What's New
- Pain -

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Past Medical History

- Cellulitis
- Chronic Kidney Disease
- Congestive Cardiac Failure
- Depression
- Hypertension
- Ischaemic Heart Disease
- Left Bundle Branch Block
- Migraine
- Obesity (BMI 35kg/m^2)
- Parkinson's Disease
- Rheumatoid Arthritis
- Spondylosis

Medicines Reconciliation

- Terbutaline inhaler
- Glyceryl Trinitrate spray
- Budesonide/Formoterol Inhaler
- Amlodipine 5mg od
- Aspirin 75mg od
- Furosemide 80mg od
- Nicorandil 30mg bd
- Ramipril 10mg od
- ISMN XL 60mg od
- Pravastatin 80mg od
- Pizotifen 500mcg od

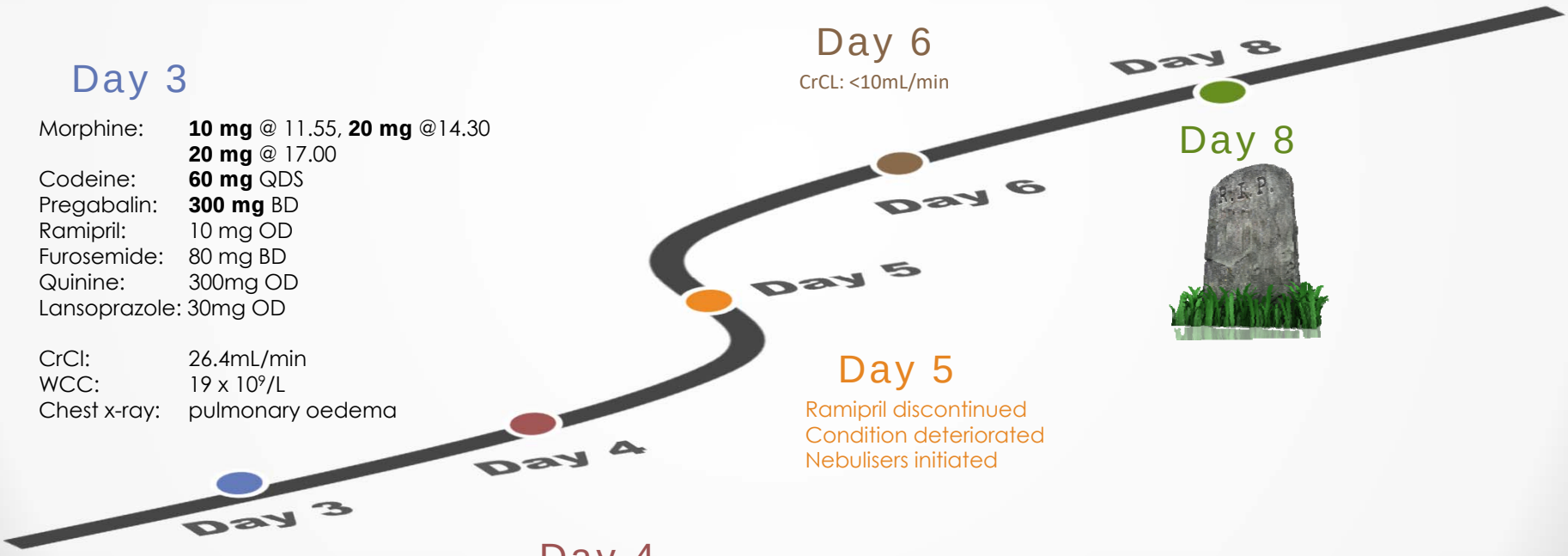
- Co-beneldopa 25mg/100mg max 6 daily
- Domperidone 10mg prn tds
- Tramadol 50-100mg qds/prn
- Pregabalin 300mg bd
- Folic Acid 5mg od
- Ferrous Sulfate 200mg bd
- Mebeverine 200mg bd
- Citalopram 40mg od
- Lansoprazole 30mg od
- Quinine Sulfate 300mg od
- Zolpidem 5mg od

TIMELINE

Day 3

Morphine: **10 mg** @ 11.55, **20 mg** @14.30
20 mg @ 17.00
Codeine: **60 mg** QDS
Pregabalin: **300 mg** BD
Ramipril: 10 mg OD
Furosemide: 80 mg BD
Quinine: 300mg OD
Lansoprazole: 30mg OD

CrCl: 26.4mL/min
WCC: 19 x 10^9/L
Chest x-ray: pulmonary oedema



Day 4

Pregabalin discontinued
Furosemide 80mg IV stat
IVABs (meropenem)
Naloxone: 400mcg @1100, 1350 and 1630
DNACPR

Day 5

Ramipril discontinued
Condition deteriorated
Nebulisers initiated

Day 6

CrCL: <10mL/min

Day 8

Toxicology

- Postmortem blood
  - Morphine 175 µg/L
  - Codeine 166 µg/L
- Toxicologist's conclusions:
  - In the absence of adequate tolerance, the reported concentration of morphine could have posed a threat to life
  - Patient was **not** opioid tolerant

Toxicology

- Additional report requested 6 months later

  Blood

  - ‘Free' morphine – 175 µg/L
  - 'Total' morphine – 225 µg/L
- In the absence of adequate tolerance, the reported concentration of morphine could have posed a threat to life
- **Concentrations of 'free' and 'total' morphine indicate that this drug may have been used/administered shortly before death**

Toxicology

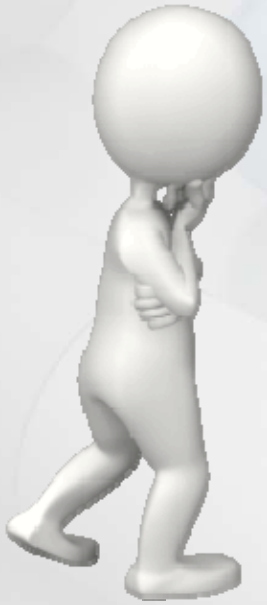
- Further analysis requested 2 months later

  Blood

  - 'Free' morphine – 265 µg/L
  - M-6-G/M-3-G – non detected

- Fatal morphine toxicity is associated with free (unmetabolised) blood concentrations >200µg/L

Did 50mg oral morphine plus 240mg codeine contribute or cause the patient's death 120 hours later?



