TOXICOLOGY AND ENVIRONMENTAL TEACHING TUE 1ST OCT 2019

CASE ONE

The ambulance bring in a 50 year old woman who has been found confused at her home by friends. There is no history available, but she was last seen well around dinner yesterday. She has no known past history and her medications are unknown.

Initial Obs:

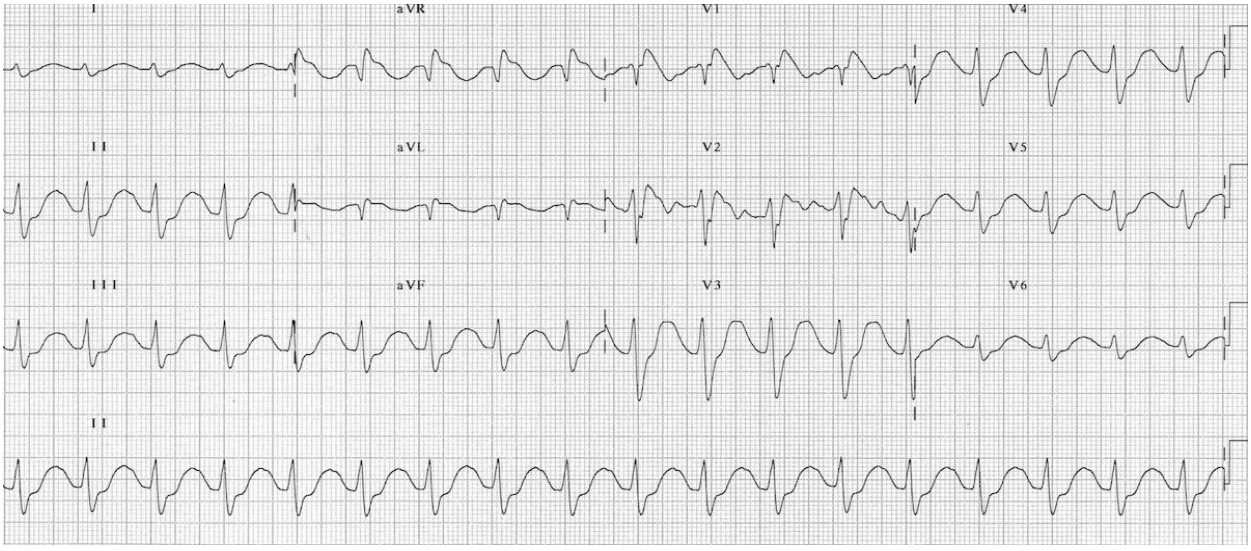
- GCS M 5, E4, V4 pupils large and reactive
- SBP 110
- HR 120
- Sats 99% o/a
- Afebrile
- BSL 8

1. **She is confused and denies any ingestion or overdose. She dose state she only took some sleeping medication. What investigations would you do and how would you manage her presentation?**

- Look up NHI: prior hx, community dispensing etc
- Investigations: Bloods, VBG, ECG
- Consider differential diagnoses : sepsis, trauma, metabolic

2. **You note a community dispensing for 60 x 20mg amitriptyline tablets a few days ago. Her ECG and VBG are shown, please describe and discuss the findings:**
    - Potential toxic dose > 10mg/kg onset, toxicity usually rapid onset in 1-2hrs

    VBG pH 7.35 PCO2 4.0 HCO3 15 Na 143 K 4.2 Lactate 3.5



- Sinus tachycardia with first-degree AV block (P waves hidden in the T waves, best seen in V1-2).
- Broad QRS complexes.
- Positive R' wave in aVR.

- **ECG Features of Sodium-Channel Blockade**

- Interventricular conduction delay — QRS > 100 ms in lead II
- Right axis deviation of the terminal QRS:
  - Terminal R wave > 3 mm in aVR
  - R/S ratio > 0.7 in aVR
- Patients with tricyclic overdose will also usually demonstrate **sinus tachycardia** secondary to muscarinic (M1) receptor blockade.

  QRS > 100 ms is predictive of seizures , QRS > 160 ms is predictive of ventricular arrhythmias (e.g. VT)

