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# Estimation Of Levodopa Concentration In The Treatment Of Parkinson's Disease

**S. Suksai+, C. Salikupata++ and P. Wandee+**
+Department of Mathematics, Faculty of science, Srinakarinwirot University, Bangkok, 10110, Thaïland.
++Department of mathematics, Faculty of Science, King Mongkut's University of Technology Thonburi, PrachaUthit Rd., Bang Mod, ThungKhru, Bangkok 10140, Thailand.

## Abstract

Parkinson's disease is currently treated with drugs as a primary treatment. Common drugs used to treat the disease are levodopa and carbodipopa. Levodopa is a substrate of the neurotransmitter called dopamine. Levodopa has a mechanism for increasing dopamine levels in the brain, which is the mechanism of dopamine neurotransmitters in the brain. Carbidopa prevents levodopa from decomposing in the blood. The delivery of drugs is done in three ways, intravenous, oral and nasal. Calculation of levodopa concentrations in the blood, peripheral, and brain of drug administration using the combination of numerical methods and computer programs. The graph of the relationship between the concentration of levodopa and the time in each form of drug administration is compared

**Keywords:** dopamine, intravenous injection, levodopa, nasal administration, oral administration

## Introduction

Parkinson's disease is caused by neurons producing dopamine in the central brain, causing degeneration or degradation of the neurons called dopamine, causing the body to move slower, causing patients to shake. Currently, drug treatment for Parkinson's disease is the main treatment of Parkinson's disease. The most commonly used drug is levodopa. Levodopa is a neurotransmitter precursor called dopamine, and is considered a standard for the treatment of Parkinson's disease. Levodopa has an action mechanism that increases the level of dopamine neurotransmitters in the brain. Levodopa can pass through a brain barrier that does not pass through dopamine. If levodopa enters the carboxyl group of the front brain, it is eliminated as dopamine, increasing dopamine levels in the brain [3, 13].To facilitate the production of dopamine through the administration of precursor levodopa, it has thus been one of the most important treatments for the treatment of Parkinson's disease. Levodopa is a powerful agent in the treatment of Parkinson's disease [1, 8, 14] and the result is to overcome blood brain barriers. Decarboyled levodopa is a dopamine receptor in brain tissues and is usually stored in neurons' pre-synaptic terminals, striatal [2,11]. Increased understanding of the concentration effects of levodopa in plasma is useful in assessing management diseases [4, 5, 7, 12]. In our work, we describe the dosage of levodopa in each cycle of all three types of levodopa delivery. In order to estimate the dosage level of Levodopa, take all three types of Levodopa dose models. The results will help us to estimate the doses of levodopa in three ways faster. Use numerical methods to estimate the concentrations of levodopa in the blood, liver, kidney, fat, etc., and brain.Results from experimental parameters can be obtained to find the concentration of levodopa and graph the relationship between time and levodopa concentration in various parts of the body.

## Materials And Methods

In Figure 1, a model of the blood supply to various organs of the body, including central, brain, and peripheral organs such as liver and kidneys, can be shown. In figure 1A, levodopa is administered directly to the bloodstream. Figure 1B shows the administration of levodopa by food and Figure 1C shows the administration of levodopa by nose. $Q$ is the dosage of Levodopa in each part of Figure 1 and various variables related by the relationships in each part of the model, namely

$$\dot{Q} = \frac{dQ}{dt} = rate\ inputs - rate\ outputs.$$

The equations (1) - (3) relate to the injection of levodopa, which corresponds to the model of Figure 1A.

$$\dot{Q}_1 = -(k_{e,iv} + k_{cp} + k_{cb})Q_1 + k_{pc}Q_2 + k_{bc}Q_3 \quad (1)$$

$$\dot{Q}_2 = k_{cp}Q_1 - k_{pc}Q_2 \quad (2)$$

$$\dot{Q}_3 = k_{cb}Q_1 - k_{bc}Q_3 \quad (3)$$




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Equations 4 to 7 are related to drugs using the simulation method of figure 1B.

$$\dot{Q}_4 = -(k_{e,po} + k_{cp} + k_{cb})Q_4 + k_a Q_7 + k_{pc} Q_5 + k_{bc} Q_6 \quad (4)$$

$$\dot{Q}_5 = k_{cp} Q_4 - k_{pc} Q_5 \quad (5)$$

$$\dot{Q}_6 = k_{cb} Q_4 - k_{bc} Q_6 \quad (6)$$

$$\dot{Q}_7 = -k_a Q_7. \quad (7)$$

The equations (8) and (10) relate to nasal levodopa administration in accordance with the models of Figure 1C.

