

Pain medication treatment Modeling Activity

Level: High school or Undergraduate

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Pain medication treatment

As soon as we take medication, the body begins to absorb it and the concentration of the drug in the blood stream increases quickly. The body also begins a slower process of eliminating the drug from our body. Therefore, the concentration of the medicine in the blood is constantly changing; first it goes up quickly and then decreases slowly. For a person to benefit from the medication, the concentration must be above the *Minimum Effective Concentration* (MEC), see Figure 1. But a concentration above the *Maximum Tolerance Concentration* (MTC) is considered harmful. For this reason it is important to maintain the amount of medicine between the MEC and the MTC.

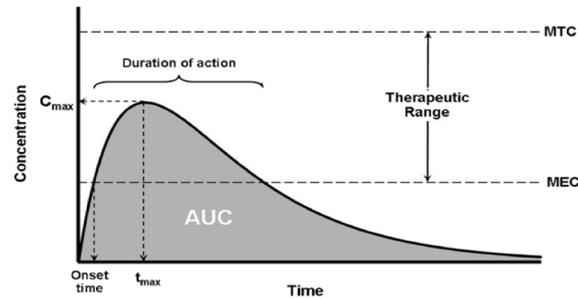


FIGURE 1. Figure taken from *The role of pharmacokinetics and pharmacodynamics in phosphodiesterase-5 inhibitor therapy*, N Mehrotra, M Gupta, A Kovar and B Meibohm. MTC means maximum tolerance concentration and MEC means minimum effective concentration.

This problem is about comparing different treatment plans for a pain medication that has an MEC of 80 mg (milligrams) and MTC of 200 mg. Suppose you or a friend has to take this pain medication for a sports injury. The doctor has the option of prescribing (a) 200 mg once a day for a week; (b) 100 mg every 12 hours for one week; or (c) 50 mg every 6 hours for one week. It has been estimated that in healthy adults, the body eliminates 6% of the medicine each hour (it has a half life of about 12 hours).

- (1) For each of the three medication treatments, what makes it effective and what are causes for concern?
- (2) Which of the three treatments would you recommend?
- (3) Are there other more effective options? Explain and propose one.
- (4) Based on your work, what questions would you ask a doctor who is about to prescribe the medication?

Notes to the instructor

These comments are based on experiences implementing this problem in a university course with Calculus I as the only prerequisite and was open to students of any major.

Issues that have come up in students' formulation of a model

1. Common Initial Assumptions

- (1) The medicine is absorbed by the body immediately (faster than in the figure above) so that the concentration of the drug in our body jumps every time the patient takes a dosage.
- (2) The body eliminates a constant proportion the medicine in the body
- (3) An effective treatment is one that maintains the medicine level in the body between 80 mg and 200 mg.
- (4) A better treatment is one that stays farther away from the harmful level while being effective.
- (5) The rate at which the body eliminates the drug is the same for all people.

2. Formulation of a model

Take for example the case of 200 mg every 24 hours. An initial dosage of $C_0 = 200$ mg is introduced into the body at time $t = 0$. The amount of medicine in the body after one hour will be denoted C_1 , after 2 hours C_2 , and so on. If the body eliminates 6% of the medicine per hour, then we conclude that after 1 hour, the amount of medicine remaining in the body is $C_1 = C_0 - 0.06C_0 = 0.94C_0 = 188$ mg.

Continuing this way, we have that $C_0 = 200$ and for $n \geq 1$

$$(1) \quad C_n = \begin{cases} 0.94C_{n-1} + 200 & \text{when } n \text{ is a multiple of 24} \\ 0.94C_{n-1} & \text{when } n \text{ is not a multiple of 24} \end{cases}$$

For the second treatment, 100 mg every 12 hours, we get $C_0 = 100$ and for $n \geq 1$

$$(2) \quad C_n = \begin{cases} 0.94C_{n-1} + 100 & \text{when } n \text{ is a multiple of 12} \\ 0.94C_{n-1} & \text{when } n \text{ is not a multiple of 12} \end{cases}$$

For the third treatment, 50 mg every 6 hours, we get $C_0 = 50$ and for $n \geq 1$

$$(3) \quad C_n = \begin{cases} 0.94C_{n-1} + 50 & \text{when } n \text{ is a multiple of 6} \\ 0.94C_{n-1} & \text{when } n \text{ is not a multiple of 6} \end{cases}$$

3. Finding a solution of the model

If we start with 200 mg and compute the drug concentration for 24 hours, we find out that after 24 hours the concentration is $200 \times (0.94)^{24} + 200 = 245.3$ mg. This is above 200 mg so we conclude that this is not a good plan.

