**Question 57**

A 24 year old man with a severe closed head injury is receiving phenytoin after having three seizures. He has received a loading dose of 1000mg and then 300mg/day via naso-enteric tube. His phenytoin concentration one week later is 8 microg/L (therapeutic range 40-80 microg/L).

A number of his other treatments are listed below. Which one is most likely to have contributed to the subtherapeutic phenytoin concentration?

A. Metronidazole  
B. Naso-enteric feeds  
C. Omeprazole  
D. Hyperventilation  
E. Erythromycin

**Answer:**

**Phenytoin**

- Primary site of action: motor cortex  
- Main anti-epileptic effect: **blocks voltage dependant sodium channels** -> promotes sodium efflux from neuron -> stabilises membrane against hyperexcitability  
- ↓ **synaptic transmission**; inhibits calcium-calmodulin protein phosphorylation  
- For **generalised** (not effective for absence) and **partial** seizures (usually 2\textsuperscript{nd} line)  
- In treatment of status epilepticus, it has slower onset (30 minutes) and longer duration (6-12 hours) compared to benzodiazepines. Needs to be given together to allow immediate and sustained seizure control  
- **Seizure prevention in neurosurgery** and treatment of certain **arrhythmias**  
- **NOT indicated for seizures secondary to metabolic causes eg hypoglycaemia**

- Phenytoin demonstrates **non-linear kinetics**
  - With linear kinetics, $t_{1/2}$ used to determine dose rate, drug accumulation and time to reach steady state  
  - With non-linear kinetics, half-life affected by absorption, saturation of metabolic pathways, dose and degree of enzyme induction  
  - Thus **large inter and intra-patient variability**

  - **Need to check levels 7-10 days after initiation, dose change, addition of new drug/ removal of drug**
    - Trough levels (just prior scheduled dose) provide information re compliance and clinically effective serum range  
    - Peak levels (at time of expected peak concentration) provide information re individual’s threshold for emergence of side effects  
    - **Extensively protein bound (90%), only the free fraction is active**  
    - **Water-insoluble and very alkali (pH 12)**

- **Unusually ↑ levels**
  - Liver disease  
  - Congenital enzyme deficiency/ different isoenzymes  
  - Drug interactions -> metabolic interference  
  - Hypoalbuminaemia of pregnancy/ uraemia -> high free levels

- **Unusually ↓ levels**
  - Non-compliance
- Hypermetabolisers of phenytoin eg congenital, acute trauma, pregnancy, young children, menstruation

- Needs initial **loading dose**
- Long $t_{1/2}$ averages 22 hours (between 7 – 44 hours)
- Steady state therapeutic range achieved after $t_{1/2}$ (usually quoted at **5.5 $t_{1/2}$**)

- **Metabolised in liver** by CYP2C9 (major), CYP2C19 (minor) and CYP3A4 (inducible)
- This enzyme system is **saturable**, thus at high plasma levels, any small increments in dose (even up to 10%) may prolong $t_{1/2}$ significantly leading to intoxication
- Excretion into bile as inactive metabolites -> reabsorbed by intestines -> **excreted in urine** via glomerular filtration (minor) and tubular secretion (major)

### Adverse effects

<table>
<thead>
<tr>
<th>Dose related (similar to other antiepileptics)</th>
<th>Neurotoxic effects</th>
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<tbody>
<tr>
<td>- Drowsiness</td>
<td>- Drowsiness</td>
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<tr>
<td>- Confusion</td>
<td>- Confusion</td>
</tr>
<tr>
<td>- Tremor</td>
<td>- Tremor</td>
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<tr>
<td>- Dysarthria</td>
<td>- Dysarthria</td>
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<tr>
<td>- Ataxia (of gait, not upper limb)</td>
<td>- Ataxia (of gait, not upper limb)</td>
</tr>
<tr>
<td>- Diplopia and nystagmus</td>
<td>- Diplopia and nystagmus</td>
</tr>
</tbody>
</table>

- Paradoxical $\uparrow$ in seizure frequency

<table>
<thead>
<tr>
<th>Idiosyncratic effect</th>
<th>Reversible:</th>
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<tbody>
<tr>
<td>- <strong>Gingival hypertrophy</strong></td>
<td>- <strong>Gingival hypertrophy</strong></td>
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<tr>
<td>- $\uparrow$ body hair</td>
<td>- $\uparrow$ body hair</td>
</tr>
<tr>
<td>- Coarsening of facial features</td>
<td>- Coarsening of facial features</td>
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<tr>
<td>- Acne</td>
<td>- Acne</td>
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</tbody>
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**Lymphadenopathy**

