# Determining appropriate Antihypertensive drug for a patient by differential equation

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***Abstract*—** Antihypertensive drugs such as captopril, losartan and perindopril are inhibitor, used for the treatment of hypertension and some types of congestive heart failure. This flow of medication operates by treating the parts of the body as compartments, so that a unit of the medication leaves one compartment and enters to another until eliminates from the body. This process is modeled by linear differential equations. The rates of absorption and elimination of drugs are computed at each stage and is compared with together. Solving IVP's determines better dose for treating different diseases on variety conditions.

***Keywords*—**Pharmacokinetics, Differential equation, Captopril, Losartan, Perindopril.

## I. Introduction

PROPER dosing of medications is important to ensure patient safety. Calculating dosages, dosage regimens, and compounding formulas involves the use of simple math principles. You can solve many of these problems by setting up ratios and proportions using the information given in the question and keeping like units consistent. Dosage calculation means figuring out the correct dose of a medication. Many times the medication dose prescribed for the patient is different from the way the medication is supplied.

A variety of work has been done in the area of modeling heterogeneous tumors. One model designed to aid clinicians is by Birkhead et al. [1]. They set up a system of four linear differential equations that describe the dynamics of the sensitive, resistant, proliferating, and non proliferating compartments of the cancer mass, thus modeling a heterogeneous cancer with four uniquely different types of cells. Cold- man and Goldie [2] developed a probabilistic model of cell mutations (which they suggest are a function of drug dose) resulting in drug resistance. With their model, they show that early detection and early therapy can lead to less chance of resistance because there is a fast change from a small to a large probability of resistance occurring as the tumor mass increases. In the mathematical model by Birkhead and Gregory [3], and subsequent clinical comparison with the model in Gregory et al. [4] and Souhami et al. [5], they investigate induced resistance in small cell lung cancer. B. C. Goodacre and R. J. Murray. Investigate about physical factors involved in intestinal drug absorption [9].

In this paper we use a system of ordinary differential equations to determining the dose of three hypertensive drugs at same family and compare them with together. In addition demonstrate the best choice of hypertensive drug by a doctor when she (he) encounters variety patients.

Blood pressure is the pressure of the blood in your arteries – the tubes that take the blood away from your heart to the rest of your body. You need a certain amount of pressure to keep the blood flowing [6]. High blood pressure develops if the walls of the larger arteries lose their natural elasticity and become rigid, and the smaller blood vessels become narrower (constrict). The highest pressure, known as systolic pressure, is the pressure when the beat or contraction of your heart forces blood round your body. The lowest pressure, diastolic pressure, is the pressure between heartbeats when the heart is resting. A blood-pressure reading gives two numbers. The first number is the systolic pressure and the second is the diastolic pressure [7].

There are two types of hypertension, essential and secondary. Essential is the type of high blood pressure that most people have. With primary hypertension there is no specific disease process involved and there is likely to be no single cause. Secondary is when the change in blood pressure comes as a result of (or secondary to) a specific disease or defect. This is rare and is caused by conditions such as kidney disease, problems with glands that produce hormones, and congenital problems affecting a blood vessel near the heart or brain. In addition some environmental factors such as smoking, fat, alcohol and … cause hypertension. Pharmacologists have classified these drugs in some categories: Diuretics, Calcium channel blockers, Angiotensin-converting enzyme (ACE) inhibitors, Angiotensin II receptor antagonists, Beta adrenoceptor antagonists. In this paper we choose three drugs from (ACE) inhibitors [6].

Last of this section we consider pharmacokinetics. Pharmacokinetics provides a mathematical basis to assess the time course of drugs and their effects in the body. It enables the following processes to be quantified: Absorption, Distribution, Metabolism and Excretion. These pharmacokinetics processes, often referred to as ADME, determine the drug concentration in the body when medicines are prescribed [8].

## II. Calculating Drug Dosage

The antihypertensive drug dissolves and releases the medications into the gastrointestinal tract. The medication diffuses from there into the blood, and the bloodstream takes each medication to the site where it has therapeutic effect. Then gradually is cleared from the blood by the kidneys and the liver. Pharmaceutical companies do a lot of testing to determine the flow of a medication through the body. This flow is modeled by treating the parts of the body as compartments then tracking the medication as it enters and leaves each compartment. A typical cold medication leaves one compartment (e.g., the GI tract) and moves into another (such as the bloodstream) at a rate proportional to the amount present in the first compartment. The constant of proportionality depends upon the medication, the compartment, and the age and general health of the individual [11].

