Poisonings: paracetamol, tricyclics and worse

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Case History 1
- 55 yr old woman admitted with confusion/drowsiness
- Complaining of chest pain
- Recently moved to a new house
- O/E:
  - PR 130, BP 120/60, RR 35, \( \text{SaO}_2 \) 99%
  - Otherwise normal CVS/Resp/GI/Neuro examination
- ECG: sinus tachycardia, widespread ST depression
- CXR: normal
- Glc: 7.0, FBC, U&Es and LFTs: normal
- ABG: \( \text{PaO}_2 \) 13.3, pH 7.11, \( \text{PaCO}_2 \) 2.8, Bicarb 10

Differential diagnosis of confusion
- Hypoglycaemia
- Vascular
- Infection
- Inflammation
- Trauma
- Tumour
- Toxic/Metabolic

Carbon monoxide poisoning
- Odourless
- Tasteless
- Colourless
- Non-irritating gas

Carbon monoxide poisoning
- Most common during the winter months
- Potential sources:
  - Poorly functioning heating systems
  - Improperly vented fuel-burning devices
  - Motor vehicles operating in poorly ventilated areas.
- Potentially fatal
- Underdiagnosed

Carbon monoxide poisoning
- CO binds to the Fe moiety of heme with 240x the affinity of oxygen, forming COHb.
- Impaired oxygen transport and utilization
- CO can also result in CNS lipid peroxidation and delayed neurologic sequelae.
CO poisoning: Presentation

- Non-specific: headache, malaise, nausea, and dizziness (may be misdiagnosed with viral syndromes)
- Confusion, seizures, coma
- Cardiac ischaemia can occur.

CO poisoning: Investigations

- Pulse oximetry is unable to distinguish between Oxyhaemoglobin and COHb.
- PaO\(_2\) normal as it reflects O\(_2\) dissolved in blood, & this process is not affected by CO.
- Cooximetry of a blood gas sample
- ECG
- Pregnancy test

CO poisoning: Management

- A, B, C, intubate those with severely impaired mental status.
- 100% O\(_2\) by non-rebreathing face mask or endotracheal tube
  - CO half-life
    - Room air: 5 hours
    - 100% O\(_2\): 1 hour
    - hyperbaric O\(_2\): 30mins
- Hyperbaric O\(_2\) therapy ↓ incidence and severity of delayed neurocognitive deficits (controversial).

Hyperbaric oxygen therapy

- CO level > 25%
- CO level > 20% in pregnancy
- End-organ ischemia:
  - Altered mental status
  - Chest pain
  - ECG changes
  - Metabolic acidosis (pH <7.1)

Case History 2

- 21-year-old woman admitted with nausea.
- She had taken 40 paracetamol tablets after an argument with her mother.
- Physical examination: normal
- Na\(^+\) 135 mmol/l, K\(^+\) 4 mmol/l, urea 5.0 mmol/l, Bicarb 18 mmol/l, PT: 16 s
- Serum paracetamol: 200mg/l
- What are the immediate treatment steps?

Paracetamol overdose: Presentation

- Patients presenting within 24 hours are generally asymptomatic.
- Patients presenting later may manifest features of hepatic injury.
- There are no early symptoms that predict toxicity.
**Therapeutic doses of paracetamol**

- Mostly metabolized in the liver to sulfate and glucuronide conjugates; excreted in urine.
- 8% metabolized via the hepatic cytochrome P450 enzymes into NAPQI*
- NAPQI: conjugated with hepatic glutathione, excreted in the urine.

* N-acetyl-p-benzoquinoneimine

**Toxic doses of paracetamol**

- Sulfation and glucuronidation pathways are saturated.
- Increased metabolism via the cytochrome P450 enzymes to NAPQI.
- Hepatic glutathione stores are depleted.
- NAPQI causes hepatic injury.