- Mostly benign lymph node hyperplasia
- Rare association with Hodgkins lymphoma

**Rash**

- Associated Steven Johnson’s and toxic epidermal necrolysis (within $1^{st}$ 8 weeks)

**Macrocytic anaemia**

- Responds to folic acid (but adding this may $\downarrow$ drug efficacy)

**Anticonvulsant Hypersensitivity Syndrome**

- Benzene ring metabolised by CYP450 to arene oxide
- Rare but life-threatening
- Within 1-4 weeks
- Fever, rash and multiorgan involvement (hepatitis, myocarditis, myositis, lymphadenopathy, pneumonitis)
- Also seen in barbiturates and carbamazepine (similar benzene ring)
- Valproate structurally different so no cross reactivity; lamotrigine cause similar syndrome but no cross reactivity
**Long term effects**

<table>
<thead>
<tr>
<th>Cerebellar degeneration</th>
<th>Sensory peripheral neuropathy</th>
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<tbody>
<tr>
<td><strong>Osteomalacia/ osteoporosis</strong></td>
<td></td>
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<tr>
<td>- By ↑ Vit D3 metabolism</td>
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</tbody>
</table>

**Drug interactions complex:**
- Induces cytochrome P450 enzymes
- Metabolised by CYP2C9 and CYP2C19 -> any drugs inhibit/ induce these enzymes affect levels
- 90% protein bound -> any drug that displaces phenytoin -> ↑ free levels
- **Oral absorption affected by enteral feeding significantly (up to 80%)** and certain drugs/ nutritional supplements
  - Continuous enteral feeds: phenytoin IV
  - Intermittent enteral feeds: 2 hours post/prior feed
  - Including calcium supplements and antacids
- Some drugs lower seizure threshold (eg antipsychotics, beta lactams) and may precipitate seizures despite therapeutic phenytoin levels

**Overdose** (Lethal dose in adults 2-5g)
- No antidote
- Poorly absorbed in stomach, so activated charcoal useless
- Death from CNS, respiratory and circulatory depression

Back to the question:
Normal adult dosage: 4-5 mg/Kg initially, then ↑ gradually to maximum of 600mg/day in divided doses. After a loading dose of 1000mg and daily oral dose of 300mg, one would expect his levels to be therapeutic by 1 week.

A. Metronidazole (anaerobic cover). It is NOT protein bound. It is excreted in the urine predominantly as metronidazole and inactive metabolites -> does not interfere with phenytoin metabolism

B. Correct. Phenytoin is very water-insoluble and crystallizes if mixed with any glucose containing solution -> drastically ↓ phenytoin absorption. In general any drug that forms precipitates or is very acidic (pH <4) are unsuitable. There are many examples, but notable ones include **fluoroquinolones** (eg ciprofloxacin), **antacids** (Al and Mg containing), **iron supplements, metoclopramide, and lithium**. Note that **warfarin**’s pharmacokinetics also affected (↓ efficacy) due to erratic gut absorption and vitamin K antagonism from the vitamin K in the feeds.

C. Omeprazole is a proton pump inhibitor -> ↓ gastric H+ secretion. It is 95% protein bound and metabolised by the hepatic cytochrome p450 enzymes. It has been shown to ↑ **plasma phenytoin levels** by ↓ plasma clearance by and displacing phenytoin from albumin.
D. Hyperventilation -> ↓ carbon dioxide concentration -> constriction of cerebral vessels -> ↓ ICP (closed head injury). Each ↓ p_aCO_2 by 1mmHg ↓ cerebral blood flow by 3%. The aim is a p_aCO_2 between 25-30mmHg only for short durations when immediate control of ICP needed. Prolonged hyperventilation may ↓ cerebral blood flow to below the “ischaemic threshold” (anecdotally quoted at a p_aCO_2 of <20 mmHg), leading to infarction of marginal areas. This may lead to infarct-related seizures but will not affect phenytoin levels.

E. Erythromycin (macrolide: binds to 50S ribosomal subunit to inhibit protein synthesis, good G+ve and G-ve cover). 75% protein bound, predominantly metabolised by liver (a substrate and inhibitor of cytochrome p450 CYP3A family) thus ↑ and prolongs t_{1/2} of phenytoin (also affects carbamazepine). Another notable side effect of erythromycin is that it prolongs the QT interval and can rarely cause interstitial nephritis.