3. How would you manage this woman?

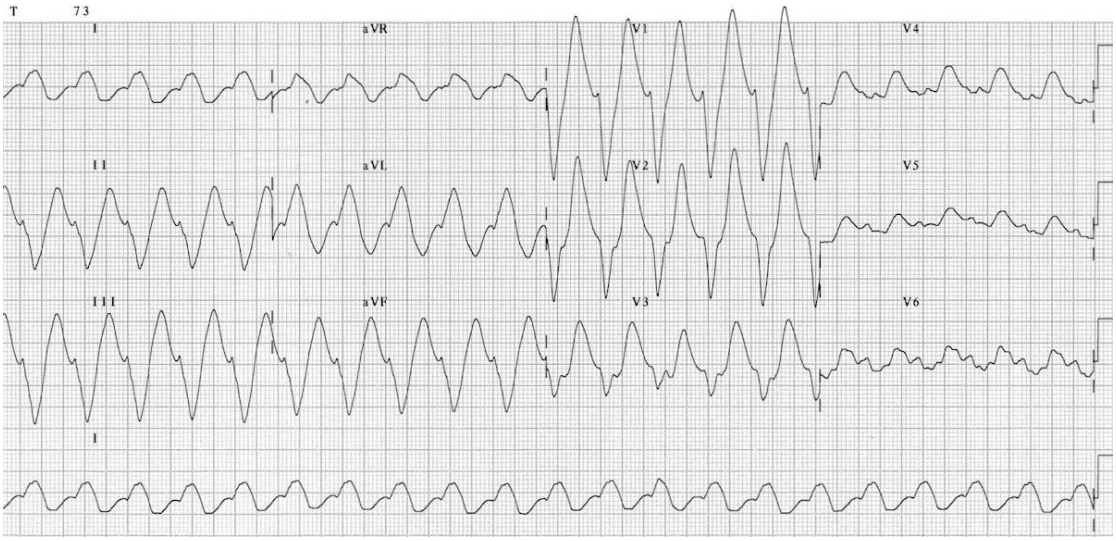
- Sodium channel blocker toxicity – medical emergency
- Risk seizures (Use BDZ)/coma and cardiac toxicity usually rapid onset
- Broad complex tachy or brady(pre arrest) pH dependent toxicity
- Anti-cholinergic features (usually later)

- Rapid escalation of care:
- Get help ICU/ED
- Resus area with monitoring
- Early aggressive sodium bicarbonate therapy
- Small IVF boluses for hypotension

- Sodium bicarbonate 1-2mmol/kg (100mmol initial)
- Aim narrowing QRS – rpt ECG
- Rpt dosing aim QRS < 110

- Consider early RSI and hyperventilation aim pH 7.5 if worsening QRS prolongation despite therapy or dropping GCS

4. **Her GCS drops to 10 and becomes hypotensive SBP 70 with broad QRS. Discuss your management ? Her ECG is repeated below.**



- High dose sodium bicarbonate repeated every few minutes
- IVF boluses
- RSI (discuss drugs) and hyperventilate aim pH 7.5
- Consider pressors (Norad) for resistant hypotension

5. **During intubation she becomes more unstable despite successful intubation and hyperventilation, she has no palpable pulse and monitor shows coarse VF. Discuss your management?**

- CPR
- Sodium Bicarbonate 100mmol every 1-2min
- Target pH 7.5
- Cardioversion and defibrillation unlikely to be effective until adequate sodium bicarbonate given and hyperventilation achieved
- Lignocaine 1.5mg/kg IV is second line when pH is established near 7.5 with bicarbonate and hyperventilation

- Resus efforts should not cease until patient intubated , treated with sodium bicarbonate and hyperventilated to pH 7.5 and prolonged resuscitation has been attempted

CASE TWO

18 year old man is found on the street intoxicated, and having fallen over. He is brought to the ED by the police in a calm drowsy state. His initial GCS is 12 (M5) with reactive pupils and no signs of external head trauma. He is placed in an assessment room.

Initial Obs:

SBP 120
HR 110
Sats 95%
RR 25
Afebrile

1. **The patient is seen by the nurse. She notes a GCS of 10 (M4), BSL is 3.2, RR is 26, SBP 110, HR 120. She is concerned and approaches you to discuss the patient. How would you manage this patient?**

- Move to resus area with monitoring
- Consider differentials : sepsis, trauma, toxicology, metabolic
- IV access
- Tox bloods, cultures, VBG, coags, Grp screen
- Hypoglycaemia treat and monitor
- Consider empiric Abs
- IVF with care
- ECG rhythm? specific changes
- Establish any background hx if possible (concerto, prescribing, family etc)
- CT head?

2. **The point of care VBG result is shown, discuss result and potential differentials?**

pH 7.01, HCO3 5, PCO2 2.4, Na 150, K 4.2, Cl 90 Lactate 20, Gluc 3.2

- Severe metabolic acidaemia and *hyperlactatemia*
- **AG** = Na – (Cl + HCO3) = 55 (uncorrected for albumin = AG + (0.25 X (40-albumin)
- **HAGMA (55)**

- Differentials for HAGMA
  M-Methanol, metformin
  U- Uraemia
  D- DKA
  P- Paracetamol (paraldehyde, propylene glycol)
  I- Infection, Iron, Isoniazid, in born errors metabolism
  L- Lactic acidosis
  E- Ethylene glycol (ethanol- lactic acidaemia or ketoacidaemia)
  S- Salicylates

3. **What other lab results and calculations would be useful?**

- Other useful lab results : Ethanol, serum osmolarity, serum lactate , urea
- **Osmolar gap** = Osmolality (measured) – Osmolarity (calculated)

    - Calculated osmolarity = (2 x [Na+]) + [glucose] + [urea] +[ETOH]
    - normal = < 10

