Deacon's Challenge

No 153 - Answer

An adult male (body weight 70 Kg) is receiving an intravenous infusion of aminophylline (the diamine salt of theophylline) at a rate of 60 mL/h. The intravenous solution was prepared by adding two ampoules of aminophylline to 500 mL of 0.9% sodium chloride. Each ampoule contains 250 mg aminophylline in a volume of 10 mL. How long will it take to achieve a plasma theophylline concentration of 10 mg/L? Assume theophylline has a volume of distribution, V_d, of 0.5 L/Kg and its elimination follows first-order kinetics with a half-life of 6h. Aminophylline is 80% theophylline by weight.

Rate of increase in plasma theophylline = Rate of infusion – Rate of elimination

Let C_p = plasma concentration (mg/L) V_d = volume of distribution (L)

V_i = rate of infusion (mg/h/L plasma) k_d = elimination rate constant (h^{-1})

t = time since start of infusion

The rate of increase in plasma theophylline (dC_p/dt) is given by the differential equation:

$$\frac{dC_p}{dt} = V_i - k_d.C_p$$

Integration of this equation (using Laplace transforms) gives an expression in terms of plasma concentration, rate of infusion and time:

$$C_p = \frac{V_i(1 - e^{-kd.t})}{k_d}$$

First calculate Vi - the rate of infusion of theophylline (mg/h/L plasma).

Since two ampoules (each containing 250 mg aminphylline in 10 mL solution) were added to 500 mL saline:

$$\text{Aminophylline concentration in infusion fluid} = \frac{2 \times 250}{(2 \times 10) + 500} \text{ mg/mL}$$

Next convert to theophylline concentration (aminophylline is 80% theophylline):

$$\text{Theophylline concentration of infusion fluid} = \frac{2 \times 250 \times 80}{\{(2 \times 10) + 500\} \times 100} = 0.769 \text{ mg/mL}$$

Since 60 mL were infused per hour, the rate of infusion is = 60 x 0.769 = 46.14 mg/h

However this amount of drug will be distributed throughout the available space. Therefore divide by Vd to give the rate of increase per L of plasma:

$$V_d\text{ (L)} = V_d\text{ (L/Kg)} \times \text{Body wt (Kg)} = 0.5 \times 70 = 35 \text{ L}$$

$$\text{Therefore } V_i = \frac{46.14}{35} = 1.32 \text{ mg/h/L plasma}$$

Next calculate k_d from the half-life:

$$k_d = \frac{0.693}{t_{1/2}} = \frac{0.693}{6} = 0.116 \text{ h}^{-1}$$

Finally substitute for C_p (10 mg/L), V_i and k_d into the integrated rate equation and solve for t:

Therefore:

$$10 = \frac{1.32(1 - e^{-0.116t})}{0.116} = 11.38(1 - e^{-0.116t})$$

$$\frac{10}{11.38} = 1 - e^{-0.116t}$$

$$0.879 = 1 - e^{-0.116t}$$

$$e^{-0.116t} = 1 - 0.879 = 0.121$$

Taking natural logarithms:

$$-0.116t = \ln 0.121 = -2.112$$

$$t = \frac{-2.112}{-0.116} = \mathbf{18.2\ h}$$

Question 154

An adult male (body weight 60 Kg) volunteered to donate one of his kidneys to his brother. The pre-op investigations included a carefully conducted creatinine clearance with the following results: plasma creatinine 80 µmol/L, 24 h volume 1.45 L and urine creatinine 8.0 mmol/L. The donor operation proceeded without any problems but a routine blood 24 h showed a plasma creatinine concentration of 162 µmol/L. A worried on-call SHO reviewing his results that evening queried whether a creatinine concentration this high would be expected so soon after the operation. In order to answer his question calculate:

a) The expected new steady state plasma creatinine concentration.

b) The time taken to achieve 95% of the new steady-state value.