COMPARTMENTAL ANALYSIS OF DRUG DISTRIBUTION

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and Medical Education
National Institutes of Health
Clinical Center
The post-absorptive transfer of drug from one location in the body to another.

- **Compartmental Models**
  (ordinary differential equations)
- **Distributed Models**
  (partial differential equations)
Pharmacokinetic Models Using Ordinary Differential Equations*

<table>
<thead>
<tr>
<th>MODEL</th>
<th>NUMBER OF COMPARTMENTS</th>
<th>MATHEMATICAL CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NONCOMPARTMENTAL</td>
<td>0</td>
<td>CURVE FITTING TO DATA</td>
</tr>
<tr>
<td>COMPARTMENTAL</td>
<td>1 – 3</td>
<td>MODEL PARAMETERS FIT TO DATA</td>
</tr>
<tr>
<td>“PHYSIOLOGICAL”</td>
<td>4 - 20</td>
<td>MODEL PARAMETERS FIXED A PRIORI</td>
</tr>
</tbody>
</table>

Mathematical vs. Physical Models*

**MATHEMATICAL MODEL:**
Functions or differential equations are employed without regard to the physical characteristics of the system.

**PHYSICAL MODEL:**
Implies certain mechanisms or entities that have physiological, biochemical or physical significance.

Goals of Drug Distribution Lecture

- **Significance** of Drug Distribution Volumes
- **Physiological Basis** of Multi-Compartment Pharmacokinetic Models
- **Clinical Implications** of Drug Distribution Kinetics
DIGOXIN DISTRIBUTION VOLUME

\[ V_d = \frac{\text{DOSE}}{C_0} = \frac{750 \, \mu g}{1.4 \, \mu g/L} = 536 \, L \]
**Body Fluid Spaces**
Catenary 3-Compartment Model

- Intravascular Space
  - capillaries
  - Elimination
- Interstitial Fluid Space
- Intracellular Fluid Space
  - cell membranes
Apparent Volume of Distribution and Physiological Fluid Spaces

**Intravascular Space:**
No drug is restricted to this fluid space

**Extracellular Fluid Space:**

- Inulin
- Proteins and other Macromolecules
- Neuromuscular Blocking Drugs (N+)
- Aminoglycoside Antibiotics (initially)


Apparent Volume of Distribution and Physiological Fluid Spaces

Total Body Water
- Urea
- Ethyl alcohol
- Antipyrine (some protein binding)
- Caffeine
Factors Affecting Volume of Distribution Estimates

Binding to Plasma Proteins
- Thyroxine
- Theophylline

Tissue Binding (partitioning)
- Lipophilic Compounds
- Digoxin (Na\(^+\) - K\(^+\) ATPase)
Effect of Plasma Protein Binding on Drug Distribution

Cell Membranes

ECF

BINDING PROTEINS

ICF

Elimination
Effect of **Plasma Protein Binding** on Apparent Volume of Distribution*

\[ V_d = ECF + f_u (TBW - ECF) \]

\( f_u \) is the “free fraction”, the fraction of drug in plasma that is not bound to plasma proteins.

Impact of Protein Binding on Thyroxine Distribution Volume*

\[ f_u = 0.03\% \]

\[ V_d = V_{ECF} \]

Impact of Protein Binding on Theophylline Distribution Volume*

\[ f_u = 60\% \]

\[ V_d = V_{ECF} + f_u V_{ICF} \]

Basis for Increased Theophylline Volume of Distribution in Pregnancy*

<table>
<thead>
<tr>
<th></th>
<th>f_U (%)</th>
<th>FLUID SPACE ESTIMATES (L)</th>
<th>TOTAL V_d (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ECF</td>
<td>TBW</td>
</tr>
<tr>
<td>PREGNANT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-26 WEEKS</td>
<td>88.9</td>
<td>13</td>
<td>34</td>
</tr>
<tr>
<td>36-38 WEEKS</td>
<td>87.0</td>
<td>21</td>
<td>40</td>
</tr>
<tr>
<td>POSTPARTUM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-8 WEEKS</td>
<td>77.4</td>
<td>12</td>
<td>33</td>
</tr>
<tr>
<td>&gt;6 MONTHS</td>
<td>71.9</td>
<td>12</td>
<td>33</td>
</tr>
</tbody>
</table>

Effect of Plasma Protein and Tissue Binding on the Volume of Distribution of Most Drugs*

\[ V_d = ECF + \Phi f_u (TBW - ECF) \]

