

Experiment 4a

Pharmacokinetics (PK) of treosulfan after intravenous infusion. Compartmental versus non-compartmental PK analysis.

Theoretical knowledge: PK analysis of drug concentration in blood after intravenous infusion in 1- and 2-compartment and non-compartmental body model, calculation of pharmacokinetic parameters: K , $t_{0.5}$, C_{max} , AUC, Cl, V_{ss}

A dose of 13 g of treosulfan has been administered as a single 2h intravenous infusion to a paediatric patient undergoing conditioning regimen prior to haematopoietic stem cell transplantation in three consecutive days. The plasma and urine samples has been collected on the third day of treosulfan administration. The concentrations of the drug in the samples were determined using a validated HPLC method with refractometric detection (HPLC-RID). The results are presented in tables 1 and 2.

Table 1. The change of concentration of treosulfan in plasma

Time [h]	Concentration [mg/L]
0.25	285.70
0.5	379.39
1.0	407.48
2	482.48
2.5	192.48
3	135.64
4	102.90
6	40.11
8	18.63

Table 2. The change of concentration of treosulfan in urine

Time [h]	Concentration [mg/L]	Urine volume [mL]
1.5	5166.10	240
2	1037.61	370
4	1039.83	350
5	402.46	270
5.5	141.75	250
7.5	451.82	170

Performance

1. Plot the drug concentrations in plasma versus time on a millimetre and semi-log paper. Discuss the drug profile obtained in the graphs.
2. Using **TopFit 2.0** choose an appropriate model for pharmacokinetic calculations.

Compartmental analysis

Enter the plasma concentrations of treosulfan into the TopFit by using the following procedure:

I. MAIN MENU

- i. Edit header (4) save (F1)
- ii. Edit data (5)
 1. FORMULATION DATA
 - a. Type of input (Bolus/Infusion)
 - b. Edit dosing table (F7)
 - i. Enter unit of time (h), unit of dosing (g/individual), time = 0 h, dose = 13 g, duration = 2h
 - ii. Save (F1)
 - c. Edit data sets (F8)
 - i. Sample matrix (plasma), 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, concentration value)
 - ii. Save (F1) × 3

II. MAIN MENU

- i. Enter methods menu (8)
- ii. Standard compartment models (2)
- iii. One compartment (1)
- iv. Select data sets (1)
 - a. Ready (F1)
- v. Start iteration (6)
- vi. Results Menu
 - a. View graphics (2)
 - 1) Edit (F3)
 - 2) Change Y-axis to logarithmic
 - 3) Graph (F1)
 - 4) Exit (F10)
 - b. View results (1)
 - 1) Select as follows: Residuals; Parameters, eigenvalues and coefficients; Statistical tests on model
 - 2) Save (F1)
- vii. Rewrite the values of pharmacokinetic parameters and statistical tests (with weightings)
- viii. Exit (F10)

Repeat the procedure described in Section II (i – vii) choosing two compartment model

Discuss the fitting of pharmacokinetic profile in 1- and 2-compartment models to experimental data and compare the values of statistical tests. Decide which model is the most appropriate for the data obtained in the patient treated with treosulfan.

Non-compartmental analysis

IV. MAIN MENU

- i. Enter methods menu (8)
- ii. Non-compartmental analysis (1)
- iii. Select methods: All (F5)
- iv. Select maximum: use F1 to mark the maximum concentration
- v. Save (F1), exit (F10)
- vi. Half-life determination: use (F1) to select points, which are excluded from the terminal elimination phase
- vii. Exit (F10) × 2
- viii. AUC upper bond selection: (F1)
- ix. AUC calculation using: linear trapezoidal rule (F1)
- x. AUC extrapolating using: last data point (F1)
- xi. Select interval for AUD: (F1) × 2
- xii. Exit (F10)
- xiii. Rewrite the values of pharmacokinetic parameters
- xiv. Exit (F10)

Compare the values of pharmacokinetic parameters obtained from plasma data using non-compartmental analysis with those obtained by compartmental modelling. Discuss the differences.

