Question 32
A 75 year old man with non small cell lung cancer and mild chronic renal failure (<his serum creatinine is usually 0.15 mmol/L (0.06-0.12)> is recovering from hip replacement surgery. He has been receiving intravenous pethidine via a patient-controlled analgesia for the past three days. Over the last 24 hours, he has developed myoclonic twitching of all limbs and then has a grand mal seizure.

The most likely cause of his neurological signs is:

- A. Brain mets
- B. Uraemia
- C. Hypercalcaemia
- D. Pethidine metabolites
- E. Stroke

Answer:

Commonest cause of seizures in those age >65 is stroke but this man has other risk factors for seizures

In the setting of renal impairment and a drug with seizure potential, the answer is D.

- Pethidine: synthetic opioid
- **Pethidine 75mg-100mg IV equivalent to morphine 10mg IV** in terms of analgesic/ euphoric/ sedative/ respiratory depressive properties, but suppressive effects on cough reflex less
- Other off-label use: 12.5mg IV stat for rigors
- Faster onset of action (more lipid soluble and more addictive) but **shorter duration of effect** compared to morphine
- 70% protein bound
- Mainly metabolised by liver

- Pethidine hydrolysed (liver) to pethidinic acid, and demethylated to norpethidine
- **Norpethidine** is neurotoxic -> dose related PAN (pethidine associated neurotoxicity)
- Causes:
  - Tremor/ twitches
  - Hallucinations
  - Mood changes
  - Seizures and myoclonus
- Long half-life (8-12 hours)
- Norpethidine mainly cleared by kidneys so accumulates in renal failure
- Half the analgesic properties of pethidine
- **Toxic effects not counteracted by opioid antagonist eg naloxone**
- Seizures should be managed supportively +/- benzodiazepines, and use of other analgesia is recommended
- Has anti-cholinergic effects
- Many drug interactions:
  - Avoid respiratory depressants/ CNS depressants
  - MAO inhibitors -> excitation, sweating, hypo/hypertension +/- fatal
  - Phenytoin/ phenobarbitone -> ↑ metabolism thus more norpethidine

Uraemia can also cause seizures but unlikely to have such high urea levels with a Cr of 150. Typically it is hypocalcaemia rather than hypercalcaemia that causes seizures.

Other clinical features of hypocalcaemia
- Tetany, myopathy and weakness, cramps, QT prolongation, papilloedema, mental changes