PHAR 7633 Basic Pharmacokinetics

Chapter 20

Non Compartmental Analysis

Typical Clinical Publication:

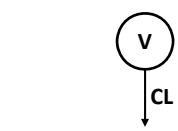
Wong SL et al., *Clin. Pharmacol. Ther*. 73: 304 (2003)

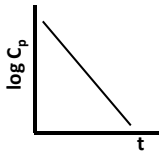
Pharmacokinetics and pharmacodynamics of abarelix, a gonadotropin-releasing hormone antagonist, after subcutaneous continuous infusion in patients with prostate cancer.

"**Noncompartmental pharmacokinetics analysis**. Pharmacokinetic parameters of abarelix, including maximum plasma drug concentration (***C_{max}***), time to reach C_{max} (***T_{max}***), area under the plasma concentration-time curve (***AUC***), apparent total volume of distribution during the terminal elimination phase (**V_β/F**) were estimated for each patient by standard noncompartmental methods. The average plasma concentration (C_{avg}) was calculated as AUC(0-t)/Duration of infusion, in which AUC(0-t) was defined as AUC from time 0 to the last measurable concentration. The area under the first moment curve (**AUMC**) was calculated with use of the trapezoidal rule. The subcutaneous mean residence time (**MRT_{SC}**) of abarelix after continuous subcutaneous infusion was calculated as AUMC/AUC – Infusion time/2.

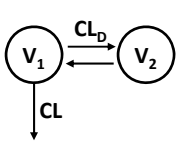
All of the pharmacokinetic calculations were performed with WinNonlin (version 3.3; Pharsight Corp., Mountain View, CA)"

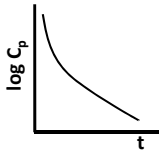
THE PROBLEM: Many Models and Curves



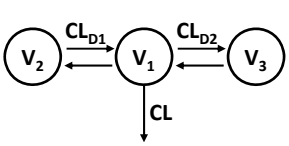


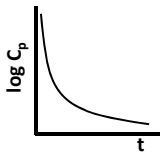
$$C_P = C_P^0 \cdot e^{-\lambda \cdot t}$$





$$C_P = C_1 \cdot e^{-\lambda_1 \cdot t} + C_2 \cdot e^{-\lambda_2 \cdot t}$$





$$C_P = C_1 \cdot e^{-\lambda_1 \cdot t} + C_2 \cdot e^{-\lambda_2 \cdot t} + C_3 \cdot e^{-\lambda_3 \cdot t}$$

Number of compartments = Number of curve exponentials.

THE QUEST: Capture Parameters Relevant to All Models and Drugs

Essential:

- **F : Bioavailability**
- **CL: Clearance**
- **V_{ss}: Steady-State Volume**

Others:

- **V_c: Central Volume**
- **$t_{1/2\beta}$: Terminal Half-life**

THE ANSWER: Moment Analysis

Definition for a continuous function, *f(t)* ; (t = time)

$$M_n \overset{\Delta}{=} \int_0^\infty t^n \cdot f(t) \cdot dt$$

Moment	Statistics	Physics	Pharmacokinetics
M_0	Numbers	Weight	AUC
M_1	Mean	Center of Mass	Mean Residence Time, AUMC
⋮			

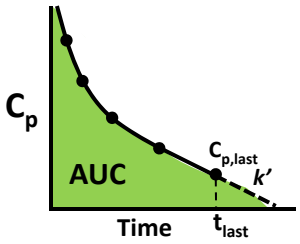
❑ Non Compartmental Analysis:

Calculate the areas of the C_p versus time curve (AUC; zero moment) and the first moment ($t \cdot C_p$) curve (AUMC) using the trapezoidal rule without making any assumption concerning the number of compartments.

