Deacon's Challenge
No 136 - Answer

A new drug for the treatment of rheumatoid arthritis is metabolised in vivo to its active metabolite (MW = 142) by a plasma enzyme. The metabolite is cleared by glomerular filtration. A patient (body weight = 75 kg, GFR = 100 mL/min) failed to respond to treatment. Kinetic studies showed that the patient's enzyme obeyed simple Michaelis-Menten kinetics with respect to drug concentration (K_m = 80 µmol/L and Vmax = 5 µmol/min/L plasma). Calculate the maximum achievable steady state plasma concentration of the active metabolite (in mg/L) and comment on the significance of this result if the therapeutic range for the metabolite is 80-140 mg/L.

In a steady state the plasma concentration of the drug metabolite is constant since:

Rate of removal = Rate of formation

The rate of removal of the drug metabolite is the GFR (volume of plasma completely cleared of the metabolite per unit time) multiplied by the steady state plasma concentration (Cp_{ss}):

Rate of removal (µmol/min) = GFR (L/min) x Cp_{ss} (µmol/L)

The maximum rate of formation of the metabolite is the V_{max} (µmol/min/L plasma) multiplied by the total plasma volume (in litres).

The human body contains approximately 5% plasma, therefore:

Rate of formation = V_{max} (µmol/min/L plasma) x Body wt (kg) x 5/100

Therefore in the maximal steady state:

GFR (L/min) x Cp_{ss} (µmol/L) = V_{max} (µmol/min/L plasma) x Body wt (kg) x 5/100

The GFR is given as 100 mL/min, division by 1,000 converts it to 0.1 L/min. Substitute GFR = 0.1 L/min, Vmax = 5 µmol/min/L plasma, body wt = 75 kg then solve for Cp_{ss}:

$$0.1 \times Cp_{ss} = 5 \times 75 \times 5/100$$

$$0.1 \times Cp_{ss} = 5 \times 75 \times 0.05$$

$$Cp_{ss} = \frac{5 \times 75 \times 0.05}{0.1} = 187.5\ \mu mol/L$$

To convert this concentration to mg/L multiply by the MW (142) and divide by 1,000:

$$Cp_{ss} = \frac{187.5 \times 142}{1{,}000} = \mathbf{27\ mg/L}\ \text{(to 2 sig figs)}$$

The maximum achievable plasma steady state concentration of the active metabolite is well below its therapeutic range so this patient will fail to respond to the drug – no matter how high the dose.

Question 137

What volume of 25% (w/w) hydrochloric acid (SG = 1.15 g/mL) would be required to prepare 3 L of 0.5 M hydrochloric acid?