents with multisystem failure → lung, kidney & hepatic ± cardiac, adrenal & cerebral

- **Metabolism**
  - herbicide with rapid GIT absorption and slow renal excretion, t½ ~ 24 hrs
  - during the first 24 hrs there is active & selective uptake by,
    - type II pneumocytes > type I pneumocytes > endothelial cells
  - this occur even against a concentration gradient, and plasma levels fall reciprocally
  - uptake is reduced by hypothermia and decreased VO₂
  - mechanism of toxicity believed to be,
    1. inhibition of superoxide dismutase
      → ↑O₂ free radicals and NADPH/NADH depletion
    2. single electron, cyclic reduction-oxidation, forming superoxide radicals
      - superoxide is nonenzymatically transformed to *singlet oxygen*
      - produces lipid hydroperoxides, which are unstable in the presence of trace metals
      - these subsequently form lipid-free-radicals
  - the reaction rate is enhanced by,
    a. high paraquat levels
    b. high F₁O₂
    c. Fe²⁺
    d. low NADPH states
    e. high BMR or body temperature
• plasma levels \( \geq 1.0 \, \mu g/ml \) are almost always fatal
• prevention is best achieved by,
  1. restricted sale
  2. adequate **labelling** and **education**
  3. emetics may also be added to the formulation

**Treatment**

**NB:** without treatment, **mortality ~ 85-100%**

.: treat all cases aggressively & early

1. gastric lavage
2. absorbents
   i. charcoal
      • one study showing equally efficacious to Fuller's earth
   ii. **Fuller's earth**
      • specific binder, paraquat is inactivated on contact with soil
      • LIGW states only 5-10% of paraquat absorbed from GIT in 24 hrs
      • 1000 ml 30% solution, 300 g/l, followed by 200 ml 20% mannitol
      • definitely require **laxative** due to risk of constipation/obstruction
      • subsequently q2h - 15% solution, 150 g/l + mannitol q4h
      • monitor biochemistry for electrolyte disturbances
3. cathartics ~ 200 ml mannitol 20%
   ~ 100 ml sorbitol 70%
4. haemoperfusion\(^8\) - limited to use within the first 12 hrs
   - may be some improvement if started early for severe cases
5. minimise lung injury
   • titrated to minimal F\(_{2}\)O\(_2\)
   • desferrioxamine - decreases Fe\(^{++}\)
   • steroids of **no use**
   • ? hypothetical - 6-7 Å molecule to block lung uptake

**NB:** \(^8\)LIGW states haemodialysis, haemoperfusion and peritoneal dialysis are **ineffective** for paraquat removal
Quinine / Quinidine Poisoning

- quinidine is the dextrostereoisomer of quinine, and has all of the pharmacological actions of this agent → antimalarial, antipyretic, oxytocic
- however, its actions on the myocardium are far more potent than quinine

**NB:** → cinchonism visual disturbance, headache, tinnitus/deafness N&V, abdominal pain, rashes

i. toxic dose ≥ 4g
ii. fatal doses usually ≥ 8g

- quinine is frequently used to lace heroin → combined poisoning

  a. CNS - fever, headache, excitement, confusion
     - vertigo, nystagmus, blindness, tinnitus, deafness
     - convulsions, coma, respiratory failure
  b. CVS - hypotension (2° α-blockade), negative inotropy
     - paradoxical rate rise with AF (vagolysis)
     - occasional VT, torsade de pointes, cardiac arrest
     ECG - ↑ QRS prolongation proportional to dose
     - SA/AV node blockade, bundle branch block
     - polymorphic VT
  c. skin - rashes, purpura, dermatitis, erythema multiforme
     - jaundice (G6PD deficiency)
  d. eyes - diplopia, toxic amblyopia, scotomata, tunnel vision
     - photophobia, night blindness, distorted colour vision
     - extraocular ophthalmoplegia
     - mydriasis, retinal oedema, optic disc pallor
  e. allergic - Stevens-Johnson syndrome (erythema multiforme major)
     - haemolytic anaemia, thrombocytopaenia
     - angioneurotic oedema
- **Treatment**