Φ is the ratio of tissue/plasma drug concentration.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Log $D_{oct}$</th>
<th>Log $\Phi$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>6.5</td>
<td>4.0</td>
</tr>
<tr>
<td>Loratidine</td>
<td>5.3</td>
<td>3.2</td>
</tr>
<tr>
<td>Clozapine</td>
<td>4.9</td>
<td>2.9</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>4.5</td>
<td>2.6</td>
</tr>
<tr>
<td>Diazepam</td>
<td>4.2</td>
<td>2.4</td>
</tr>
<tr>
<td>Imipramine</td>
<td>3.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>3.7</td>
<td>2.1</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>3.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>3.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Clonidine</td>
<td>3.1</td>
<td>1.8</td>
</tr>
<tr>
<td>Propranolol</td>
<td>3.0</td>
<td>1.7</td>
</tr>
<tr>
<td>Digoxin</td>
<td>2.9</td>
<td>1.6</td>
</tr>
</tbody>
</table>

LIPID SOLUBILITY ($D_{oct}$) and $\Phi$
**Apparent Volume of Distribution for Digoxin**

\[
V_d = \text{ECF} + \Phi f_u (\text{TBW} - \text{ECF})
\]

ECF = 11.2 L, TBW = 45.5 L, \( f_u = 0.75 \), \( \Phi = 20.4 \)

\[
V_d = 11.2 + (20.4) (0.75) (34.3) \text{ L}
\]

\[
V_d = 536 \text{ L}
\]

\( \Phi \) includes binding to \( \text{Na}^+\text{-K}^+\text{ATPase} \).
Tissue vs. Plasma **Digoxin** Levels
GOALS OF DRUG DISTRIBUTION LECTURE

• Significance of drug distribution volumes

• **Physiologic basis of multi-compartment pharmacokinetic models**

• Clinical implications of drug distribution kinetics
First Multicompartmental Analysis of Drug Distribution*

* From Teorell T. Arch Intern Pharmacodyn 1937;57:205-25.
Number of exponential phases in plasma level vs. time curve determines the number of compartments.
TECHNIQUE OF CURVE PEELING
COMPARTMENTAL ANALYSIS

Data Equation:
\[ C = A \ e^{-\alpha t} + B \ e^{-\beta t} \]

Model Equation:
\[ \frac{dX_1}{dt} = -(k_{01} + k_{21})X_1 + k_{12}X_2 \]
TWO-COMPARTMENT MODEL

Dose

\[ V_{d(ss)} = V_1 + V_2 \]
3 DISTRIBUTION VOLUMES

\[ V_{d (\text{extrap.})} = \frac{\text{DOSE}}{C_0} \]

\[ V_{d (\text{area})} = \frac{t^{1/2} \cdot CL_E}{0.693} \]

\[ V_{d (\text{ss})} = V_1 + V_2 + \ldots + V_n \]
TWO-COMPARTMENT MODEL

Central
\( V_1 \)

Periph.
\( V_2 \)

Dose

\( CL_I \)

\( CL_E \)

\( k_{01} \)

\[ CL_E = k_{01} V_1 \]
TWO-COMPARTMENT MODEL

\[ V_1 = \frac{CL_{I}}{k_{21}} \]
\[ V_2 = \frac{CL_{I}}{k_{12}} \]

\[ CL_I = k_{21} V_1 = k_{12} V_2 \]
INTERCOMPARTMENTAL CLEARANCE*

Volume-Independent Parameter
Characterizing the Rate of Drug Transfer
Between Compartments of a Kinetic Model

Is Central Compartment Intravascular Space?

- Usually **not** identified as such **unless** drug is given **rapidly IV**.

- **NEED TO CONSIDER:**
  - If distribution is **limited to ECF**, compare the central compartment volume with **plasma** volume.
  - If distribution volume **exceeds ECF** compare central compartment with **blood** volume.*

*(account for RBC/Plasma partition if [plasma] measured)*
### Analysis of Procainamide and NAPA Central Compartment Volumes*

<table>
<thead>
<tr>
<th>DRUG</th>
<th>$V_c$ (L)</th>
<th>RBC/P</th>
<th>INTRAVASCULAR SPACE (L)</th>
<th>PREDICTED</th>
<th>OBSERVED</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA</td>
<td>6.7</td>
<td>1.52</td>
<td>5.6</td>
<td>5.5</td>
<td>5.5</td>
</tr>
<tr>
<td>NAPA</td>
<td>7.5</td>
<td>1.62</td>
<td>5.6</td>
<td>6.0</td>
<td></td>
</tr>
</tbody>
</table>

If Central Compartment Volume is Based on Plasma Concentration Measurements

\[
V_{c(\text{corr.})} = \frac{V_{c(\text{meas.})}}{\left[ (1 - Hct) + Hct \left( \frac{\text{RBC}}{\text{P}} \right) \right]}
\]

**RBC/P = red cell/plasma partition ratio**

**Hct = hematocrit**
Analysis of Inulin Kinetics with a 2-Compartment Model*

3-Compartment Model of Inulin Kinetics
Kinetic Heterogeneity of IF Space

The interstitial fluid (IF) compartment is “kinetically heterogeneous” with regard to rate of drug distribution.

