Clinical Pharmacokinetics: Use in Drug Development
Presentation Outline

• Background on Roche
• Overview of Drug Development Process
• Pharmacokinetics Introduction
• PK Study design Exercise
Our History

• F. Hoffmann-La Roche & Co. Founded October 1, 1896.

Founder Fritz Hoffmann recognized early that the industrial manufacture of standardized medicines would be a major advance in the fight against disease.

• Early products included antiseptics (Airol), cough syrups (Sirolin), heart stimulants (Digalen), and pain medicines (Pantopon).
Priority Disease Areas in Palo Alto

Areas of high unmet medical need

**Inflammation/AutoImmune/Transplant**
- Rheumatoid
- Osteoarthritis
- Arthritis
- Chronic Obstructive Pulmonary Disease
- Asthma, Emphysema
- Transplant

**Viral Diseases**
- HIV/AIDS
- Hepatitis C

**Central Nervous System/Neuropsychiatry**
- Depression/Anxiety
- Schizophrenia

**Genitourinary**
- Incontinence, Pelvic Hypersensitivity
- Benign Prostatic Hyperplasia
- Overactive Bladder
# Treating Serious Diseases:
Roche’s Top Ten Prescription Medicines

<table>
<thead>
<tr>
<th>Roche Medicine</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. NeoRecormon, Epogin**</td>
<td>anemia</td>
</tr>
<tr>
<td>3. Pegasys + Copegus***</td>
<td>Hepatitis C</td>
</tr>
<tr>
<td>4. Herceptin*</td>
<td>metastatic breast cancer</td>
</tr>
<tr>
<td>5. CellCept***</td>
<td>transplantation, prevention of rejection</td>
</tr>
<tr>
<td>6. Rocephin***</td>
<td>bacterial infections</td>
</tr>
<tr>
<td>7. Avastin****</td>
<td>First-line treatment in combination with chemotherapy of metastatic colorectal cancer</td>
</tr>
<tr>
<td>8. Tamiflu***</td>
<td>treatment and prevention of influenza A and B</td>
</tr>
<tr>
<td>9. Xeloda***</td>
<td>colorectal or breast cancer</td>
</tr>
<tr>
<td>10. Xenical</td>
<td>weight loss/management</td>
</tr>
</tbody>
</table>

*Jointly marketed by Roche, Genentech and Chugai **Marketed by Chugai ***Jointly marketed by Roche and Chugai ****Jointly marketed by Roche and Chugai
Overview of the Drug Development Process

**Discovery**

*Find it!*

- **Early Research / Preclinical Testing**
  - Years: 5
  - Test Population: Laboratory and animal studies
  - Purpose: Assess safety and biological activity
  - Success Rate: 5,000 compounds evaluated
  - Years: 0 Years
  - Test Population: File Investigational
  - Purpose: New Drug Application (IND)

**Development**

*Test it!*

- **Phase I**
  - Years: 1
  - Test Population: 20 to 80 healthy volunteers
  - Purpose: Determine safe dose range PK
  - Success Rate: 5 enter trials

- **Phase II**
  - Years: 1.5
  - Test Population: 100 to 300 patient volunteers
  - Purpose: Evaluate dose, look for side effects and efficacy

- **Phase III**
  - Years: 2.5
  - Test Population: 1,000 to 3,000 patient volunteers
  - Purpose: Confirm effectiveness, monitor adverse reactions

**Marketing**

- **NDA**
  - Years: 1
  - Test Population: 1 approved
  - Purpose: Review data, approve drug and package insert

- **Phase IV**
  - Years: 12
  - Test Population: Postmarketing testing required by FDA
  - Purpose: Study additional uses, populations, dosage forms, etc

- **Years**
  - 6.5 Years
  - File Investigational
  - New Drug Application (IND)

- **Years**
  - 10.5 Years
  - File New Drug Application (NDA)
What is Pharmacokinetics (PK)?

