

PHAR 7632 Chapter 20

Non Compartmental Analysis

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Student Objectives for this Chapter

- To understand and use the non compartmental approach to parameter estimation

Non Compartmental Analysis

Table 20.1.1 Typical Cp versus Time Data after 100 mg IV Bolus Administration

| Time (hr) | Cp (mg/L) | Cp • t (mg.hr/L) | AUC (mg.hr/L) | AUMC (mg.hr ² /L) |
|-----------|-----------|------------------|---------------|------------------------------|
| 0 | 8 | 0 | 0 | 0 |
| 1 | 7.09 | 7.09 | 7.54 | 3.54 |
| 2 | 6.29 | 12.6 | 14.2 | 13.4 |
| 3 | 5.58 | 16.74 | 20.2 | 28.1 |
| 4 | 4.95 | 19.8 | 25.4 | 46.3 |
| 6 | 3.89 | 23.4 | 34.3 | 89.5 |
| 9 | 2.71 | 24.5 | 44.2 | 161 |
| 12 | 1.89 | 22.7 | 51.1 | 232 |
| 18 | 0.92 | 16.6 | 59.6 | 350 |
| 24 | 0.44 | 10.8 | 63.7 | 432 |
| ∞ | | | 67.43 | 553.2 |

Non compartmental methods can be used to determine certain pharmacokinetic parameters without deciding on a particular compartmental model. The basic calculations are based on the area under the plasma concentration versus times curve (zero moment) and the first moment curve (AUMC). The AUC can be calculated as before [using the trapezoidal rule](#). The first moment is calculated as concentration times time (Cp • t). The AUMC is the area under the concentration times time versus time curve. Maybe best covered with an example. Consider a drug given both by IV and oral administration. Both the AUC and AUMC were calculated using the trapezoidal rule without making any assumption concerning the number of compartments. The final segment of the AUC curve is calculated as Cp(last)/k, where k is the last exponential term (the slowest). The last segment for the AUMC curve is:

$$AUMC_{(last-\infty)} = \frac{C_{p_{last}} \cdot t_{last}}{k} + \frac{C_{p_{last}}}{k^2}$$

Equation 20.1.1 Equation of the last segment AUMC

Various parameters can be calculated as:

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

Equation 20.1.2 Equation for Mean Residence Time (MRT)

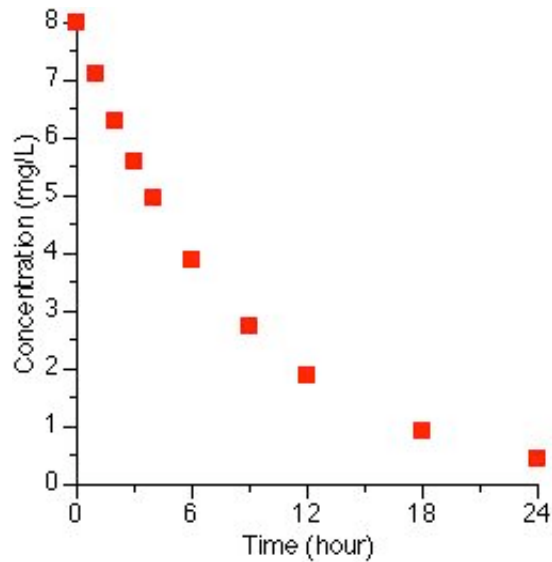
$$k' = \frac{1}{MRT}$$

Equation 20.1.3 Equation for Apparent Elimination Rate constant (k')

$$CL = \frac{Dose}{AUC}$$

Equation 20.1.4 Equation for Total Body Clearance (TBC)

$$V_{ss} = CL \bullet MRT = \frac{Dose \bullet MRT}{AUC}$$

Equation 20.1.5 Equation for Apparent Volume of Distribution, Steady State (V_{ss})**Figure 20.1.1 Plot of C_p versus Time (IV)**

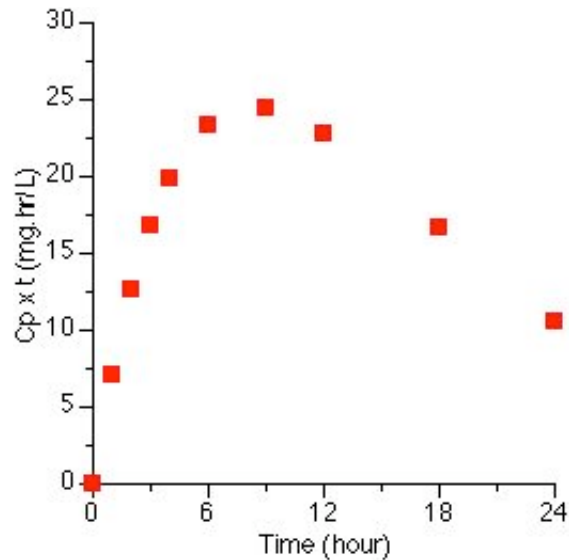


Figure 20.1.2 Plot of Cp x Time versus Time (IV)

