Deacon's Challenge

No 129 - Answer

A 22 year old man (body weight 75 Kg) was referred to a Neurologist by his GP with a history of 8 seizures over the previous 3 months. He was previously successfully treated for grand mal epilepsy for many years with sodium phenytoin 100 mg bd. After obtaining a trough plasma phenytoin level of 8 mg/L the neurolgist increased the dose to 150 mg bd. However, the patient misunderstood the Neurologist's instructions and continued to take his old tablets in addition to his new dose (so that he was actually taking 250 mg bd). Over the next few weeks he became increasingly unwell, complaining of tiredness, nausea and vomiting. In A&E nystagmus was noted, a plasma phenytoin level (30 mg/L) confirmed phenytoin toxicity and medication was stopped immediately. The Neurologist has asked you to estimate how long it will take for the plasma level to return to the relatively safe concentration of 10 mg/L by endogenous clearance alone, at which point medication will be resumed.

Assume a volume of distribution of 0.65 L/Kg, normal renal and hepatic function and that phenytoin clearance follows saturation kinetics. Using the direct linear plot of Mullen to evaluate previous data, his K_m was estimated at 5.0 mg/L and V_{max} at 312 mg/24 h/total vol.

Phenytoin is metabolised by hepatic oxidases which may become saturated. Therefore the rate of metabolism is non-linearly related to dose and mirrors the Michaelis-Menten equation used in enzyme kinetics. However, we are now dealing with concentrations and times rather than rates so the integrated form of the Michaelis Menten equation is used (see Wagner GW, *J Pharmokinetics Biopharmaceutics* 1973, **1(Part 2):** 103-121)

$$V_{max}.t = C_0 - C_t + K_m \ln(C_0/C_t)$$

Where C_0 = initial concentration = 30 mg/L
C_t = concentration at time t = 10 mg/L
K_m = Michaelis-Menten constant = 5.0 mg/L
V_{max} = maximal velocity = 312 mg/24 h/total vol

Note that the units of V_{max} determined from the Mullen nomogram are mg/24 h/total volume of distribution and need to be converted to mg/h/L since plasma drug concentrations are mg/L and we need to calculate time in hours. Therefore the V_{max} needs to be divided by 24 and the total volume of distribution:

Total volume of distribution (V_d) = Body weight (Kg) x Vol distribution (L/Kg)
= 75 x 0.65 = 48.75 L

$$V_{max}\ (mg/h/L) = \frac{V_{max}\ (mg/24\ h/total\ V_d)}{24 \times Total\ V_d}$$

$$= \frac{312}{24 \times 48.75} = 0.267\ mg/h/L$$

Substitute these values into the integrated Michaelis-Menten equation and solve for t:

$0.267\ t = 30 - 10 + 5.0 \ln (30/10)$

$0.267\ t = 20 + 5.0 \ln 3$

$0.267\ t = 20 + (5.0 \times 1.10)$

$0.267\ t = 20 + 5.5 = 25.5$

$t = \frac{25.5}{0.267} =$ **96 h** (to 2 sig figs)

Therefore it will take 4 days for the plasma phenytoin to fall to 10 mg/L. ■

Question 130

Haemochromatosis, a cause of abnormal liver function tests (LFTs), has a UK allele frequency of 0.07. Iron overload due to haemochromatosis can be demonstrated in 80% of men aged over 40, using a raised serum transferrin saturation. A commoner cause of abnormal LFTs is non-alcoholic fatty liver disease (NAFLD), with a reported prevalence of 5%. Unfortunately, raised TSat has also been reported in 7.4% of patients with abnormal LFTs due to NAFLD (and there is no association between NAFLD and haemochromatosis).

Assuming that there are no other causes of raised TSat, in what percentage of male patients over 40 with abnormal LFTs will a raised TSat indicate haemochromatosis? State any assumptions made.

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