Management of Poisoning

Dr Muhammad Elamin
Consultant in Clinical Toxicology

Objectives

- At the end of the session you should be able to:
  - Manage acute paracetamol toxicity
  - Describe the management of patients with cardiovascular collapse secondary to poisoning
  - Formulate a differential diagnosis of toxic metabolic acidosis

2

Case 1

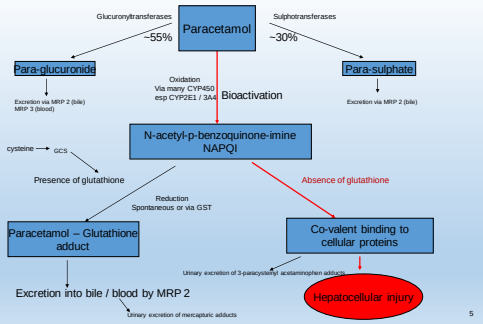
- 17 year old girl presents to hospital via ambulance at 04:00 having been found slumped in her bedroom by her father. She was last seen at 22:00. It is reported by the paramedic crew that 4 empty packets of paracetamol were next to her as well as an empty bottle of alcohol.
- On examination she has GCS 14/15, uncommunicative and smells of vomit. She has tenderness in her epigastrium but examination is otherwise normal.

3

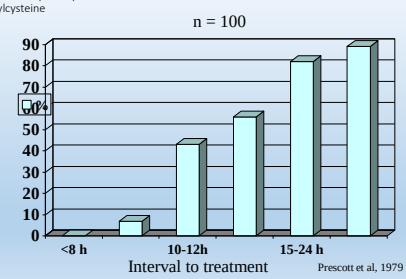
What is the correct management?

1. Start NAC based on history
2. She does not require antidote based on history
3. Take bloods and start NAC if elevated paracetamol
4. Start methionine

4



Proportion of patients above '200 line' developing severe hepatic dysfunction after i.v. acetylcysteine

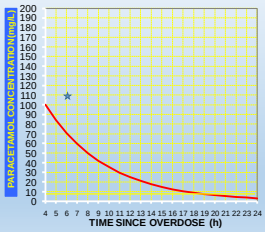


Prescott et al, 1979

Case 1
Bloods @ 6 hours

- Hb *14.3 g/dL* Plt *225 x 10^9/L* WCC *6.1 x 10^9/L* PT *14 sec*
- Para *110 mg/L*
- Na *141 mmol/L* K *4.4 mmol/L* Ur *4.1 mmol/L* Cr *87 µmol/L*
- Alk Phos *54* U/L ALT *18 U/L* Bili *11 µmol/L*
- CRP *21 mg/L*

UK Paracetamol treatment nomogram (new)



Case 1

- She is commenced on treatment
- 5 minutes into her second bag she tells the nurse that she is feeling unwell
- You note a rash on her face, she is sweaty and itchy.

10

What is the right course of action?

1. Stop NAC, give IV hydrocortisone, chlorpheniramine and IM adrenaline
2. Stop NAC, give IV hydrocortisone and IV chlorpheniramine
3. Stop NAC, give IV chlorpheniramine
4. Continue NAC and give IV chlorpheniramine

11

Case 1

- Treatment finishes and these are her blood results.
  - PT 16 sec [11-13]
  - ALT 98 U/L [0-30]
  - Creatinine 75 µmol/L [60-110]

12

Should she receive further NAC?

1. Yes
2. No
3. Abstain

13

Case 1

- Refer if worsening coagulopathy, acidosis, hypoglycaemia, renal impairment
- Rate of deterioration is important

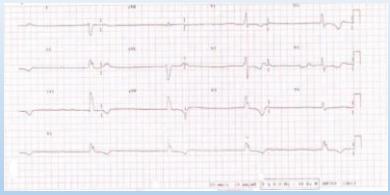
- Kings criteria for transplant (paracetamol)
  - pH below 7.3 despite fluid resuscitation
  - Creatinine > 300 micromol/L
  - PT > 100 (INR>6.5)
  - Grade 3 or 4 encephalopathy
- Lactate >3 post fluid resuscitation

14

Case 2

- 31yr male, 90 kg
- Past Medical History: Cluster headaches, Asthma, depression
- Out of hospital asystolic arrest reported
- Paramedics gave CPR & atropine 3mg IV
- Now BP 55/31, pulse 29/min, responsive to pain
- ECG…

15



16

Which is the most likely cause?

