Deacon's Challenge

No 104 - Answer

A patient who weighed 75 Kg presented with rapid atrial fibrillation. He was given a first 250 mcg oral dose of digoxin on admission. Twelve hours later he is reviewed by a cardiologist who notes that he is still in atrial fibrillation and recommends a loading dose of digoxin in order to bring his next pre-dose plasma digoxin concentration to approximately 1.5 µg/L 12 hours later. Calculate the dose that should now be given. Assume the following:

- *Digoxin volume of distribution 7.3 L/Kg*
- *Oral bioavailability 0.62*
- *Single first order half life of 36 hours*

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Two equations are needed to solve this problem:

$$Cp_0 = \frac{\text{Dose} \times \text{Bioavailability}}{Vd} \quad \text{..... (i)}$$

where Cp_0 = initial plasma drug concentration

V_d = volume of distribution

$$\ln CR = -0.693\,N \quad \text{..... (ii)}$$

where CR = ratio of concentrations at times t_2 and t_1 i.e. Cpt_2/Cpt_1

N = number of half-lives which have elapsed between t_2 and t_1 i.e. $(t_2\text{-}t_1)/t_{1/2}$

Equation (ii) is derived from the integrated first-order rate equation. The first-order rate equation could be used directly to solve this problem but most people find version (ii) easier to use.

The first step is to calculate the target plasma digoxin concentration at 12 h after the initial dose (and after the second dose has been absorbed and equilibrated) using the target value of 1.5 µg/L after a further 12 h (i.e. at 24 h).

$$N = \frac{t_2 - t_1}{t_{1/2}} = \frac{24 - 12}{36} = 0.333$$

$$-0.693\,N = -0.693 \times 0.333 = -0.231$$

So that $\ln CR = -0.231$ and $CR = \text{antilog}_e\,-0.231 = 0.794$

$$CR = \frac{Cp_{24}}{Cp_{12}} = 0.794$$

Therefore $Cp_{12} = \frac{Cp_{24}}{CR} = \frac{1.5}{0.794} = 1.89$ µg/L

This concentration is derived from two sources:

(i) The digoxin remaining from the initial dose of 250 µg given 12 h earlier.

(ii) The loading dose given.

In order to calculate (i) it is first necessary to find the initial plasma concentration (Cp_0) using equation (i).

Bioavailability = 0.62

V_d = 7.3 L/Kg which, for a 75 Kg patient = 7.3 x 75 = 548 L

$$Cp_0 = \frac{\text{dose} \times \text{bioavailability}}{V_d} = \frac{250 \times 0.62}{548} = 0.283 \text{ µg/L}$$

This value is then used to find the plasma digoxin concentration remaining after 12 h i.e. $C_{p12'}$ using equation (ii).

Since the time interval is 12 h the value for CR is the same as calculated previously i.e. 0.794 so that:

$$C_{p12'} = CR \times Cp_0 = 0.794 \times 0.283 = 0.23 \text{ µg/L}$$

The following expression can now be written for the target concentration at 12 h (C_{p12}):

$$C_{p12} = C_{p12'} + CpL$$

Where CpL = plasma concentration component from loading dose

Therefore $CpL = C_{p12} - C_{p12'} = 1.89 - 0.23 = 1.66$ µg/L

All that remains is to use equation (i) to calculate the loading dose required to achieve this concentration:

$$1.66 = \frac{\text{Loading dose} \times 0.62}{548}$$

$$\text{Loading dose} = \frac{1.66 \times 548}{0.62} = \mathbf{1500\ \mu g}$$

The answer is only given to 2 significant figures since the target plasma concentration is only given to 2 figures. Furthermore, the size of tablets available is limited and the digoxin dose would probably be administered as 6 x 250 µg tablets.

Question 105

Recent draft UK national guidelines for the use of newer agents in the treatment of Type 2 Diabetes have recommended that thiozolidinedione drugs (e.g. pioglitazone) should only be continued if their introduction results in a reduction in HbA1c of at least 0.7 HbA1c units (%). If the biological within-subject variance is 0.01, what analytical precision must the assay achieve in order to be able to detect a true fall of 0.7 with greater than 95% certainty?

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