- **MEANING OF A HIGH OSMOLAR GAP**

- presence of an abnormal solute present in significant amounts
- must have: a low molecular weight and be uncharged -> can elevate the osmolar gap
- if the ethanol levels are measured they can be added to the calculated osmolarity to exclude the presence of an additional contributor to the osmolar gap. [NB: To convert ethanol levels in mg/dl to mmol/l divide by 4.6]

- **CAUSES OF HIGH OSMOLAR GAP**

If elevated consider presence of other osmotically active particles

- mannitol
- methanol
- ethylene glycol
- sorbitol
- polyethylene glycol (IV lorazepam)
- propylene glycol (IV lorazepam, diazepam and phenytoin)
- glycine (TURP syndrome)
- maltose (IV IG – Intragram)

- **Serum lactate**: Presence of unmeasured osmoles will falsely elevate the lactate on our blood gas machine. Serum lactate will give true level.

4. **Blood results are returned as below, interpret the results?**

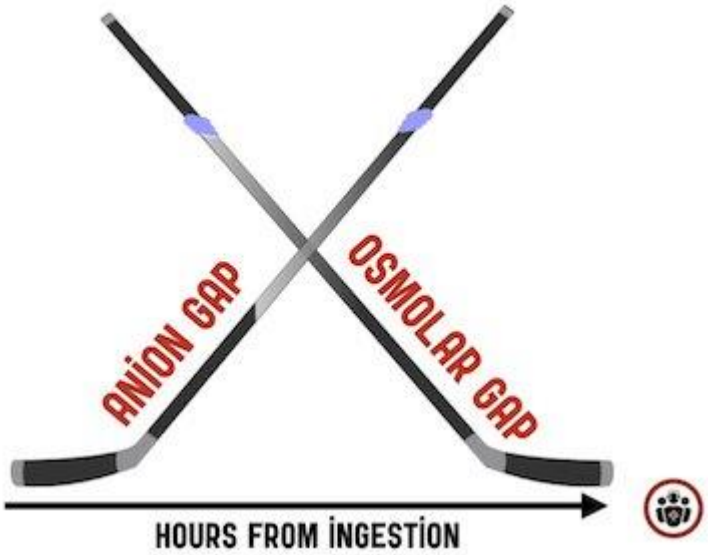
Na 150, K 4, Ur 10, Cr 110, ETOH 20, Gluc 4 , serum lactate 2.5, serum osmolarity 340

- Osmolar gap = 350 – ([2 x 150] + 4 + 10 + 20 = 16 (high normal)

- Severe HAGMA with high normal OG and serum lactate and mildly elevated serum ETOH : In clinical context concern for toxic alcohol ingestion (EG/Methanol)

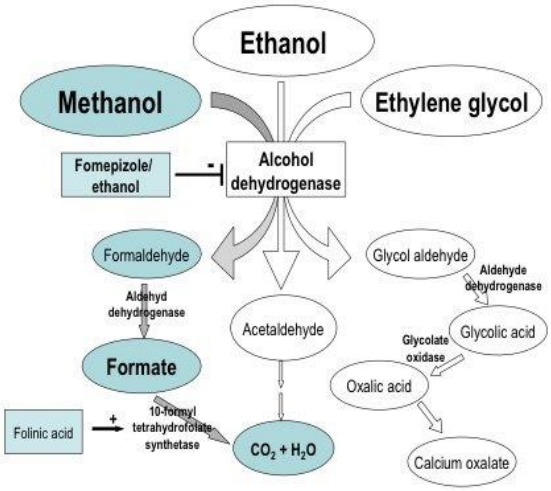
5. **How do you interpret the anion gap and osmolar gap in the setting of toxic alcohol ingestion?**

Key concept: *The acidosis and osmolality in toxic alcohol poisoning are inversely related. As the patient becomes more acidotic the osmolality decreases so that a normal osmolar gap does* not *rule out toxic alcohol poisoning. Think of their relationship like a pair of hockey sticks in a cross formation.*



6. **What are the clinical and lab indications to suggest toxic alcohol ingestion?**

- Clinical suspicion or hx is of up most importance
- Early signs of both methanol and ethylene glycol toxicity are the same as for ethanol.
- As the toxic alcohol is metabolized to an acid, hypotension develops, tachycardia, tachypnea, fixed dilated pupils for methanol, depressed level of awareness and potentially seizures. The symptoms usually develop over 6-24hrs but can be delayed up to 4 days if ethanol is co- ingested.



- The 4 clinical clues to toxic alcohol poisoning are:

1. **Tachypnea** in absence of respiratory illness caused by patient's effort to blow off CO2 with their metabolic acidosis.
2. **Visual changes** with methanol include the classic *'snowstorm' vision*, blurry vision and ultimately blindness with fixed dilated pupils. The finding of extraocular movement paralysis with ethylene glycol is a very late finding and rarely seen in the ED.
3. **Not sobering up** as expected.
4. **Seizure** may occur with severe toxic alcohol poisoning late in the presentation.