$$\dot{Q}_8 = -(f_{ke,n} k_{e,n} + k_{cb,n})Q_8 + k_{a,n} Q_{10} + k_{bc,n} Q_9 \quad (8)$$

$$\dot{Q}_9 = k_{cb,n} Q_8 - k_{bc,n} Q_9 \quad (9)$$

$$\dot{Q}_{10} = -k_{a,n} Q_{10}. \quad (10)$$

(1) - (10) is the relationship between time and levodopa volume. In the relationship between time and levodopa concentration, we form the equation (1)-(10). The concentration and amount of levodopa is $Q = CV$. Whenthe amount of levodopa $Q$ is the concentration of levodopa and $C$ is the volume of the distribution of levodopa. Replacing equations (1) – (10) and simplifying them into a new form, then equations (1) – (3) are produced.

$$\dot{C}_1 = -(k_{e,iv} + k_{cp} + k_{cb})C_1 + k_{pc} C_2 + \frac{k_{bc} C_3 V_b}{V_{c,iv}} \quad (11)$$

$$\dot{C}_2 = k_{cp} C_1 - k_{pc} C_2 \quad (12)$$

$$\dot{C}_3 = \frac{k_{cb} C_1 V_{c,iv}}{V_b} - k_{bc} C_3. \quad (13)$$

From equation (4) - (7) become

$$\dot{C}_4 = -(k_{e,po} + k_{cp} + k_{cb})C_4 + k_a C_7 + k_{pc} C_5 + \frac{k_{bc} C_6 V_b}{V_{c,po}} \quad (14)$$

$$\dot{C}_5 = k_{cp} C_4 - k_{pc} C_5 \quad (15)$$

$$\dot{C}_6 = \frac{k_{cb} C_4 V_{c,po}}{V_b} - k_{bc} C_6 \quad (16)$$

$$\dot{C}_7 = -k_a C_7. \quad (17)$$

And equation (8) - (10) get

$$\dot{C}_8 = -(f_{ke,n} k_{e,n} + k_{cb,n})C_8 + k_{a,n} C_{10} + k_{bc,n} C_9 \quad (18)$$

$$\dot{C}_9 = k_{cb,n} C_8 - k_{bc,n} C_9 \quad (19)$$

$$\dot{C}_{10} = -k_{a,n} C_{10}. \quad (20)$$

Applying the compartment parameters [16] to the equations (11)-20, and using the Runge Kutta method together with computer programs, locate the levodopa concentration in the blood, various organs (heart, kidneys, fat, etc.). The algorithm for assessing levodopa concentration is as follows: step 1-4 select $h$ and $t = a$. For $i = 1, 2, ..., m$, let $u_i = \alpha_i$ then get the results $(t, u_1, u_2, ..., u_m)$ for $j = 1, 2, ..., N$. Next do step 5-11, for $i = 1, 2, ..., m$. Let

$$k_{1,i} = h f_i(t, u_1, u_2, ..., u_3),$$




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$$k_{2,i} = hf_i\left(t+\frac{h}{2}\,,\, u_1+\frac{1}{2}k_{1,1}\,,\, u_2+\frac{1}{2}k_{1,2}\,,\ldots,\, u_m+\frac{1}{2}k_{1,m}\right),$$

$$k_{3,i} = hf_i\left(t+\frac{h}{2}\,,\, u_1+\frac{1}{2}k_{2,1}\,,\, u_2+\frac{1}{2}k_{2,2}\,,\ldots,\, u_m+\frac{1}{2}k_{2,m}\right).$$

For $j=1,2,\ldots,m$, let $u_i = u_i+\frac{1}{6}(k_{1,i}+2k_{2,i}+2k_{3.i}+k_{4,i})$ and $t=a+jh$ then get the results $(t,u_1,u_2,\ldots,u_m)$. Stop routine after get the results.

## Results

### Levodopa Concentration by Intravenous Injection

For $0\le t\le 36$, choose $h=0.001$ then $j=0,1,2,\ldots,3600$. Let $E_{1,j}$ is levodopa concentration in blood, $E_{2,j}$ is levodopa concentration in various organs and $E_{3,j}$ is levodopa concentration in brain which the initial conditions are $E_{1,0}$ , $E_{2,0}$ , $E_{3,0}$ then equation (11) – (13) become

$$f_1(t_j\,,\,C_1\,,\,C_2\,,\,C_3) = -(k_{e,iv}+k_{cp}+k_{cb})C_1+k_{pc}C_2+\frac{k_{bc}C_3V_b}{V_{c,iv}},$$

$$f_2(t_j\,,\,C_1\,,\,C_2\,,\,C_3) = k_{cp}C_1-k_{pc}C_2,$$

$$f_3(t_j\,,\,C_1\,,\,C_2\,,\,C_3) = \frac{k_{cb}C_1V_{c,iv}}{V_b}-k_{bc}C_3.$$

After the results of graphing Figure 2, you can see that intravenous injections at initial blood concentrations are 12.74 mg/l (milligrams per liter). The concentration of levodopa in the blood vessels is decreasing rapidly, but the concentration of levodopa in various organs is increasing rapidly and also decreasing rapidly. The concentration of dosing in the brain increases rapidly, but slows down, taking about 36 hours to completely escape the brain.

