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*

* From Atkinson AJ Jr, et al. Trends Pharmacol Sci 1991;12:96-101.

Noncompartmental models require curve fitting to data.

Compartmental analysis requires model parameters fit to data.

“Physiological” models fix parameters a priori.

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.

*Berman M: The formulation and testing of models. Ann NY Acad Sci 1963;108:182-94

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

Graph showing a biexponential plasma concentration versus time curve for digoxin and the estimation of the apparent volume of distribution by extrapolation.

Body Fluid Spaces

Catenary 3-Compartment Model

Graph illustrating the intravascular, interstitial, and intracellular fluid spaces with a catenary (chain links) 3-compartment model.

Volume of Distribution and Physiological Fluid Spaces

Intravascular Space:

None

Extracellular Fluid Space:

Inulin

Proteins and other Macromolecules

Neuromuscular Blocking Drugs (N+)

Aminoglycoside Antibiotics (initially)

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

Graph illustrating that highly protein-bound drugs distribute in the extracellular fluid space.

Effect of Plasma Protein Binding on Apparent Volume of Distribution*

* Atkinson AJ Jr, et al. Trends Pharmacol Sci 1991;12:96-101.

Formula to estimate apparent volume of distribution as the sum of extracellular fluid volume plus the product of the drug unbound (free) fraction times the intracellular fluid volume.

Impact of Protein Binding on Thyroxine Distribution Volume*

- From Larsen PR, Atkinson AJ Jr, et al. J Clin Invest 1970;49:1266-79.

Graph illustrating that highly protein-bound thyroxine distributes in the extracellular fluid space.

Impact of Protein Binding on Theophylline Distribution Volume*

*** From Atkinson AJ Jr, et al. Trends Pharmacol Sci 1991;12:96-101.**

Graph illustrating that theophylline is 40% protein-bound and its volume of distribution exceeds extracellular fluid space but is less than total body water.

Basis for Increased Theophylline Volume of Distribution in Pregnancy*

- From Frederiksen MC, et al. Clin Pharmacol Ther 1986;40;321-8.

Table illustrating that theophylline protein binding is reduced during pregnancy and results in a higher apparent volume of distribution.

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

*** Atkinson AJ Jr, et al. Trends Pharmacol Sci 1991;12:96-101.**

Formula to estimate apparent volume of distribution accounting for protein binding and tissue: plasma partition ratio.

LIPID SOLUBILITY(D_{oct}) and Φ

Graph showing a good correlation between drug lipid solubility and plasma: tissue partitioning.

Apparent Volume of Distribution for Digoxin

Φ includes binding to Na+-K+ ATPase.

Formula estimating the volume of distribution for digoxin that factors in protein binding and tissue: plasma partitioning. Digoxin binds to sodium-potassium Adenosine Triphosphatase in tissues.

Tissue vs. Plasma Digoxin Levels

Graph showing higher tissue levels of digoxin relative to plasma 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.**

Graph illustrating Teorell's original compartmental model of drug distribution proposed in 1937.

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*

Graph illustrating the technique of curve peeling for a multiexponential plasma concentration versus time curve.

COMPARTMENTAL ANALYSIS

Data and model equations for a 2-compartment model.

TWO-COMPARTMENT MODEL

Graph illustrating volume and clearance perameters for the model.

3 DISTRIBUTION VOLUMES

Slide with formulae to estimate VD (extrap), VD (area), and VD (steady-state).

TWO-COMPARTMENT MODEL

Slide emphasizing the elimination clearance parameter.

TWO-COMPARTMENT MODEL

Slide emphasizing the intercompartmental clearance perameter.

INTERCOMPARTMENTAL CLEARANCE*

Volume-Independent Parameter

Characterizing the Rate of Drug Transfer

Between Compartments of a Kinetic Model

*** From Saperstein et al. Am J Physiol 1955;181:330-6.**

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*

* **From Stec GP, Atkinson AJ Jr. J Pharmacokinet Biopharm 1981;9:167-80.**

Table illustrating that the central compartment volume for procainamide and NAPA is larger than the intravascular space due to partitioning into red blood cells.

If Central Compartment Volume is Based on Plasma Concentration Measurements

Correction formula for central compartment volume that accounts for hematocrit and red blood cell drug partitioning.

Analysis of Inulin Kinetics with a 2-Compartment Model*

*** Gaudino M. Proc Soc Exper Biol Med 1949;70:672-4.**

Graph of inulin kinetics using a 2-compartment model.

3-Compartment Model of Inulin Kinetics

3-compartment model parameters for inulin kinetics.

Basis for Kinetic Heterogeneity of Interstitial Fluid Space

The splanchnic bed has fenestrated capillaries with large pores.

Somatic tissues have continuous capillaries with small pores.

ENDOTHELIAL FENESTRAE IN HEPATIC SINUSOIDS

Picture of hepatic capillary vessel with large pores.

INTERENDOTHELIAL CELL JUNCTION IN CONTINUOUS CAPILLARY

Picture of a continuous capillary with tight endothelial cell junctions.

UREA-$^{15}N_2$ KINETICS IN A NORMAL SUBJECT

Plasma-concentration versus time curve for urea (tri-exponential decline after a single intravenous dose requires a 3-compartment model).

Multicompartment Model of Inulin and Urea Kinetics*

Diagram of 3-compartment model for inulin distribution in the extracellular fluid space.