- **The 5 big lab clues to toxic alcohol poisoning are:**

1. ***Anion gap metabolic acidosis.*** *Consider MUDPILES differential diagnosis of AG metabolic acidosis. Ethylene glycol may cause renal failure with an* ***elevated creatinine*** *contributing to the AG metabolic acidosis, while both methanol and ethylene glycol may cause an* ***elevated lactate****. Note that very early after ingestion an anion gap metabolic acidosis has not had time to develop. Absence of an anion gap metabolic absence does not rule out toxic alcohol poisoning.*

- ***Clinical Pearl:*** *The differential for a metabolic acidosis with a very low bicarbonate level of 1 or 2 is small – severe sepsis, metformin induced and toxic alcohols.*

2. ***High osmolality and osmolar gap.***

- ***Limitations of Osmolar Gap:*** *If a patient at baseline has a osmol gap of -14, and now has a osmol gap of 10, they have a elevated Osm Gap, even though it is considered normal by textbook definition. Sick patients from a variety of causes can have baseline osmol gap between +10 to +20. In fact, a majority of patients with an elevated osmolal gap will not have toxic alcohol poisoning. As the toxic alcohol is being metabolized to acid, the osmolarity decreases so that by the time you draw your blood work, the osmolar gap may be normal. High osmolar gaps are generally only seen* early *after toxic alcohol ingestion. Overall, the osmolar gap has poor positive and negative predictive value for toxic alcohol poisoning.*

- ***Key concept:*** *The acidosis and osmolality in toxic alcohol poisoning are inversely related. As the patient becomes more acidotic the osmolality decreases so that a normal osmolar gap does* not *rule out toxic alcohol poisoning. Think of their relationship like a pair of hockey sticks in a cross formation.*

3. ***Low ethanol level in an intoxicated patient.*** *While an ethanol level does not need to be drawn in every patient who presents to the ED inebriated, the serum ethanol may be a clue to a toxic alcohol ingestion. The patient with a decreased LOA with a negligible ethanol concentration must be investigated for other pathology. Ethanol is metabolized at the rate of ~ 5.5 mmol/L/hr in an induced patient. You can predict when the serum ethanol level should be low enough for that patient to mobilize safely out of the ED. If the patient is not improving in that estimated time, rethink the diagnosis and re-assess. For the toxic alcohol ingestion patient, who has co-ingested ethanol, the patient has treated themselves (for the time being), and does not need another intervention. Finally, the serum ethanol must be taken into account when calculating the osmolar gap.*

- ***Pearl:*** *The triad of acidosis, high osmolality and low or zero ethanol level is highly suspicious for a toxic alcohol ingestion.*

4. ***Hypocalcemia with a prolonged QT*** *is sometimes seen with ethylene glycol toxicity as the calcium is bound to oxalate and deposits in the kidneys causing renal failure and in the brain causing the late findings of parkinsonism and basal ganglia hemorrhages.*

5. ***Bilateral basal ganglia hemorrhages*** *on CT (late finding) with ethylene glycol ingestion.*

- *Note that urinary* calcium oxalate crystals *have very poor sensitivity and specificity for ethylene glycol toxicity and are therefore rarely helpful in the ED. In addition, wood's lamp examination of urine to detect fluorescein is rarely helpful in detecting ethylene glycol poisoning, with frequent false negatives and false positives making the test unreliable.*

7. **What are the key treatment and management aims?**

- Call for help : ED, ICU, TOX (Chip, poisons centre)
- IV access, IVF and :

1. **Block the toxic metabolites** with fomepizole or ethanol
2. **Correct pH** to 7.2 with bicarb
3. **Eliminate toxic metabolites** with dialysis (especially methanol)

- **Prevent toxic metabolites:** Consider **fomepizole** ideally within 30 minutes. If you do not have access to fomepizole, consider **ethanol**.

- **Fomepizole dosing:** loading dose of 15mg/kg, then 10mg/kg q12h for the first 48 hours, after which the dose is increased to 15mg/kg q12h
- **Ethanol dosing:** oral ethanol q1h to a target serum ethanol level = 22-23 mmol/L. Note that if the patient comes in having co-ingested ethanol, they will not require fomepizole or additional ethanol as long as their serum ethanol remains above 22-23 mmol/L.

- **Replenish cofactors:** Folic acid (50mg IV q4-6h) or folinic acid (1-2mg/kg IV q4-6h) for methanol; thiamine (100mg IV q6h) and pyridoxine (100mg IV q6h) for ethylene glycol.
- **Correct acidosis** with a bicarbonate infusion to target pH = 7.2.
- **Consider dialysis**: Dialysis may not be required if fomepizole is started early in ethylene glycol poisoning assuming there is no acidaemia or renal dysfunction. Methanol is eliminated too slowly for antidotal treatment alone to be effective and so usually requires dialysis.

