PHARM / TOX

ANSWER PAPER

SUNDAY 03/01/2016
(a) List the risk factors for and the clinical and laboratory findings of propofol infusion syndrome.

**Risk Factors**
- Large doses (> 4mg/kg/hr for > 48 hours in adults): typically, but not always, large dose, long time
- Younger age
- Acute neurological injury
- Low carbohydrate intake
- Catecholamine and/or corticosteroid infusion

**Clinical and laboratory findings**
- Unexplained lactic acidosis
- Increasing inotrope support (Lipaemic serum, propofol levels / chromatography (if available??))
- Brugada-like ECG abnormalities (Coved-type = convex-curved ST elevation in V1-3)
- (Green urine)
- Cardiovascular collapse, reflected in PICCO / PAC / ECHO
- Rhabdomyolysis, high CK, hyperkalaemia
- Arrhythmia / heart block
- Renal failure

(b) Outline your management of a patient with suspected propofol infusion syndrome.

**Management:**
- High index of suspicion
- Discontinue immediately
- Monitor for early warning signs: lactate, CK, Urine myoglobin, ECG Standard cardio-respiratory support
- Consider pacing (bradycardia often resistant to high dose CA and pacing)
- Adequate carbohydrate intake (6-8mg/kg/min)
- Carnitine supplementation: theoretical benefit
- Haemodialysis and haemoperfusion, used, unproven benefit
- ECMO: 2 case reports, readily reversible pathology

**Discussion**

Propofol infusion syndrome is discussed elsewhere.

It is well covered in an article by Prof Kam.

*Pathophysiology of propofol infusion syndrome*
This tends to happen after about 48 hours of infusion, at over 4mg/kg/hr. The mechanism is likely the inhibition by propofol of coenzyme Q and Cytochrome C. This results in a failure of the electron transport chain, and thus the failure of ATP production. In the event of such a breakdown of oxidative phosphorylation the metabolism becomes increasingly anaerobic, with massive amounts of lactate being produced. Furthermore, fatty acid metabolism is impaired - the conversion of FFAs to acetyl-CoA is blocked, and thus no ATP is produced by lipolysis. On top of that, unused free fatty acids leak into the bloodstream, contributing to the acidosis directly.

a) **Risk factors for propofol infusion syndrome**

- Propofol infusion dose of >4mg/kg/hr for over 48 hrs
- Traumatic brain injury
- Catecholamine infusion
- Corticosteroid infusion
- Carnitine deficiency
- Low carbohydrate intake: because energy demand is met by lipolysis if carbohydrate intake is low, thus leading to the accumulation of free fatty acids.
- Children more susceptible than adults - probably because their glycogen store is lower, and they depend on fat metabolism.
- Congenital weirdness: Medium-chain acyl CoA dehydrogenase (MCAD) deficiency

**Clinical features and laboratory findings in propofol infusion syndrome**

- Acute bradycardia leading to asystole.
  - A prelude to the bradycardia is a sudden onset RBBB with ST elevation in V1-V3; Kam’s article has the picture of this ECG.
- Arrhythmias
- Heart failure, cardiogenic shock
- Metabolic acidosis (HAGMA) with raised lactate (and also due to fatty acids)
- Rhabdomyolysis, raised CK and myoglobin
- Hyperlipidaemia
- Fatty liver and hepatomegaly
- Coagulopathy
- Raised plasma malonylcarnitine and C5-acylcarnitine

**Management of propofol infusion syndrome**

Enhanced elimination

- Stop the propofol infusion!
- “decontamination” might be impossible, but **haemodialysis** should be commenced to wash out propofol and its toxic metabolites
- **Plasma exchange** may be required (Da Silva et al, 2010)

Specific antidote

- **Carnitine** has been mentioned as one of the potential antidotes to propofol infusion syndrome (Uezono et al, 2005). The authors observed a patient who developed a propofol-infusion-like syndrome in response to intravenous lipid emulsion, while in the context of an acquired carnitine deficiency. This led to the hypothesis that "acute fat burden in the setting of inadequate delivery of carbohydrate and acquired carnitine deficiency may impair fatty acid oxidation, leading to the conditions similar to those seen in mitochondrial beta-oxidation defects."

Supportive care

- Pacing and atropine may be useless (the bradycardia is refractory)
- Vasopressors and inotropes are also usually ineffective
- ECMO is the only answer if circulatory collapse with bradycardia has developed

**Nutrition with a satisfactory amount of carbohydrate** to reduce the use of fat for metabolism. The college answer quotes a dose rate (6-8mg/kg/min) but it is unclear where the got this value from.