Moment Functions in PK: AUC

$$M_0 = \int_0^\infty t^0 \cdot C_p dt = \int_0^\infty C_p dt = AUC$$

❑ Numerical Calculation:



$$AUC = \underbrace{AUC_{0-t_{last}}}_{\text{Calculated Interval Areas (Trapezoidal Rule)}} + \underbrace{\frac{C_{P,last}}{k'}}_{\text{AUC (last-}\infty\text{) (Extrapolate from } t_{last} \text{ to } t=\infty\text{)}}$$

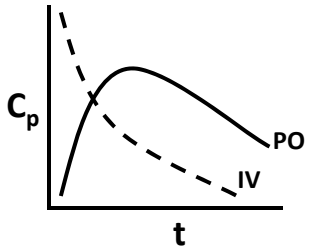
where k' is the terminal slope from semi-log graph of Cp vs. time

Utility of AUC

❑ Bioavailability (F)

The fraction of the dose available to the systemic circulation

$$F = \frac{AUC_{PO} \times Dose_{IV}}{AUC_{IV} \times Dose_{PO}}$$



❑ Total Clearance (CL)

CL = Dose/AUC

$$CL = \frac{dA_e / dt}{C_p} = \frac{\text{Elimination Rate}}{C_p}$$

$$Thus: \frac{dA_e}{dt} = CL \cdot C_p \quad \text{Rearrange}$$

$$Integrate: \int_0^\infty dA_e = CL \cdot \int_0^\infty C_p \cdot dt$$

$$A_e^\infty = Dose = CL \cdot AUC$$

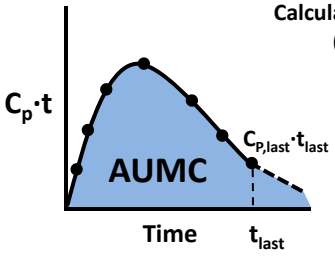
Does not depend on shape of IV disposition curve.
Requires elimination from plasma compartment.

Moment Functions in PK: AUMC

$$M_1 = \int_0^\infty t \cdot C_p dt = AUMC$$

❑ Numerical Calculation:

$$AUMC = \underbrace{AUMC_{0-t_{last}}}_{\text{Calculated Interval Areas (Trapezoidal)}} + \underbrace{\frac{C_{P,last} \cdot t_{last}}{k'} + \frac{C_{P,last}}{k'^2}}_{\text{AUMC (last-}\infty\text{) (Extrapolation)}}$$



where k' is the terminal slope from semi-log graph of Cp vs. time

AUMC: Area under the first moment curve

Numerical Calculation of AUMC: $= \int_0^\infty t \cdot C_p dt$

Table from: http://www.boomer.org/c/p4/c20/c2001.html

Time (hr)	Cp (mg/L)	Cp • t (mg.hr/L)	AUC (mg.hr/L)	AUMC (mg.hr²/L)
0	8	0	0	0
1	7.09	7.09	7.55	3.55
2	6.29	12.58	14.24	13.39
3	5.58	16.74	20.18	28.05
4	4.95	19.80	25.45	46.32
6	3.89	23.34	34.29	89.46
9	2.71	24.39	44.19	161.06
12	1.89	22.68	51.09	231.67
18	0.92	16.56	59.52	349.39
24	0.44	10.56	63.60	430.75
∞			**67.27**	**549.31**

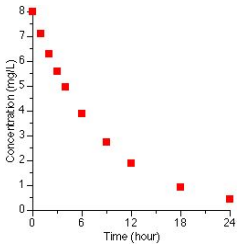


Figure 20.1.1 Plot of Cp vs Time (IV)

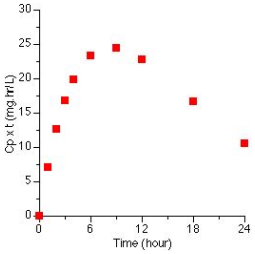


Figure 20.1.2 Plot of Cp x t vs Time (IV)

