Experiment 3

Noncompartmental approach to analysis of drug disposition

Theoretical knowledge: Noncompartmental analysis, statistical moment theory, AUC, AUMC, MRT, MAT, Cl, Vd

Noncompartmental analysis does not require the assumption of a specific compartmental model for a drug. It can be applied to any drug behaving in the body according to linear pharmacokinetics.
The time course of drug concentration in plasma can usually be regarded as a statistical distribution curve. For pharmacokinetic analysis statistical moments of the concentration-time curve are used, usually the first two moments (zero and first) .

The zero moment: $$AUC = \int_0^\infty C \cdot dt$$

The first moment: $$MRT = \frac{AUMC}{AUC}$$,

where MRT is the mean residence time,
AUMC is the area under a plot of the product of concentration and time versus time, often referred to as the area under the first moment curve.

Estimation of AUC
Noncompartmental methods are based on the estimation of the area under a plot of drug concentration versus time. AUC is calculated in two steps. AUC from 0 time to t is estimated by means of the trapezoidal rule. The method involves the calculation of a sum of the individual areas determined by measurements of the drug concentration in specific time points. The areas possess a trapezoidal shape and threfore should be calculated from the formula:

$$area = \frac{(C_n + C_{n+1})}{2} \cdot (t_{n+1} - t_n)$$

In the second step, AUC from t to infinity is estimated from the following equation:

$$AUC_{t-\infty} = \frac{C_{last}}{\lambda}$$,

where λ is the slope of the terminal exponential phase of a plot of ln concentration versus time, Clast is the last measured concentration.
The same approach must be used to estimate AUMC. The area under the first moment curve from t to infinity is estimated as follows:

$$AUMC_{t-\infty} = \frac{t_{last} \cdot C_{last}}{\lambda^*} + \frac{C_{last}}{(\lambda^*)^2}$$,

where λ* is the slope of the terminal exponential phase of a plot of ln(C×t) versus time.

Bioavailability
Bioavailability refers to the fraction (F) of an oral dose that reaches the systemic circulation. F is estimated from:

$$F = \frac{D_{iv} \cdot AUC_{oral}}{D_{oral} \cdot AUC_{iv}}$$

Clearance

Clearance is regarded as the most important parameter to describe the pharmacokinetics of a drug. It can be defined as the reciprocal of the zero moment of a plasma level-time curve normalized for dose:

$$Cl = \frac{D_{iv}}{AUC}$$

Fraction F should be taken into account if the parameter is estimated after oral administration of a drug:

$$Cl = \frac{F \cdot D_{oral}}{AUC}$$

Mean residence time

Mean residence time (MRT) is the statistical moment analogy to half-life (t0.5). It represents the time for 63.2% of the administered dose to be eliminated. MRT is given by the following equation:

$MRT_{iv} = \frac{1}{K}$, where K is the first order elimination rate constant.

Therefore, half-life can be described by:

$t_{0.5} = 0.693 \cdot MRT$

Mean absorption time

For estimating absorption rate after oral administration differences in mean residence times after different modes of administration are calculated.

Mean absorption time (MAT) = MRT_{ni}- MRT_{iv}

MRT_{ni} – mean residence time after administration of the drug in a non-instantaneous manner.

When drug absorption can be desribed by a single first-order proces:

$$MAT = \frac{1}{k_a}$$,

where k_a is the apparent first-order absorption rate constant.

Volume of distribution

The most useful parameter describing drug distribution is the apparent volume of distribution at steady state, V_{ss}.

According to statistical moment theory V_{ss} is the product of clearance and mean residence time after a single intravenous administration of a drug:

$$V_{ss} = Cl \cdot MRT = \frac{D_{iv} \cdot AUMC}{AUC^2}$$

0.5 g of sulfacarbamide in a single oral dose has been administered to a patient. The plasma concentrations of drug in patient 1 and 2 and are shown in the table below.

Time, h	Concentration, μg/mL	
	Patient 1	Patient 2
0.5	5.38	4.15
1.0	8.83	6.95
1.5	10.87	8.74
2.0	11.90	9.80
2.5	12.23	10.30
3.0	12.06	10.42
3.5	11.58	10.25
6.0	7.58	7.66
9.0	3.66	4.41
12.0	1.60	2.34
15.0	0.67	1.21
18.0	0.28	0.61

1. Calculate t C values in order to prepare the graph: t C = f(t)
2. Plot the graphs on a semilog paper:
    a. Ln C = f(t)
    b. Ln (t C) = f(t)
3. Obtain the slope (a), the y-intercept (b) and regression coefficient of the terminal, elimination, phase by the least square method for both logarithmic graphs. The slope is equal to ***–K***.
4. Estimate the AUC and AUMC by the trapezoidal rule
    a. First area has a triangular shape
    b. The area under the curve from last time points to the infinity is given by:
        i. $AUC_{t\to\infty} = \frac{C_t}{\lambda_n}$ where λ_n is the slope of the terminal exponential phase a plot of ln drug concentration versus time
        ii. $AUMC_{t\to\infty} = \frac{t\,C_t}{\lambda_n} + \frac{C_t}{\lambda_n^2}$ where λ_n is the slope of the terminal exponential phase a plot of ln (t C) versus time
    c. Calculate total AUC and AUMC
        i. $AUC_{0\to\infty} = AUC_{0\to t} + AUC_{t\to\infty}$
        ii. $AUMC_{0\to\infty} = AUMC_{0\to t} + AUMC_{t\to\infty}$
5. Calculate:
    a. Mean residence time, MRT
    b. Mean residence time after intravenous administration, MRT_{iv} knowing that AUC_{iv} = 108.41 [mg h L^{-1}] and $AUMC_{iv}$=341.31 [mg h^2 L^{-1}]
    c. Half-life time, $t_{0.5}$
    d. Bioavailability, F
    e. Clearance, Cl
    f. Mean absorption time, MAT
    g. Apparent volume of distribution
6. Write the laboratory report