**References:**


Schenkman KA, Yan S. Propofol impairment of mitochondrial respiration in isolated perfused guinea pig hearts


a) Outline the clinical features and laboratory abnormalities likely to be found in a patient with envenomation due to an Australian snake-bite. (50% marks)

b) Outline the management of a patient with confirmed snake envenomation. (50% marks)

College Answer

a) Clinical features

Local pain, swelling and bruising. This may be absent
Sudden collapse – associated with hypotension and loss of consciousness, rarely cardiac arrest and seizure (5%)
Non-specific systemic symptoms – nausea, vomiting, diarrhoea, headache, sweating.
Neurotoxicity – descending flaccid paralysis – starting with ptosis, diplopia, blurred vision, and then progressing to bulbar weakness, respiratory and limb muscle paralysis.
Myotoxicity – local and generalised myalgia and muscle tenderness. Haemorrhage – rare – intracranial, gastrointestinal or from cannula sites

Laboratory abnormalities

Venom induced consumptive coagulopathy – characteristic of Australian snake bite – INR >3, APPT >100, fibrinogen < 1, raised D-dimers – can be 100 times assay cut off, Thrombocytopenia <100
CK – 1000 to over 100,000 u/L associated with myotoxicity
Acute renal failure – raised potassium, urea and creatinine.
Fragmented red cells in blood film – microangiopathic haemolytic anaemia.

b) Management

First aid – Pressure bandage with immobilisation of the limb and the patient, pressure similar to that for a sprained ankle.
Monitor the patient in critical care area with resuscitation facilities – ED, HDU, ICU – neurological state, HR, BP, respiration, bleeding
Resuscitation as appropriate with two large bore cannulas and collect blood for laboratory tests – Coags (INR, APTT, Fibrinogen, D-Dimers), platelets, Urea, creatinine, electrolytes, CK.
Identify the likely snake type; the site of the bite can be swabbed and a venom detection kit (VDK) used or urine but not blood, or consultation with an herpetologist. Administer anti-snake venom (ASV) only if clinical symptoms or signs or lab abnormalities such prolonged INR. Current guidelines are for one vial ASV only and
then correct subsequent coagulopathy with FFP

Release pressure bandage only after administration of ASV.

Type of ASV (monovalent or polyvalent) depends on clinical presentation, geography and VDK.

Monitor closely for anaphylactic reaction. Treat with adrenaline. Premedication with adrenaline, steroids or antihistamines not recommended.

Repeat lab investigations at 6, 12 and 24 hours to monitor response such as improvement in coagulopathy (INR).

Supportive treatment such ventilation for muscle paralysis and respiratory failure, dialysis for acute renal failure, inotropes for cardiovascular collapse and FFP for severe coagulopathy and bleeding complications.
A 46-year-old male from a foreign fishing vessel presents unconscious to the Emergency Department. He complained of visual disturbance prior to his deterioration.

The following blood results are obtained:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient Value</th>
<th>Normal Adult Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>144 mmol/L</td>
<td>135 – 145</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.0 mmol/L</td>
<td>3.5 – 5.0</td>
</tr>
<tr>
<td>Chloride</td>
<td>102 mmol/L</td>
<td>95 – 110</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>8.2 mmol/L*</td>
<td>22.0 – 30.0</td>
</tr>
<tr>
<td>Urea</td>
<td>6.4 mmol/L</td>
<td>3.0 – 7.0</td>
</tr>
<tr>
<td>Creatinine</td>
<td>127 μmol/L*</td>
<td>44 – 97</td>
</tr>
<tr>
<td>Glucose</td>
<td>5.0 mmol/L</td>
<td>3.5 – 7.8</td>
</tr>
<tr>
<td>Calcium (ionised)</td>
<td>1.10 mmol/L</td>
<td>1.03 – 1.23</td>
</tr>
<tr>
<td>Lactate</td>
<td>4.1 mmol/L*</td>
<td>0.6 – 2.4</td>
</tr>
<tr>
<td>Osmolality</td>
<td>324 mOsm/kg*</td>
<td>275 – 295</td>
</tr>
</tbody>
</table>

a) What is the most likely diagnosis? *(10% marks)*

b) What is the pathophysiology of the visual disturbance? *(20% marks)*

c) List three specific treatments you would institute. *(15% marks)*

College Answer

a)
Methanol toxicity

b)
Methanol - > formaldehyde - > formate which is neurotoxic (especially retina and basal ganglia)

c)
Sodium bicarbonate
ADH inhibition with Ethanol (or fomepizole if available)
Dialysis
Cofactor therapy with either folic or folinic acid
Discussion

So as to be fair to the other no-less-toxic alcohols, here is a table of the common alcohol toxidromes

