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Review Article

# Two Compartmental Pharmacokinetics Modeling

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**Abstract:** A system of differential equations for compartmental model of pharmacokinetics is discussed. Example of medication for two- compartmental models are given. Discrete approximation of the system will result in a system of difference equations. Eigenvalues and eigenvector are used to find powers of a matrix which will be used to find approximate solution of difference equation.

**Keywords:** compartmental model, pharmacokinetics, matrix.

## INTRODUCTION

Knowledge of pharmacokinetics is critical in drug therapy. Pharmacokinetics is the science of absorption, distribution, metabolism and excretion function of each drug. Shargel *et al*. (2015) contains basic concepts of pharmacokinetics. Koda-Kimble, M. A. (2012) covers applied therapeutics. Knowing pharmacokinetics parameters such as onset of action, peak and trough concentrations, steady state, area under the curve, half- life, rate of absorption and elimination help us understand how long, it takes for drugs to work; what concentrations are therapeutic and sub -therapeutic or toxic; when to anticipate the highest concentration; when to start the next dose; how long it takes for a drug to leave the system and etc. In summary, by understanding pharmacokinetics parameters, practitioners are better able to calculate the right dose which will result in an effective (therapeutic) concentration.

To best access the effectiveness of a drug is by measuring the drug concentration when the drug reaches the steady state. It takes about 5 half-lives for a drug concentration to reach the steady state. Also to determine the effective concentration of a drug in the tissue, the drug in the tissue has to reach equilibrium with the drug in plasma. This equilibrium between the tissues and blood happens fast with one-compartmental drugs, and happens slowly with two-compartmental drugs. One-compartmental drugs follow a first order process and a single exponential equation is used to calculate the concentration. In a two-compartmental model, drugs follow the sum of more than one first order process and a bi-exponential equation is used to measure the concentration. To measure concentration changes over time the log scale concentration versus time is used. Pharmacokinetics parameters used in one and bi-exponential equations to measure concentration in compartmental modeling include half-life, volume of distribution, clearance, elimination rate, and distribution rate.

Mathematicians have discovered more sophisticated methods to calculate the pharmacokinetics parameters for one and two-compartmental drugs when pharmacokinetics parameters are unstable or steady state concentration is difficult to obtain. Laplace transform, Bayesian statistics Method of Moments, Stochastic and fractional calculus are some of the methods used to calculate the pharmacokinetics parameters in more difficult situations. Bayesian and Method of Moments use non-linear regression to calculate the parameters in more complicated situations mainly for two-compartmental drugs. One of the programs that uses Bayesian theory is called DrugCalc written by Doctor Dennis Mungall. This program is used to calculate the dose for digoxin, lidocaine, and lithium. In the case of lidocaine, since in most cases patients are not on lidocaine long enough to achieve the steady state, linear method cannot be used. So by entering patients' demographic and concentration-time information in the computer program, practitioners are able to calculate the pharmacokinetics parameters. Laplace transform, Stochastic and fractional calculus

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are other mathematical methods which are used to calculate the pharmacokinetics parameters. Laplace transform uses differential equation and Stochastic uses differential equation and probability and statistics to calculate the parameters.

**One compartment model:**

The simplest compartment is the one compartment model. In one- compartment model, the whole body is assumed as one compartment and drug distribution between blood and tissues happens fast. Drug enters the body (compartment 1), distributes from the blood into the tissues, and gets eliminated via elimination rate constant (Ke). It's important to note that changes in drug concentration in the plasma reflects the changes of the drug in the tissue and that the equilibrium between blood and tissues happens rapidly. A log scale concentration versus time results in a straight line and it follows a first order process and one exponential equation is used to measure the concentration. Followings are examples of mathematical equations for concentration, half- life, elimination rate, and clearance after a IV bolus (used for amino glycosides in particular). These equations may change depending on the route of administration. In one-compartmental model half- life and clearance are constant.

Logarithm of concentration as a function of time is a straight line. Slop of linear regression line is equal to elimination rate.

**Two-compartment model:**

In a two-compartment model body is assumed to consist of two compartments, central and peripheral. Central compartment includes blood and well perfused organs such as heart, kidneys, and lung, and peripheral compartment consists of skin and muscle, and fat tissues. A characteristic of a two-compartmental drug is an initial rapid serum concentration decline, and a long distribution phase. The rapid initial serum concentration decline is due to drug leaving the vascular system and distributing into peripheral tissue. Contrary to one-compartment model the equilibrium between plasma and tissues happens slowly.

