# Pharmacodynamic Models

Modeling Drug Effect versus Time

## Pharmacodynamic Models

- Objective
  - Understand the different types of concentration - effect relationships
  - Understand the mathematical relationships involved with Direct Reversible Pharmacological Effect Kinetics

## Concentration - Effect Relationships

- Direct Reversible Effects
  - Blood pressure control
  - Muscle Relaxant
- Indirect Reversible Effects
  - Anticoagulation
  - Anti-diabetic
- Irreversible Effects
  - Antibiotics
  - Anti-cancer

## Direct Reversible Effect

- Drug Effect proportional to Receptor Site Drug Concentration

$C_p$ <===> $C_r$ + Receptor <===> Drug Receptor Complex ---> Response

- Relationship between Effect and Concentration described using the Hill Equation

$$\text{Effect} = \frac{E_{max} \cdot C_r^{\gamma}}{C_{r,50\%}^{\gamma} + C_r^{\gamma}}$$

$E_{max}$ Maximum Response

$C_r^{\gamma}$ Slope, response factor

$C_{r,50\%}^{\gamma}$ Concentration producing 50% maximum

$C_r$ Concentration at Receptor

## Data Analysis

- Non linear Regression using the Hill Equation (Boomer or SAAM II or …)
- Or could rearrange to give a straight line

$$\text{Effect} = \frac{E_{max} \cdot C_r^{\gamma}}{C_{r,50\%}^{\gamma} + C_r^{\gamma}}$$

Rearranging gives: $\frac{E_{max}}{E} = \frac{C_{r,50\%}^{\gamma} + C_r^{\gamma}}{C_r^{\gamma}}$

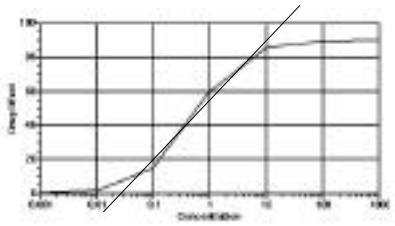
$$\log\left[\frac{E}{E_{max} - E}\right] = \gamma \cdot \log C_r - \log C_{r,50\%}^{\gamma}$$

## Linearization

$$\log\left[\frac{E}{E_{max} - E}\right] = \gamma \cdot \log C_r - \log C_{r,50\%}^{\gamma}$$

- Plot of log ($E/E_{max}$-E) versus log $C_r$ should give a straight line plot with a Slope of $\gamma$
- Exact if a single response

## Alternate Linearization



Approximately Linear from 20 to 80% of the maximum intensity

## Alternate Linearization …

- From 20 to 80% of the maximum effect

$$E = a \cdot \log C_r + b$$

this is also useful if the dose or concentration is not high enough to get a good estimate of $E_{max}$

## Continuing with this Thread

$$E = a \cdot \log C_r + b$$

Rearranging gives: $\log C = \frac{E - b}{a}$

For an IV Bolus one compartment model: $\log C = \log C_0 - \frac{kel \cdot t}{2.303}$

Thus E declines linearly with time: At least over the 20 to 80% part of the curve

$$\frac{E - b}{a} = \frac{E_{max} - b}{a} - \frac{kel \cdot t}{2.303}$$

$$E = E_{max} - \frac{m \cdot kel \cdot t}{2.303}$$

## An Example

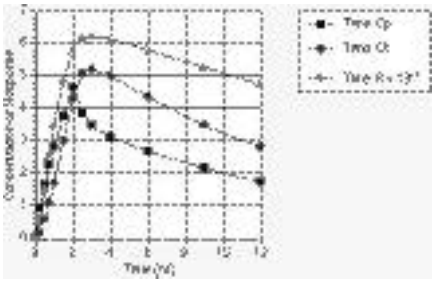
RR-Labetalol after one week
Last Dose

Derendorf, H. and Hochhaus, G. Handbook of Pharmacokinetic/Pharmacodynamic Correlation, CRC Press, 1995 page 207

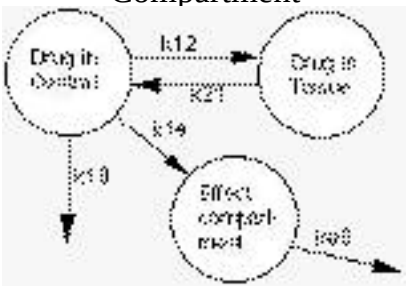
## Where is the Receptor?

- Pharmacokinetic Compartment
  - Central Compartment
  - Peripheral Compartment
- "Hypothetical" Receptor Compartment
- Plot Effect versus 'Concentration'

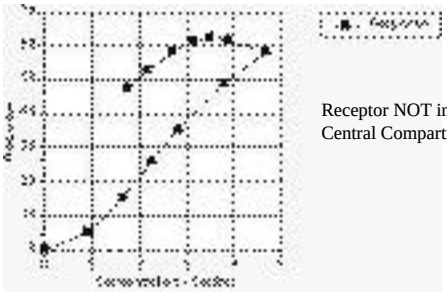
## Example Data



## PK Model with Effect Compartment




## Hysteresis in Plot



Receptor NOT in the Central Compartment

## Further reading?

- Hypothetical Response Compartment
  - Sheiner Model (Muscle Relaxants): L.B. Sheiner., et al. 1979 Clin. P'col. Therap., 25:358-371
- Indirect Reversible Response
  - Warfarin: R.A. O'Reilly, et al. 1963 J. Clin. Invest., 42:1542
- Irreversible Response
  - Antibiotics, Anti-cancer drugs: W.J. Jusko 1973 J. Pharm. Sci., 60:892

## Objectives

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