**Factors influencing hepatotoxicity (1)**

- Concomitant use of alcohol, other drugs, herbal supplements
- Advancing age
- Nutritional status
- Mechanism:
  - Increased cytochrome P450 activity: shunting of greater fraction through the CYP2E1 pathway, generation of NAPQI
  - Depletion of glutathione stores

**Factors influencing hepatotoxicity (2)**

- Acute alcohol ingestion is NOT a risk factor for hepatotoxicity.
- Chronic alcohol ingestion:
  - Increases CYP2E1 activity & depletes glutathione levels
  - Increased risk for hepatotoxicity following ingestion of multiple supratherapeutic doses, but not after a single overdose.
- Chronic liver disease: if do not regularly ingest alcohol, risk not increased (have low cytochrome P450 enzyme activity)
- Pattern of use: higher rates of severe hepatotoxicity in cases of accidental poisoning with repeated excessive doses

**Paracetamol overdose: Treatment (1)**

- GI decontamination:
  - Activated charcoal 1 g/kg (maximum dose 50 g) by mouth in those presenting within 4 hours
- Plot serum paracetamol concentration on the normogram.
- Key to effective treatment: start therapy before the onset of ALT elevation (within 8 hours of an acute ingestion).
Paracetamol overdose: Treatment (2)

- IV acetylcysteine
- Measure the ALT and serum paracetamol conc prior to stopping acetylcysteine
- Treatment may be stopped when:
  - Serum paracetamol conc is undetectable
  - ALT is clearly decreasing (> 50% from the peak measurement or 3 consecutive decreasing values, < 1000 IU/L)
  - INR < 2
- 10-20% of patients treated with IV acetylcysteine develop an anaphylactoid reaction.

King’s College Hospital criteria

- Referral for liver transplantation in paracetamol-induced acute liver failure:
  - Arterial pH < 7.3 (irrespective of the grade of encephalopathy) OR
  - Grade III or IV encephalopathy AND
  - PT > 100 seconds AND
  - Serum creatinine > 301 µmol/L

Case History 3

- 19-year-old girl admitted with shortness of breath, nausea and tinnitus.
- SaO\(_2\): 96%
- ABG (on room air):
  - PaO\(_2\): 15 kPa
  - pH: 7.5
  - PaCO\(_2\): 2.5 kPa
  - Bicarb: 12 mmol/l

Salicylate overdose: Presentation

- Tachypnoea
- Tinnitus
- Nausea & vomiting
- Acid-base abnormalities
- Severe cases: hyperthermia, altered mental status, pulmonary oedema

Salicylate overdose: Investigations

- Salicylate level
- ABG, U&Es, glucose, CXR
- Repeat salicylate level every 2 hours until level declining.
- Repeat blood gas every 2 hours until acid-base status improving.

Salicylate overdose: Management

- Supplemental oxygen as needed
- Activated charcoal
- Supplemental glucose in those with altered mental status
- IV saline
- IV sodium bicarbonate
- Alert the Renal team early in the patient’s clinical course
- Consider haemodialysis:
  - Profoundly altered mental status
  - Pulmonary/cerebral oedema
  - Fluid overload
  - Plasma salicylate concentration > 1000 mg/l
- Clinical deterioration despite supportive care
Case History 4

- 65-year-old man with metastatic prostate cancer
- Admitted following a collapse at home
- Had been taking analgesics for back pain
- O/E:
  - Drowsy, GCS 8
  - PR 120, BP 105/65, RR 10
  - ABG on 60% $O_2$: pH 7.2, $PaCO_2$ 9, $PaO_2$ 24, Bicarb 28
- What is the immediate treatment?

Opioid overdose: Presentation

- Miotic pupils
- Depressed mental status
- Decreased respiratory rate
- Decreased bowel sounds
- The best predictor of opioid poisoning is a RR < 12.
- Normal pupil examination does NOT exclude opioid overdose.

Opioid overdose: Management

- Support airway and breathing.
- Naloxone (short-acting opioid antagonist)
  - IV route is preferred, may be given SC or IM.
- The goal of treatment is NOT a normal level of consciousness, but adequate ventilation.
- If a clinical effect does not occur after 5-10 mg, reconsider the diagnosis.

Case History 5

- A 40-year-old drug addict is brought to hospital by his brother.
- Found unresponsive in bed
- Recently visited a private clinic in central London
- Given a withdrawal regimen (cocktail of 4 drugs)
- Shortly after admission had a seizure
- On examination:
  - $SaO_2$ 96% on air
  - GCS 12 (Eyes 3, Motor 5, Speech 4)
  - PR: 125, BP: 80/50, RR 18, Temp 36.8
  - Dilated pupils

TCA overdose: Presentation

- Neurological
  - Sedation, coma, seizures
- Cardiac
  - Tachycardia, arrhythmia, hypotension
- Anticholinergic
  - Dilated pupils, dry mouth, urinary retention, reduced bowel sounds
**TCA overdose: Investigations**

