COMPARTMENTAL ANALYSIS OF DRUG DISTRIBUTION

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DRUG DISTRIBUTION

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>NONCOMPARTIMENTAL</td>
<td>0</td>
<td>CURVE FITTING TO DATA</td>
</tr>
<tr>
<td>COMPARTIMENTAL</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.


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**Goals of Drug Distribution Lecture**

- Significance of Drug Distribution Volumes
- Physiological Basis of Multi-Compartment Pharmacokinetic Models
- Clinical Implications of Drug Distribution Kinetics

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**DIGOXIN DISTRIBUTION VOLUME**

\[ V_d = \frac{DOSAGE}{C_s} = \frac{750 \text{ mg}}{1.4 \mu g/L} = 536 \text{ L} \]
Body Fluid Spaces
Catenary 3-Compartment Model

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

ECF

Cell Membranes

ICF

Effect of Plasma Protein Binding on Apparent Volume of Distribution*

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

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**

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

\( \Phi \) is the ratio of tissue/plasma drug concentration.


**LIPID SOLUBILITY**

- **Log \( \Phi \)**
- **Log \( D_{oct} \)**

**Apparent Volume of Distribution for Digoxin**

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

- ECF = 11.2 L, TBW = 45.5 L, \( f_u = 0.75 \), \( \Phi = 20.4 \)
- \( V_d = 11.2 + (20.4)(0.75) \) (14.3) L
- \( V_d = 536 \) L

\( \Phi \) includes binding to Na⁺-K⁺ 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.
Analysis of Experimental Data

How many compartments?

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

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

3 DISTRIBUTION VOLUMES

\[
\begin{align*}
V_{d(\text{extrap.})} &= \frac{\text{DOSE}}{C_0} \\
V_{d(\text{area})} &= \frac{t^{1/2} \cdot \text{CL}_E}{0.693} \\
V_{d(ss)} &= V_1 + V_2 + \ldots + V_n
\end{align*}
\]

TWO-COMPARTMENT MODEL

\[
\text{CL}_E = k_{01} V_1
\]
**TWO-COMPARTMENT MODEL**

\[
\begin{align*}
CL_I &= k_{21} V_1 = k_{12} V_2 \\
CL_{IE} &= k_{21} V_1 = k_{12} V_2
\end{align*}
\]

**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

$$V_{C\text{(corr.)}} = V_{C\text{(meas.)}} / \left[ (1 - \text{Hct}) + \text{Hct} \times (\text{RBC/P}) \right]$$

RBC/P = red cell/plasma partition ratio

Hct = hematocrit

Analysis of Inulin Kinetics with a 2-Compartment Model*

Compartment Model of Inulin Kinetics

3-Compartment Model of Inulin Kinetics

EXTRACELLULAR FLUID

Dose → \( V_C \) → \( CL_F \) → \( V_F \)

CELL MEMBRANES

\( CL_S \) → \( V_S \)

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\(^{15}\text{N}_2\) KINETICS IN A NORMAL SUBJECT

[Graph showing urea\(^{15}\text{N}_2\) kinetics over time]
ROLE OF TRANSCAPILLARY EXCHANGE

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*

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

\( Q = \text{capillary blood flow} \)

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

SIMULTANEOUS ANALYSIS OF INULIN AND UREA-15N2 KINETICS

3-COMPARTMENT MODEL

For Each Peripheral Compartment

3 UNKNOWNS:

3 EQUATIONS:

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

U = urea;  I = inulin
D = free water diffusion coefficient
SIMULTANEOUS ANALYSIS OF INULIN AND UREA-\(^{15}\text{N}_2\) 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)</th>
<th>(Q_S)</th>
<th>(Q_F + Q_S)</th>
<th>% CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEAN†</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>Dm @ 37º C (x 10^-5 cm²/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**

![Chemical Structures]

**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

\[ \text{CO} = Q_F + Q_S \]

PK-PD Study of INSULIN Enhancement of Skeletal Muscle Glucose Uptake*

DISTRIBUTION TERMINATES EFFECT BOLUS LIDOCAINE DOSE

CONSEQUENCES OF VERY SLOW DRUG DISTRIBUTION

- "Flip-Flop" Kinetics
- Effective Half-Life
- Pseudo Dose Dependency

GENTAMICIN Elimination Phase Precedes 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**

\[ CF = \frac{1}{1 - e^{-k\tau}} \]

**TOLRESTAT CUMULATION**

Predicted C.F. from \( T_{1/2} = 31.6 \text{ hr} \): 4.32

Observed C.F.: 1.29

**EFFECTIVE HALF- LIFE**

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

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

EFFECTIVE HALF-LIFE OF TOLRESTAT*

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

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

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


CONSEQUENCES OF VERY SLOW DRUG DISTRIBUTION

• “Flip-Flop” Kinetics

• Effective Half-Life

• Pseudo Dose Dependency

AREA UNDER THE CURVE

Measure of Dose Proportionality

$$\text{CL} = \frac{\text{ABSORBED DOSE}}{\text{AUC}}$$

PLASMA LEVEL VS. TIME CURVE

AUC

HOURS
HYPOTHETICAL Phase I Trial Results

<table>
<thead>
<tr>
<th>DOSE (mg)</th>
<th>DOSE 1</th>
<th>DOSE 2</th>
<th>INCREASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>100</td>
<td>4 x ↑</td>
<td></td>
</tr>
<tr>
<td>AUC (μg·hr/mL)</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

C₀ = 2.1 μg/mL, V₁ = 47.6 L, CL = 5.6 L/hr
C₀ = 1.8 μg/mL, V₁ = 13.9 L, CL = 18.9 L/hr

DISTRIBUTION VOLUME Representative Macromolecules

<table>
<thead>
<tr>
<th>MACROMOLECULE</th>
<th>MW (kDa)</th>
<th>V₁ (mL/kg)</th>
<th>Vd(ss) (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>
"The $V_{\text{ss}}$ (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."