For the second treatment, at $t = 0$ the amount of medicine in the body is $C_0 = 100$ mg. We can compute the amounts

$$\begin{aligned}
 C_0 &= 100 \text{ mg} \\
 C_{12} &= 100 \times (0.94)^{12} + 100 = 147.59 \text{ mg} \\
 C_{24} &= 147.59 \times (0.94)^{12} + 100 = 170.24 \text{ mg} \\
 (4) \quad C_{36} &= 170.24 \times (0.94)^{12} + 100 = 181.02 \text{ mg}
 \end{aligned}$$

Instead of listing all the values, we can plot the amount of medicine in the body every hour.

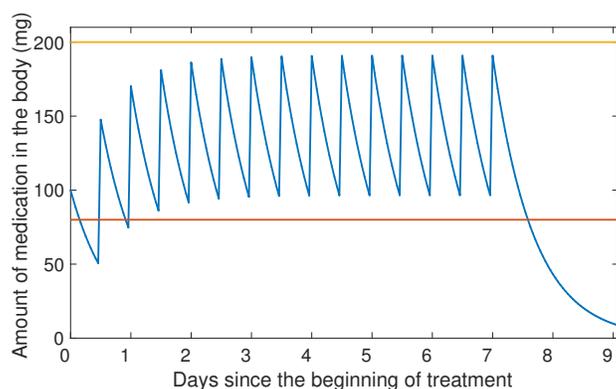


FIGURE 2. Amount of medicine in the body starting with 100 mg and adding 100 mg every 12 hours as the body eliminates 6% of the medicine every hour.

We can see in Figure 2 that after about 24 hours, the amount of medicine in the body stays within 80 mg and 200 mg until we stop taking the medication.

We can follow the same procedure for the third treatment, where 50 mg of the medicine is taken every 6 hours. We use the same model but change the values as shown in Table 1. The results are shown in Figure 3.

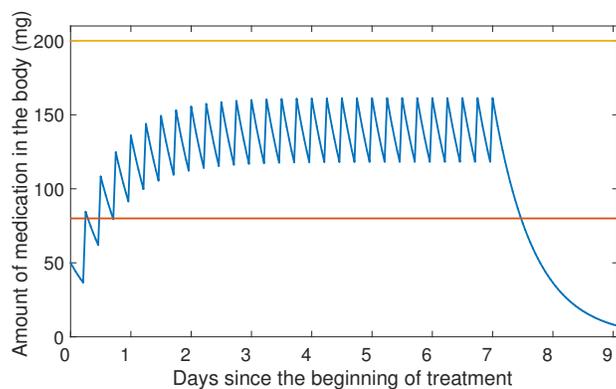


FIGURE 3. Amount of medicine in the body starting with 50 mg and adding 50 mg every 6 hours as the body eliminates 6% of the medicine every hour.

We see that it also takes about 24 hours for the amount of medicine in the body to stay within 80 mg and 200 mg.

4. Interpretation

By analyzing Figures 2 and 3, we can see that the amount of medicine in the body cycles up and down: up when the person takes a new dosage and down as the body constantly eliminates a proportion of the medicine.

Since the initial dosage (at time $t = 0$) is not completely eliminated from the body by the time of the next dosage, the peaks in the amount of medicine in the body increase at first. After some time (about 72 hours), the peaks and valleys reach constant values. These values depend on the parameters of the treatment. The larger the time interval between dosages, the larger the difference between peak and valley (because the dosage will be larger).

Note. Getting the values of the sequence in Eq. (4): $C_0, C_{12}, C_{24}, C_{36}$, etc. connects to finite geometric series. Following the pattern, we get that at peak k , the medicine level is

$$C_{12k} = (0.94^{12})^k C_0 + 100[(0.94^{12})^{k-1} + (0.94^{12})^{k-2} + \dots + (0.94^{12}) + 1]$$

The second term is a finite geometric series, which has a formula. For example, if s is a number between -1 and 1 , then

$$1 + s + s^2 + s^3 + \dots + s^{k-1} = \frac{1 - s^k}{1 - s}$$

In our case $s = 0.94^{12}$ so that we can write

$$(5) \quad C_{12k} = (0.94^{12})^k C_0 + 100 \frac{1 - (0.94^{12})^k}{1 - (0.94^{12})}$$

k	1	2	3	4	5	6	7	8	9	10	11	12
C_{12k}	100	147.6	170.2	181.0	186.2	188.6	189.8	190.3	190.6	190.7	190.8	190.8

The instructor can prompt the question of what are the final peak and valley values of a given treatment? We need to make sure they are between 80 mg and 200 mg. One way to determine these is by noting that starting at the peak concentration, the amount eliminated by the body before the next dosage is exactly equal the dosage so that the pattern repeats. For treatment 2 this means

$$C_{peak} \times (0.94)^{12} = C_{valley}, \quad C_{peak} = C_{valley} + 100$$

so that $C_{peak} = 190.8$ mg. For treatment 2 the result is $C_{peak} = 161.22$ mg.