1. Atenolol
2. Verapamil
3. Digoxin
4. Amitriptyline
5. Salbutamol

17

Cardiac action potential

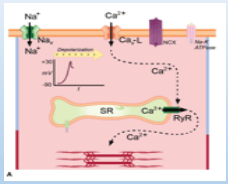


Image from Goldfrank's Toxicologic Emergencies 9th edition
Chapter 60 p885

Adrenergic NS

Heart

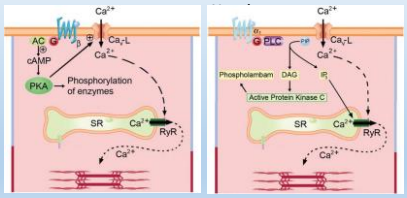


Image from Goldfrank's Toxicologic Emergencies 9th edition
Chapter 23, p331-332

Resuscitation

- He has IV access secured
- Given 500ml IV fluid
- Remains hypotensive and bradycardic
- What next?

Well Dr?

1. Adrenaline
2. Dobutamine
3. Digibind
4. Calcium
5. Glucagon
6. Insulin
7. TPN

Calcium

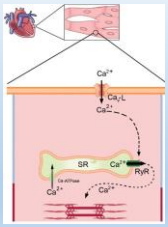


Image from Goldfrank's Toxicologic Emergencies 9th edition Chapter 60 p885

22

Calcium

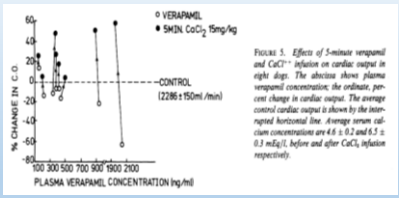


FIGURE 5. *Effects of 5-minute verapamil and $CaCl^{++}$ infusion on cardiac output in eight dogs. The abscissa shows plasma verapamil concentration; the ordinate, percent change in cardiac output. The average control cardiac output is shown by the interrupted horizontal line. Average serum calcium concentrations are 4.6 ± 0.2 and 6.5 ± 0.3 mEq/l, before and after $CaCl_2$ infusion respectively.*

Hariman et al, 1979

23

Calcium

- 10% calcium chloride 0.2 mL/kg up to 10 mL over 5 minutes
  - Give 2-3 times the dose if calcium gluconate is used (0.6 mL/kg up to 30 mL of 10% calcium gluconate over 5 minutes)
  - To achieve the effect intended high doses are required
  - Repeat the bolus dose of calcium every 10-20 minutes until a maximum of 4 doses given, or consider an infusion at 0.2 mL/kg/hour (maximum 10 mL/hour). Monitor the calcium level if repeat doses or infusion given
  - **Caution:** In cases of concomitant digoxin overdose, administration of calcium should be avoided

24

Progress

- He remained
  - Hypotensive
  - Bradycardic
  - Semi-conscious
  - Anuric
- Therefore transferred to critical care
- Started on Dobutamine and nor adrenaline
  - No improvement

25

What next?

1. Glucagon 10mg IV
2. Insulin 90 units IV
3. TPN 135mls of 20% IV

26

bolus

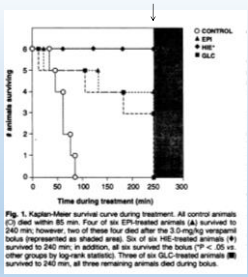


Fig. 1. Kaplan-Meier survival curve during treatment. All control animals (○) died within 85 min. Four of six EPI-treated animals (▲) survived to 240 min; however, two of these four died after the 3.0-mg/kg verapamil bolus (represented as shaded area). Six of six HIE-treated animals (◆) survived to 240 min; in addition, all six survived the bolus (*P < .05 vs. other groups by log-rank statistic). Three of six GLC-treated animals (■) survived to 240 min, all three remaining animals died during bolus.

