Question 31

A patient, previously untreated, is commenced on phenytoin therapy with an intravenous loading dose of 1000mg, followed immediately by oral administration of 300mg/day as a single daily dose.

Assuming that phenytoin has an elimination half-life of 30 hours, what is the best estimate of the length of time after the initial loading dose that then patient will achieve steady state conditions with respect to phenytoin?

A. Immediately
B. One day
C. Three days
D. Six days
E. Twelve days

Refer to 2002P2Q57 (also on phenytoin)

Estimation of length of time to achieve steady state in phenytoin = 5-7 half-lives

Usually quoted as $5.5 \times t_{1/2}$ ($5.5 \times 30$ hours = 165 hours = 6.8 days) = closest answer is D

**Half life**
- Time required for 50% of drug to be eliminated

**Steady state**
- A point during *chronic* drug administration
- Amount of drug administered per unit time = amount of drug eliminated per unit time
- During continuous IV: plasma drug concentrations at steady state are stable
- During chronic oral administration: plasma drug concentration may vary during dosing interval but the time-concentration profile between intervals is stable

**Loading doses**
- For some drugs, indication may be urgent so time to steady state levels is too long
- Loading dose -> rapid plasma elevations -> achieves therapeutic effect faster
- However time taken to achieve *true steady state is still determined only by half-life*
- Only appropriate if there’s a *defined relationship between drug dose and clinical effect*
- Loading dose = $C \times V$
  - $C$ is the desired plasma concentration
  - $V$ is the volume of distribution

**OR**
- Loading dose = $Fr \times MD$
  - $Fr$ is the fraction of drug eliminated during dosing interval
  - $MD$ is the planned maintenance dose

**Linear kinetics**
- Drug concentration $\propto$ dose
- Rate of elimination $\propto$ drug concentration

Thus – if doubling of steady state concentration is desired, the dose should be doubled

**Non-linear kinetics**
- Drug concentration is not proportional to dose (and/or)
- Rate of elimination is not proportional of drug concentration
- The main reason is that drug elimination is dependant on enzymes
  - Enzyme concentrations may vary according to genetics, illness, nutrition
  - Enzyme systems also saturable, affected by agonists, can be induced/ inhibited

Thus - plasma concentrations change disproportionately with small dose alterations