Splanchnic vascular bed
  Fenestrated capillaries - large pores

Somatic tissues vascular beds
  Continuous capillaries – small pores
UREA-$^{15}$N$_2$ KINETICS IN A NORMAL SUBJECT
Multicompartment Model of **Inulin** and **Urea** Kinetics*

The central compartment for both urea and inulin is the intravascular space.

Therefore, transcapillary exchange is the rate-limiting step in the distribution of urea and inulin to the peripheral compartments of the mammillary 3-compartment model.
RENKIN EQUATION*

\[ CI = Q \left( 1 - e^{-\frac{P}{Q}} \right) \]

Q = capillary blood flow

P = capillary permeability coefficient-surface area product (sometimes denoted P•S).

SIMULTANEOUS ANALYSIS OF INULIN AND UREA-$^{15}$N$_2$ KINETICS

SUBJECT 1

PLASMA CONCENTRATION (µg/ml)

MINUTES

0 60 120 180 240 300 360 420 480

INULIN

UREA
3-COMPARTMENT MODEL

\[ CL_F = Q_F \left(1 - e^{PF/Q_F}\right) \]

\[ CL_S = Q_S \left(1 - e^{PS/Q_S}\right) \]
For Each Peripheral Compartment

3 UNKNOWNS:

\( Q, \ P_U, \ P_I \)

3 EQUATIONS:

\[
\begin{align*}
P_U &= Q \ln \left( \frac{Q}{Q - Cl_U} \right) \\
P_I &= Q \ln \left( \frac{Q}{Q - Cl_I} \right) \\
P_U / P_I &= D_U / D_I
\end{align*}
\]

\( U = \text{urea}; \ I = \text{inulin} \)

\( D = \text{free water diffusion coefficient} \)
SIMULTANEOUS ANALYSIS OF INULIN AND UREA-$^{15}$N$_2$ KINETICS

How does $Q_F + Q_S$ compare with C.O.?
**CARDIAC OUTPUT AND COMPARTMENTAL BLOOD FLOWS**

<table>
<thead>
<tr>
<th></th>
<th>$Q_F$ (L/min)</th>
<th>$Q_S$ (L/min)</th>
<th>$Q_F + Q_S$ (L/min)</th>
<th>% CO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MEAN†</strong></td>
<td>3.87</td>
<td>1.52</td>
<td>5.39</td>
<td>99</td>
</tr>
</tbody>
</table>

† MEAN OF 5 SUBJECTS

TRANSCAPILLARY EXCHANGE
Mechanisms

TRANSFER OF SMALL MOLECULES (M.W. < 6,000 Da):

• Transfer proportional to D
  - Polar, uncharged (urea, inulin)

• Transfer rate < predicted from D
  - Highly charged (quaternary compounds)
  - Interact with pores (procainamide)

• Transfer rate > predicted from D
  - Lipid soluble compounds (anesthetic gases)
  - Facilitated diffusion (theophylline)
## Urea and Theophylline Diffusion Coefficients

<table>
<thead>
<tr>
<th>MOLECULAR WEIGHT (DALTONS)</th>
<th>CORRECTED STOKES-EINSTEIN RADIUS (Å)</th>
<th>$D_m @ 37^\circ C$ (x $10^{-5} \text{ cm}^2/\text{sec}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UREA</td>
<td>60</td>
<td>2.2</td>
</tr>
<tr>
<td>THEOPHYLLINE</td>
<td>180</td>
<td>3.4</td>
</tr>
</tbody>
</table>

PRESUMED CARRIER-MEDIATED TRANSCAPILLARY EXCHANGE

THEOPHYLLINE

HYPOXANTHINE

ADENINE
GOALS OF DRUG DISTRIBUTION LECTURE

• Significance of drug distribution volumes

• Physiologic basis of multi-compartment pharmacokinetic models

• Clinical implications of drug distribution kinetics
SIGNIFICANCE OF DRUG DISTRIBUTION RATE

1. Affects toxicity of IV injected drugs
   Theophylline, lidocaine

2. Delays onset of drug action
   Insulin, digoxin

3. Terminates action after IV bolus dose
   Thiopental, lidocaine
PK Model of THEOPHYLLINE Distribution

IV Dose

CNS

HEART

IVS

SPLANCHNIC

SOMATIC

CO = \( Q_F + Q_S \)