Since the second and third treatments stay within 80 mg and 200 mg (after some initial ramp-up period), we conclude that both treatments are effective. However, since the peaks in treatment 3 are farther away from the harmful level, we declare treatment 3 to be better.

5. Validation

Although the treatments are eventually effective, they are not effective during the first 24 hours when the amount of medicine in the body dips below 80 mg. Also, we have assumed the body absorbs the drug instantaneously, which is not what is described in the pharmacokinetics paper. Perhaps these issues can be improved. Additionally, we may want to make sure the medication level is never too close to 200 mg.

6. Revised models

The following ideas have been inspired by student comments but not all of them have been developed by the students. These represent additional ideas to pursue.

Variable	Value	Description
Treatment 2		
D	100 mg	Dosage amount
r	6% per hour	Proportion of medicine the body eliminates
T	12 hours	Time interval between dosages
Treatment 3		
D	50 mg	Dosage amount
r	6% per hour	Proportion of medicine the body eliminates
T	6 hours	Time interval between dosages

TABLE 1. Variables and values for both treatments used in the model.

Let's assume that we want to be safe and we would like to keep the medication level under 180 mg. The two treatments under consideration are listed in Table 1. These can be generalized as follows: if we take the medication every m hours, we should take a dosage of $D = 100(m/12)$ so that $D = 100$ when $m = 12$ and $D = 50$ when $m = 6$. Then the highest peak is

$$C_{max} = \frac{100m}{12} \frac{1}{1 - (0.94^m)}$$

The figure below shows the value of the highest peaks for different values of m (the frequency of taking the medication). To stay below a value of 180 mg, the medicine should more frequently than every 10 hours.

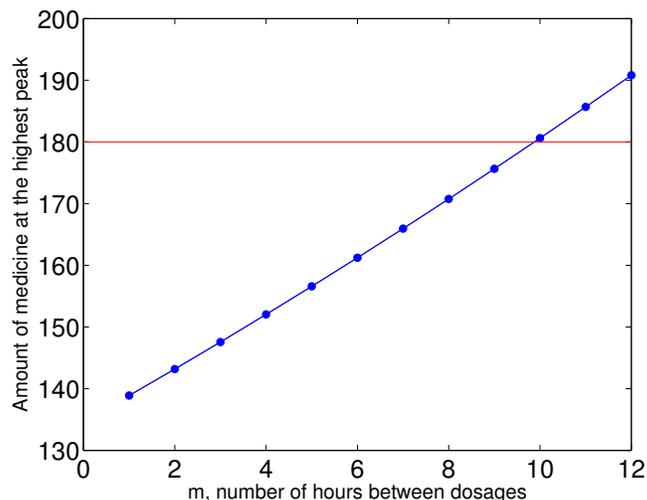


FIGURE 4. Maximum amount of medicine in the body given by the highest peak shown in the previous figures.

We can also conclude that if we take an initial dosage equal to C_{max} and then take a dosage of $D = 100(m/12)$ mg every m hours, we can eliminate the 'ramp-up' period at the beginning.

For example the figure below shows what happens if we take an initial dosage of 161 mg and then 50 mg every 6 hours.

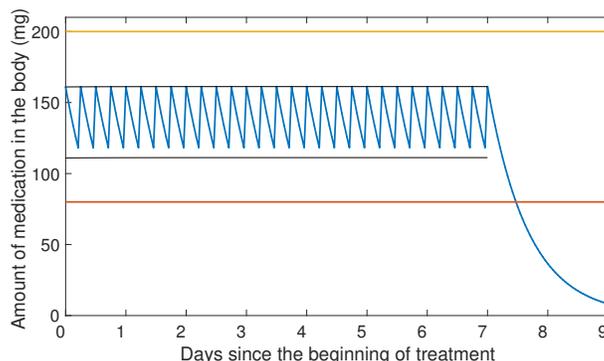


FIGURE 5. Amount of medicine in the body starting with 161 mg and adding 50 mg every 6 hours as the body eliminates 6% of the medicine every hour.

Out of curiosity, suppose you are taking 100 mg every 12 hours. What would happen if you skip one dosage?