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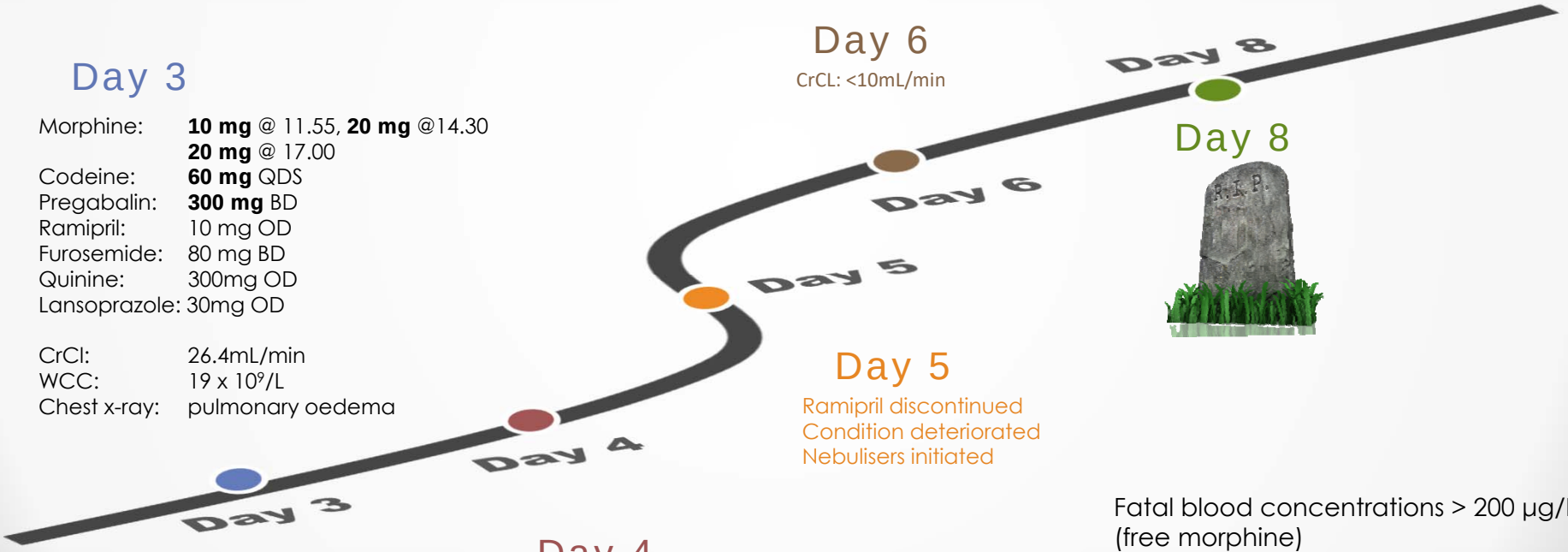

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Fatal blood concentrations > 200 µg/L (free morphine)

1st toxicology report – 175 µg/L

2nd toxicology report – 175 µg/L

3rd toxicology report - 265 µg/L

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Why such high PM morphine levels?

- What could have potentiated morphine?
- Factors affecting pharmacokinetics:
  - Co-morbidity - renal function, obesity
  - Drug interaction
  - Genetics

Why such high PM morphine levels?

- Oral bioavailability of morphine - wide interpatient variation from 15-69%; average value of 30-40%
- Morphine undergoes rapid first-pass metabolism
  - Renal clearance of morphine is low
- M6G and M3G are mainly eliminated by renal clearance with some biliary excretion
  - enterohepatic recycling
- M6G has a half-life of about 50 hours (38-103) in patients with end stage renal failure
  - 3-5 hours in the presence of normal renal function

Why such high PM morphine levels?

- Quinine & lansoprazole are P-gp inhibitors
- Both drugs *could* have:
  - increased the absorption of morphine from the GI tract
  - enhanced enterohepatic recirculation of morphine
- Net effect - increase oral bioavailability of morphine
- Quinine *could* have reduced CYP2D6 activity
  - ↓ analgesic benefit from codeine (↓ morphine)

Toxicology

- After death, drugs may move from one area of the body to another
  - post-mortem redistribution
- Is extremely difficult to interpret significance of post-mortem drug concentrations and cause of death
- Reported concentrations may not be representative of those at time of death
- Incorrect sample storage (e.g. temperature) can cause M6G to be cleaved back to morphine

Final Report

- Causes of death:
  - 1a Congestive Cardiac Failure/ AKI/early acute bronchopneumonia
  - 1b Fractured ankle
  - 2 Morphine administration
- High free morphine in blood most likely due to accumulation of metabolites
  - most likely caused by renal impairment, with unknown contribution from P-gp inhibitors
- After death and probable inappropriate storage, metabolites converted back to free morphine