Describe the pharmacology of Phenytoin (75% of marks) and Levetiracetam (25% of marks). → 35% pass rate

### Anticonvulsants

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<th>Phenytoin</th>
<th>Levetiracetam</th>
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| **Indications** | Anticonvulant and antiarrhythmic (V-W class 1b)  
Epilepsy  
Trigeminal neuralgia  
TCA toxicity  
Digoxin-induced arrhythmias | Epilepsy in the case of partial seizures  
Adjunctive therapy for partial, myoclonic and tonic-clonic seizures |
| **PC** | - Hydantoin derivative  
- Routes of administration PO and IV  
- Precipitates at pH < 7  
  o → variable oral absorption  
  o → IM contraindicated  
- Doses 10-20 mg/kg (plasma levels required aim 10-20µg/mL)  
- Rapidly achieves peak [ ] (<20mins after loading)  
- Duration 30mins-1hr but highly variable | - Pyrroolidine  
- Highly lipid soluble  
- Steady state after two days of a twice daily administration schedule.  
- Dose: PO/IV 1000 mg daily given as 500 mg 2 times a day |
| **PD** | - Slows inward Na and Ca ion flux during depolarisation and delays outward K flux.  
  o Stabilises the inactive state of V-gated Na channels limiting repetitive generation of APs.  
  ▪ Limits spread of seizure  
  o Reduce glutamate release and thus attenuating Ca entry  
- Enhance action of GABA | 1. Partial inhibition of N-type Ca2+ currents and reduced release of Ca2+ from intra-neuronal stores causing reduced intra-neuronal Ca.  
2. Inhibition of synaptic vesicle protein 2A (SV2A) involved in vesicle fusion and neurotransmitter exocytosis  
  - → membrane hyperpolarisation → ↓NT release. |
| **PK** | **Absorption**  
- IV  
- PO – variable (above) 30-75%  
**Distribution**  
- 90% protein bound  
**Metabolism**  
- Hepatic to parahydroxyphenyl (inactive)  
  o hydroxylation by CYP450 2C9  
    ▪ Metabolism effected by inducers or inhibitors of CYP450 2C9  
  o induces its own CYP450  
- Mixed 1st and zero order kinetics as process is saturatable  
  o 1st order at plasma [ ] < 10 µg/mL  
    ▪ t1/2 ~ 24hr  
  o 0th order at plasma [ ] > 10 µg/mL  
    ▪ t1/2 dose dependent  
**Excretion** | **Absorption**  
- IV  
- Rapidly absorbed after oral administration. Oral BA 100%.  
**Distribution**  
- <10% protein bound  
**Metabolism**  
- Enzymatic hydrolysis (24%) in a large number of tissues including whole blood but not plasma.  
**Excretion**  
- T1/2 7hrs  
- 95% excreted in the urine  
- 65% unchanged |
### Tox

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<th>Mixed kinetics $\rightarrow$ plasma level strongly influenced by drugs which induce/inhibit CYP450 2C9</th>
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#### Toxicity

- **Dose dependent**
  - $> 20$ µg/mL $\rightarrow$ ataxia, nystagmus, drowsiness
  - Rapid infusion $\rightarrow$ hypotension, arrhythmia
  - GI irritation, rash
- **Idiosyncratic**
  - Rash, acne, gum hyperplasia, SLE, porphyria, peripheral neuropathy
- **Other**
  - Teratogenesis (hydatoin syndrome)
  - Hypoglycaemia/calcaemia

**Therapeutic Drug monitoring available**

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- Somnolence, asthenia, and dizziness
- Does not induce or inhibit CYP and is not a substrate
  - $\rightarrow$ devoid of known interactions with other anti-seizure drugs, oral contraceptives, or anticoagulants

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**Examiner Comments**

The knowledge of phenytoin was often superficial and many answers were too brief and didn’t adequately cover the required material. The knowledge around levetiracetam seemed very limited with many candidates guessing (incorrectly) what the pharmacokinetics might be. Most answers demonstrated a structured approach to this type of question.

Better answers were able to distil major issues such as the narrow therapeutic window for phenytoin or the potential clinical impact of differing ordered kinetics or altered metabolism. Candidates are reminded to read each question carefully; levetiracetam should not be confused with levosimendin.