Clinical pharmacokinetics of phenytoin

Purpose:

1. Calculation of V_{max} and K_m using Topfit .
2. Designing a dosing regimen for a patient treated with phenytoin.
3. Solving problems arising during therapy with phenytoin.

1. Calculation of V_{max} and K_M

A) A man, who had taken phenytoin in a single oral dose of 30 mg/kg, was admitted to hospital because of toxic effects after administration of the drug. The plasma concentrations of phenytoin are shown in the table below.

Table 1. The plasma concentrations of phenytoin as a function of time

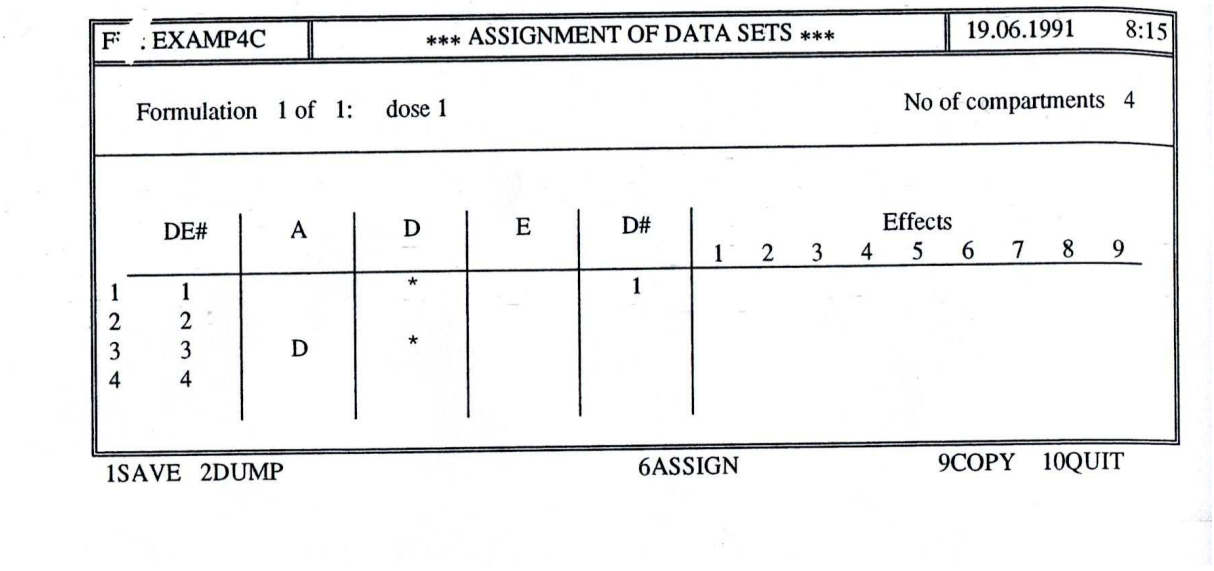
time (h)	Concentration (mg/L)
5	29.7
15	27.1
25	24.5
35	21.9
45	19.4
55	17.0
75	12.5
85	10.5
105	7.4
115	5.3
125	4.0
135	3.0

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

I. MAIN MENU
   i. Load Topfit file **FENYTO2.TOP**
   ii. Edit header (4) save (F1)
   iii. Edit data (5)
      1. FORMULATION DATA
         a.Type of input (Absorption - tablet)
         b. Edit dosing table (F7)
            i. Unit of time (h), unit of dosing (mg/kg), time = 0, Dose = 30
            ii. Save (F1)

c. Edit data sets (F8)
   i. Sample matrix (plasma), type of weighting function (w=1), 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) × 3

II. MAIN MENU
   i. Enter methods menu (8)
   ii. Nonlinear compartment model (4)
   iii. List selection – select appropriate model (**MM1PO**) (F1)
   iv. Select data sets (1)
      1. Ready (F1)
   v. Assignment of data sets (4)
   vi. Describe the data according to the scheme given below