CASE THREE

R40 from ambulance services 68 year old male found collapsed in a paddock next to his truck. His vitals are:

GCS 12 (M5), HR 45, RR 30, SBP 180, 37.5, Sats 90% (o/a)

1. He is placed in the Resus area. On arrival he is SOB with noisy breathing and vomiting. Handover from ambulance is that he was found by his son collapsed in the paddock next to his truck attached to a spreading machine. He was spreading an insecticide called RAMPAGE 20g (**Chlorpyrifos 200mg/kg**). **What is your concern?**

- Potential toxic exposure ? Organophosphate
- Will need full PPE (full gown/gloves/suitable masks ?)
- Simultaneous supportive care and decontamination (remove clothes/sheets-place in plastic bags/wipe warm water) [nosocomial poisoning of staff rare]
- Consider differentials (medical, trauma etc)
- Tox input

2. **What is the mechanism of these toxins and the effect? (Acute/intermediate/chronic)**

- Organophosphates inhibit acetylcholinesterase enzyme increase ACh at muscarinic and nicotinic receptors
- Ageing may occur depending on agent with permanent binding to AChE
- Effects and timing depend on specific agent, route of exposure
- Chlorpyrifos associated with early cholinergic symptoms

- Muscarinic Effects:

Killer BBB's (Bradycardia, bronchorrhoea, bronchospasm) and hypotension

D diarrhoea
U urination
M miosis
B bronchospasm
B bronchorrhoea
E emesis
L lacrimation
S salivation

- Nicotinic effects
- Faciculations, tremor, weakness, resp muscle paralysis, tachycardia, hypertension
- CNS: agitation, seizure, coma

- Some agents display a intermediate toxicity with delayed paralysis at 2-4 days (ie malathion, diazinon)

- Delayed syndrome (ie chlorpyrifos)
- Organophosphate induced delayed polyneuropathy (rare) 1-5 weeks is an ascending mixed neuropathy

- Chronic organophosphate induced neuropsychiatric disorder

3. **How do you treat this man? He is obviously agitated, has noisy breathing, and tremulous; his observations are :**

   SBP 100, HR 30, RR 35, Sats 90% (10L), BGL 8, GCS 10 (M5)

- Simultaneous resuscitation and decontamination
- High flow O2
- Cholinergic features (miosis, salivation, bronchospasm, bronchorrhoea, bradycardia, hypostension etc) **early atropine**
- 1.2mg (50mcg/kg) IV and double dose every 5 minutes until resolution of bradycardia and drying of secretions (may need huge amounts up to 100mg – no supply ?)
- Glycopyrrolate for resp secretions 200-400mcg (4hrly if needed) may help reduce amount of atropine needed
- Seizure careful BDZ use, Coma resp support
- Pralidoxime (reactivates AChE if given before ageing occurs) indicated in all patients with objective intoxication initial load 2g, then infusion.

- Prolonged admission for observation and oxime (ICU)

- RSI avoid suxamethonium use Rocuronium

- Direct depolarising agent may worsen some nicotinic features
- Dependent on cholinesterase metabolism results in prolonged paralysis and apnea
- Rocuronium is a non-depolarising competitive antagonist metabolised by liver. May help inhibit nicotinic cholinergic effects of OGP

CASE FOUR

75 year old woman presents with 2 days of lethargy and diarrhoea. She has a background of mild CHF, hypertension, but is otherwise fully independent and active. Her obs are:

HR 50, RR 18, SBP 90, GCS 14, afebrile, BGL 8, Sats 92%

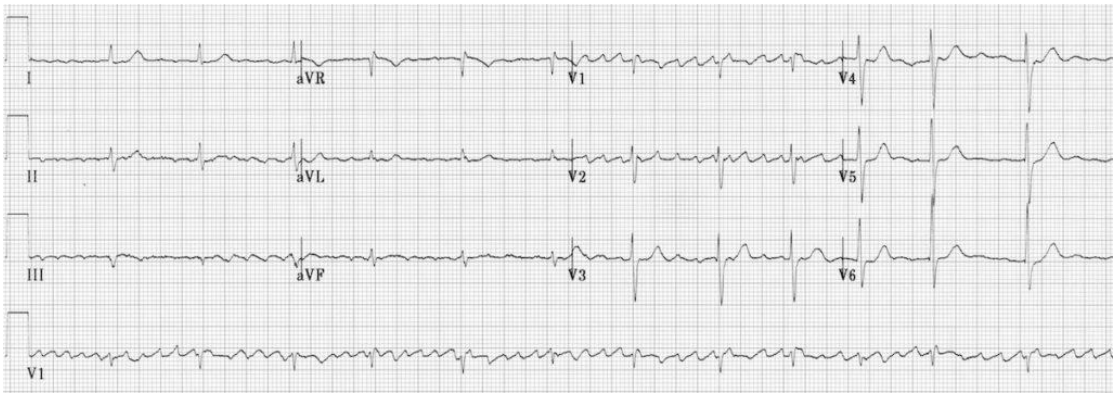
Medications: Furosemide, cilazapril, simvastatin, aspirin, digoxin, felodipine