From the AUC and AUMC values we can calculate the mean residence time, MRT. This is the average time that the drug stays in the body (or plasma as measured here). It can be related to the average elimination rate constant as $1/\text{MRT}$. The values from the above data are $\text{MRT} = 553.2/67.43 = 8.2 \text{ hr}$ and $k = 1/8.2 = 0.122 \text{ hr}^{-1}$. Remember we can also calculate the clearance, $\text{CL} = \text{Dose}/\text{AUC} = 100/67.43 = 1.48 \text{ L.hr}^{-1}$. Finally a steady state volume can be calculated as $\text{CL} \cdot \text{MRT} = 1.48 \times 8.2 = 12.2 \text{ L}$.

Table 20.1.2 Typical Cp versus Time Data after 250 mg Oral Administration

| Time (hr) | Cp (mg/L) | Cp • t (mg.hr/L) | AUC (mg.hr/L) | AUMC (mg.hr ² /L) |
|-----------|-----------|------------------|---------------|------------------------------|
| 0 | 0 | 0 | 0 | 0 |
| 1 | 12.18 | 12.2 | 6.09 | 6.09 |
| 2 | 14.12 | 28.3 | 19.2 | 26.3 |
| 3 | 13.43 | 40.3 | 33.0 | 60.6 |
| 4 | 12.16 | 48.6 | 45.8 | 105 |
| 6 | 9.64 | 57.9 | 67.6 | 212 |
| 9 | 6.73 | 60.6 | 92.2 | 389 |
| 12 | 4.69 | 56.4 | 109 | 565 |
| 18 | 2.28 | 41.2 | 130 | 857 |
| 24 | 1.11 | 26.7 | 141 | 1061 |
| ∞ | | | 149.8 | 1361 |

Other parameters can be calculated as:

$$MAT = \text{MRT}_{PO} - \text{MRT}_{IV}$$

Equation 20.1.6 Equation for Mean Absorption Time (MAT)

$$ka' = \frac{1}{MAT}$$

Equation 20.1.7 Equation for Apparent Absorption Rate Constant (ka')

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

Equation 20.1.8 Equation for Oral Bioavailability (F)

The data were calculated after a 250 mg oral dose of the same drug. From these data a MRT was calculated as $1361/149.8 = 9.08$ hr. We can subtract from this MRT(PO) the MRT(IV) to get an idea of the absorption process, the mean absorption time (MAT). That is $MAT = MRT(PO) - MRT(IV) = 9.08 - 8.20 = 0.88$ hr. From this we can calculate an average absorption rate constant $= 1/MAT = 1/0.88 = 1.14 \text{ hr}^{-1}$. Of course we can calculate the bioavailability of the oral dosage form using the dose adjusted AUC ratio.

Thus $F = (149.78/67.43) \times (100/250) = 0.89$.

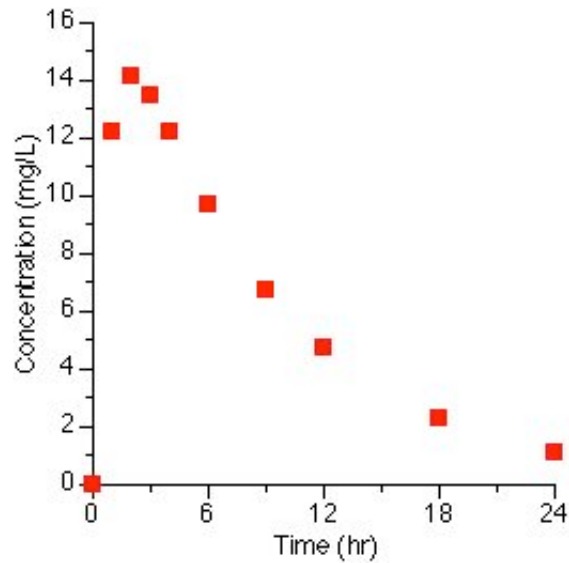


Figure 20.1.3 Plot of Cp versus Time (PO)