A log scale concentration versus time results in a biphasic line which include distribution phase and elimination phase. In the first phase which is the distribution phase drug distributes between blood and the tissues. In the second phase which is the elimination phase drug eliminates from the body and the log plot of this phase is a straight line. To measure the concentration, mathematicians use a bi-exponential (the sum of usually two linear processes) equation. It's important to note that since the drug concentration in peripheral tissues is small, and as a result very small amount gets eliminated from the peripheral tissues, the elimination rate from the central compartment is dominant. In a two-compartmental mode, half- life and clearance are not constant. Also calculating the effective concentration is a challenge due to a long distribution phase, time needed for the equilibrium and also because several pharmacokinetics parameters and constants are involved. These parameters and constants include a, b, alpha, beta, $K_{12}$ (the elimination rate constant from central to periphery), $K_{21}$ (the elimination rate constant from periphery to central), $k_{10}$ (the elimination rate constant from central to outside the body). Linear regression analysis of extrapolated and residual lines are used to measure a, b, alpha, and beta. Another important thing to note is that $K_{12}$ is negative as drug is being removed from the central compartment, $K_{21}$ is positive as drug is being added to the central compartment, and $K_{10}$ is also negative as the drug is being removed from the central. It's also important to note that in a two-compartmental model the volume of distribution is a useful parameter as it relates the concentration to the amount of a drug in the body. Although each compartment has it's own volume of distribution, during distribution and after the equilibrium is reached, calculating the volume of distribution at the steady state will be more useful for the purpose of finding the right dose and calculation of concentration. At the steady state, equilibrium between the central and peripheral is reached, and volume of distribution at this point is a function of the elimination rate constant between the two compartments ($K_{12}$, and $K_{21}$), and it's calculated as follow:

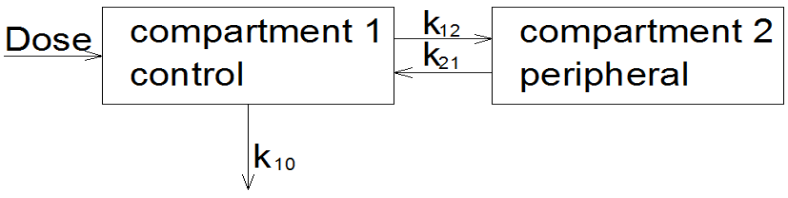
(Vd)ss = Dp + Dt/Cp Where Dp= (Cp)(Vp)

Dt =$K_{12}$CpVp/$K_{21}$ Because at steady state (Dt)($K_{21}$) = (Dp)($K_{12}$)

$$(Vd)ss = \frac{(Cp)(Vp) + (K12)(Cp)(Vp)/k_{21}}{Cp}$$

(Vd)ss = Vp + ($K_{12}$/$K_{21}$)(Vp)

The following diagram is used for two compartmental models.



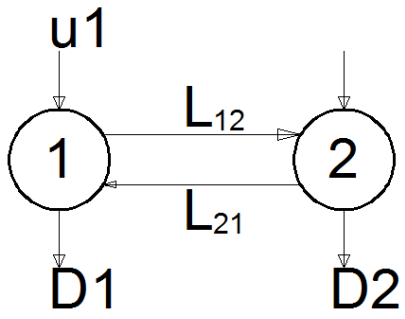
Equation of concentration as a function of flow for two-compartmental model which is a bi–exponential decline in plasma is given below.

$$C_{P_{(t)}} = ae^{-\propto t} + be^{-\beta t}$$

Where:

$$K_{21} = \frac{\propto \beta + b \propto}{a + b}$$
$$K_{10} = \frac{\propto \beta}{K_{21}}$$
$$K_{12} = \propto + \beta - K_{10} - K_{21}$$

The mathematical model for two-compartmental model is given below (see [1], [3]):




$D_1$= Degradation from com$P_1$
$D_1$= Degradation from com$P_1$
.$m_1$= mass in $Pool_1$
.$m_2$= mass in $Pool_2$
.$v_1$= volume of $Pool_1$
.$v_2$= volume of $Pool_2$
.$x_1$= mass per unit volume in $Pool_1$
.$x_2$= mass per unit volume in $Pool_2$

$$\frac{dm_1}{d_t} = -L_{12}m_1 + L_{21}m_2 - D_1m_1 + u_1$$
$$\frac{dm_2}{d_t} = L_{12}m_1 - L_{21}m_2 - D_2m_2 + u_2$$

$$\frac{dx_1}{dt} = -k_1x_1 + k_{21}x_2 + w_1$$
$$\frac{dx_2}{dt} = k_{12}x_1 + k_2x_2 + w_2$$
$$k_1 = L_{12} + D_1$$
$$k_2 = L_{21} + D_2$$
$$k_{21} = \frac{L_{21}V_2}{V_1}$$
$$k_{12} = \frac{L_{12}V_1}{V_2}$$
$$w_1 = \frac{u_1}{V_1} \ \& \ w_2 = \frac{u_2}{V_2}$$

Where:
.$w_1$= concentration
.$u_1$= dose
.$v_1$= volume of distribution

The outline solution of the homogeneous system of differential equations for two-compartmental pharmacokinetics models as a discrete approximation is given below:

Let A denote the coefficient matrix and $X = [x(t), y(t)]^t$ concentration of time t. then the system can be written as

$$\frac{dX}{dt} = AX(t)$$

Use approximation for derivation $\frac{dX}{dt}$ by

$$\frac{X(t + \Delta t) - x(t)}{\Delta t} = AX(t)$$

Assume $\Delta(t)$ is one unit of time.
Then

$$X(t + 1) - X(t) = AX(t)$$

We obtain the following equation

$$X(t + 1) = (A + I)X(t)$$

When I denote a 2×2 identity matrix.