F: EXAMP4C | *** ASSIGNMENT OF DATA SETS *** | 19.06.1991 8:15

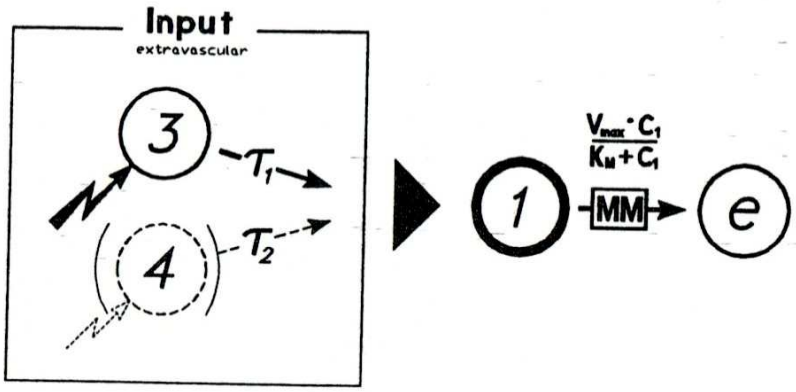
Formulation 1 of 1: dose 1 — No of compartments 4

	DE#	A	D	E	D#	Effects 1 2 3 4 5 6 7 8 9
1	1		*		1	
2	2					
3	3	D	*			
4	4					

1SAVE 2DUMP 6ASSIGN 9COPY 10QUIT

DE# - compartment number
A – dosing compartment
D – disposition compartment
E – elimination compartment
D# - data set number of the formulation (e.g. plasma, urine, subject)

MM1PO



vii. Go to data assignment (F6)
viii. Enter number of entry compartment (3)
ix. Save (F1)×2
x. Start iteration (6)
xi. 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)

Rewrite values of V_{max} and K_M calculated in Topfit.

B) Calculate a daily dose of phenytoin for the patient that will result in a steady-state level of approximately 15 mg/L. Assume that the patient weigh 70 kg and phenytoin will be given as a 100 mg tablet that can be split in half.

$$DR = \frac{V_{max} \quad C_{ss}}{K_M + C_{ss}}$$

$$C_{ss} = \frac{DR_{new} \quad K_M}{V_{max} - DR_{new}}$$

2. Designing a dosing regimen for maintenance therapy with phenytoin

J.P., a 12-year-old boy with a seizure disorder, had been taking 200 mg/day of acid phenytoin. After this dose a steady-state level of the drug in plasma was 5.65 mg/l. As his seizures were poorly controlled, phenytoin dose was increased to 250 mg/day that resulted in plasma concentration of 8.44 mg/l. In spite of increasing phenytoin dose, the boy still suffered from seizures. Calculate a new daily dose of phenytoin that will result in a steady-state level of approximately 15 mg/l. Take into account that phenytoin will be given to the patient as a 100 mg tablet that can be split in half.

$$K_M = \frac{C_{ss}^1 \cdot C_{ss}^2 \cdot (DR_2 - DR_1)}{DR_1 \cdot C_{ss}^2 - DR_2 \cdot C_{ss}^1}$$

$$V_{\max} = \frac{DR \cdot (K_M + C_{ss})}{C_{ss}}$$

$$DR_3 = \frac{V_{\max} \cdot C_{ss}^3}{K_M + C_{ss}^3}$$

$$C_{ss} = \frac{DR_{new} \cdot K_M}{V_{\max} - DR_{new}}$$

3. Therapeutic problem - hypoalbuminemia

J.M. is an epileptic patient being treated with phenytoin. He has hypoalbuminemia (albumin = 2.2 g/dL) and normal renal function (creatinine clearance = 90 mL/min). His total phenytoin concentration is 7.5 µg/mL. Calculate an estimated normalized total and unbound phenytoin concentration for this patient.

$$C_{normal\_binding} = \frac{\text{patient's phenytoin concentration}}{\left[0.9 \times \frac{\text{patient's serum albumin}}{4.4(g/dL)}\right] + 0.1}$$

$C_{unbound} = 0.1 \times C_{normal\ binding}$