3. Using TopFit 2.0 calculate pharmacokinetic parameters of treosulfan based on urine data
 - a. Calculate amounts of treosulfan excreted in urine samples using the equation:
$$X_{ui} = C_i \cdot V_i$$
 - b. Calculate cumulative amounts (U) of treosulfan in urine samples
 - c. Draw the cumulative graph representing the relationship: $U = f(t)$
 - d. Enter the cumulative amounts of treosulfan in urine into the TopFit by using the following procedure:

V. MAIN MENU

- iii. Edit header (4) save (F1)
- iv. Edit data (5)
 1. FORMULATION DATA
 - a. Type of input (Bolus/Infusion)
 - b. Edit dosing table (F7)
 - i. Enter unit of time (h), unit of dosing (g/individual), time = 0 h, dose = 13 g, duration = 2h
 - ii. Save (F1)
 - c. Edit data sets (F8)
 - i. Sample matrix (urine), type of weighting function ($1/y^2$), unit of measurement (mg), unit of time (h)
 - ii. Save (F1)
 - d. Edit data sets (F8) table (F8)
 - i. File the measurement table (time, cumulative amounts)
 - ii. Save (F1) × 3

Compartmental analysis

VI. MAIN MENU

- i. Enter methods menu (8)
- ii. Standard compartment models (2)
- iii. Two compartment (2)
- iv. Select data sets (1)
 - a. Ready (F1)
- v. Start iteration (6)
- vi. Results Menu
 - a. View graphics (2)
Exit (F10)
 - b. View results (1)
 - 1) Select as follows: Residuals; Parameters, eigenvalues and coefficients
 - 2) Save (F1)
- vii. Rewrite the values of pharmacokinetic parameters
- viii. Exit (F10)

Non-compartmental analysis

VII. MAIN MENU

- i. Non-compartmental analysis (1)
- ii. Select methods: All (F5)
- iii. Half-life determination (based on the excretion rate): use (F1) to select points excluded from the half-life determination
- iv. (F10) × 2
- v. Select interval for AUD: (F1) × 2
- vi. Exit (F10)
- vii. Half-life determination (based on $\ln(U_{\infty} - U) = f(t)$): mark points excluded from the half-life determination (F1) × 2
- viii. (F10) × 2
- ix. Cumulative excretion: (F10)
- x. Rewrite the values of pharmacokinetic parameters
- xi. Exit (F10)

Compare the values of pharmacokinetic parameters obtained from urine data using non-compartmental analysis with those obtained by compartmental modelling. Discuss the differences.

Experiment 4b.

Computer simulation of pharmacokinetic parameters after intravenous infusion

Performance

1. Start the software
2. Enter the parameters, as follows:
 - a. Time of the infusion, $t(\text{doz})$ 5 h
 - b. The infusion speed, k_0 200 mg h⁻¹
 - c. Elimination rate constant, K 0.8 h⁻¹
 - d. Apparent volume of distribution, V_d 20 L
3. Analyse the drug concentration in plasma during and after constant rate intravenous infusion.
4. Change the infusion parameters
 - a. Type "zm" → "enter"
 - b. The question says: Which parameter do you want to change?
 - c. Enter the parameter symbol you want to change (every time change only one parameter)
 - d. An order of the parameter changing is as follows:
 - i. Time of the infusion: 2.5 h and 10 h
 - ii. The infusion speed: 100 mg h⁻¹ and 400 mg h⁻¹
 - iii. Elimination rate constant: 0.4 h⁻¹ and 1.6 h⁻¹
 - iv. Apparent volume of distribution: 10 L and 40 L
 - e. Observe an influence of the parameter changing on the graph $c=f(t)$ by typing "w" and "enter"
5. Attach a printout of the simulation results to your report.