Université Libre de Bruxelles

Rational drug deisgn and PKPD modeling

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PKPD Report

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1 Renal clearance

We can calculate the renal clearance with the total clearance.

$CL_R = CL_{total} \times f_{excreted}$
$CL_R = 2\text{L/h} \times 0.7$
$CL_R = 1.4\text{L/h}$

The hepatic clearance is the clearance not done by the kidneys.

$CL_H = CL_{total} - CL_R$
$CL_R = 2\text{L/h} - 1.4\text{L/h}$
$CL_R = 0.6\text{L/h}$

The drug is considered as secreted if the renal clearance is bigger than the fraction filtered through the glomerule : $CL_R > f_{\text{unbound plasma}} \times GFR$. 1.4 L/h is smaller than 5.6 L/h (0.8×7L/h), so this means that further in the kidney the drug is reabsorbed. The drug clearance is thusly prey to the change in the urine flow or the pH. If the urine flow increases, the clearance of the drug will consequently increase as the re-absorption could not be able to compensate. As for the pH influence, we would need to know if the drug is an acid or base, thusly implicating that the re-absorption process could be influenced by the change in the pH which would change the charges of the drug.

We estimate that there would be a problem in the case of renal failure because a large fraction of the drug is excreted unchanged, meaning that the larger part of the drug is cleared through the kidneys. A renal failure would considerably reduce the renal clearance, meaning it could be very dangerous, more so considering the therapeutic window is narrow.

2 Two compartment models

We used the plot to establish the half-life.

$t_{1/2} \approx 1\text{h}$

$$k_e = \frac{ln2}{t_{1/2}} = 0.693$$

The total clearance is obtained with the following formula : $CL = \frac{dose}{AUC}$.

The AUC is obtained with the following formula : $(\sum \frac{C_i + C_{i+1}}{2} \times (t_{i+1} - t_i)) + \frac{C_n}{ln2/t_{1/2}}$

$$AUC = \frac{260 + 130.7}{2} \times 0.25 + \frac{130.7 + 103.6}{2} \times 0.25 + \frac{103.6 + 84.3}{2} \times 0.25 + \frac{84.3 + 70.1}{2} \times 0.25 + \frac{70.1 + 50.7}{2} \times 0.5 + \frac{50.7 + 38.1}{2} \times 0.5 + \frac{38.1 + 29.1}{2} \times 0.5 + \frac{29.1 + 22.5}{2} \times 0.5 + \frac{22.5 + 13.6}{2} + \frac{13.6 + 8.2}{2} + \frac{8.2}{ln2} = 243.7951118$$

$CL = 2.05\text{L/h}$

$$V = \frac{CL}{k_e} = 2.96\text{L}$$

The two compartment models follow the formula : $C_{p(t)} = Ae^{-\alpha t} + Be^{-\beta t}$ The plot is composed of two parts : the first part represents the distribution phase and the second one the elimination phase. By extrapolating the second part to the y-axis, we can find the value of the B variable (here around 85). The extrapolation of the first part gives the initial concentration (around 260). The initial concentration is equal to the sum of a and b, so we can calculate A (around 175). β is the negative slope of the curve of the second part we extrapolated. $\beta = -\frac{C_2 - C_1}{t_2 - t_1} = 20.$ α is obtained by tracing the residual curve of the difference between the curve we extrapolated from the second part and the real observed values in the first part. $\alpha = -\frac{residual_2 - residual_1}{t_2 - t_1} = 60.$

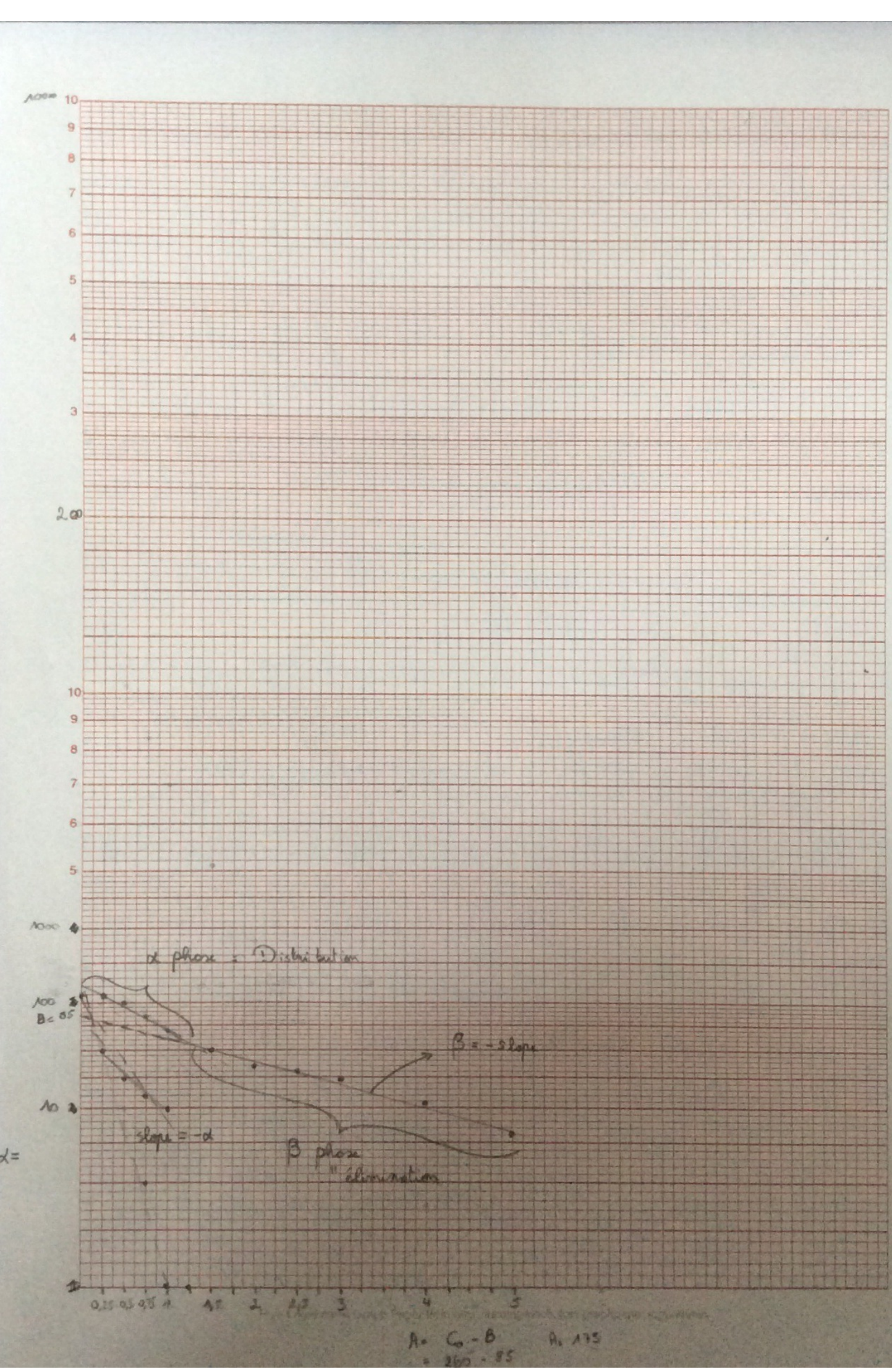
We use the two compartment models to model the distribution of a drug in tissues. This is because the body is composed of a heterogeneous group of tissues each with

different degree of blood flow and affinity for drug. When a drug enters the body, this drug distributed in the central compartment and at the same time, in a slower process, to another compartment. This other compartment represents other tissues that needs more time for the drug to go to.

3 Loading and maintenance doses

$CL = 0.1 \times 75 \times 60 = 0.45\text{L/h}$
$V = 0.2 \times 75 = 15\text{L}$
$Dose_{maintenance} = \frac{C_{SS} \times CL \times \tau}{F} = 165$ mg every 4 hours
$Dose_{loading} = \frac{V \times C_{SS}}{F} =$ for minimum constant dose 1000 mg and for the maximum 1750 mg.

The loading dose is an initial high dose of the drug in order to reach more quickly the desired steady state concentration.


α phase : Distribution
β = - slope
slope = -α
β phase
" élimination
A = C₀ - B
= 260 - 85
A = 175