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Toxin</th>
<th>Clinical and Laboratory Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholic ketoacidosis</td>
<td>• β-hydroxybutyric acid</td>
<td>• Metabolic acidosis</td>
</tr>
<tr>
<td></td>
<td>• Acetoacetic acid</td>
<td></td>
</tr>
<tr>
<td>Methanol intoxication</td>
<td>• Formic acid</td>
<td>• Metabolic acidosis</td>
</tr>
<tr>
<td></td>
<td>• Lactic acid</td>
<td>• hyperosmolality</td>
</tr>
<tr>
<td></td>
<td>• Ketones</td>
<td>• retinal damage with blindness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Basal ganglia (putamen) damage</td>
</tr>
<tr>
<td>Ethylene glycol intoxication</td>
<td>• Glycolic acid</td>
<td>• Cardiovascular collapse</td>
</tr>
<tr>
<td></td>
<td>• Calcium oxalate</td>
<td>• Myocardial damage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cerebral damage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Renal failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Metabolic acidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hypocalcemia</td>
</tr>
<tr>
<td>Diethylene glycol intoxication</td>
<td>• 2-Hydroxyethoxyacetic acid</td>
<td>• Neurological damage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Renal failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Metabolic acidosis</td>
</tr>
<tr>
<td>Propylene glycol intoxication</td>
<td>• Lactic acid</td>
<td>• Metabolic acidosis</td>
</tr>
<tr>
<td>Isopropyl alcohol intoxication</td>
<td>• Isopropanol</td>
<td>• Coma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• hypotension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No acidosis! Only acetone is the metabolic product</td>
</tr>
</tbody>
</table>

Management of toxic alcohol poisoning:

**Decontamination**

- Activated charcoal is useless. Absorption is too rapid.

**Enhanced elimination**

- **Haemodialysis**: toxic alcohols and their metabolites are rapidly cleared in this manner
- **Thiamine** enhances metabolism of ethylene glycol to alpha-hydroxy-beta-ketoadipate
- **Pyridoxine** enhances metabolism of ethylene glycol to glycine (and ultimately hippuric acid).
- **Folate and leucovorin** enhance the clearance of formate
- **Alkalization of urine** with a bicarbonate infusion promotes dissociation of formic acid (it is less toxic in its ionised state) and improves its clearance by ion trapping in the urine

**Specific antidotes**

- **Alcohol** - the precise use of this substance in overdose is discussed in the chapter on ethylene glycol and its toxic acid metabolites.
- In brief, one should sustain a blood ethanol concentration of 20 to 30 mmol/L (100 to 150 mg/dL) - this equates to a blood alcohol level of 0.1-0.15%.
- **Fomepizole** as it is known, is basically a competitive antagonist to alcohol dehydrogenase. It does what ethanol would do, except it does so with great expense, and without ethanol intoxication. The advantage of using it is its lack of CNS effects - if the patient is confused already you do not want to add alcohol into the mix.

**Supportive management**

- Boring supportive care is all that is required.
- **Airway control and mechanical ventilation**: the patient may be uncooperative and with a foul manner.
- **Circulatory support** in case of significant haemodynamic collapse
- **Sedation and analgesia** with short acting substances
References:


A 58 year old farmer with a history of depression was found collapsed in his shed. On arrival at the Emergency Department, his GCS was 10 (E2, V3, M5), respiratory rate was 23, and mouth ulceration was noted with a green coloured substance staining his lips, hands and clothes.

His arterial blood gas and biochemistry on admission were as follows:

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FiO2</td>
<td>0.5</td>
</tr>
<tr>
<td>pH</td>
<td>7.29</td>
</tr>
<tr>
<td>PCO2 (mmHg)</td>
<td>35 (4.6 kPa)</td>
</tr>
<tr>
<td>PaO2</td>
<td>68 (9.0 kPa)</td>
</tr>
<tr>
<td>HCO3 (mmol/L)</td>
<td>16</td>
</tr>
<tr>
<td>Base Excess (mmol/L)</td>
<td>-9</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>140</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.3</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>111</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>7.2</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>5.2</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>162</td>
</tr>
<tr>
<td>Creatinine micromole/L</td>
<td>230</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>(Normal Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.3-7.4</td>
</tr>
<tr>
<td>PCO2 (mmHg)</td>
<td>4.5-6.5 kPa</td>
</tr>
<tr>
<td>PaO2</td>
<td>95-105 kPa</td>
</tr>
<tr>
<td>HCO3 (mmol/L)</td>
<td>24-28</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>135-145</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>3.5-5.0</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>95-105</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.0-6.0</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>&lt;2.5</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>130-160</td>
</tr>
<tr>
<td>Creatinine micromole/L</td>
<td>60-120</td>
</tr>
</tbody>
</table>

**a. What is the likely diagnosis?**

**b. How can you confirm this?**

**c. List 4 important principles of management specific to this condition.**
College Answer

a. What is the likely diagnosis?
Paraquat ingestion

b. How can you confirm this?
Serum paraquat levels
History of exposure

c. List 4 important principles of management specific to this condition.
1) Risk assessment based on estimate of quantity of Paraquat ingested
2) Gastrointestinal decontamination with diatomaceous earths, activated charcoal or sodium resonium
3) Monitoring for organ dysfunction (respiratory, CVS, renal, GIT, adrenal, hepatic, CNS)
4) Avoid high FiO2

Discussion

Though the most likely diagnosis is an overdose of some sort of horrible herbicide (and past history suggests the college likes their paraquat questions), one should still go through the motions of analysing a blood gas from basic principles.