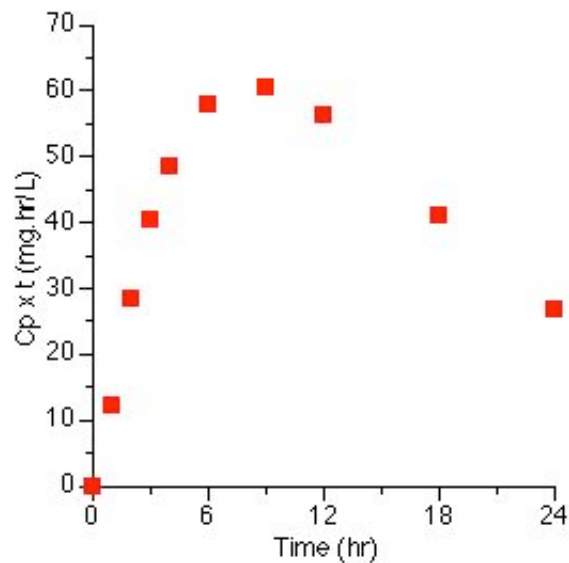


Figure 20.1.4 Plot of Cp x Time versus Time (PO)

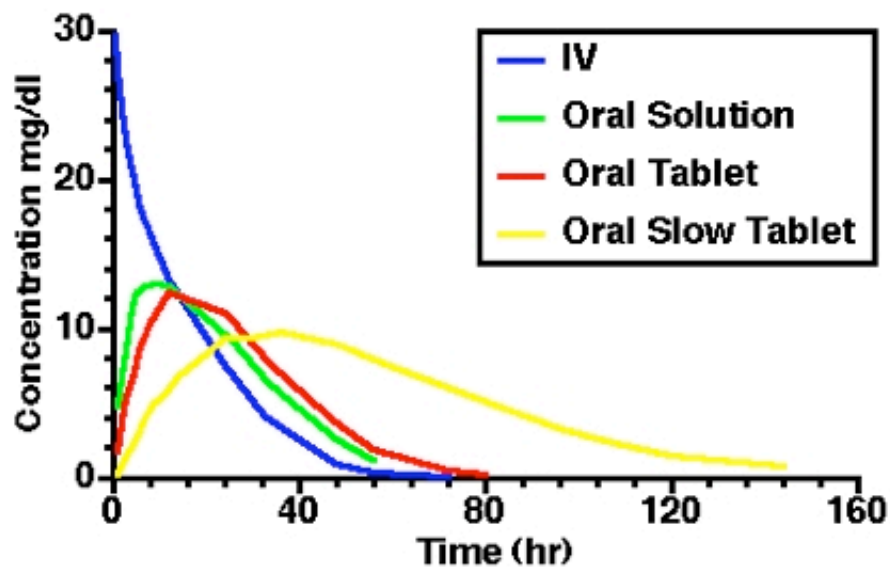
Another Example

using Data from [Bevill et al. 1977](#)

Pharmacokinetics of Sulfamethazine in Cattle following IV and Three Oral Dosage Forms Dosage Forms

- IV Bolus
- Oral Solution
- Oral Rapid Release Tablet
- Oral Sustained Release Tablet

Plasma Concentration



IV 107 mg/kg; Oral Solution 107 mg/kg
Oral Tablet 105 mg/kg; Oral Slow Tablet 249 mg/kg

Figure 20.1.5 The Average Data from Each Dosage Form

Non compartmental Analysis

| | AUC | AUMC | MRT | MAT | MDT |
|------------------------|------------|-------------|------------|------------|------------|
| IV | 437 | 6393 | 14.6 | - | - |
| Solution | 431 | 9454 | 21.9 | 7.3 | - |
| Tablet | 450 | 11303 | 25.1 | 10.5 | 3.2 |
| Slow Tablet | 765 | 45484 | 59.5 | 44.9 | 37.6 |

Figure 20.1.6 Non Compartmental Analysis Results

Comparison

| | Curve Fitting SAAM | Non Compartmental |
|--------------|-----------------------|----------------------|
| k' | 0.077 | 0.068 |
| ka' | 0.11 | 0.14 |
| kd' (fast) | 0.41 | 0.31 |
| kd' (slow) | 0.026 | 0.027 |

Curve fitting - One compartment model

Non compartmental analysis - $k' = 1/\text{MRT}$; $ka' = 1/\text{MAT}$; $kd' = 1/\text{MDT}$

Figure 20.1.7 Comparison with Non Linear Regression Analysis

[Want more practice with this type of problem!](#)

References

- Bevill, R.F., Dittert, L.W. and Bourne, D.W.A. 1977 Pharmacokinetics of Sulfamethazine in Cattle following IV and Three Oral Dosage Forms, *J. Pharm. Sci.*, **66**, 619-23

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