- Serum TCA levels do not help to guide therapy.
- ECG changes in severe poisoning:
  - QRS duration >100 msec
  - Deep S wave in leads I, AVL
  - Tall R wave in lead AVR

**TCA overdose: Management**

- **Airway**: Many require intubation.
- **Breathing**: Supplemental oxygen.
- **Circulation**: IV crystalloid, if remain hypotensive consider norepinephrine.
- **GI decontamination**: activated charcoal if present within 2 hrs of ingestion (unless ileus/obstruction suspected).
- **Conduction abnormalities**: If QRS > 100 msec, challenge with IV sodium bicarbonate.
  - If QRS narrows: start continuous infusion
- **Seizures**: Treat with benzodiazepines, NOT phenytoin

**Case History 6**

- A 50-year-old alcoholic man found collapsed outside a hospital.
  - O/E
    - GCS: 5
    - PR: 110, BP: 85/55, RR: 24, temp: 37°C
    - Resp & GI exam: normal
    - Fundoscopy:

- **ABG**: PaO$_2$ 9kPa, pH: 7.2, PaCO$_2$ 2.5, Bicarb 15

**Case history 6**

- Na$: 135$ mmol/l
- K$: 5 mmol/l
- Urea: 5$ mmol/l
- Glucose: 5$ mmol/l
- Plasma osmolality: 320 mOsm/l
- Bicarb: 15$ mmol/l
- Chloride: 100$ mmol/l

**Methanol poisoning**

- **Toxicity**: converted to Formic acid by alcohol dehydrogenase
- **Presentation**
  - Acute: intoxication
  - 10-30 hours:
    - Metabolic acidosis
    - Visual loss, optic disc hyperaemia
    - Basal ganglia: parkinsonism/dystonia

**Methanol poisoning: Treatment**

- IV sodium bicarbonate if serum pH < 7.3.
- Alcohol dehydrogenase inhibition therapy with fomepizole (or ethanol):
  - Strong clinical suspicion
  - Plasma osmolal gap > 10, pH < 7.3, Bicarb < 20
  - Methanol conc > 6.2 mmol/l
- Consultation with a medical toxicologist and the renal team
Case History 7

- Asked by the A&E team to see a fireman admitted with confusion after attending a fire.
- Seizure while in hospital
- O/E:
  - PR: 120, BP: 110/70, RR: 26, SaO\textsubscript{2}: 99% on oxygen
  - No external evidence of trauma
  - CVS/Resp/GI exam: normal
  - Pupils: equal, reactive to light
- Glucose: 5.3 mmol/l
- Carboxyhaemoglobin 7%
- What diagnosis should be considered?

Cyanide poisoning

- Source:
  - Domestic fires (combustion: wool, silk, nylon, plastics)
  - Industrial exposure (mining, plastic manufacturing)
  - Plants and fruit (plum, peach, pear, apple, bitter almond)
  - Drugs: Sodium nitroprusside
- Mechanism:
  - Binds to the Fe\textsuperscript{3+} of cytochrome oxidase a3 (final enzyme in the mitochyctochrome complex)
  - Oxidative phosphorylation stops
  - Anaerobic metabolism, formation of lactic acid, metabolic acidosis

Cyanide poisoning: Presentation

- CNS: Headache, anxiety, confusion, seizures, coma
- CVS: Initial tachycardia and hypertension, then bradycardia and hypotension, AV block, ventricular dysrhythmias
- Respiratory: initial tachypnoea, then bradypnoea, pulmonary oedema
- GI: vomiting, abdominal pain
- Flushing, Not cyanotic
- Renal failure, Hepatic necrosis

Cyanide poisoning: Investigations

- Metabolic acidosis
  - Assess anion gap
  - Serum lactate
- Central venous blood gas: ↓ arterial-venous PO\textsubscript{2} gradient (↑ venous [oxyhemoglobin], venous blood bright red)
- Blood cyanide levels may be obtained for diagnosis confirmation.

Cyanide poisoning: Treatment

- Sodium thiosulphate & hydroxocobalamin:
  - Sodium thiosulphate: Sulfur donor in the reaction catalyzed by rhodanese which converts cyanide to thiocyanate, excreted in the urine.
  - Hydroxocobalamin: combines with cyanide to form cyanocobalamin, excreted in the urine.
- Activated charcoal in cases of oral ingestion
- Seek assistance from a medical toxicologist

Thank you