• “The science of what your body does to drugs.”
• The study of the time course of its absorption, distribution, metabolism, and excretion (ADME).
Absorption (A)

- Process involving the movement of drug from its extravascular site of administration into the systemic circulation.
- Various routes of administration requiring absorption (including oral, transdermal or subcutaneous)
Oral Absorption

- Oral Absorption
- GI Tract
- Dissolution
- Chemical Degradation
- Absorption
- Gut Wall Metabolism
- Fecal Excretion
- Systemic Circulation
- Liver
- Portal Vein
- Biliary Excretion
Distribution (D)

The transfer of drug between various locations in the body

Peripheral Compartment
- Fat Cells
- Muscle
- Brain

Central Compartment
- Highly-Perfused Tissues
  - Blood
  - Heart
  - Kidney
  - Lungs
  - Liver

\[ D = \text{Drug} \]
Metabolism (M)

• Process by which a drug is changed or chemically converted to another chemical entity/compound.

• Major Site: Liver

• Importance: converts active parent drug to a more water soluble form which may be more readily excreted.
Excretion (E)

- The irreversible removal of the drug/metabolite from the body.
- Major route: Kidney
Pharmacokinetic Overview

Distribution

Dose

Absorption

Blood/Plasma

Site of Action

Elimination

\[ \frac{dA}{dt} = \frac{dA_a}{dt} - CL \cdot C \]

Rate of Change of Drug amount in the body

Rate of absorption

Rate of elimination
Plasma Concentration-Time Curve

- $C_{\text{max}}$: Maximum Plasma Concentration
- $AUC$: Area Under Curve
- $T_{1/2}$: Half-Life
- $T_{\text{max}}$: Time to $C_{\text{max}}$
Pharmacokinetic Parameters

- **Cmax** - Maximum concentration
- **Tmax** – Time at which maximum concentration is observed
- **AUC** – (Area under the curve) – exposure
- **T1/2** – half-life
Area Under the Curve (AUC)

- The total exposure to the drug
- Why is it important? So we know if the body is getting optimal exposure for efficacy and not over-exposed leading to toxicity
- $AUC = \int_{0}^{\infty} C \, dt$
- The AUC may be calculated using the trapezoidal rule where:

\[
AUC_{tn-1} = C_{n-1} \frac{t_n - t_{n-1}}{2} + C_{n} (t_n - t_{n-1})
\]
Half Life ($t_{1/2}$)

- The time in which half of the drug has cleared from the plasma, etc.

- Why do we care? So we know how long the drug stays in the body so we can determine time points and optimum dosing intervals to maintain average drug concentration over time.
Example of Phase I Study

- Drug: ROxxxxx is being evaluated for the treatment of asthma.
- Study Design: Phase I, single dose study in healthy volunteers
- Dose: 50 mg
- Pharmacokinetic sampling: Plasma samples were collected at predose (0), 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120 and 144 hours following an overnight fast
Sample Processing and Data Analysis

Blood samples drawn into labeled tube

- Mixed 
- & Centrifuged at 4°C to obtain plasma

- Plasma transferred to fresh tube

- !!!Well-validated analytical methods!!!

- Analysis & Quantitation of Drug and/or metabolites

- !!!Accurate recording of dates, times, etc.!!!

- Transport to analytical lab

- !!!Proper labeling and handling essential!!!

- Frozen @ -20°C until transport
## Plasma Concentration Data following a single 50mg dose of ROxxxxx

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Plasma Conc of Drug ROxxxxx (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.5</td>
<td>4.08</td>
</tr>
<tr>
<td>1</td>
<td>6.75</td>
</tr>
<tr>
<td>2</td>
<td>9.55</td>
</tr>
<tr>
<td>4</td>
<td>10.8</td>
</tr>
<tr>
<td>6</td>
<td>10.5</td>
</tr>
<tr>
<td>8</td>
<td>9.86</td>
</tr>
<tr>
<td>12</td>
<td>8.59</td>
</tr>
<tr>
<td>24</td>
<td>5.64</td>
</tr>
<tr>
<td>36</td>
<td>3.71</td>
</tr>
<tr>
<td>48</td>
<td>2.44</td>
</tr>
<tr>
<td>72</td>
<td>1.05</td>
</tr>
<tr>
<td>96</td>
<td>0.454</td>
</tr>
<tr>
<td>120</td>
<td>0.196</td>
</tr>
<tr>
<td>144</td>
<td>0.0846</td>
</tr>
</tbody>
</table>
Plasma Concentration-Time Profile Following a Single dose of ROxxxxxx
## Calculation of Area under the Curve (AUC)