### Levodopa Concentration by Oral Administration

Let $E_{4,j}$ is levodopa concentration in blood, $E_{5,j}$ is levodopa concentration in various organs, $E_{6,j}$ is levodopa concentration in brain and $E_{7,j}$ is levodopa concentration in storage area (depot) which the initial conditions are $E_{4,0}$ , $E_{5,0}$ , $E_{6,0}$ , $E_{7,0}$ then equation (14) – (17) become

$$f_4(t_j\,,\,C_4\,,\,C_5\,,\,C_6\,,\,C_7) = -(k_{e,po}+k_{cp}+k_{cb})C_4+k_aC_7+k_{pc}C_5+\frac{k_{bc}C_6V_b}{V_{c,po}},$$

$$f_5(t_j\,,\,C_4\,,\,C_5\,,\,C_6\,,\,C_7) = k_{cp}C_4-k_{pc}C_5,$$

$$f_6(t_j\,,\,C_4\,,\,C_5\,,\,C_6\,,\,C_7) = \frac{k_{cb}C_4V_{c,po}}{V_b}-k_{bc}C_6,$$

$$f_7(t_j\,,\,C_4\,,\,C_5\,,\,C_6\,,\,C_7) = -k_aC_7.$$

In Figure 3, the initial concentration of levodopa in drug storage cells is 116 mg/l. The concentration of drugs in the storage organs of levodopa is very high and decreases over a long period of time. However, levodopa concentrations in various organs and blood gradually increase to the maximum concentrations and decrease over 40 hours. The concentration of levodopa in the brain increases rapidly from the beginning to the peak, and gradually expelled from the brain after 40 hours.

### Levodopa Concentration by Nasal Administration

Let $E_{8,j}$ is levodopa concentration in blood, $E_{9,j}$ is levodopa concentration in brain and $E_{10,j}$ is levodopa concentration in depot which the initial conditions are $E_{8,0}$, $E_{9,0}$ , $E_{10,0}$ then equation (18) – (20) yield



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$$f_8(t_j\ ,\ C_8\ ,C_9\ ,\ C_{10}) = -(f_{ke,n}k_{e,n} + k_{cb,n})C_8 + k_{a,n}C_{10} + k_{bc,n}C_9\ ,$$
$$f_9(t_j\ ,\ C_8\ ,C_9\ ,\ C_{10}) = k_{cb,n}C_8 - k_{bc,n}C_9\ ,$$
$$f_{10}(t_j\ ,\ C_8\ ,C_9\ ,\ C_{10}) = -k_{a,n}C_{10}\ .$$

In the graphs of Figure 4, when a nasal levodopa is given, the initial concentration in the levodopa storage area is 26.67 mg/l. The concentration of levodopa in the drug storage region decreases rapidly, but blood and brain intensity increases rapidly to the peak of the concentration of levodopa and gradually reduces the concentration of levodopa completely removed from blood vessels and brain in about 6 hours.

## Discussion And Conclusion

From the assessment of the concentration of levodopa in the system equations, three doses of levodopa are administered by injection, food and nose. We are interested in determining brain levodopa concentrations and see what dosages yield the best results. By providing 20 mg levodopa, we estimate the concentration of levodopa in the brain and the compartment parameter [16]. The graph we summarized as follows, Levodopa injection delivery, is evident that the concentration of levodopa in the brain lasts quite long in the brain and has a high concentration completely expelled from the brain, which takes approximately 36 hours completely expelled. As far as food administration is concerned, the concentration of drugs in the brain is relatively small compared to injection. However, the advantages are that the brain has a long period of time, removing all levodopa takes about 40 hours.From the nasal passage; the concentration of levodopa in the brain is quite high. However, there are a few disadvantages in the brain, and after 7 hours, the drug will be completely eliminated. Therefore, three ways of administering levodopa can be seen as the best as the dose is relatively stable because of the drug. But it takes a long time to be expelled. Oral and nasal administration has different advantages and disadvantages: nasal administration has the advantage that the drug is very concentrated, but the brain period is relatively short compared to injections. It is more likely that you need the medication than injecting the medication. Oral administration has the advantage that the drug stays in the brain for the same period of injection. However, the concentration of the drug in the brain is relatively low and requires doses to increase therapeutic effects. The results of our work enable faster assessment of levodopa concentrations. And it is possible to use concentration estimation to calculate the amount of levodopa in the brain that should be used for the best effect of patients in the treatment of Parkinson's disease. Furthermore, the dosage of the drug that patients should take at each cycle of Levodopa can be applied.