Firstly, what we have here is a hypoxia with a widened A-a gradient.
The PAO2 should be \((0.5 \times 713) - (35 \times 1.25)\), or 311mmHg - so the gradient is a whopping 246.

Next, we have a metabolic acidosis (the BE is -9)
This disorder is inadequately compensated by ventilation. No matter which equation you use, the CO2 should be lower. If you apply the '7.xx' rule, the CO2 should be the last two digits of the pH - 29. If you apply Winter's Formula, the CO2 should be around 32. Thus, a mild respiratory acidosis also exists.
The anion gap is only slightly raised, 17.3 \((140+4.3 - 111 - 16)\)
The delta ratio is therefore 0.66 \((5.3 / 8)\) - if we take the normal anion gap to be 12.
The metabolic acidosis is therefore a mixed disorder.
The serum osmolality and urea are not provided, so we cannot calculate an osmolar gap.
Anyway... The gas exchange defect suggests pulmonary oedema, the bloods suggest renal failure, and the history screams herbicide. Paraquat selectively attacks the alveoli and causes renal necrosis. Ergo, its a case of paraquat poisoning.
Diagnosis consists of a suspicious history, confirmed by formal paraquat levels.
Management consists of supportive care of multi-organ system failure, and decontamination by Fuller's Earth, which is essentially calcium montmorillonite, or bentonite - a absorbent aluminium phyllosilicate, formed from the weathering of volcanic ash.
Dialysis is probably going to be useless, as paraquat is rapidly eliminated and by the time you get the circuit set up most of it will have gone already. The alveolar and renal damage will have been done by then, so you have nothing to gain (other than a more rapid control of the acid-base disturbance).
Hyperoxia is to be avoided, as it has been demonstrated to exacerbate the oxidative toxicity of paraquat.

References:


Clark, D. G. "Inhibition of the absorption of paraquat from the gastrointestinal tract by adsorbents." *British journal*

A 62-year-old female is brought into hospital with suspected organophosphate poisoning.

a) List six acute clinical features associated with this condition.

b) List the antidotes indicated in this condition and the rationale for their use.

The following data are taken from this patient:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient Value</th>
<th>Normal Adult Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinesterase</td>
<td>0.3 KU/L*</td>
<td>3.4 – 9.0</td>
</tr>
<tr>
<td>Cholinesterase mixing</td>
<td>33%*</td>
<td>100%</td>
</tr>
</tbody>
</table>

c) What does the result of the mixing test indicate?

[Hide Answer]

College Answer

a) 
- Diarrhoea
- Urination
- Miosis
- Bronchospasm
- Bronchorrhoea
- Emesis
- Lachrymation
- Salivation
- Fasciculations
- Tremor
- Weakness
- Respiratory muscle weakness
- Bradycardia (tachycardia may be present)
- Hypotension
- Agitation
- Coma
- Seizures

b) 
- Atropine to control clinical features of cholinergic excess - anti-muscarinic. Large doses may be required
- Pralidoxime to reactivate acetyl choline esterase - only effective before irreversible binding or "ageing" takes place

c) 
- This mixing test is suggestive of free organophosphate present in the blood OR inadequate dose of pralidoxime.
Discussion

The first part of the question asks the candidate to produce 6 features of the cholinergic toxidrome. This should be a piece of cake. One recalles the mnemonic SLUDGEM:

- Salivation
- Lacrimation
- Urination
- Diarrhoea
- Gastrointestinal upset
- Emesis
- Miosis

The college answer does not lend itself well to being so easily memorised, and has broken at least one anagram engine. However, Yun from Canberra has pointed out that it is taken directly from the Australian Toxicology Handbook. The first six points are DUMBBELS (the muscarinic features), and the rest are nicotinic.

b)

Atropine and pralidoxime were asked for. The brevity of the college answer cannot be improved upon.

c)

In the mixing test, the patients serum and some random reference serum are both tested for plasma cholinesterase, and then a 50-50 mixture of the two is tested.

If there is enough pralidoxime being given, there will be little free organophosphate in the patient's sample, and the mixed sample will have a plasma cholinesterase level which is exactly between the patients sample and the reference sample.

If there is still free organophosphate present, then it will disable the plasma cholinesterase in the reference sample, and the cholinesterase level of the mixed sample will be surprisingly low.

References:

Brian Kloss from LITFL has a superb cartoon to illustrate the horrors of the cholinergic toxidrome.


Briefly outline the mechanism of effectiveness of sodium bicarbonate in the management of tricyclic antidepressant overdose.

**College Answer**

Increased serum pH, TCAs are weak bases and therefore increasing serum pH will increase the proportion of non-ionised drug thus causing a greater proportion of drug to be distributed throughout the body away from the heart. Increased serum Na also overcomes the Na receptor blockade. Alkalisation also accelerates recovery of sodium channels by neutralizing the protonation of the drug receptor complex.

**Discussion**

The indication for the use of bicarbonate in tricyclic overdose is the widening of the QRS interval, rather than the metabolic acidosis (which may or may not accompany TCA poisoning).

