Deacon's Challenge

No 128 - Answer

A newly diagnosed epileptic commenced treatment with a daily oral phenytoin dose of 150 mg. After 2 months of treatment his average steady state plasma phenytoin concentration was 4.1 mg/L. Since there had been little clinical improvement the dose was increased to 200 mg per day and after a further 2 month period the new plasma phenytoin concentration was 7.5 mg/L. However, seizure control was still not ideal and the Neurologist has asked you to calculate the expected plasma phenytoin concentration if the dose is further increased to 250 mg.

Assume that phenytoin clearance follows saturation kinetics and bioavailability, F = 1, salt conversion factor, S = 0.92 and the dosing interval, τ = 24 h.

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:

$$v = \frac{V_{max}\,[s]}{K_m + [s]}$$

In a steady state, [s] = average plasma concentration of the drug, C_{ss}, and the rate of metabolism must be equal to the rate of administration, which is given by F x S x Dose/τ. Substituting these into the Michaelis-Menten equation gives the useful expression:

$$\frac{F \times S \times Dose}{\tau} = \frac{V_{max}\,C_{ss}}{K_m + C_{ss}}$$

Calculation of the plasma steady state concentration when the dose is increased to 250 mg requires knowledge of the constants F, S, K_m and V_{max}. Only the first two are given but values for K_m and V_{max} can be calculated from the two simultaneous equations which results when two pairs of values for dose and C_{ss} are substituted into the above equation. For simplicity it is best to work with one of the linear transformations of the Michaelis-Menten equation (it doesn't matter which one). The double reciprocal transformation of Lineweaver & Burk gives the following equation:

$$\frac{\tau}{F \times S \times Dose} = \frac{K_m}{V_{max}\,C_{ss}} + \frac{1}{V_{max}}$$

When dose = 150 mg, C_{ss} = 4.1 mg/L, therefore

$$\frac{24}{1 \times 0.92 \times 150} = \frac{K_m}{4.1\,V_{max}} + \frac{1}{V_{max}}$$

and when dose = 200 mg, C_{ss} = 7.5 mg/L

$$\frac{24}{1 \times 0.92 \times 200} = \frac{K_m}{7.5\,V_{max}} + \frac{1}{V_{max}}$$

Simplifying these two equations:

$$0.174 = \frac{0.244\,K_m}{V_{max}} + \frac{1}{V_{max}}$$

and

$$0.130 = \frac{0.133\,K_m}{V_{max}} + \frac{1}{V_{max}}$$

Subtraction of the second equation from the first eliminates the $1/V_{max}$ term:

$$0.044 = 0.111\,K_m/V_{max}$$

Therefore $K_m/V_{max} = \frac{0.044}{0.111} = 0.396$

Substitute this value for K_m/V_{max} into one of the simultaneous equations (it doesn't matter which) and solve for V_{max}. Using the first equation:

$$0.174 = 0.244 \times 0.396 + \frac{1}{V_{max}}$$

$$\frac{1}{V_{max}} = 0.174 - (0.244 \times 0.396) = 0.174 - 0.0966 = 0.0774$$

$$V_{max} = 1/0.0774 = 12.9 \text{ mg/h/L}$$

Substitute this value into K_m/V_{max} = 0.396 and solve for K_m:

$$\frac{K_m}{12.9} = 0.396$$

$$K_m = 0.396 \times 12.9 = 5.1 \text{ mg/L}$$

To calculate the plasma concentration at the new dose of 250 mg substitute dose = 250 mg, F = 1, S = 0.92, τ = 24 h, K_m = 5.1 mg/L and V_{max} = 12.9 mg/h/L into the Michaelis-Menten equation, and solve for the C_{ss} term:

$$\frac{1 \times 0.92 \times 250}{24} = \frac{12.9 \times C_{ss}}{5.1 + C_{ss}}$$

$$9.58 = \frac{12.9 \times C_{ss}}{5.1 + C_{ss}}$$

$$9.58\,(5.1 + C_{ss}) = 12.9 \times C_{ss}$$

$$48.9 + 9.58\,C_{ss} = 12.9 \times C_{ss}$$

$$12.9\,C_{ss} - 9.58\,C_{ss} = 48.9 \text{ mg/L}$$

$$3.32\,C_{ss} = 48.9 \text{ mg/L}$$

$$C_{ss} = \frac{48.9}{3.32} = 15 \text{ mg/L (to 2 sig figs)}$$

Note that as metabolism becomes saturated a relatively small increase in phenytoin dose results in a marked increase in plasma concentration. ■

Question 129

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 Neurologist 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.