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

\[ C_r \iff C_r + \text{Receptor} \iff \text{Drug Receptor Complex} \implies \text{Response} \]

- Relationship between Effect and Concentration described using the Hill Equation

\[ \text{Effect} \begin{array}{c} \equiv \ \frac{E_{\text{max}} \cdot C_r^\gamma}{C_r^{50\%} + C_r^\gamma} \\ \end{array} \]

Maximum Response Concentration producing 50% maximum

Effect of $E_{\text{max}}$ 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

\[ \text{Effect} = \frac{E_{\text{max}} \cdot C_r^\gamma}{C_r^{50\%} + C_r^\gamma} \]

Rearranging gives:

\[ E_{\text{max}} = \frac{C_r^{50\%} + C_r^\gamma}{C_r^\gamma} \]

\[ \log \left( \frac{E}{E_{\text{max}} - E} \right) = \gamma \cdot \log C_r - \log C_r^{50\%} \]

Linearization

\[ \log \left( \frac{E}{E_{\text{max}} - E} \right) = \gamma \cdot \log C_r - \log C_r^{50\%} \]

- Plot of $\log (E/E_{\text{max}} - E)$ 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

\[ E = a \log C_r + b \]

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

\[ E = a \log C_r + b \]

Rearranging gives:

For an IV Bolus one compartment model

\[ \log C = \log C_0 - \frac{k_{el} t}{2.303} \]

Thus \( E \) declines linearly with time. At least over the 20 to 80% part of the curve

\[ E_{\max} - \frac{E - b}{a} = \frac{E_{\max} - b}{a} - \frac{k_{el} t}{2.303} \]

\[ E = E_{\max} - \frac{m \cdot k_{el} t}{2.303} \]
An Example

R.R.-Labetalol after one week
Last Dose

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

Further reading?
- Hypothetical Response Compartment
- Indirect Reversible Response
- Irreversible Response
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