Exactly how this works is a topic of some debate. In general, the QRS prolongation in TAC overdose seems to result from voltage-gated sodium channel blockade.

Some authors have been able to demonstrate that amitryptilline enjoys greater protein binding in a more alkaline environment, which decreases the fraction of free drug.

Other authors have correctly identified sodium (rather than bicarbonate) as the more important ion in sodium bicarbonate; the administration of hypertonic saline seemed to have greater antiarrhythmic effect than sodium bicarbonate!

The last part of the college answer I could find no evidence for, at least not in the way it was worded. A good paper on the molecular mechanisms of sodium channel blockade by imipramine seems to report that intracellular alkalosis seems to favour the unbinding of imipramine from the voltage-gated sodium channel, which vaguely sounds like the thing that the college said.

In summary, bicarbonate in TCA overdose works in the following ways:

- **Increased protein binding of TCAs** in an alkaline bloodstream, thus decreasing the biologically active free fraction.
- **Increased availability of sodium** in sodium bicarbonate, as a substrate for the voltage-gated channels.
- **Decreased binding of TCAs to the voltage gated sodium channel**
- **Correction of metabolic acidosis**
- **Volume expansion** because of the dilutional effect on TCA concentration
- **Cellular membrane hypopolarisation** results from bicarbonate-induced intracellular shift of potassium.

**References:**


A two-year-old boy is suspected of ingesting iron tablets.

a) List the clinical features, and the underlying pathophysiology, of iron poisoning.

b) Briefly outline your management of this child.

[ Hide Answer ]

College answer

a)

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, vomiting, diarrhoea</td>
<td>Direct corrosive effect on GIT</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Direct corrosive effect on GIT</td>
</tr>
<tr>
<td>Gut ischaemia</td>
<td>Disruption of cellular metabolism</td>
</tr>
<tr>
<td>Shock</td>
<td>Fluid losses from GIT</td>
</tr>
<tr>
<td>Anion gap metabolic acidosis</td>
<td>Disruption of cellular metabolism</td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>Disruption of cellular metabolism</td>
</tr>
<tr>
<td>Jaundice, coma, low BSL, coagulopathy</td>
<td>Shock and hypovolaemia</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Disruption of cellular metabolism</td>
</tr>
<tr>
<td>Oliguria</td>
<td>Shock and hypovolaemia</td>
</tr>
</tbody>
</table>

b) Management consists of:

- Resuscitation as indicated with concurrent specific assessment and management of the toxidrome.
- Resuscitation:
  - ABCs
  - Priority is early restoration of circulating volume
  - Boluses of 10-20 ml/kg crystalloid and assess response
- Assessment for signs and symptoms indicative of iron toxicity.
- Risk assessment:
  - History of ingestion – type, quantity of tablets and time of ingestion
  - Iron preparations differ in the amount of elemental iron contained.
• < 20 mg/kg elemental iron is asymptomatic
• 20 – 60 mg/kg causes GI symptoms
• > 60 mg/kg causes systemic toxicity
• > 120 mg/kg is potentially lethal
• Children rarely ingest more than 60 mg/kg.

- Specific investigations
  - BSL
  - Serum iron level
  - ABG
  - AXR – useful in confirming ingestion

- Disposition
  - Asymptomatic at 6hr and negative AXR may be discharged home
  - Monitoring and treatment in paediatric centre (ward, HDU, ICU depending on severity)

- Ongoing assessment of response to resuscitation and antidotes.

- Antidotes
  - Desferrioxamine chelation therapy in cases of systemic toxicity (high serum iron level or metabolic acidosis on ABG)

- Decontamination
  - Iron not absorbed to activated charcoal
  - Whole bowel irrigation indicated for confirmed ingestions > 60 mg/kg – difficult and potentially hazardous in 2-year-old
  - Surgical or endoscopic removal of tablets if lethal ingestion or WBI not feasible

Discussion

The pediatric aspect of this question does not feature prominently in the answer. The only time it is mentioned is in the discussion of whole bowel irrigation, and how foolish it would be to subject a two-year old to this.

a) is well presented by the college.

A flowchart of the mechanisms of high anion gap metabolic acidosis due to iron poisoning is presented elsewhere.