  a. gastric lavage
  b. repeated charcoal and purgatives
  c. correct biochemistry  
     * hyperkalaemia & hypocalcaemia potentiate toxicity
  d. respiratory and cardiovascular support  
     - may require PA catheter, pacing, rarely IABP
  e. agents useful in the treatment of *ventricular tachyarrhythmias* caused by quinidine,  
     i. sodium lactate
     ii. glucagon
     iii. catecholamines
     iv. magnesium sulphate
  f. toxic amblyopia  
     - Na-nitrite
     - nicotinamide
     - stellate ganglion blockade
Salicylate Overdose

- inhibits many enzymes including,
  a. cyclooxygenase - platelet > endothelial
  b. oxidative phosphorylation
  c. Kreb's cycle - succinate dehydrogenase
     - α-ketoglutarate dehydrogenase
  d. hyaluronidase
- the uncoupling in oxidative phosphorylation results in,
  a. increased heat production
  b. glycogenolysis → early hyperglycaemia
  c. increased energy requirement → late hypoglycaemia
  d. increased lactate production, liberation of FFA's and ketogenesis → metabolic acidosis
- produces central respiratory stimulation, in addition to the ↑ VO₂ and CO₂ production → the net effect being a respiratory alkalosis
- hyperpyrexia may occur if sweating decreases due to excessive dehydration
- the therapeutic level is 150 - 300 µg/ml (2200 µmol/l)
- toxicity and serum levels correlate poorly but usually ≥ 350-500 µg/ml
  1. maximal therapeutic doses ~ 4-6g/d
  2. toxic dose ≥ 10g
  3. fatal doses are usually ≥ 30g
- GIT absorption is usually rapid and within 1 hr
- large single doses may delay gastric emptying and prolong absorption for up to 24 hrs
- displays dose-dependent kinetics, ie. half-life increases with larger doses,
  a. 300 mg → 2.5 hr
  b. 1000 mg → 5-7 hrs
  c. 4000 mg → 15-30 hrs
- small changes in plasma pH significantly alter free fraction,
  pH ~ 7.4 → 7.2 free fraction ↑ 2x
**Clinical Features**

- **neurological**
  - altered mental state, confusion
  - agitation, tremor, seizures, coma (esp. children)
  - tinnitus, deafness
  - hyperthermia
  - Kussmaul breathing
- **metabolic**
  - respiratory alkalosis
  - metabolic acidosis
  - ↑ anion gap ⇐ ↑ lactate & ketones
  - fluid & electrolyte loss, esp. K⁺
  - early hyperglycaemia, later hypoglycaemia
- **GIT**
  - nausea, vomiting and epigastric pain
  - liver dysfunction, usually mild
  - gastritis & haemorrhage
- **haematological**
  - platelet dysfunction → ↑ SBT
  - ↓ Factor VII → ↑ INR

**Treatment**

- **gastric lavage**
  - avoid alkalis
- **activated charcoal**
  - ~ 8g/g of salicylate
  - repeated q2h → * decreases t½β from 24-30 hrs to < 4 hrs
- **fluid & electrolyte replacement**
  - glucose to avoid hypoglycaemia
- **hyperventilation & bicarbonate**
  - aimed at correction of respiratory & metabolic acidoses respectively
- **Vit.K for coagulopathy**
- **forced alkaline diuresis**
  - NaHCO₃ ± acetazolamide → pH > 7.5
  - may worsen acidemia & increase free fraction, .: check AGA’s
  - salicylate excretion is only marginally increased at urine pH > 7.5
  - excretion is not enhanced by the use of diuretics
  - complications of fluid overload, pulmonary oedema, electrolyte disturbance
  - really of marginal benefit
- **cooling measures**
- **anticonvulsants prn**
- **haemodialysis**
  - clinically severe intoxication
    - coincident pulmonary oedema, acute renal failure, coma
  - acidosis unresponsive to Rx
  - salicylate level > 750 µg/ml (range: 500-1000 µg/ml)
Strychnine

