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A Geometric Inequality in Pharmacokinetics

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Abstract. The arithmetic-geometric mean inequality is used to give a lower bound for the average concentration in a two-compartmental model in pharmacokinetics. A geometric interpretation is given to relate concentration to the area of a rectangle as a function of time. Generalization to multi-compartmental models is discussed. Formulas for a variable dosage regimen are derived using concepts from engineering economy and mathematics of finance.

1 Introduction

Pharmacokinetics deals with study and characterization of drug absorption, distribution and elimination as a function of time. Drugs are eliminated from the body by metabolism and excretion. For a study of basic definitions in pharmacokinetics we refer the reader to the textbooks by Bauer [1], Gibaldi [3], and Shargel [8]. We will review required definitions as they are needed.

The arithmetic mean of two non-negative numbers is their average. Their geometric mean is the square root of their product. A simple inequality which can be proved using algebra states that, the arithmetic mean is greater than or equal to the geometric mean with equality if and only if the two numbers are equal. That is, if $a \geq 0$, and $b \geq 0$, then

$$\frac{a+b}{2} \geq \sqrt{ab} \tag{1}$$

Concentration of a drug $c(t)$ as a function of time is important in pharmacokinetics. Using first order kinetic for one-compartmental model the concentration is given by

$$c(t) = \frac{D}{V}\, e^{-kt} \tag{2}$$

where D denotes the dosage, V is the apparent volume of distribution and k is called elimination rate.

In one-compartmental model the blood is the main medium to transport the drug. In two-compartmental model the concentration is distributed in tissues and the blood. Examples of these drugs which follow two-compartmental model are lidocaine, digoxin and lithium line.

Digoxin is a poisonous cardiotonic steroid $C_{41}H_{64}O_{14}$ obtained from a foxglove (*Digitalis lanata*) and is used for congested heart failure (CHF).

Lidocaine is a crystalline compound $C_{14}H_{22}N_2O$ that is used in the form of its hydrochloride as a local anesthetic and as an anti-arrhythmic agent.

Lithium line is used for psychiatric disorders partially for bipolar depression. The book by Winter [9] has detail discussion of these drugs as well as basic concepts in pharmacokinetics.

In section 2 we introduce concepts from pharmacokinetics and mathematical preliminaries. In section 3 we give a lower bound for average concentration of drug in two compartmental model and interprete corresponding geometric results. Generalizations for multi-compartmental model and higher dimensional geometry are given. In section 4 we will derive formulas for constant and variable dosage regimen and explore the analogy to mathematics of finance and engineering economy.

2 Preliminaries

In two-compartmental models the drug is distributed in a central compartment and another compartment. The apparent volume of the central compartment is usually larger than the blood volume. The second compartment is the tissues. If the drug absorption is fast then the concentration can be expressed as the sum of two exponentials

$$c(t) = Ae^{-k_1 t} + Be^{-k_2 t} \tag{3}$$

The drug interaction for a multi-compartmental model obey a system of homogeneous linear differential equation with constant coefficients. Using standard solution techniques, we can obtain equation (3) for two-compartmental model.

A good mathematical treatment of pharmacokinetics is discussed in [2]. For multi-compartmental model the concentration $c(t)$ is expressed as

$$c(t) = \sum_{i=1}^{n} A_i e^{-k_i t} \tag{4}$$

We can use the Laplace transform to obtain the area under the concentration curve

$$[AUC] = \sum_{i=1}^{n} \frac{A_i}{k_i} \tag{5}$$

Recall the Laplace transform of $f(t)$ is given by

$$\tilde{f}(s) = \int_0^\infty e^{-st} f(t) dt \tag{6}$$

We now consider a rectangle with side lengths a and b. The perimeter $L = 2a + 2b$ and the area is $A = ab$. Using inequality (1) we obtain

$$L^2 \geq 16A. \tag{7}$$

Equality holds if and only if $a = b$. Inequality (7) is a simple geometric inequality for a rectangle. In fact for any convex quadrilateral inequality (7) is satisfied. This inequality is referred to as the isoperimetric inequality for quadrilaterals. There are many references on geometric inequalities. Two useful references on geometric inequalities are Kazarinoff [5] and Mitrinovic [6].

