Deacon's Challenge

No 139 - Answer

A patient is given a loading dose of 250 µg of a new drug (MW = 781). After 12 hours, his serum drug concentration is estimated at 1.0 nmol/L. After a further 12 hours, the concentration is re-measured and is estimated at 0.8 nmol/L. Assuming the elimination of this drug follows first-order kinetics, calculate the volume of distribution and the rate constant of elimination.

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The linear form of the integrated first-order rate equation can be used to determine the initial drug concentration (Cp_0) and elimination rate constant (K_d):

$$\ln Cp_t = \ln Cp_0 - K_d t$$

where $\ln Cp_t$ is the natural logarithm of the plasma drug concentration at time t.

As there are two unknowns to determine the easiest approach is to set up two simultaneous equations with a concentration of 1.0 nmol/L at 12 h and 0.8 nmol/L at 24 h:

$$\ln 1.0 = \ln Cp_0 - 12K_d$$

$$\ln 0.8 = \ln Cp_0 - 24K_d$$

working out the natural logarithms:

$$0 = \ln Cp_0 - 12K_d$$

$$-0.223 = \ln Cp_0 - 24K_d$$

Subtraction of the second equation from the first eliminates the $\ln Cp_0$ term and since -(-0.223) = 0.223 and $-12K_d - (-24K_d) = -12K_d + 24K_d = 12K_d$, this results in:

$$0.223 = 12K_d$$

Therefore $K_d = \frac{0.223}{12} = \mathbf{0.0186\ h^{-1}}$ (to 3 sig figs)

The value of $\ln Cp_0$ can be obtained by substitution of this value for K_d into either of the rate equations. Using the first equation the calculation is:

$$0 = \ln Cp_0 - (12 \times 0.0186)$$

$$\ln Cp_0 = 12 \times 0.0186 = 0.223$$

$$Cp_0 = \text{antilog}_e\, 0.223 = 1.25\ \text{nmol/L}$$ (to 3 sig figs)

An alternative approach would be to plot $\ln Cp_t$ against t, join up and extrapolate the points. The slope would equal to $-K_d$ and the intercept on the $\ln Cp_t$ axis would give $\ln Cp_0$. This would be the preferred approach if there were more than two pairs of data.

The volume of distribution can be calculated from the value of Cp_0 and the administered dose:

$$\text{Volume of distribution} = \frac{\text{Dose (nmol)}}{Cp_0\ \text{(nmol/L)}}$$

Dose = 250 µg = 250,000 ng

$$\text{Dose (nmol)} = \frac{\text{Dose (ng)}}{\text{MW}} = \frac{250{,}000}{781} = 320\ \text{nmol}$$

$$\text{Volume of distribution} = \frac{320}{1.25} = \mathbf{256\ L}$$

Question 140

You have been asked to check the calibration of your laboratory's spectrophotometer. Using a solution of potassium dichromate (50.0 mg/L) in dilute sulphuric acid, you obtain absorption values of 0.523, 0.521, 0.524 and 0.523 at 350 nm. The absorptivity index of potassium dichromate at this wavelength is 10.7 ± 0.11 $g^{-1}\ cm^{-1}$. Given you have used cuvettes with a pathlength of 1 cm, calculate the probability that the spectrophotometer is correctly calibrated.

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