I will reproduce it here, for convenience.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachypnoea</td>
<td>• Metabolic acidosis</td>
</tr>
<tr>
<td>Shock, circulatory collapse</td>
<td>• Third space fluid losses</td>
</tr>
<tr>
<td></td>
<td>• Blood and fluid loss from the ulcerated gut</td>
</tr>
<tr>
<td></td>
<td>• Cardiotoxic effects, with cardiogenic shock</td>
</tr>
</tbody>
</table>

![Flowchart of the mechanisms of high anion gap metabolic acidosis due to iron poisoning](chart.png)
Vasodilation due to SIRS

Hypoglycaemia

Coma

Acute hepatotoxicity

High anion gap metabolic acidosis

Lactic acidosis

Ketosis

Minor contribution from iron itself (conversion of Fe$^{3+}$ to Fe$^{2+}$ produces a net loss of a cation, and therefore contributes to the decrease in the SID)

Hyperlactatemia

Acute hepatotoxicity and liver failure

Shock state

Direct mitochondrial toxicity

Renal failure

Shock state

mitochondrial (tubular) toxicity, ATN

Gastric ulceration

direct corrosive effect of the drug

Haemorrhage, melaena

from ulcerated gut surface

Toxicity manifests in four stages:

- Stage I: GI toxicity (0-6 h since ingestion): vomiting, haematemesis, abdominal pain and lethargy
- Stage II: “apparent stabilization” (6-12 h since ingestion) - symptoms subside
- Stage III: mitochondrial toxicity and hepatic necrosis (12-48 h since ingestion)- acute liver failure, coagulopathy, acute tubular necrosis, metabolic acidosis and shock.
- Stage IV: GI scarring (4-6 weeks since ingestion) - gastric scarring and pyloric stricture

b) A systematic approach to an answer would resemble the following:

- Immediate management:
  - ABCs
  - Circulatory support with fluid resuscitation and inotropes if indicated
- Diagnostic studies
  - ABG - to assess extent of acidosis
  - AXR - to directly visualise the bezoar
  - Serum iron level

Decontamination

- Activated charcoal has no role to play
- Whole bowel irrigation - until effluent turns clear - is a good strategy; much of the toxicity is related to gut ulceration, and by diluting the iron in the gut lumen you may be able to ameliorate this direct corrosive effect, even if you don’t manage to prevent toxic absorption.
- Surgical removal of tablets - if a bezoar is clearly visible on the AXR

Enhanced elimination

- Exchange transfusion: the removal of iron-poisoned blood is ery old-school, but it works (Movassaghi et al, 1969)
- Haemodialysis can be considered to help remove the iron-desferrioxamine complexes, as they are renally excreted and there may not be enough renal function to remove this product. Otherwise, apart from correcting acidosis there is no role for dialysis.

Specific antidote

- Administer desferrioxamine, a sideramine product derived from Streptomyces pilosus.
- Desferrioxamine is indicated if metabolic acidosis is present or iron levels are over 90 micromol/L.
- Total intravenous dose should not exceed 80mg/kg/24hrs.
- The resulting iron-desferrioxamine complex is water-soluble and biologically inert.

Supportive care

- Intubation will likely be required to protect the airway not only from the decreased level of consciousness but also from the risks of aspiration associated with whole bowel lavage.
- Mechanical ventilation will likely be with mandatory mode, to decrease the demands on the failing myocardium
- Circulatory support should consist of simultaneous fluid resuscitation, inotrope and vasopressor infusions
- Sedation should be rationalised, given that the patient is already in a coma before the sedation is given, and that the liver is doing little metabolically.
- Correction of acidosis with bicarbonate may be indicated if catecholamine responsiveness is lost.
- Electrolyte replacement - losses must be anticipated, the leaky gut and bowel lavage will result in potassium and phosphate depletion.
- Haemodialysis may be required to maintain metabolic normality, as well as to remove ammonia which may accumulate due to the acute hepatocellular necrosis
- Hypoglycaemia and ketosis will likely develop. The patient will need a dextrose infusion, as hepatic and skeletal muscle glycogen stores will be depleted.
- Nutrition will likely be parenteral for some time, depending on the extent of gastric ulceration.
- Coagulopathy will develop due to hepatocellular necrosis. Coagulation factor replacement will be required.
References:

The Royal Childrens Hospital has a good set of guidelines for iron overdose.


What key cardiac effects are observed with acute digoxin toxicity? List two rhythm disturbances highly associated.

List three drugs known to enhance digoxin serum level. Provide a mechanism for each.

Other than drugs, what other factors are known to exacerbate digoxin toxicity?

With respect to the use of digoxin specific Fab fragments:

- Outline your indications for use in suspected acute digoxin toxicity.
- Total serum digoxin level continues to remain high after the administration of an appropriate dose of digoxin specific Fab fragments. What action would you take and why?

College Answer

a) Key cardiac features are increased automaticity combined with AV conduction block.

Rhythms suggestive: PAT with variable block
Accelerated junctional rhythms
Bidirectional ventricular tachycardia (specific for Digoxin).
Other (a variety are seen): SA node arrest, premature ventricular contractions, bradycardia, non paroxysmal junctional tachycardia, AV nodal blockade, ventricular tachycardia, ventricular flutter and fibrillation.

**Note:** Features of digoxin effect (e.g. T wave flattening/inversion) do not correlate well with toxicity.

b) Verapamil, Diltiazem, Amiodarone via inhibition of P-glycoprotein (efflux pump that excretes many drugs, including Digoxin, into the intestine or proximal renal tubule) - effectively reducing renal and GI secretion.