Utility of AUMC

$$MRT = \frac{AUMC}{AUC}$$

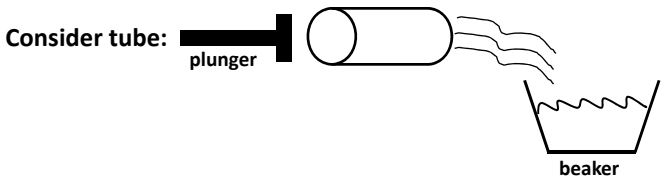
- MRT: Mean Residence Time, the average time that drug molecules remain in the body after dosing.
- Apparent elimination rate constant (*kel'*)

$$kel' = \frac{1}{MRT}$$ **for an IV dose of drug**

- Used for calculation of other parameters, particularly $V_{ss} = MRT \cdot CL$

Noncompartmental Generation of V_{ss}

Volume of Distribution: $V_{ss} = CL \cdot MRT$



If 1 mL leaves in 1 sec: CL = 1 mL/sec
If it takes 10 sec for plunger to traverse tube: MRT = 10 sec
Then tube V must be: 10 sec x 1 mL/sec = 10 mL

Hamilton Flow/Volume Principle (1931).

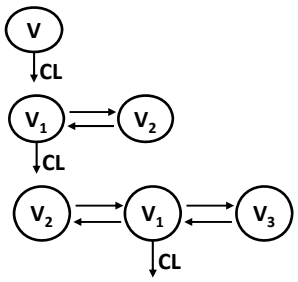
V_{ss}: All Methods Yield Equivalent Values

- $\underline{V_{ss}}$: Compartment Models

  1 CMT $V_{ss} = V$

  2 CMT $V_{ss} = V_1 + V_2$

  3 CMT $V_{ss} = V_1 + V_2 + V_3$



- Noncompartment Analysis

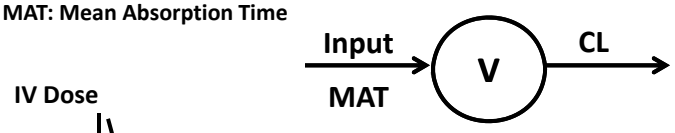
  $V_{ss} = MRT \cdot CL$

- Physiological Models

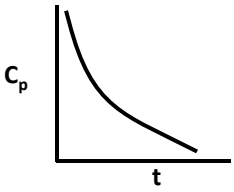
  $V_{ss} = V_{plasma} + \sum P_i \cdot V_{tissue}$

Mean Residence Time: Drug Absorption

MAT: Mean Absorption Time

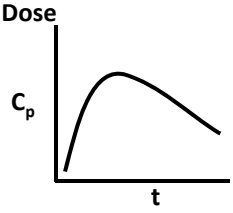


IV Dose



$$MRT_{IV} = \frac{AUMC_{IV}}{AUC_{IV}} = \frac{V_{SS}}{CL} \qquad kel' = \frac{1}{MRT_{IV}}$$

PO Dose



$$MRT_{PO} = \frac{AUMC_{PO}}{AUC_{PO}} = MAT + MRT_{IV}$$

$$MAT = MRT_{PO} - MRT_{IV} \qquad ka' = \frac{1}{MAT}$$

ka': Apparent Absorption Rate Constant

NOTE: We don't calculate CL or V_{ss} using oral data.

Limitations of Noncompartmental Analyses

- While AUC and AUMC are easily generated, they are **UNABLE** to visualize or predict plasma concentration-time profile for other dosing regimens.
- Requires the kinetics to be linear and stationary (i.e., time-independent) for simple applications.

Summary: Noncompartment Methods

- Calculation of AUC, AUMC, and MRT are valuable initial steps in PK data analysis.
- Calculation of
  CL = Dose/AUC
  is relevant for all traditional PK models regardless of numbers of exponentials.
- Calculation of
  $\mathbf{V_{ss} = MRT \cdot CL}$
  is easy and relevant for all linear models.