Q3 Describe the pharmacology of phenytoin (March 2012, Q2 March 2010))

Phenytoin is an anticonvulsant used in the management of grand mal and partial seizures, trigeminal neuralgia, and ventricular arrhythmias (possesses Class 1 antiarrhythmic properties). It is not indicated for absence seizures.

PHARMACEUTICALS - presented as capsules, syrup and solution for injection.

PHARMACODYNAMICS
MECHANISM OF ACTION → binds to and stabilises inactivated sodium channels, preventing further generation of action potentials required for seizure generation (sodium channel blockade also occurs in cardiac tissue, hence its antiarrhythmic actions). May also reduce calcium influx into neurons to reduce neurotransmitter release, enhance the effects of GABA, and block glutamate receptors.

SIDE EFFECTS → There is a large genetic variation in the metabolism of phenytoin (slow hydroxylation) and a narrow therapeutic window, requiring regular levels. It is a potent enyzme inducer and increases the metabolism of warfarin, benzodiazepines and the OCP. Rapid administration of loading IV dose can cause hypotension.

Idiopathic side effects - cardiac arrhythmias, blood dyscrasias, SIADH, hirsuitism in females, gingival hyperplasia
Concentration dependent side effects - n/v, behavioural disturbance, paradoxical seizures, peripheral neuropathy.

PHARMACOKINETICS
ADMINISTRATION
Route - PO or IV
Dose – 15-20mg/kg IV loading dose then daily dose depending on levels, aiming 10-20mcg/ml.
Bioavailability - ~100%
Time to onset - 30-60min

DISTRIBUTION
Vd - 0.6-0.7L/kg
Protein binding - 90%

METABOLISM - hepatic metabolism via hydroxylation and glucuronidation (CYP 450 system). Zero order kinetics at higher doses (ie, saturable hepatic hydroxylation, meaning metabolism is independent of plasma concentrations). Metabolism may be inhibited by metronidazole, chloramphenicol and isoniazid.

ELIMINATION - urine as glucuronides (<5% unchanged). Half life normally 10-15hrs however can increase with drug accumulation.