Erythromycin, omeprazole via increased Digoxin absorption.

c) Low potassium, magnesium, pH, high calcium.

d) Early recognition of toxicity and prompt administration of Fab fragments essential for severe poisoning. The serum Digoxin concentration does not necessarily correlate with toxicity.

Indications Include:

- Life threatening arrhythmia with cardiovascular instability
- Evidence of end organ dysfunction
- Hyperkalaemia (> 5.0 – 5.5 mEq/l)
- Ingestion of 10mg or more in total
After Fab administration free Digoxin levels are decreased to zero within minutes. Total Digoxin level will increase markedly since assays measure bound and free. Bound fraction rises due to an increase in Digoxin-Fab complex. These high levels have no correlation with toxicity and the serum level may be unreliable for several days and no action should be taken based on total level after digoxin-specific Fab fragments administration.

Discussion

a)

The features of digoxin toxicity can be divided into cardiac and non-cardiac.

- **Cardiac:**
  - Bradycardia
  - AV block
  - Ventricular ectopics
  - Tachyarrhythmia- pretty much any variety which does not involve rapid AV conduction
  - Bidirectional ventricular tachycardia is ridiculously rare, but digoxin seems to be among the few drugs which can actually produce this.

- **Non-cardiac:**
  - Nausea/vomiting
  - Abdominal pain
  - Diarrhoea
  - Weakness
  - Confusion
  - Xanthopsia (seeing yellow)
  - Hyperkalemia (in acute overdose)

b)

Drug interactions of digoxin are a massive topic. The ones which result in overdose can be divided into inhibition of clearance (by inhibition of P-glycoprotein) and increase of absorption.

- **P-glycoprotein inhibitors:**
  - Calcium channel blockers like verapamol and diltiazem
  - Spironolactone
  - Quinidine
  - Amiodarone

- **Absorption enhancers**
  - Macrolides (by killing gut bacteria which normally digest some of the orally administered digoxin)
  - Proton-pump inhibitors (by increasing the permeability of the gastric mucosa)

c)

Digoxin toxicity is exacerbated by the following factors:

- Hypokalemia
- Hypomagnesemia
- Hypocalcemia
- Acidosis
d)

Indications for the use of digoxin-specific Fab fragments are strange.

Life-threatening arrhythmia, hyperkalemia and altered mental status are mentioned, but the article in UpToDate recommends that digoxin antibodies be used in every poisoning, because there is no therapy with a comparable efficacy and safety.

> "Total serum digoxin level continues to remain high after the administration of an appropriate dose of digoxin specific Fab fragments. What action would you take and why?"

One appropriate action would be to do nothing. The digoxin assay measures the total digoxin, whereas the free digoxin level after Fab may in fact be reduced to nearly zero. One is then confronted with a situation where the measured digoxin level is still very high, but the patient looks perfectly fine.

In such a situation, one should ignore the total level. I thank Yun from Canberra for pointing out the error in my
initial reading of this question. If the clinical features of toxicity have resolved, the total digoxin level is meaningless. If they have not resolved, the patient requires another dose of the specific Fab fragments. If for whatever reason this is inadequate, one may attempt resin hemoperfusion. However, this is not universally acknowledged as a useful strategy. Fab fragments together with plasmapheresis is another experimental technique.

References:

UpToDate has a nice article.


Marcus, Frank I. 'Pharmacokinetic interactions between digoxin and other drugs.' Journal of the American College of Cardiology 5.5s1 (1985): 82A-90A.


A 45-year-old male is admitted to the Emergency Department after ingesting an unknown quantity of "headache tablets". His initial complaints are nausea, vomiting, shortness of breath and tinnitus. Fluid resuscitation has been commenced. You are asked to assess him as he is getting more dyspnoeic.

His serum biochemistry and arterial blood gas profile are as follows:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient Value</th>
<th>Normal Adult Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>138 mmol/L</td>
<td>135 – 145</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.2 mmol/L*</td>
<td>3.4 – 5.0</td>
</tr>
<tr>
<td>Chloride</td>
<td>108 mmol/L</td>
<td>100 – 110</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>10 mmol/L*</td>
<td>22 – 27</td>
</tr>
<tr>
<td>FiO₂</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.32*</td>
<td>7.35 – 7.45</td>
</tr>
<tr>
<td>PO₂</td>
<td>125 mmHg (16.4 kPa)</td>
<td></td>
</tr>
<tr>
<td>PCO₂</td>
<td>20 mmHg (2.6 kPa)*</td>
<td>35 – 45 (4.6 – 6.0)</td>
</tr>
<tr>
<td>Base Excess</td>
<td>-10 mmol/L*</td>
<td>-2 – +2</td>
</tr>
<tr>
<td>Salicylate level</td>
<td>105 mg/dL*</td>
<td>3 – 10</td>
</tr>
<tr>
<td>Paracetamol level</td>
<td>&lt; 20 mg/L (&lt; 130 µmol/L)</td>
<td>&lt; 20 (&lt; 130)</td>
</tr>
</tbody>
</table>

a) Describe the acid-base status. (20% marks)
b) What are four severe complications of this toxidrome? (20% marks)
c) What coagulopathy may be present in this toxidrome and what is the treatment? (10% marks)
d) What are the treatment options for severe toxicity, and what is their rationale? (50% marks)