Suppose that there are *A* units of antihypertensive drug in the GI tract at time 0 and that *x(t)* is the number of units remaining at any later time *t.* The Balance Law applies:

Net rate = Rate in − Rate out

Since we start with *A* units and the medication moves out of the GI tract and into the blood at a rate proportional to the amount in the GI tract, we have the IVP [11]:

$$\frac{dx(t)}{dt} = -k_1 x(t),\ x(0) = A \quad (1)$$

Where $k_1$ is a positive constant, time is measured in hours and $k_1$ in hour $^{-1}$.

The level y(t) of antihypertensive drug in the blood, builds up from zero but then falls as the kidneys and liver do their job of clearing foreign substances from the blood. The Balance Law applied to the antihypertensive drug in the blood compartment leads to the IVP [10]:

$$\frac{dy(t)}{dt} = -k_1 x(t) - k_2 y(t),\ x(0) = A \quad (2)$$

The first term on the right side of the rate equation in (2), models the fact that the exit rate of antihypertensive drug from the GI tract equals the entrance rate, into the blood. The second rate term models the clearance of antihypertensive from the blood. The clearance constant $k_2$ is measured in hours $^{-1}$.

Putting (1) and (2) together, we have a system of two first-order ODEs with initial data:

$$\begin{cases} \dfrac{dx}{dt} = -k_1 x\ ,\ x(0) = A \\ \dfrac{dy}{dt} = k_1 x - k_2 y,\ y(0) = 0 \end{cases} \quad (3)$$

IVP (3) is our mathematical model for the flow of a single dose of *A* units of medication through the GI tract and blood compartments. The first equation is a separate differential equation then:

$$\frac{dx}{x} = -k_1 dt \Rightarrow \ln x = -k_1 t \Rightarrow x = e^{-k_1 t}$$

The second equation is the first order differential equation with initial value. Integrate factor of this equation is: $e^{k_2 t}$

$$\frac{dy}{dt} + k_2 y = k_1 \underbrace{Ae^{-k_1 t}}_{x(t)},\ y(0) = 0$$

$$(k_2 e^{k_2 t} y - k_1 A e^{k_2 t} e^{-k_1 t})dt + dy = 0 \Rightarrow$$

$$(k_2 y e^{k_2 t} - k_1 A e^{-k_1 t} e^{k_2 t})dt + e^{k_2 t} dy = 0$$

$$f(y,t) = \int (k_2 e^{k_2 t} y - k_1 A e^{k_2 t} e^{-k_1 t})dt = y e^{k_2 t} - \frac{k_1 A}{k_2 - k_1} + g(y)$$

$$\frac{\partial f(y,t)}{\partial y} = e^{k_2 t} + g'(y) = e^{k_2 t} \Rightarrow g'(y) = 0 \Rightarrow g(y) = c$$

$$y(0) = 0 \Rightarrow y(t) = \frac{k_1 A}{k_1 - k_2}(e^{-k_2 t} - e^{-k_1 t})$$

We see that the antihypertensive drug levels in the GI tract and blood are given by the formulas:

$$x(t) = Ae^{-k_1 t},\ y(t) = \frac{k_1 A}{k_1 - k_2}(e^{-k_2 t} - e^{-k_1 t}) \quad (4)$$

From the formulas in (4), we see that the antihypertensive drug levels in the GI tract when t=0 is highest (A) then tends to zero. Also when t=0 amount of drug into blood is zero then the level of it reaches a maximum value at some positive time and then drops back.

## III. Samples

1) According to Pharmacokinetics of captopril, %70 of drug absorbs in GI tract (without food consumption) [12]. Assume a patient consume A unit of captopril. This drug starts to absorb in GI tract after 15 min. Then it maintains into bloodstream until 12 hours after consuming. Finally %10 of A unit will excrete without any acting. Putting these data in system (4):

$$\frac{75}{100} A = Ae^{-k_1(\frac{1}{4})} \Rightarrow k_1 = 1.1507$$

$$\frac{10}{100}A=\frac{1.1507A}{1.1507-k_2}(e^{-k_2 11\frac{3}{4}}-e^{-1.1507\times 11\frac{3}{4}})\Rightarrow k_2=0.21343$$