- fatal dose ~ 15-30 mg
- produces glycine receptor blockade on post-synaptic inhibitory neurones
- similar effects cf. tetanus (tetanospasmin TT)
  \[\rightarrow\] prevents glycine release from presynaptic terminal

### Clinical Features

a. increased muscle tone  
b. extensor spasms  
c. respiratory paralysis  
d. seizures  
e. lactic acidosis  
f. hyperthermia  
g. rhabdomyolysis

### Management

1. support respiration  
2. maintain CVS status  
3. control spasms  
4. prevent seizures

**NB:** normal excretion / detoxification is rapid, *no* specific therapy required  
prognosis is good providing patient supported for 6-12 hrs
Theophylline Toxicity

- **Clinical Effects**
  
a. GIT - transient motility depression  
  - nausea and vomiting with toxicity  
b. CNS - general stimulation, increased arousal  
  - antagonism of benzodiazepine depression  
  - respiratory centre stimulation and \( \uparrow V_m \)  
  - vasomotor stimulation, vasoconstriction, \( \uparrow \) MAP and HR  
  - stimulation of *vomiting centre*

c. CVS - positive inotropic & chronotropic effect  
  - \( \uparrow \) CO and CMRO_2  
  - direct vasodilatation ? reflex from baroreceptor stimulation  
  \( \rightarrow \) central effects predominate  
  - potentiates effects of \( \beta \)-adrenergic agonists

d. RS - bronchodilatation (5-20 µg/ml)  
  - \( \downarrow \) histamine release  
  - \( \uparrow V_m \)  
  ? improved mucociliary transport

e. renal - \( \uparrow \) RBF/GFR \( \propto \) \( \uparrow \) CO & MAP  
  - direct depression of tubular reabsorption \( \rightarrow \) diuresis

e. metabolic - hyperglycaemia, hypercalcaemia  
  - hypokalaemia, hypomagnesaemia, hypophosphataemia  
  - *lactic acidosis* proportional to severity of toxicity  
  - respiratory alkalosis  
  - rhabdomyolysis

- toxic doses are usually \( \geq 10 \) mg/kg  
- in severe intoxication, the overall *mortality* \( \sim 10\% \)  
- hepatic clearance becomes saturated \( \rightarrow \) *zero order kinetics*  
- effective plasma half-life, \( t_{1/2} \beta \sim 8-30 \text{ hrs} \)
- blocks both *adenosine receptors* and *phosphodiesterase III*  
- plasma levels and clinical features correlate reasonably well

<table>
<thead>
<tr>
<th>Plasma Level</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>µmol/l</td>
<td>µg/ml</td>
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<tr>
<td>30-110</td>
<td>5-20</td>
</tr>
<tr>
<td>&gt; 200</td>
<td>&gt; 36</td>
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<tr>
<td>&gt; 500</td>
<td>&gt; 90</td>
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<tr>
<td>&gt; 500-800</td>
<td>&gt; 90-145</td>
</tr>
</tbody>
</table>
- plasma levels should be monitored 2-4 hourly until level plateaus
- indications for **ICU admission**,
  a. > 220 µmol/l (**40 µg/ml**) - chronic toxicity
     - elderly or child
  b. > 275 µmol/l (**50 µg/ml**) - adult with acute toxicity

### Treatment
- a. gastric aspiration and lavage
- b. **charcoal** and mannitol via NG tube * repeat q2h
- c. haemoperfusion
  - effective in removing systemic theophylline
  - **no evidence** that it reduces morbidity / mortality
- d. plasmapheresis ? better than haemoperfusion
- e. supportive therapy
  i. CVS - verapamil, esmolol, propranolol
  ii. GIT - ranitidine, metoclopramide
     * avoid cimetidine & phenothiazines (↓ Cl & epileptogenic)
  iii. CNS - phenobarbitone
     * phenytoin is **ineffective**

### Indications for Extracorporeal Techniques
- a. severe clinical toxicity - refractory arrhythmias
  - refractory seizures
  - refractory vomiting
- b. serum level
  - > 350 µmol/l in acute (LIGW: > 550 µmol/l)
  - > 220 µmol/l in chronic
- c. severe hepatic/cardiac/respiratory disease and level > 220 µmol/l
Tricyclic Overdose

**NB:**
- **hot** as a hare
- **dry** as a bone
- **red** as a beet
- **blind** as a bat
- **mad** as a hatter

Severe toxicity occurs at doses > 1000 mg (70 kg).