[ Hide Answer ]

College Answer

a) Acid-base status:
   Increased anion gap metabolic acidosis Concomitant normal anion gap metabolic acidosis Respiratory alkalosis
   Decreased delta ratio
b) Hypoglycaemia
   Pulmonary oedema Cerebral oedema Arrhythmias Hyperpyrexia
c) Hypoprothrombinaemia

Vitamin K

d)

Forced alkaline diuresis. Renal excretion of salicylates becomes important when the metabolic pathways become saturated. There is a 10-20 fold increase in elimination when the urine pH increased from 5 to 8.

Haemodialysis. Most of the drug is protein-bound, and is concentration dependant. The volume of distribution is small, and binding site saturation leads to large levels of free drug, which is easily dialyzable.

Multiple-dose charcoal. Many aspirin forms are slow release and after ingestion they clump together in the GI tract, forming a large slow release preparation. It is also poorly soluble in the stomach leading to delayed absorption.

Additional Examiners’ Comments:

Most candidates understood the acid-base abnormalities but not all were able to provide cogent answers relating to the complications and management. Few were able to describe all the treatment options for severe toxicity with the rationale for these strategies.

Discussion

This question is identical to Question 10 from the second paper of 2012.

b) Complications of salicylate overdose:

<table>
<thead>
<tr>
<th>Serum level 30-50mg/dL:</th>
<th>Serum level 50-75mg/dL:</th>
<th>Serum level &gt;75mg/dL:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Tachypnoea</td>
<td>• Tachypnoea</td>
<td>• Coma</td>
</tr>
<tr>
<td>• Respiratory alkalosis</td>
<td>• Respiratory alkalosis</td>
<td>• Hallucinations</td>
</tr>
<tr>
<td>• Nausea</td>
<td>• Fever</td>
<td>• Seizures</td>
</tr>
<tr>
<td>• Vomiting</td>
<td>• Sweating</td>
<td>• Cardiogenic shock</td>
</tr>
<tr>
<td>• Tinnitus</td>
<td>• Dehydration</td>
<td>• Coagulopathy, with raised INR.</td>
</tr>
<tr>
<td>• Dizziness</td>
<td>• Agitation</td>
<td>• Oliguria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Renal failure.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lactic acidosis and ketoacidosis</td>
</tr>
</tbody>
</table>

b) Coagulopathy in salicylate overdose? Its not just platelet inhibition. According to UpToDate, this is because of hepatotoxicity and interference with the synthesis of vitamin K dependent factors. Specifically, it is well known that salicylate toxicity can cause a decrease in prothrombin. Vitamin K (if not prothrombinex) is the answer.

c) Management of severe salicylate overdose consists of the following measures:

Decontamination

- **Multiple dose activated charcoal** is recommended by the UpToDate toxicology authors. Aspirin is well adsorbed by charcoal. Three 25g doses separated by two hours is the recommended regimen.
- **Whole bowel irrigation** is relevant in the context of sustained release preparations, and has been useful in animal models.

Direct and indirect antidotes

- **There is nothing specific.** Urinary alkalisation is generally held to be the nearest thing to a direct antidote.

Enhancement of clearance

- **Alkalise the urine.** This is vital. An alkaline blood environment also prevents the movement of salicylate into the CSF. Raising the urine pH from 5 to 8 can increase total salicylate excretion by twenty times.
- **Haemodialysis** may be required in severe cases, particularly where you cannot give any more bicarbonate (i.e. the patient is already fluid overloaded) or where the overdose is supermassive (levels in excess of 100mg/dL). Even though salicylate is highly protein bound this technique can usually move enough molecules to make a difference. One must also keep in mind the nonlinear kinetics of elimination - the higher the dose, the longer the half-life, and therefore the more prominent the effects of extracorporeal clearance.

Supportive ICU therapies

- **Intubation** may be indicated, but must be carried out carefully (see next point)
- **Mechanical (hyper)ventilation** will be required: if the patient ends up being intubated, their minute volume must be maintained at least as high as it was prior to intubation. Respiratory alkalosis keeps the salicylate ions trapped in the blood; if a post-intubation acidosis is allowed to develop the sudden influx of salicylate into the CNS may cause seizures, cerebral oedema and death.
- **Vaspressors and inotropes** may be useful in some cases, but in the majority of cases the patient will be hypotensive because of volume depletion.
- **Supplemental glucose:** these people are neuroglycopenic at normal BSL, and so the BSL should be kept at the higher range of normal.
Correction of hypokalemia is vital, because hypokalemia promotes $K^+$ reabsorption at the distal tubule (where $K^+$ is exchanged for $H^+$). Ergo, hypokalemia interferes with the attempt to alkalinise urine.

References:


