Clinical pharmacokinetics of cyclosporin

1. Calculation of population pharmacokinetic parameters of cyclosporine

400 mg of cyclosporine in a single oral dose has been administered to 16 patients. The average blood concentrations of the drug are shown in the table below.

Table 1. The average blood concentrations of cyclosporine as a function of time

time (h)	Concentration (mg/L)
0.5	0.09
1.0	0.52
1.5	0.75
2.0	0.85
3.0	0.79
4.0	0.68
6.0	0.52
8.0	0.41
10.0	0.33
24.0	0.05

Enter the blood concentrations into the Topfit program and calculate population pharmacokinetic parameters by using the following procedure:

I. MAIN MENU
   i. Edit header (4) save (F1)
   ii. Edit data (5)
      1. FORMULATION DATA
         a.Type of imput
         b. Edit dosing table (F7)
            i. Unit of time (h), unit of dosing (mg), time = 0, Dose = … (mg)
            ii. Save (F1)
         c. Edit data sets (F8)
            i. Sample matrix (blood), type of weighting function ($1/y^2$), unit of measurement (mg/L), unit of time (h)
            ii. Save (F1)
         d. Edit data sets (F8) table (F8)
            i. File the measurement table (time, value)
            ii. Save (F1) $\times$ 3

II. MAIN MENU
   i. Enter methods menu (8)
   ii. Standard compartment models (2)
   iii. One compartment (1)

iv. Select data sets (1)
    1. Select data (press ↵)
    2. Ready (F1)

v. Start iteration (6)

vi. Results Menu
    1. View graphics
        a. Change Y-axis to logarithmic Edit (F3)
        b. Graph (F1)
        c. Exit (F10)
    2. View results
        a. Result section (F1)

Table 1. Pharmacokinetic parameters of cyclosporine following a single oral dose

Parameter	Value
k_a (h^{-1})	
k_e (h^{-1})	
$t_{0.5}$ (h)	
C_{max} (mg/L)	
t_{max} (h)	
V/F (L)	
Cl/F (mL/min) (L/h)	
AUC (mg·h/L)	

2. Designing a dosing regimen for long-term maintenance therapy with cyclosporine

A 25-year-old woman (weight - 50kg, height - 160cm), who received unrelated renal transplant two weeks ago, is being treated with cyclosporine 5 mg/kg every twelve hours. Following transplantation her serum creatinine stabilized to 1.2 mg/dL.

A) What is the expected C_{trough} and C_2 at steady state with this regimen? Apply values of population pharmacokinetic parameters calculated in Topfit.

Dose = 5 mg/kg × weight = ……. mg

$$C_{trough} = \frac{F \cdot D \cdot k_a}{V \cdot (k_a - k_e)} \cdot \left(\frac{e^{-k_e \cdot \tau}}{1 - e^{-k_e \cdot \tau}} - \frac{e^{-k_a \cdot \tau}}{1 - e^{-k_a \cdot \tau}} \right)$$

$$C_n = \frac{F \cdot D \cdot k_a}{V \cdot (k_a - k_e)} \cdot \left(\frac{e^{-k_e \cdot t}}{1 - e^{-k_e \cdot \tau}} - \frac{e^{-k_a \cdot t}}{1 - e^{-k_a \cdot \tau}} \right)$$

τ - dosing interval
C_n – steady state concentration at time t

C_{trough} (mg/L) =

C_2 (mg/L) =

Table 2. C_{trough} and C_2 monitoring targets in renal transplantation

Time after transplantation (months)	**C_{trough} (mg/L)**	**C_2 (mg/L)**
0 – 3	*0.2 – 0.3*	*1.0 – 1.5*
3 – 6	*0.15 – 0.2*	*0.8 – 1.0*
> 6	*0.1 – 0.15*	*0.4 – 0.6*

Conclusion:

……

……

B) Design new dosing regimens for 1-year therapy allowing to obtain C_2 values given in Table 2. Cyclosporine is available as 25 mg and 100 mg capsules.

$$D_{desired} = \frac{C_2^{\ desired}}{C_2^{\ current}} \cdot D_{current}$$

Table 3. New dosing regimen for 1-year treatment:

Time after transplantation (months)	New dose (mg)	dosing interval (h)
0 – 3		
3 – 6		
> 6		

3. Simulation of pharmacokinetic parameters

A. Check if the designed regimen is appropriate using program for simulation of pharmacokinetic parameters.

Table 4. Values obtained using program for simulation of pharmacokinetic parameters:

Time after transplantation (months)	Dose (mg)	τ (h)	C_{trough} (mg/L)	C_{peak} (mg/L)	C_{ave} (mg/L)	C_2 (mg/L)
0 – 3						
3 – 6						
> 6						

Conclusion:

……..

B. Determine the influence of changing a dose and time interval on cyclosporine concentration. Suggest alternative doses and time interval allowing to obtain C_2 monitoring target.

Table 5. Alternative dosing regimen for cyclosporine treatment:

Time after transplantation (months)	Dose (mg)	τ (h)	C_{trough} (mg/L)	C_{peak} (mg/L)	C_{ave} (mg/L)	C_2 (mg/L)
0 – 3						
3 – 6						
> 6						

4. Therapeutic problem

After 5 months of treatment with cyclosporine patient's serum creatinine increased to 2.3 mg/dL and the steady state cyclosporine trough concentration was 0.35 mg/L.

- Calculate the current creatinine clearance and compare with the value obtained from the creatinine concentration at the beginning of the therapy (1.2 mg/dL)

$$Cl_{cr}\ (ml/\min) = 0.85 \cdot \frac{(140 - age)(weight)}{72 \cdot C_{cr}(mg/dL)}$$

Current Cl_{cr}: ……..

Cl_{cr} at the beginning of the cyclosporine therapy: ……

- What question would you ask the patient to evaluate the reason for the observed increase in the cyclosporine concentration?

  ……

  ……

  ……

- How would you adjust patient's cyclosporine regimen to achieve a new steady-state cyclosporine concentration of approximately 0.15 mg/L?

  Current dose (5th month of treatment, Table 3): ……..

  New dose =

Situation 2

A 39-year-old woman (weight - 51kg) who had a renal transplant is being treated with cyclosporine 250 mg every twelve hours. Her cyclosporine steady state through concentration is 0.2 mg/l. Evaluate the elimination process of cyclosporine in the patient based on the $t_{0.5}$ value.

- Assuming F = 0.3 and V = 4 L/kg, calculate the steady state peak concentration

  V = 4 L/kg · weight =

  $$C_{peak} = C_{trough} + \frac{F \cdot D}{V} =$$

- Calculate k_e and $t_{0.5}$

  $$k_e = \frac{\ln\left(\frac{C_{peak}}{C_{trough}}\right)}{\tau} =$$

  $$t_{0.5} = \frac{\ln 2}{k_e} =$$

Conclusion:

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