- Most complications occur **within 1 hour** of admission and are almost never seen if patient remains alert with a normal ECG for over an hour.
- However, complications may occur up to 6 days after ingestion (when severe).
- **Anticholinergic** effects may slow GIT transit and absorption.
- Avid tissue binding \( \rightarrow \) large \( V_{ass} \approx 10-50 \, l/kg \).
- **Hypalbuminaemia** and **acidaemia** increase the free drug fraction & toxicity.
- Increasing plasma pH from 7.38 to 7.5 decreases free fraction by \( \approx 21\% \).
- Mechanism of effects includes,
  1. **Anticholinergic** effects
  2. **Quinidine-like** effects
  3. Blockade of **catecholamine reuptake**

**Clinical Effects**

- **CVS**
  - Postural hypotension
  - Prolonged QTc and RAD
  - Some argue evidence for \( \uparrow \) QTc minimal
  - Tachyarrhythmias: AF, SVT, VEB’s, VT, VF
  - \( \uparrow \) QRS duration, \( \uparrow \) PR interval, AV block
  - \( \downarrow \) VF threshold
  - Acute congestive failure

- **CNS**
  - Central **anticholinergic syndrome**
    - Respiratory depression
    - Nystagmus, ataxia, dysarthria
    - Choreoathetosis, myoclonic jerks
    - Extensor plantars
    - Seizures, coma

- **Metabolic**
  - Hypothermia | hyperthermia
  - Hypokalaemia, metabolic acidosis
  - Rhabdomyolysis
Monitoring

a. blood levels correlate poorly with CNS / CVS toxicity
b. if maximal limb lead QRS > 0.10s at 6 hrs then monitor for 24 hours
   • correlates with blood level > 3.7 µmol/l & severe intoxication
c. seizures & ventricular arrhythmias may occur up to 6-24 hours post-ingestion

Treatment

a. supportive therapy
b. drug absorption / elimination
   i. gastric lavage (up to 24 hrs)
   ii. activated charcoal - repeated administration
   iii. sorbitol / mannitol
c. CNS toxicity
   i. airway support / protection as required
   ii. control of seizures - diazepam or thiopentone
      + phenytoin
      • seizures worsen acidaemia & CVS toxicity, ∴ control promptly
   iii. physostigmine may reduce central depression
      • lasts ~ 30-60 min and has no effect on CVS toxicity
      • contraindicated if seizures or bradycardia are present
d. CVS toxicity
   i. phenytoin, magnesium, or lignocaine for ventricular arrhythmias
   ii. alkalisation may decrease cardiotoxicity
      • hyperventilation & bicarbonate
   iii. DCCV for VT - low energy (50J)
   iv. temporary pacing wire - torsade or CHB

NB: dialysis is unhelpful due to large V_{ass} and high lipid solubility
repeated charcoal is of probable benefit
<table>
<thead>
<tr>
<th>Specific Antidotes</th>
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<tbody>
<tr>
<td>paracetamol</td>
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<tr>
<td>• N-acetylcysteine</td>
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<tr>
<td>methanol, ethylene glycol</td>
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<tr>
<td>• ethanol</td>
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<td>• 4-methylpyrazone</td>
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<tr>
<td>cyanide</td>
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<td>• dicobalt EDTA</td>
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<td>• Na-thiosulphate</td>
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<td>• B₁₂</td>
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<tr>
<td>carbon monoxide</td>
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<tr>
<td>• 100% F₁O₂</td>
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<td>• hyperbaric oxygen</td>
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<tr>
<td><em>Amanita phalloides</em></td>
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<td>• penicillin</td>
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