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Plasma Conc</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.5</td>
<td>4.08</td>
<td>1.02</td>
</tr>
<tr>
<td>1</td>
<td>6.75</td>
<td>2.71</td>
</tr>
<tr>
<td>2</td>
<td>9.55</td>
<td>8.15</td>
</tr>
<tr>
<td>4</td>
<td>10.8</td>
<td>20.4</td>
</tr>
<tr>
<td>6</td>
<td>10.5</td>
<td>21.3</td>
</tr>
<tr>
<td>8</td>
<td>9.86</td>
<td>20.4</td>
</tr>
<tr>
<td>12</td>
<td>8.59</td>
<td>36.9</td>
</tr>
<tr>
<td>24</td>
<td>5.64</td>
<td>85.4</td>
</tr>
<tr>
<td>36</td>
<td>3.71</td>
<td>56.1</td>
</tr>
<tr>
<td>48</td>
<td>2.44</td>
<td>36.9</td>
</tr>
<tr>
<td>72</td>
<td>1.05</td>
<td>41.9</td>
</tr>
<tr>
<td>96</td>
<td>0.454</td>
<td>18.1</td>
</tr>
<tr>
<td>120</td>
<td>0.196</td>
<td>7.8</td>
</tr>
<tr>
<td>144</td>
<td>0.0846</td>
<td>3.37</td>
</tr>
<tr>
<td><strong>0 - 144</strong></td>
<td><strong>Σ</strong></td>
<td><strong>360.4</strong></td>
</tr>
</tbody>
</table>
## Summary of PK Results

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cmax (mcg/mL)</strong></td>
<td>10.8</td>
</tr>
<tr>
<td><strong>Tmax (hr)</strong></td>
<td>4</td>
</tr>
<tr>
<td><strong>AUC (mcg*hr/mL)</strong></td>
<td>360.4</td>
</tr>
<tr>
<td><strong>Half-life (hr)</strong></td>
<td>20</td>
</tr>
</tbody>
</table>
Next Challenge: Dose Selection

• The project team is ready to move into a Phase II study in asthmatic patients. Preclinical data suggest that the minimum effective concentration for ROxxxxx is 20 mcg/mL. However, toxicity in animals were observed at concentrations above 30 mcg/mL. The team needs to select a dose to move into Phase II.
Use of Modeling in Drug Development
Pharmacokinetic Models

- Simplify very complex body processes and structures.
- Quantitatively describe real physiological processes.
- Serve to predict the time course of drug concentrations in fluids and tissues.
- Basic type = Compartmental model
- May be used to simulate to predict plasma concentrations at other doses
1 compartment open, 1st order

\[ C = C_0 \cdot (e^{-\lambda z t} - e^{-k_a t}) \]

where \( C_0 = \frac{FD \cdot k_a}{V_z (k_a - \lambda_z)} \)
Simulation of Multiple Doses
Rate of absorption

- \( \frac{dA_a}{dt} = -ka \cdot A_a \)

\( ka = \) first order rate constant for absorption

\( A_a = \) the amount of drug at the absorption site remaining to be absorbed
Rate of Elimination

- CL*C

Where CL = clearance (represented in volume per time)
and C = drug concentration (amount/volume)
Clinical Pharmacokinetics

• The application of PK principles for the purpose of providing safe and effective therapeutic management of patients.

• Goals of Clinical PK:
  – Optimal dosage regimen design
  – Successful drug therapy => Optimal therapeutic response with minimal adverse events. (↑ efficacy, ↓ toxicity)
  – Proper drug labeling
Area under the Curve (AUC)

- The AUC may be calculated using the trapezoidal rule where:

\[
AUC_{tn}^{tn-1} = \frac{C_{n-1} + C_n}{2} (t_n - t_{n-1})
\]