\( CL_F = Q_F \)  

\( CL_S = Q_S \)  

\( CL_E \)
PK-PD Study of **INSULIN** Enhancement of Skeletal Muscle Glucose Uptake*

DISTRIBUTION TERMINATES EFFECT
BOLUS LIDOCAINE DOSE*

THERAPEUTIC RANGE

CONSEQUENCES OF VERY SLOW DRUG DISTRIBUTION

• “Flip-Flop” Kinetics

• Effective Half-Life

• Pseudo Dose Dependency
GENTAMICIN
Elimination Phase Preceeds Distribution Phase*

GENTAMICIN ELIMINATION
Nephrotoxic vs. Non-Toxic Patient*

CONSEQUENCES OF VERY SLOW DRUG DISTRIBUTION

- “Flip-Flop” Kinetics
- Effective Half-Life
- Pseudo Dose Dependency
TOLRESTAT
Cumulation with Repeated Dosing*

CUMULATION FACTOR

\[ CF = \frac{1}{\left(1 - e^{-k\tau}\right)} \]
Predicted C.F. from $T_{1/2} = 31.6$ hr: 4.32

Observed C.F.: 1.29
EFFECTIVE HALF- LIFE*

\[
k_{\text{eff}} = \frac{1}{\tau} \ln \left( \frac{\text{CF}_{\text{obs}}}{\text{CF}_{\text{obs}} - 1} \right)
\]

\[
t_{\text{1/2 eff}} = \frac{\ln 2}{k_{\text{eff}}}
\]

Since $\tau = 12 \text{ hr}$ and Observed CF = 1.29:

$$k_{eff} = \frac{1}{12} \ln\left(\frac{1.29}{1.29 - 1}\right) = 0.124 \text{ hr}^{-1}$$

$$t_{1/2 eff} = \frac{\ln 2}{0.124} = 5.6 \text{ hr}$$

CONSEQUENCES OF VERY SLOW DRUG DISTRIBUTION

• “Flip-Flop” Kinetics

• Effective Half-Life

• Pseudo Dose Dependency
AREA UNDER THE CURVE
Measure of Dose Proportionality

\[ \text{CL} = \frac{\text{ABSORBED DOSE}}{\text{AUC}} \]
## HYPOTHETICAL Phase I Trial Results

<table>
<thead>
<tr>
<th></th>
<th>DOSE 1</th>
<th>DOSE 2</th>
<th>INCREASE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DOSE (mg)</strong></td>
<td>25</td>
<td>100</td>
<td>4 x ↑</td>
</tr>
<tr>
<td><strong>AUC (μg·hr/mL)</strong></td>
<td>1.32</td>
<td>17.91</td>
<td>13.6 x ↑</td>
</tr>
</tbody>
</table>
Dependency of PK Estimates on Identified Terminal Phase

Increase: Dose = 4-Fold

- 100 mg Dose  AUC = 17.91 μg.hr/ml
- 25 mg Dose  AUC = 1.32 μg.hr/ml

\( C_0 = 2.1 \mu g/mL, V_d = 47.6 \text{ L}, CL = 5.6 \text{ L/hr} \)

\( C_0 = 1.8 \mu g/mL, V_d = 13.9 \text{ L}, CL = 18.9 \text{ L/hr} \)
<table>
<thead>
<tr>
<th>MACROMOLECULE</th>
<th>MW (kDa)</th>
<th>V₁ (mL/kg)</th>
<th>V₃₃ (mL/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INULIN</td>
<td>5.2</td>
<td>55</td>
<td>164</td>
</tr>
<tr>
<td>FACTOR IX (FIX)</td>
<td>57</td>
<td>136</td>
<td>271</td>
</tr>
<tr>
<td>INTERLEUKIN-2 (IL-2)</td>
<td>15.5</td>
<td>60</td>
<td>112</td>
</tr>
<tr>
<td>INTERLEUKIN-12 (IL-12)</td>
<td>53</td>
<td>52</td>
<td>59</td>
</tr>
<tr>
<td>GRANULOCYTE COLONY STIMULATING FACTOR (G-CSF)</td>
<td>20</td>
<td>44</td>
<td>60</td>
</tr>
<tr>
<td>RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR (RT-PA)</td>
<td>65</td>
<td>59</td>
<td>106</td>
</tr>
</tbody>
</table>
CLOTTING FACTOR PHARMACOKINETICS*

• “The $V_{d(ss)}$ always exceeds the actual plasma volume, implying that no drug, not even large molecular complexes as F-VIII, is entirely confined to the plasma space.”

• “A too short blood sampling protocol gives flawed results not only for terminal T1/2 but also for the model independent parameters.”