The geometric progression (8) given below will be used for a determination of constant dosage regimen.

$$1 + x + x^2 + \ldots + x^{n-1} = \frac{1 - x^n}{1 - x} \tag{8}$$

If we take the derivative of both sides of (8) we obtain (9).

$$1 + 2x + 3x^2 + \ldots + (n-1)x^{n-2} = \frac{(n-1)x^n - nx^{n-1} + 1}{(1-x)^2} \tag{9}$$

We will use (9) for a variable dosage.

3 Inequalities

In this section we discuss inequalities regarding concentration and give their geometric interpretations. Recall that for a two-compartmental model the concentration is given by

$$c(t) = Ae^{-k_1 t} + Be^{-k_2 t}$$

Let $\bar{k} = \dfrac{k_1 + k_2}{2}$. That is, we assume $\bar{k}$ is the average of the two elimination rates in each compartment. Assume $\bar{c}(t)$ is the average of concentration between the two compartments. Using arithmetic-geometric mean inequality given by (1), we obtain

$$\bar{c}(t) = \frac{Ae^{-k_1 t} + Be^{-k_2 t}}{2} \geq \sqrt{ABe^{-(k_1+k_2)t}} = \sqrt{AB}\ e^{-\bar{k}t}$$

This inequality indicates that the average concentration between two-compartments is at least as large as the geometric mean of the two initial concentration multiplied by a negative exponential with an average elimination rate. The difference between both sides of this inequality gives a measure of closeness to a one-compartmental model. We now give a geometric interpretation.

This can be viewed as a rectangle with length and width of $a(t)$ and $b(t)$ shrinking with negative exponential rates k_1 and k_2. That is assume $a(t) = ae^{-k_1 t}$, $b(t) = be^{-k_2 t}$, where a and b denotes the initial size of the rectangle. The perimeter $L(t)$ is given by

$$L(t) = 2[a(t) + b(t)] = 2(ae^{-k_1 t} + be^{-k_2 t})$$

hence,

$$\frac{L(t)}{4} = \frac{ae^{-k_1 t} + be^{-k_2 t}}{2}.$$

Using the arithmetic-geometric mean inequality we obtain the following generalization of the isoperimetric inequality given in (7).

$$L^2(t) \geq 16Ae^{-\bar{k}t} \tag{10}$$

The isoperimetric inequality for a rectangular box in 3-dimentions is given below. See Kazarinoff [5].

$$L^3(t) \geq 12^3 V \tag{11}$$

The dynamic version of (11) is the following

$$L^3(t) \geq 12^3 Ve^{-\bar{k}t} \tag{12}$$

where $\bar{k}$ is the average shrinking rate of each side $a(t) = ae^{-k_1 t}$, $b(t) = be^{-k_2 t}$, and $c(t) = ce^{-k_3 t}$.

Here again a, b and c are the initial sizes of the rectangle box. The geometric inequalities in turn imply that the average concentration of drugs in three-compartmental model is at least as large as the geometric mean of individual concentrations multiplied by negative exponential with a mean elimination factor. In fact, the above results generalize for n-dimensional rectangle boxes which in turn will give a lower bound for the mean concentration. The arithmetic-geometric mean inequality for n variables gives the following geometric inequality

$$L^n \geq 2^{n(n-1)} n^n V \tag{13}$$

Similarly the dynamic version of (13) is given by

$$L^n(t) \geq 2^{n(n-1)} n^n V e^{-\bar{k}t} \tag{14}$$

Equalities for (13) and (14) hold if and only if the object is an n-dimensional cube.

The inequality regarding concentrations are equal if and only if the elimination rates are equal and the initial concentrations are equal. Although, in a clinical setting the initial concentrations are not equal. In fact, drug transfers from a central compartment to other compartments with a rate using Fick's law. Fick's law states that the rate of diffusion across a membrane is proportional to the difference in drug concentration on each side of the membrane. Note that we have not used average concentration between compartments. Using the mean value theorem of integral calculus there is average value given by

$$\bar{c} = \frac{[AUC]}{T}$$

where $[AUC]$ is the area under curve given by (5), and T is the time interval when drug is eliminated.