Then:

$$x(t)=Ae^{-1.1507t}\ ,\ y(t)=1.1721(e^{-0.21343t}-e^{-1.1507t})$$

Two functions above are absorption of captopril in GI tract and medication in bloodstream respectively. Their graphs are following:

$$x(t)=Ae^{-1.1507t}$$
$$y(t)=1.1721(e^{-0.21343t}-e^{-1.1507t})$$

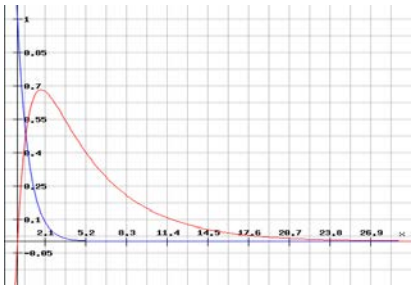

Figure 1

As you see the graph of absorption of captopril in GI tract (blue graph) when t=0 is the highest level: A=1. After 5 hours it drops to zero. After less than 2 hours about %75 of drug is absorbed. Then medication enters into blood (red graph). At t=0 amount of medication is zero then increases to highest level (less than %70 of entered drug to blood) then decreases and tend to zero after 24 hours.

2) According to Pharmacokinetics of losartan, %35 of drug absorbs in GI tract at 30 min and clearance rate by the kidneys and the liver is %12 and it maintain in body for 8 hours [13]. Substituting these data in system (4):

$$\frac{35}{100}A=Ae^{-k_1(\frac{1}{2})}\ \Rightarrow\ k_1=2.0996$$

$$\frac{12}{100}A=\frac{2.099A}{2.099-k_2}(e^{-8k_2}-e^{-2.099\times 8})\Rightarrow k_2=0.28309$$

Then:

$$x(t)=Ae^{-2.0996t}\ ,\ y(t)=1.1721(e^{-0.28309t}-e^{-2.0996t})$$

Two functions above are absorption of losartan in GI tract and medication in bloodstream respectively. Their graphs are following:

$$x(t)=Ae^{-1.1507t}$$
$$y(t)=1.1721(e^{-0.21343t}-e^{-1.1507t})$$

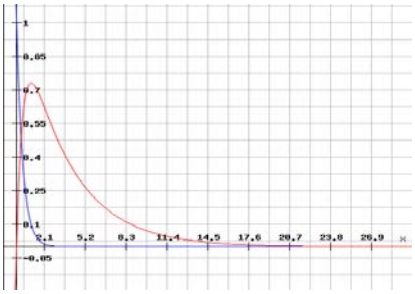

Figure 2

We see the graph of absorption of losartan in GI tract (blue graph) when t=0 is the highest level: A=1. After 2 hours it drops to zero. After less than half an hour about %75 of drug is absorbed in GI. Then medication enters into blood (red graph). At t=0 amount of medication is zero then increases to highest level (more than %70 of entered drug to blood) then decreases and tend to zero after 20 hours.

3) According to Pharmacokinetics of perindopril, %75 of drug absorbs in GI tract at 20 min and clearance rate by kidneys and liver is %10 and it will be in body for 24 hours [14]. Again putting these data in system (4):

$$\frac{75}{100}A=Ae^{-k_1(\frac{1}{3})}\ \Rightarrow\ k_1=0.8630$$

$$\frac{10}{100}A=\frac{0.8630A}{0.8630-k_2}(e^{-24k_2}-e^{-24\times 0.8630})\Rightarrow k_2=0.11829$$

Then:

$$x(t)=Ae^{-0.8630t}\ ,\ y(t)=1.1721(e^{-0.11829t}-e^{-0.8630t})$$

Two functions above are absorption of perindopril in GI tract and medication in bloodstream respectively. Their graphs are following:

$$x(t)=Ae^{-0.8630t}$$
$$y(t)=1.1558(e^{-0.11829t}-e^{-0.8630t})$$

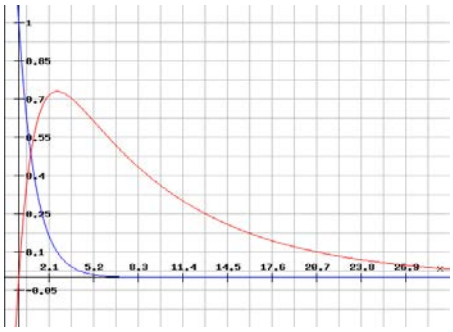


Figure 3

## IV. COMPARSION

If we compare absorption three drugs: captopril (blue graph), losartan (red graph) and perindopril (green graph) in GI tract we can conclude:

Losartan has the highest absorption speed in GI. If a patient needs to speed treatment, losartan is appropriate. Perindopril has the lowest absorption in GI. Therefore it is fit, when the patient's condition is no emergency.

