Deacon's Challenge No. 74 Answer

Calculate the loading dose of intravenous aminophylline required to achieve a plasma theophylline concentration of 15 mg/L in a 55 kg man, given that the volume of distribution of theophylline is 0.5 L/kg and that aminophylline is 80 % w/w theophylline. What infusion rate would be required to maintain this concentration if the half-life is 8 hours?

MRCPath, Autumn 2006

It is helpful to think of the body as a volumetric flask! The volume of the flask is the hypothetical volume in which the drug is dissolved i.e. the volume of distribution (V_d). The concentration of the drug in the volumetric flask is equivalent to the plasma drug concentration (C_p). The weight of drug required to achieve the desired concentration in the "volumetric flask" i.e. the loading dose (LD) is the product of concentration and volume (ensuring that the units are compatible):

$$LD = V_d \times C_p$$

If the drug is not given in the free form but as a salt or other derivative then this figure is divided by the salt factor (S). S is the proportion of free drug in the preparation (expressed on a weight basis). Therefore the above formula becomes:

$$LD = \frac{V_d \times C_p}{S}$$

If the drug was not given intravenously then it would also be necessary to correct for bioavailability.

V_d = 0.5 L/kg. Patient's weight is 55 kg. Therefore total V_d = 0.5 x 55 L

C_p = target plasma concentration = 15 mg/L

S = "salt factor". Since preparation is 80% theophylline, S = 80/100 = 0.8

Substituting these values to obtain LD:

$$LD = \frac{0.5 \times 55 \times 15}{0.8} = \mathbf{520\ mg}\ \text{(2 sig figs)}$$

The maintenance dose is the amount required to replace drug cleared by metabolism and/or excretion. The aim is to achieve the following steady state:

Rate of administration = Rate of clearance

The rate of drug clearance is the product of plasma concentration (C_p) and clearance (Cl) and the rate of administration is the maintenance dose (in this case infusion rate) corrected for any salt factor (and bioavailability if given orally). Therefore the steady state can also be written:

$$\text{Infusion rate} = \frac{C_p \times Cl}{S}$$

We are given the drug half-life ($t_{1/2}$) not its clearance. The clearance is calculated from the elimination rate constant (k_d) and the volume of distribution (V_d):

$$Cl = V_d \times k_d$$

The value for k_d can be calculated from the half-life using the expression $k_d = 0.693/t_{1/2}$.

Therefore $$Cl = \frac{0.693 \times V_d}{t_{1/2}}$$

Combining expressions for infusion rate and clearance gives:

$$\text{Infusion rate} = C_p \times \frac{0.693 \times V_d}{S \times t_{1/2}}$$

where C_p = target plasma concentration = 15 mg/L

V_d = volume of distribution = 55 x 0.5 L

$t_{1/2}$ = half-life = 8 h

S = "salt factor" = 0.8

Substituting these values gives the infusion rate (in mg/h):

$$\text{Infusion rate} = \frac{15 \times 0.693 \times 55 \times 0.5}{0.8 \times 8} = \mathbf{45\ mg/h}\ \text{(2 sig figs)}$$

Question 75

A man with a weight of 70 kg was admitted in a diabetic coma with a plasma sodium concentration of 135 mmol/L and a glucose concentration of 40 mmol/L. During the first two hours of treatment with 2 L 0.9% saline and insulin, he produced two litres of urine with a total sodium excretion of 40 mmol and his plasma glucose concentration had fallen to 15 mmol/L. What would you expect his plasma sodium concentration to be at this stage?

MRCPath, November 2006