PART 1. POPULATION PHARMACOKINETICS

Calculation of population pharmacokinetic parameters of digoxin

Twelve healthy subjects (six men and six women) received a single oral dose of 250 μg of digoxin. The mean serum digoxin concentration-time profile is presented in the table:

time [h]	mean serum concentration of digoxin[μg/L]
0.25	0.416
0.50	0.937
1.00	1.320
2.00	0.911
3.00	0.792
4.00	0.680
6.00	0.515
8.00	0.455
12.00	0.409
18.00	0.356
24.00	0.370

Calculate the pharmacokinetic parameters of digoxin (all subjects had normal BMI, mean weight was 69.7 kg).

1. MAIN MENU
    a. Edit header (4) – save F1
    b. Edit data (5)
        i. FORMULATION DATA
            1. Type of input
            2. Edit dosing table F7
                a. Unit of time (h); unit of dosing (μg); time = 0; dose = 250 μg
                b. Save F1
            3. Edit data sets F8
                a. Sample matrix (plasma); type of weighting function (1); unit of measurement (μg/L); unit of time (h)
                b. Save F1
            4. Edit data sets F8 – table F8
                a. File the measurement table (time; concentration)
                b. Save F1 x 3
2. MAIN MENU
    a. Enter methods menu (8)
    b. Standard compartment models (2)
    c. Two compartments (2)
    d. Select data sets (1)
        i. Select data (press ENTER)
        ii. Ready F1
    e. Start iteration (6)
    f. Results menu
        i. View graphics
            1. Change Y-axis to logarithmic – edit F3
            2. Graph F1
            3. Exit F10
        ii. View results
            1. Result section – mark: title page; dosage type and schedules; residuals; parameters, eigenvalues and coefficients;
            2. Ready F1

FLIP FLOP SOLUTION NO 2
Elimination rate constant = b1 = k_e
Distribution rate constant = b2 = α
Absorption rate constant = k01 = k_a
Volume of distribution (steady-state) = $V_{ss}/f = V$

pharmacokinetic parameter		value
volume of distribution (V)	[L/kg]	
absorption rate constant (k_a)	[1/h]	
elimination rate constant (k_e)	[1/h]	
clearance (Cl)	[mL/kg/min] [L/kg/h]	
distribution half-life ($\alpha t_{0.5}$)	[h]	
elimination half-life ($t_{0.5}$)	[h]	
AUC_{0-24}	[µg/(L·h)]	
t_{max}	[h]	
C_{max}	[µg/L]	

PART 2. CASE STUDY

Situation 1

A 57-year-old patient (female, weight 60 kg and height 1.68 m) with a serum creatinine of 1.2 mg/dL is being treated for congestive heart failure (CHF).Estimate a digoxin loading dose that will produce a plasma concentration of 1 µg/L. Recommend the dosing regimen that will maintain her plasma digoxin concentrations within the therapeutic range (between 0.8 and 2.0µg/L).

- Digoxin is available in immediate-release tablets of 62.5, 125 and 250µg
- Bioavailability for parenteral administration of digoxin is 1.0 and for oral administration the average bioavailability from tablets is 0.7 (for soft gelatin capsules it is 1.0)
- The factor connected to the chemical structure of digoxin (S) is 1.0, because digoxin is not administered as a salt

Information that have to be considered for further calculations:

Parameter		***Conclusion***
BMI of the patient	value: …….. kg/m^2	☐ underweight ☐ normal weight ☐ overweight ☐ obesity
Ideal Body Weight (**IBW**) men: $IBW\ [kg] = 50.0 + 0.9 \cdot (height\ [cm] - 152.4)$ women: $IBW\ [kg] = 45.5 + 0.9 \cdot (height\ [cm] - 152.4)$	value: …… kg	Has to be considered in further calculations? ☐ yes ☐ no

Calculate the pharmacokinetic parameters of digoxin (concerning patient's creatinine concentration) and compare its values derived from above population data:

Parameter	***Values concerning creatinine clearance***
creatinine clearance (Cl_{cr}) men: $Cl_{cr}\ \left[\frac{mL}{min}\right] = \frac{(140 - age) \cdot weight\ [kg]}{72 \cdot C_{cr}[\frac{mg}{dL}]}$ women: $Cl_{cr}\ \left[\frac{mL}{min}\right] = 0.85 \cdot \frac{(140 - age) \cdot weight\ [kg]}{72 \cdot C_{cr}[\frac{mg}{dL}]}$	…… **mL/min** …… **L/h**
volume of distribution (V) *Volume of distribution of digoxin is decreased in patients with renal disease.* ***In obese patients, the volume of distribution appears to correlate better with ideal body weight (IBW)*** *than total body weight. Volume of distribution of digoxin can be calculated considering creatinine clearance:* V [L] = 3.8 · weight [kg] + 3.1 · Cl_{cr} [mL/min]	…… **L**
total clearance (Cl) *Total clearance of digoxin is a sum of renal clearance (equal to Cl_{cr}) and metabolic clearance (0.8 mL/kg/min · weight in kg) values.* ***Digoxin's metabolic clearance correlates best with ideal body weight (IBW).***	…… **mL/min** …… **L/h**
elimination rate constant (k_e) **k_e** [h^{-1}] **= Cl** [L/h] **/ V** [L]	…… **h^{-1}**
elimination phase half-life ($t_{0.5}$) **$t_{0.5}$** [h] **= ln2 / k_e** [h^{-1}]	…… **h**

Estimate digoxin loading dose that will produce plasma concentration C = 1 µg/L:

	Calculated concerning patient's renal function (PART 2)	Calculated concerning population parameters (PART 1)
Loading dose [µg] $D_{load} = \frac{V \cdot C}{S \cdot F}$		

The recommended loading dose (possible for oral administration):

…… µg.

Calculate the daily dose of digoxin for maintenance therapy that will achieve an average plasma digoxin concentration of 1.0 µg/L.
Calculate C_{ave}, C_{peak} and C_{trough} resulting from different dosing regimens.

STEADY-STATE AVERAGE CONCENTRATION

$$C_{ss,ave} = \frac{F \cdot S \cdot D}{Cl \cdot \tau}$$

STEADY-STATE PEAK CONCENTRATION

$$C_{peak} = \frac{F \cdot S \cdot D}{V} \cdot \frac{1}{1 - e^{-k_e \tau}}$$

STEADY-STATE TROUGH CONCENTRATION

$$C_{trough} = C_{peak} \cdot e^{-k_e \cdot \tau}$$

Calculation of maintenance doses:

calculated maintenance dose $\mathbf{D_{calc}}$ [µg/day]	*dose possible to oral administration* $\mathbf{D_{p.o.}}$[µg/day]	*average steady-state concentration* $\mathbf{C_{ave}}$ [µg/L]	*peak steady-state concentration* $\mathbf{C_{peak}}$ [µg/L]	*trough steady-state concentration* $\mathbf{C_{trough}}$ [µg/L]

……µg/day

$$D = \frac{Cl \cdot C_{ss,ave} \cdot \tau}{S \cdot F}$$

Conclusion:……

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