*** From Atkinson AJ Jr, et al. Trends Pharmacol Sci 1991;12:96-101.**

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*

Q = capillary blood flow

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

Q and P are determinants of CL

*** From Renkin EM. Am J Physiol 1953;183:125-36.**

SIMULTANEOUS ANALYSIS OF INULIN AND UREA-$^{15}N_2$ KINETICS

Plasma concentration versus time curves for inulin and urea given simultaneously by the intravenous route to a healthy human subject.

3-COMPARTMENT MODEL

Diagram of 3-compartment model with emphasis on fast and slow intercompartmental clearances according to the Renkin equation.

For Each Peripheral Compartment

Equations to estimate the blood flow and permeability parameters for the distribution of urea and inulin.

SIMULTANEOUS ANALYSIS OF INULIN AND UREA-$^{15}N_2$ KINETICS

Plasma concentration versus time curves for urea and inulin with intermittent recording of cardiac output for 8 hours.

CARDIAC OUTPUT AND COMPARTMENTAL BLOOD FLOWS*

	QF L/min	QS L/min	QF + QS L/min	% CO
MEAN†	3.87	1.52	5.39	99

†MEAN OF 5 SUBJECTS

* From Odeh YK, et al. Clin Pharmacol Ther 1993;53;419-25.

TRANSCAPILLARY EXCHANGE
Mechanisms

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

- 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*

	MOLECULAR WEIGHT (DALTONS)	CORRECTED STOKES-EINSTEIN RADIUS (Å)	Dm @ 37º C (x 10-5 cm2/sec)
UREA	60	2.2	1.836
THEOPHYLLINE	180	3.4	1.098

*** From Belknap SM, et al. J Pharmacol Exp Ther 1987;243;963-9.**

PRESUMED *CARRIER-MEDIATED* TRANSCAPILLARY EXCHANGE

Chemical structures for Theophylline, Hypoxanthine, and Adenine.

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- **Significance of drug distribution volumes**

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- **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

Scheme of a 3-compartment model for theophylline emphasizing rapid equilibration of the intravascular space with heart and brain tissues.

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

* From Sherwin RS, et al. J Clin Invest 1974;53:1481-92.

Graph of insulin kinetics in plasma and tissue compartments. Effects correlate best with insulin levels in tissue (3-compartment model).

DISTRIBUTION TERMINATES EFFECT BOLUS LIDOCAINE DOSE*

* From Atkinson AJ Jr. In: Melmon KL, ed. Drug Therapeutics: Concepts for Physicians, 1981:17-33.

Graph of Lidocaine kinetics after a single intravenous dose. Therapeutic effect is short-lasting due to drug distribution to peripheral tissues.

CONSEQUENCES OF *VERY SLOW* DRUG DISTRIBUTION

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

GENTAMICIN
Elimination Phase Precedes Distribution Phase*

* From Schentag JJ, et al. JAMA 1977;238:327-9.

Graph of gentamicin plasma levels after multiple doses. The elimination phase precedes the distribution phase (example of “Flip-Flop” kinetics).

GENTAMICIN ELIMINATION
Nephrotoxic vs. Non-Toxic Patient*

* From Coburn WA, et al. J Pharmacokinet Biopharm 1978;6:179-86

Gentamicin plasma levels compared between a patient with nephrotoxicity and a patient without toxicity. Tissue reservoirs of gentamicin are larger in the nephrotoxic patient.

CONSEQUENCES OF *VERY* *SLOW* DRUG DISTRIBUTION

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TOLRESTAT
Cumulation with Repeated Dosing*

*** From Boxenbaum H, Battle M: J Clin Pharmacol 1995;35:763-6.**

Tolrestat plasma levels after the first dose (sampling for 24 hours) and the last dose (sampling for 72 hours allows definition of the terminal elimination phase with a half-life of 31.6 hours).

CUMULATION FACTOR

Formula to estimate the cumulation factor.

TOLRESTAT CUMULATION

Predicted C.F. from T½ = 31.6 hr: 4.32

Observed C.F.: 1.29

EFFECTIVE HALF- LIFE*

*** From Boxenbaum H, Battle M. J Clin Pharmacol 1995;35:763-66.**

Formula to estimate the "effective" half life.

EFFECTIVE HALF-LIFE OF TOLRESTAT*

*** From Boxenbaum H, Battle M. J Clin Pharmacol 1995;35:763-66.**

Example estimating the "effective" half-life for Tolrestat at 5.6 hours.

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AREA UNDER THE CURVE
Measure of Dose Proportionality

Example of AUC and its use in estimating clearance of elimination as the ratio of absorbed dose over AUC.

HYPOTHETICAL
Phase I Trial Results

	DOSE 1	DOSE 2	INCREASE
DOSE (mg)	**25**	**100**	**4 x ↑**
AUC (µg·hr/mL)	**1.32**	**17.91**	**13.6 x ↑**

Dependency of PK Estimates on Identified Terminal Phase

Graph illustrating biased estimates of PK parameters and lack of dose-proportionality due to a short plasma sampling period and limited drug assay sensitivity.

DISTRIBUTION VOLUME FOR MACROMOLECULES

EXAMPLES OF DISTRIBUTION VOLUME FOR MACROMOLECULES

CLOTTING FACTOR PHARMACOKINETICS*

- "The Vd(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."