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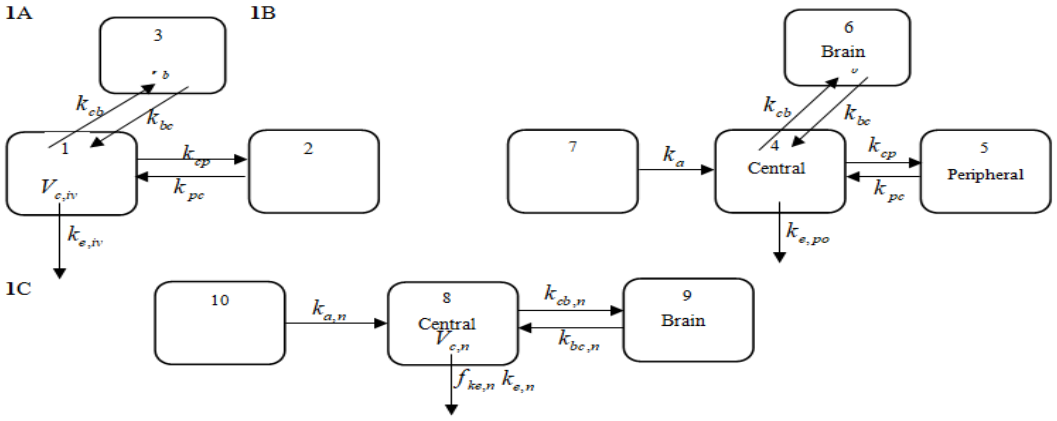


**Figure 1 The plasma and brain concentration models of levodopa are modelled after intravenous injections of levodopa 1A and oral injections of levodopa 1B and nasal injections of levodopa 1C.**