Kline, 1993

27

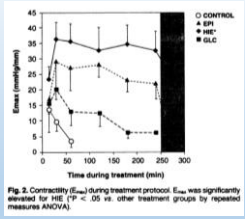


Fig. 2. Contractility (E_{max}) during treatment protocol. E_{max} was significantly elevated for HIE (*P < .05 vs. other treatment groups by repeated measures ANOVA).

Kline, 1993

28

Microvascular dysfunction

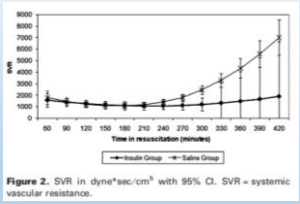
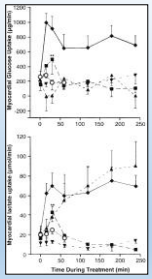


Figure 2. SVR in dyne*sec/cm^5 with 95% CI. SVR = systemic vascular resistance.

Holger et al, 2010

29

Figure 2



Beneficial myocardial metabolic effects of insulin during verapamil toxicity in the anesthetized canine.
Kline, Jeffrey; Leonova, Elena; Raymond, Richard

Critical Care Medicine. 23(7):1251-1260, July 1995.

Figure 2. Myocardial glucose (top) and lactate (bottom) uptake. Insulin significantly increased myocardial glucose and lactate uptake (p < .01, repeated measures). At 10 mins, glucagon increased both myocardial glucose and lactate uptake (**p < .01 vs. control, contrast analysis), but this increase was not sustained. With epinephrine, myocardial lactate uptake paralleled [lactate]. Open circles, control; inverted triangles, calcium chloride; triangles, epinephrine; squares, glucagon; diamonds, hyper-insulinemia-euglycemia. Mean +/- SEM values.

30

Insulin - clinical experience

Review - Engbretsen et al, Clin Tox, 49,2011

- High dose
  - Bolus
    - 0.1 – 10U/Kg [most 1U/Kg]
  - Infusion
    - 0.015-22U/Kg/Hr [most 0.5-2U/Kg/Hr]
- Monitoring
  - Biochemistry and lactate more helpful than haemodynamics
- Adverse effects
  - Hypokalaemia
  - Hypoglycaemia
    - Concurrent 10-20% dextrose infusion

31

Glucagon

- Pancreatic polypeptide
- Glucagon receptor
  - Gs linked receptors
  - Adenylate cyclase
  - Increased cAMP [+/- arachidonic acid]
  - Inotropic & Chronotropic
  - Less effective in heart failure

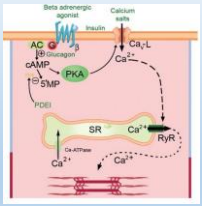


Image from Goldfrank's Toxicologic Emergencies 9th edition

32

Decision

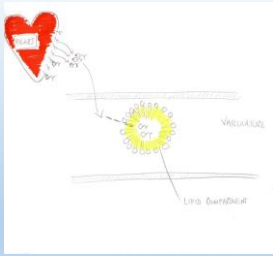
- His BP is now 35/10 and pulse 27/min
- Insulin isn't working
- Glucagon isn't working
- Inotropes aren't working
- He is going to die…
- Anything else?