1. **What are your differentials and your investigations?**

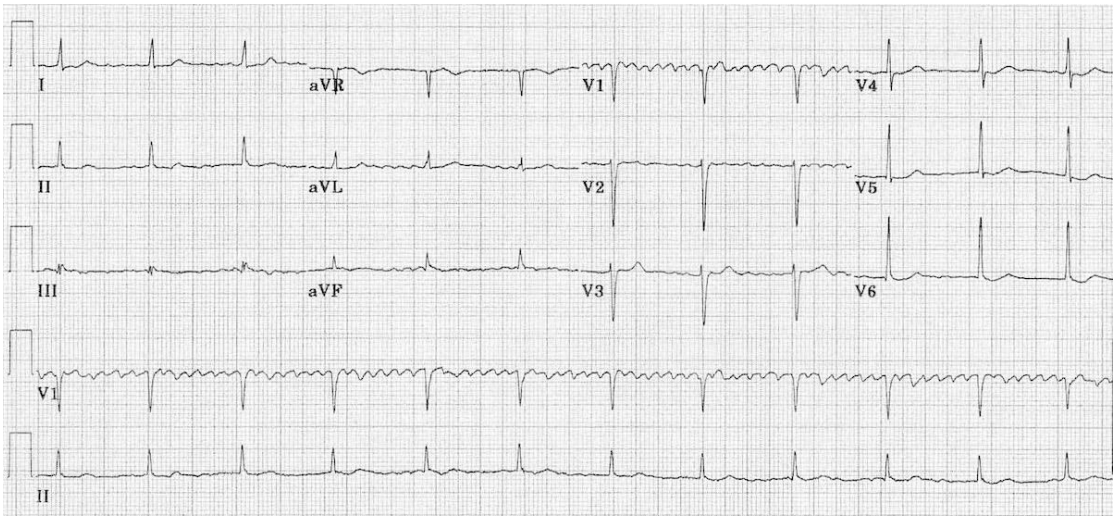
- Broad: Infective, cardiac, ischaemic bowel, drugs?

- ECG
- Bloods : VBG, U+E, FBC, LFT, ? trop, **Digoxin** level
- CXR
- MSU

2. **This is her ECG's describe and discuss?**



Slow AF ? block



Slow regularised type AF

- Slow regularised AF, AF with block common in digoxin toxicity
- AVB, AF rate < 60bpm
- Increased automaticity : PVC, bigeminy
- SVT with AV block
- VT

3. Her bloods are below please interpret in the clinical setting?

Na 150, K 6.1, Cr 240, Hb 130, Gluc 8, Digoxin level 3 nmol/L

- Hyperkalaemia and renal impairment with elevated digoxin level; in clinical setting of non-specific GIT illness, hypotension and bradycardia consistent with possible chronic digoxin toxicity. High risk mortality!

4. What are the clinical manifestations of digoxin toxicity and the mechanism?

- Membrane Na-K-ATPase pump inhibition
- Increase intracellular Ca (+ve automaticity, +ve inotropy)
- Increase extracellular K (hyperkalaemia esp with renal impairment)
- Enhanced vagal tone reduced SA/AV node conduction

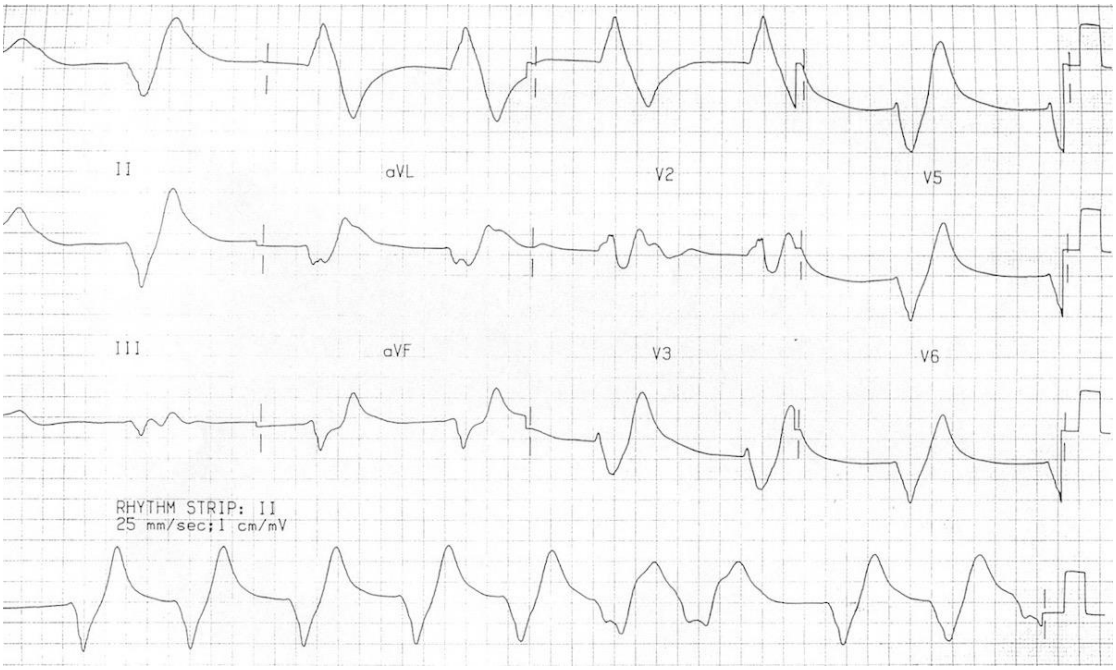
- CVS – brady, tachy, hypotension
- GIT- mild N/V/D/abdo pain (more prominent in acute OD)
- CNS- confusion, lethargy
- Vision- blurred, yellowing (chromatopsia), yellow halos (xanthopsia)