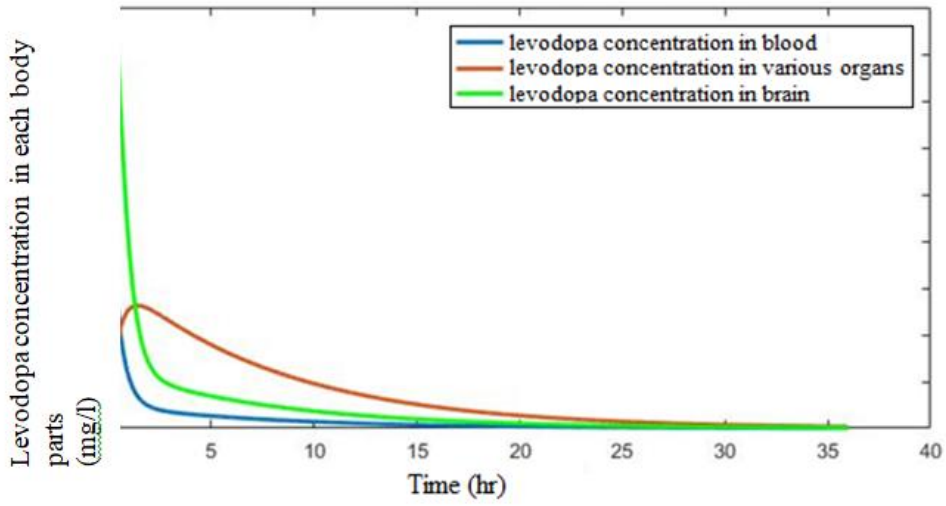


**Fig. 2 The time-to-concentration relationship of Levodopa in different parts of injections**

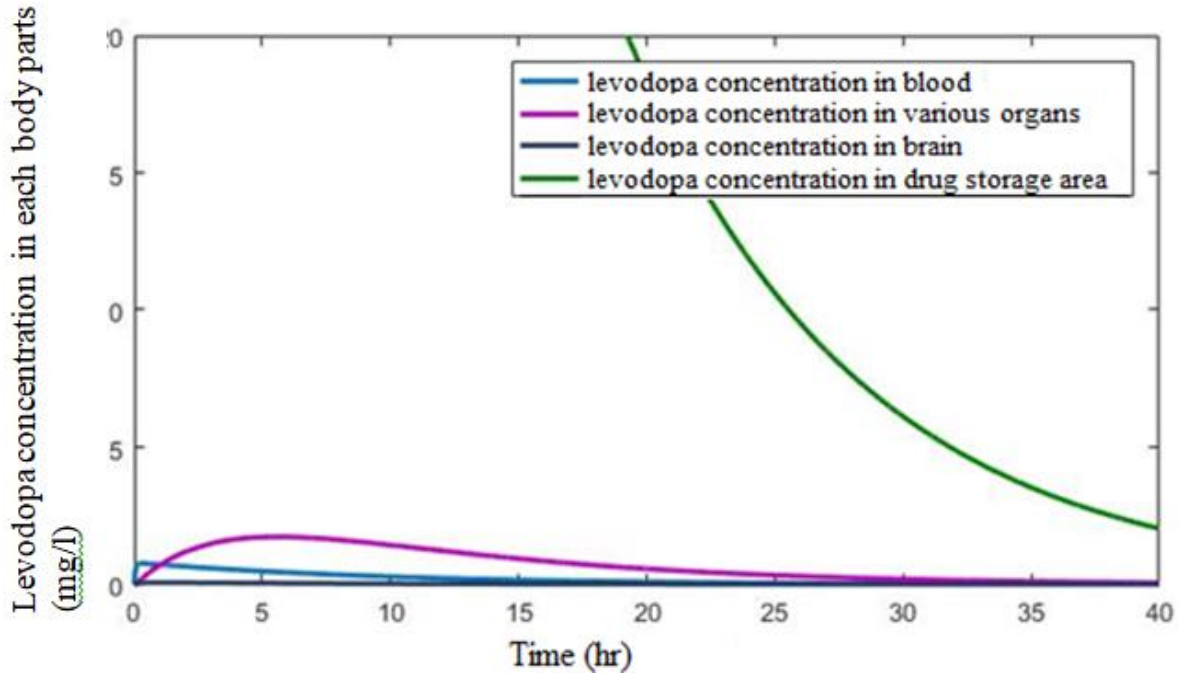


**Figure 3 The time and concentration of levodopa in various parts of the oral administration**

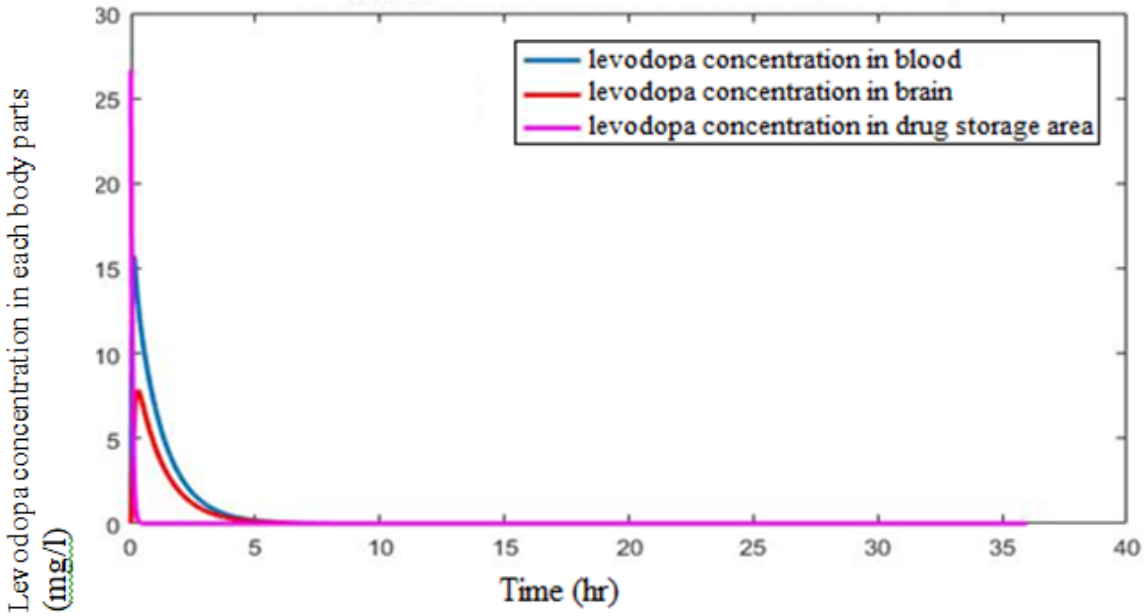


**Figure 4 The time and concentration of levodopa in different parts of the nasal delivery.**