33

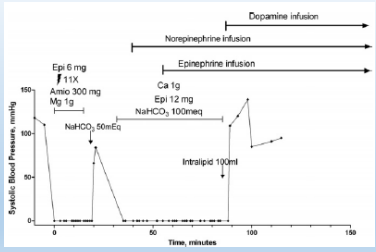
Intralipid – mechanism

- Unclear
  - Lipid sink
  - Fatty acid metabolism
  - Increased intracellular calcium
  - Charge-charge interaction
  - Transmembrane pH gradient alteration
- For lipophyllic drugs

34



35



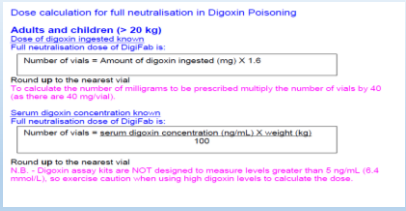
36

Digoxin specific antibodies

- For
  - life-threatening tachyarrhythmias
  - Bradyarrhythmias unresponsive to atropine
    - Hyperkalaemia
    - High digoxin level >6hrs post ingestion [eg >10μg/L]

37

Toxbase DigiFab



Dose calculation for full neutralisation in Digoxin Poisoning

Adults and children (> 20 kg)

Dose of digoxin ingested known
Full neutralisation dose of DigiFab is:

Number of vials = Amount of digoxin ingested (mg) X 1.6

Round up to the nearest vial
To calculate the number of milligrams to be prescribed multiply the number of vials by 40 (as there are 40 mg/vial).

Serum digoxin concentration known
Full neutralisation dose of DigiFab is:

Number of vials = serum digoxin concentration (ng/mL) X weight (kg) / 100

Round up to the nearest vial
N.B. - Digoxin assay kits are NOT designed to measure levels greater than 5 ng/mL (6.4 mmol/L), so exercise caution when using high digoxin levels to calculate the dose.

Case 3

- 38 yr old female mechanic
- Acting bizarrely at work
- Collapses in the waiting room in A&E and has a brief seizure
- Brought into resus
- Bloods sent
- BP 160/95, HR 88/min, RR 32/min, O2 Sats 98%

ABG

• pH	7.11	[7.35-7.45]
• PaCO2	2.5 kPa	[4.7 - 6.0]
• PaO2	41.6 kPa	[10.5 - 14.0]
• HCO3	9 mmol/L	[22 – 30]
• Base Excess (BE)	-16 mmol/L	[-2.5 to +2.5]

What is the likely diagnosis?

1. Carbon monoxide poisoning
2. Post seizure acidosis
3. Lead toxicity
4. Ethylene Glycol
5. Ethanol

Bloods

- Na 131 mmol/L (133-146), K 5.0 mmol/L (3.5 – 5),
  Urea 7.0 mmol/L (2.3 - 6.7), Creatinine 155 µmol/L (60-110)
- Glucose 8.0 mmol/L (3.5 - 11.0), lactate 5.7 mmol/L (<2.2)
- Bicarbonate 11 mmol/L (22-30), Chloride 105 mmol/L (95-105)
- Serum osmolarity 322 mOsm/kg (mmol/kg) (275–295)
- Ethanol not detected

42

What is the correct management?

1. IV Fomepizole
2. IV Ethanol
3. Oral ethanol
4. Await toxic alcohol levels
5. No immediate treatment required

43

Osmolal gap

- Measured – calculated osmolality
- Calculated
  - (2x[Na]) + [K] + [urea] + [glucose]= 282
- Measured 322
- OG = 40 mOsm/Kg H2O
- Normal ~ 10 mOsm/Kg H2O

44

Anion Gap

- ([Na] + [K]) – ([HCO3] + [Cl])
- 136 – 116
- AG = 20 mmol/L
- Normal is ~ 12-16

45

Worsens

- She is managed with IV fomepizole infusions but develops renal impairment with creatinine 205 and ongoing metabolic acidosis
- Ethylene glycol level is high at 2600mg/L

46

Haemodialysis will remove ethylene glycol

1. True
2. False

47

Objectives

- At the end of the session you should be able to:
  - Manage acute paracetamol toxicity ✓
  - Describe the management of patients with cardiovascular collapse secondary to poisoning ✓
  - Formulate a differential diagnosis of toxic metabolic acidosis ✓

48