- Probability of toxicity predicted by considering digoxin level and clinical manifestations

5. How would you manage this patient?

- Get help, Tox input, ICU
- Early treatment with Digoxin immune Fab reduces mortality
- 1-2 ampoules usually sufficient
- Hyperkalaemia
- NaHCO3
- Insulin dextrose
- Ca contraindicated
- AVB
- Atropine 0.6mg (20mcg/kg) rpt up to 1.8mg max
- Pacing rarely effective
- Vent tachydysrhytmias
- Lignocaine 1mg/kg (100mgmax)
- Correct ypotension
- Correct hypokalaemia
- Treat any intercurrent illness ? Abs etc

6. Despite 500ml saline, and 2amps of immune Fab she has a brady-arrest. Her ECG is below. How would you manage this patient?



- Commence CPR
- 5amps immune Fab
- NaHCO3 for hyperkalaemia
- CPR continue for at least 30min post digoxin immune Fab

CASE FIVE

A 23 year old woman presents with diarrhoea and vomiting for the last few hours. She is triaged to the ED assessment area. She has no significant past history and is on no regular medications. Her observations are:

SBP 100, HR 120 sinus, Afebrile, Sats 98%, GCS 15

1. What are your differential diagnoses and what investigations would you undertake?

- Common presentation most likely infective gastroenteritis
- Consider alternative causes sepsis, surgical, toxicology, medical

- Investigations: FBC/U+E/LFT/BHCG/VBG?

She is given anti-emetics and 2L saline over 2 hours while in ED. She continues to have some vomiting and diarrhoea, her BP remains 90-100 systolic with mild tachycardia. She is placed in short stay for on-going IVF.

Her blood results are below:

VBG pH 7.3, CO2 3.2, HCO3 16, Na 150, K 3.2, Gluc 4.5, Lactate 3.5
Hb 100 microcytic + hypochromic
Cr 110, LFTs normal

2. Later in the evening the short stay nurse notes that she is more unwell with some coffee ground vomitus,tender abdomen, HR 120, BP 80 systolic, RR 25. The nurse approaches you, how will you manage this patient?