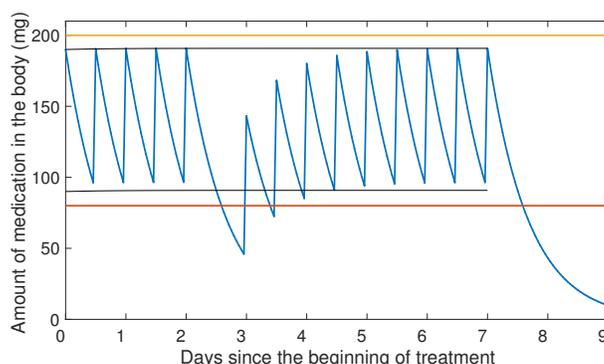


FIGURE 6. Amount of medicine in the body starting with 161 mg and adding 50 mg every 6 hours as the body eliminates 6% of the medicine every hour. This is what happens when one dosage is skipped.

Revised Assumption about the rate at which the body eliminates the drug.

In other contexts such as radiation decay, heat transfer, and chemical reactions, the decay of these quantities is modeled by an exponential function of the form $C(t) = C_0 e^{-at}$ where a is a constant. In our problem, the amount of medicine in the body follows a decay of the form $C(t) = C_0 (0.94)^t$. It is a good idea to pause and use this opportunity to let the students realize that these are equivalent as long as $e^{-a} = 0.94$ but that $a \neq 0.06$.

The assumption that the body eliminates a constant proportion of the medicine in the body is an approximation. It is more likely that the body uses what is known as *capacity-limited metabolism*, which is based on the fact that as the amount of medicine in the body increases, the proportion eliminated per hour decreases! A possible revised assumption is

- (1) The body eliminates a proportion the medicine in the body based on capacity-limited metabolism

$$r(t) = \frac{15}{130 + C(t)}$$

The constants in the formula have been chosen so that when $C(t) = 120$ mg (in the effective range), the proportion is $r = 6\%$ mg per hour.

New Model Formulation. The model we had developed before was of the form $C_n = (1-r)C_{n-1}$ where $r = 0.06$ originally. In the updated model, the proportion r is not constant but given by the capacity-limited metabolism formula $r(t)$. This leads to the model where $C_0 = D$ and

$$(6) \quad C_n = C_{n-1} \left(1 - \frac{15}{130 + C_{n-1}} \right)$$

with the additional dosage of D mg every T hours.

Equation (6) is a *nonlinear* equation and we are not able to solve the recursion exactly. However, we can compute the values of C_n at every hour and plot them. The results are

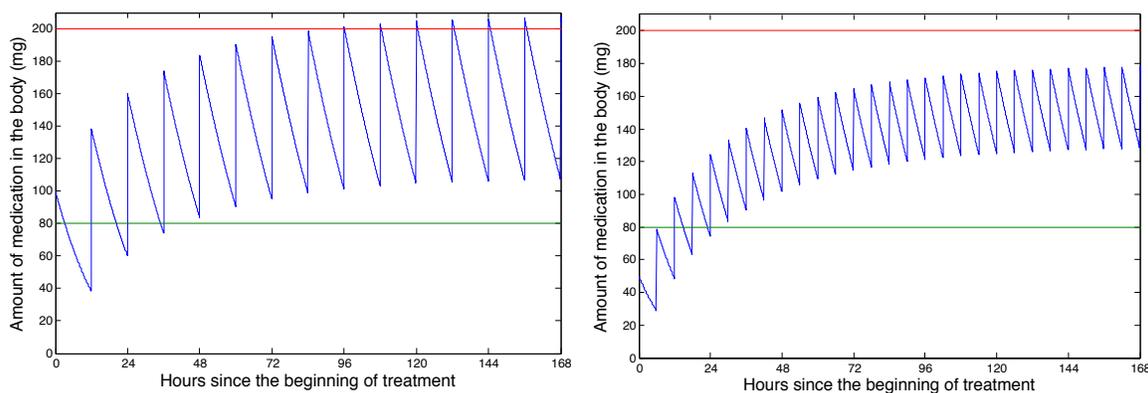


FIGURE 7. Amount of medicine in the body starting with $D = 100$ mg and $T = 12$ hours (left); and $D = 50$ mg and $T = 6$ hours (right). The body eliminates the drug based on the capacity-limited metabolism formula.

We note that Treatment 2 is no longer considered safe since it's peaks go above the harmful level of 200 mg. Treatment 3 is considered effective and safe.

Revised Assumption about the rate at which the body absorbs the drug.

So far we have assumed that the body absorbs the drug instantaneously. The original problem statement shows a figure of what the absorption function might look like. The new assumption might be that for $0 \leq n \leq 12$, the concentration changes according to $C_n = 100(0.94)^n H(n) C_0$ where $H(n)$ is a function that quickly and smoothly increases from 0 to 1. For example $H(n) = 1 - e^{-n/2}$ is a possible choice shown below.