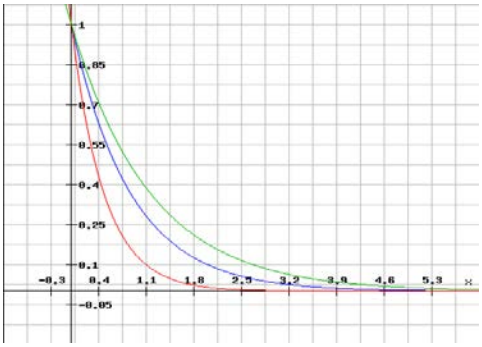


Figure 4

And if we compare absorption three medication of drugs: captopril (blue graph), losartan (red graph) and perindopril (green graph) in bloodstream we can see:

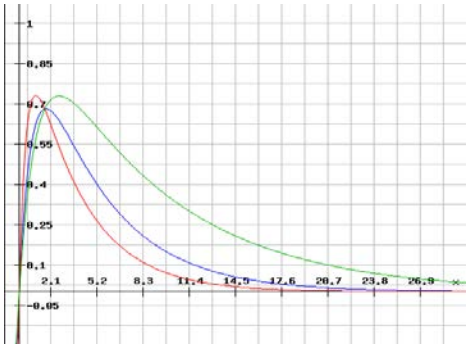


Figure 5

Losartan reaches to its peak earlier than the others and perindopril reaches to its peak later than all (After more than 2 hours). But medication of perindopril maintain into blood more than 24. This time is the longest. Then if a patient has a weak defense mechanism and her or his condition isn't emergency the best appropriate choice is perindopril. Losartan maintain into blood the shortest time but it reaches to its peak after an hour. It is appropriate for emergency conditions. Absorption rate of captopril in GI tract and its medication into blood is the middle of two others.

## V. CONCLUSION

Mathematics can help doctors to choose the appropriate drug for prescription. For example three antihypertensive drugs from the same group with variety pharmacokinetics data are evaluated. Putting data in created model (system of IVPs) gives benefit information for selecting appropriate drug.

[1] B.G. Birkhead, E. M. Rakin, S. Gallivan, L. Dones, and R. D. Rubens, A mathematical model of the development of drug resistance to cancer chemotherapy. Eur. J. Cancer Clin. Oncol. 23(9):1421-1427 (1987).

[2] A.J. Coldman and J. H. Goldie, Role of mathematical modeling in protocol formulation in cancer chemotherapy. Cancer Treat. Rep. 69(10):1041-1045 (1985).

[3] B. G. Birkhead and W. M. Gregory, A mathematical model of the effects of drug resistance in cancer chemotherapy. Math. Biosci. 72(1):59-69 (1984).

[4] W.M. Gregory, B. G. Birkhead, and R. L. Souhami, A mathematical model of drug resistance applied to treatment for small-cell lung cancer. J. Clin. Oncol. 6(3):457-461 (1988).

[5] R.L. Souhami, W. M. Gregory, and B. G. Birkhead, Mathematical models in high-dose chemotherapy. Antibiot. Chemother. 41:21-28 (1988).

[6] K. Halder and S.N. Ghosh," Effect of a magnetic field on blood flow through a indetented tube in the presence of erythrocytes", Indian J. Pure Appl. Math,V ol.25(3),1994,343-352.

[7] Kannel WB, Gordon T, Schwartz MJ. Systolic versus diastolic blood pressure and the risk of coronary heart disease. *Am J Cardiol.* 1971;27: 335–346.

[8] Agatonovic-Kustrin, S. & R. Beresford: Basic concepts of artificial neural network (ANN) modeling and its application in pharma- ceutical research. *J. Pharm. Biomed. Anal*. 2000, **22,** 717–727.

[9] B. C. Goodacre and R. J. Murray. A, Mathematical model of drug absorption. J. Clin. Hosp. Pharm. 6:117-133(1981).

[10] L. E. Thomas, A Model for Drug Concentration, *SIAM Review*. Vol. 19, No. 4 (Oct., 1977), pp. 732-735
[11] Donald Erdman, SAS Institute Inc., Cary, NC Maurice M. Morelock, Boehringer Ingelheim Pharmaceuticals, Inc. Research and Development Center, Ridgefield, CT
[12] Öhman, K. Peter; Kågedal, Bertil; Larsson, Rutger; Karlberg, Bengt E. Pharmacokinetics of Captopril and Its Effects on Blood Pressure During Acute and Chronic Administration and in Relation to Food Intake.
[13] *Y.S. Tanwar, M. Jamini, and B. Srivastava,* Formulation and *In Vitro* Evaluation of Floating Tablets of Losartan Potassium, Mahidol University Journal of Pharmaceutical Sciences 2013; 40 (2), 17-24
[14] Campbell DJ: A review of perindopril in the reduction of cardiovascular events. Vasc Health Risk Manag, 2006, 2, 117–124.

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