Let B=A+I. then the solution to the difference equation

$$X(t + 1) = BX(t)$$

Is given by

$$X_n(t) = B^nX(0)$$

Using diagonalization for matrix B, there is a matrix P such that $P^{-1}B$ P is a diagonal matrix D. the diagonalization can be used to find a formula for the power of the matrix B.

That is

$$B^n = PD^nP^{-1}$$

The diagonal matrix D in the matrix of eigenvalue of B and the matrix B has column eigenvectors. Diagonalization of matrix is treated in many texts on linear algebra for example Strang G. (1993).

It will be interesting to get clinical data to find eigenvalues for two-compartmental medications such as Digoxine, Lidocaine, and Lithium. In the following we discuss examples of two-compartmental medications.

**Two-compartment drugs**
**Digoxin:**

Digoxin from digitalis glycoside class is used for treatment of congestive heart failure due to it is inotropic effects, and atrial fibrillation due to it's chronotropic effects. Digoxin follows a two-compartment model. The distribution phase is long and takes about 8 to 12 hours at which point the drug in the blood reaches equilibrium with the drug in the tissues. The serum concentration decline rapidly during the

distribution phase as at this phase drug leaves the blood rapidly and moves into the tissues. So the concentration during this time does not reflect the concentration in the myocardial tissues. The best time to measure the drug concentration is after the distribution phase is over. The concentration time curve show a rapid decline during the distribution phase and more slowly decline in the elimination phase.

Steady-state serum concentration range of 0.5-1.5 ng/rnl is considered therapeutic where serum concentration range of 0.5- 1 ng/rnl results in inotropic effect and is beneficial for heart failure, and 0.8-1.5ng/rnl concentration results in chronotropic and is beneficial in atrial fibrillation. Concentrations higher than 2ng/rnl increase the risk of side effects.

**Lidocaine:**

Lidocain is a class IB antiarrhythmic agent as well as a local anesthetic. By lowering the conduction velocity, lidocaine is used as a second line drug for the treatment of ventricular tachycardia. Lidocaine follows a two- compartment model with a rapid serum concentration decline and a long distribution phase. The best time to measure concentration is after 3-5 half life. Because drug concentration in blood and tissues are not at equilibrium while drug is still distributing from central compartment to the peripheral compartment, serum concentration should be measured after the distribution phase is finished. At he end of the distribution phase, when the equilibrium happens, drug concentration in blood reflects the amount of the drug in the heart tissues. Half-life is 1-1.5hr in a normal adult and 5 hours or more in patients with compromised liver function. To achieve and maintain the therapeutic concentration, a loading dose is given first, followed by an IV continuous infusion . In some cases one loading dose may not maintain the drug concentration within the normal range and a recurrence of ventricular tachycardia may happen. So in this situation an additional dose (or a second loading dose which is 50% of the first loading dose)) should be given after 20-30 minutes. EKG (electrocardiogram) monitoring is the best way of monitoring the effectiveness of Lidocaine therapy. But in patients who have the recurrence of ventricular tachycardia or patients who experience side effects, serum concentration should be monitored. Lidocaine is mainly eliminated by hepatic metabolism through cytochrome P450 (CYP3A).

**Lithium**:

Lithium is administered mainly as lithium carbonate for bipolar disorder in patients who meet DSM-IV-TR diagnostic criteria. In bipolar disorder there's an imbalance of neurotransmitters such as dopamine, norepinephrine and serotonin. Lithium limits norepinephrine release, inhibits the formation of dopamine, and blocks amphetamine-induced euphoric effect. Lithium exhibit a two-compartment model with rapid serum concentration decline and long distribution phase of 12 hours. The elimination phase or beta happens slower and depends on the kidney function. During the distribution phase drug is in the process of leaving the vascular system and entering the peripheral tissues and it is concentration does not reflect the amount of the drug in the tissues.

Lithium is mainly eliminated by the kidneys. It's half-life is about 24 hours, volume if distribution is about 0.9L/kg, and clearance is about 20ml/min in patients with normal renal function. Half -life in renal failure is about 40-50 hours as kidneys are the main route of elimination.

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