It is also possible to obtain various mathematical inequalities. For example, using equation (5) and the arithmetic-geometric mean inequality we obtain

$$[AUC] \geq n \sqrt[n]{\prod_{i=1}^{n} \frac{A_i}{k_i}} \tag{15}$$

If we denote A_G and k_G geometric mean of initial concentrations and elimination rates, then (15) simplifies to

$$k_G[AUC] \geq nA_G \tag{16}$$

In the following section we discuss constant and variable dosage regimen.

4 Variable Dosage regimen

The mathematics in this section is very similar to mathematics of finance with continuous compounding interest. If a present value of P is financed with continuous compounding interest rate r, then the future value at time t is given by $F = Pe^{rt}$.

Thus $P = Fe^{-rt}$.

This means, if we look back in time, the interest rate is the analogous of elimination rate for a pharmacokinetics. The constant dosage value, which is useful for various clinical setting is analogous to constant monthly payments.

The formula for constant dosing with fixed time interval T and constant dosage c_0 is given in Schoenwald [7, p. 139] by the following expression

$$c_n = c_0 \left[\frac{1 - e^{-nkT}}{1 - e^{-kT}} \right] e^{-kT} \tag{17}$$

To maintain a minimum level of concentration in various clinical applications the constant dosage is used. The concentration at time interval n is given by level of concentration by

$$c_n = [c_0 + c_0 e^{-kT} + c_0 e^{-2kT} + \ldots + c_0 e^{-(n-1)kT}] e^{-kT} \tag{18}$$

Using (18) and the geometric progression (8) we can obtain a mathematical derivation of (17). Expression (18) together with the arithmetic-geometric mean inequality implies that

$$c_n \geq n c_0 e^{-kT\left(\frac{n+1}{2}\right)} \tag{19}$$

This gives a lower bound for the amount of concentration in n^{th} time interval. If a minimum level of concentration is desired, then we can solve for one of the parameters n, k and T as long as two of these parameters are specified.

In finance there is a gradient payment plan when at each period we add a fixed payment. In contrast in a clinical situation, one may want to add or decrease the amount of drug by a fixed amount. For example in some mental health situations through counseling, education and therapeutic techniques the patient may learn to deal with life situations better with a less need of the drug as time goes on. If we decrease the concentration c_0 by amount of A at each time then, the concentration c_2 is

$$c_2 = \{[c_0 e^{-kT} + (c_0 - A)] e^{-kT} + (c_0 - 2A)\} e^{-kT}$$

and more generally

$$\begin{aligned} c_n &= c_0 e^{-nkT} + c_0 e^{-(n-1)kT} + \ldots - Ae^{-(n-1)kT} - 2Ae^{-(n-2)kT} \\ &= c_0 \left(\frac{1 - e^{-(n+1)kT}}{1 - e^{-kT}} \right) - A \left[\sum_{i=1}^{n} i e^{-(n-i))kT} \right] \\ &= c_0 \left(\frac{1 - e^{-(n+1)kT}}{1 - e^{-kT}} \right) - Ae^{-(n-1)kT} \left[\sum_{i=1}^{n} i e^{-(i-1))kT} \right] \end{aligned}$$

The last summation can be obtained by using (9). We obtain

$$c_n = c_0 \left(\frac{1 - e^{-(n+1)kT}}{1 - e^{-kT}} \right) - Ae^{-(n-1)kT} \left[\frac{1 - (n+1)e^{-nkT} + ne^{-(n+1))kT}}{(1 - e^{-kT})^2} \right]$$

Another example of dosage reduction is, half-dosing, which is application applicable for narcotic patients. The mathematical derivation for this procedure is as follows.

After three time intervals, the concentration c_3 is expressed by

$$c_3 = \left\{ \left[\left(c_0 e^{-kT} + \frac{c_0}{2} \right) e^{-kT} \right] + \frac{c_0}{4} \right\} e^{-kT}$$

In general, we can obtain c_n by

$$c_n = c_0 e^{-nkT} \sum_{i=1}^{n-1} \frac{e^{ikT}}{2^i}$$

Using geometric progression (8), the above expression yields

$$c_n = \frac{c_0 \left(e^{-nkT} - \dfrac{1}{2^n} \right)}{1 - \dfrac{e^{kT}}{2}}$$

As n approaches higher values, the concentration tends to zero, which is desired.

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