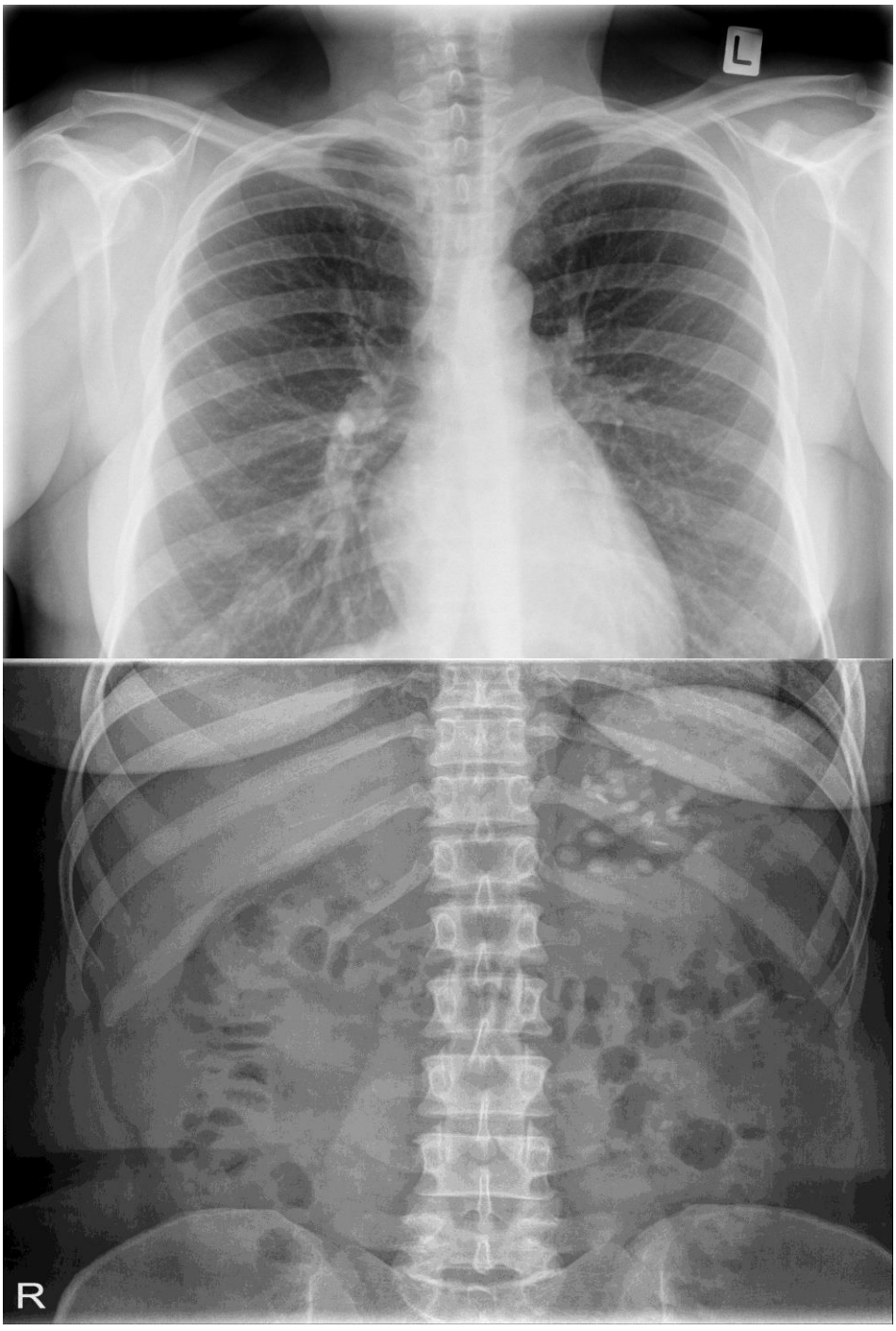
- Shocked patient move to resus
- IVF resuscitation
- Review patient for potential causes – history/exam/family
- Review community dispensing and access to medications
- Rpt blood tests : VBG, U+E, LFTs. FBC, Coags, Gluc, ECG, CXR/AXR
- Other specific tests : paracetamol, Fe level, salicylates
- Senior review, ICU input

3. Her investigation results are below, please discuss and interpret?

VBG pH 7.1, CO2 3, HCO3 12, Gluc 4, K 3.1, Na 148, Cl- 90, Lactate 5.5
AST 200, ALT 190, Alb 35
Cr 120
Hb 88
Paracetamol < 30

- HAGMA – low HCO3, high lactate
- Transaminitis
- AKI

CXR/AXR



- Radiopaque tablets in stomach concern for toxic Fe overdose
- High risk with likely prolonged and ongoing toxicity
- Elemental Fe > 60mg/kg systemic toxicity likely, >120mg/kg potentially lethal
- Elemental content dependent on type Fe supplement (need to work it out)
- Peak Fe levels > 90 micromol/L predictive for toxicity
- Peak level as early as 4-6hrs but may be delayed with bezoar/large ingestion

4. What is the mechanism of Fe toxicity and clinical features?

- Mechanism
- GIT: direct corrosive V/D/pain, GIT bleeding/hypovolaemia
- Systemic toxicity does not occur without initial GIT symptoms
- Systemic: direct cellular toxin liver/Cardiovascular, liberation H+ and lactic acidaemia. Coagulopathy

- Two pathophysiologic stages GIT and systemic

- Classical description 5 stages not distinct or the same in all patients:

0-6 hrs GIT
6-12 hrs absorption iron, latent period
12-48hrs systemic academia, vasodilation, hepatic failure
2-5days liver failure – coma/hypoglycaemia , coagulopathy, death
2-6 weeks delayed cirrhosis, GIT strictures

5. How would you manage this patient?

- Shock with systemic Fe toxicity needs urgent antidotal treatment and removal of tablet bezoar
- Urgent SMO/ICU/Tox/Gastro input
- Fluid resuscitation and stabilise ABC
- Fe level – should not delay treatment if high clinical suspicion

- Desferrioxamine indicated if systemic toxicity, and/or predicted by Fe level > 90 micormol/L at 4-6hrs (serial Fe levels and VBG useful)
- In delayed presentation Fe levels may have dropped
- Binds intravascular free ferric Fe creates water soluble GU excreted complex
- 15mg/kg/hr (reduce if hypotension) increasing to 40mg/kg/hr if not responding of severe toxicity
- End points stable patient and stable Fe < 60 micromol/L
- AE : hypotension, hypersensitivity, ARDS > 24hrs, yersina sepsis

- Decontamination :
- WBI (risk balance) > 60mg/kg confirmed on AXR

- Endoscopic removal (confirmed on AXR) in established toxicity or failed WBI or as primary option in large OD

- Disposition ICU