Drug Delivery

Group F

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1 Problem Statement

"Infections can often be alleviated by injecting drugs into the bloodstream. However, once in the bloodstream, the drug is quickly cleared by the kidneys, so the quantity of drug in the bloodstream available to fight infection will reduce swiftly unless replenished. Whilst sufficient drug is required to effectively fight infection, too much drug can be toxic to the system. You are asked to advise doctors on appropriate dosing regimes which will maintain drug levels within the therapeutic range. You are given the following experimental data for an injection of 300mg of a drug:

Time since injection (hours)	1	3	5	7	9	11	13	15	17	19
Measured concentration in blood (mg/l)	10.0	7.0	5.0	3.5	2.5	2.0	1.5	1.0	0.7	0.5

This drug is ineffective if the concentration in the blood is below 5 mg/l, whilst it is toxic at levels above 20 mg/l."

2 Introduction

The kidneys are a fundamental part of the body, constantly working to remove ions, toxic waste, urea, and water from its system. When the drug is injected into the bloodstream, the kidneys quickly get to work in removing it.[1] As the drug only fulfils its purpose when its concentration in the blood is within the range of $5mg/L$ to $20mg/L$, it is important to consider and understand the rate at which the kidneys remove the drug from the bloodstream over time. This allows us to develop an effective dose regimen.

3 Methods and Analysis

3.1 Assumptions

Here we define our global assumptions that are used in all models:

- The kidneys begin to remove the drug immediately after it enters the bloodstream.

- The rate of change of the concentration of the drug in the blood can be modelled as exponential decay.
- The rate at which the drug is removed is not affected by the consumption of any food or drink, or by the patient sleeping.

3.2 Model 1

3.2.1 Assumptions for Model 1

First we list the assumptions specific to Model 1:

- The whole dose of drug injected enters the bloodstream instantaneously.
- The kidneys begin removing the drug immediately.

3.2.2 Modelling Drug Concentration Decline Over Time

Plotting the data provided in the problem statement gives the following graph:

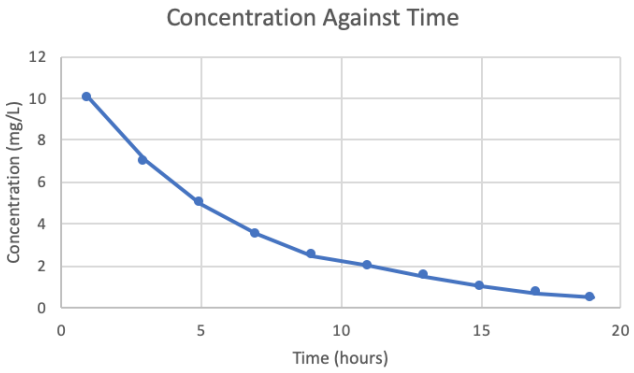

Figure 1: Relationship between drug concentration in the blood and time.

The curve generated is comparable to one of exponential decay, and hence the concentration of the drug in mg/L compared to time is modelled using the following equation:

$$x = x_0 \cdot e^{-\lambda \cdot t}, \text{[2]} \tag{3.1}$$

where x is the concentration of the drug in mg/L, x_0 is the initial concentration, λ is the decay constant, and t is the time in hours.

Also, consider that

$$\lambda \cdot t_{\frac{1}{2}} = ln(2), \text{[3]} \tag{3.2}$$

where $t_{\frac{1}{2}}$ is the half-life of the concentration. This can be re-arranged to give:

$$\lambda = \frac{ln(2)}{t_{\frac{1}{2}}}$$

The given data shows that the concentration halves after 4 hours, so we can say that

$$t_{\frac{1}{2}} = 4$$

and therefore

$$\lambda = \frac{ln(2)}{4}. \tag{3.3}$$

The maximum time in which the concentration remains within the therapeutic range will be achieved if the initial concentration is $20mg/L$ - the maximum safe concentration. Plotting the curve of the equation

$$x = 20 \cdot e^{-\frac{ln(2)}{4}t}, \tag{3.4}$$

gives that 8 hours is the maximum amount of time before another injection is needed.

3.2.3 Injection Doses

We can approximate the curve shown in Figure 1, which is given by the experimental data of drug concentration against time, using the equation $x = 11.89 \cdot e^{-\frac{ln(2)}{4} \cdot t}$ - the graph of which is shown below.

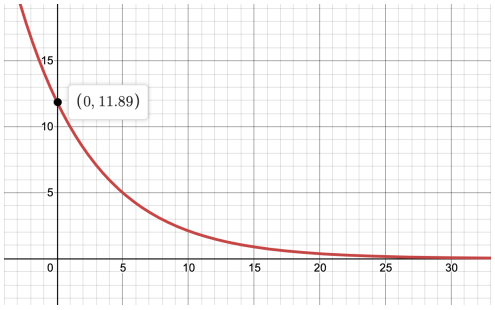

Figure 2: Graphical approximation from data provided.

The extrapolation of the data given suggests that a $300mg$ dose results in an initial concentration of $11.89mg/L$. It follows that a $25.23mg$ injection would give an initial concentration of $1mg/L$.
The initial injection should be $504.63mg$, which gives a concentration of $20mg/L$. After 8 hours an injection of $378.45mg/L$ is then required to return the concentration to the maximum possible therapeutic level of $20mg/L$.
For a suggested dose regimen see section 4.

3.3 Model 1 Adaptations

The assumptions in Model 1 state that the rate of removal of the drug from the bloodstream is not affected by activities such as eating. However, some other activities *will* affect the rate at which the drug is removed, for example, undergoing exercise.

When the patient exercises, assuming that their heart rate is double that for the same period spent resting, the blood will pass through the kidneys twice as quickly, meaning more blood will pass through the kidneys than it otherwise would during this period.

Model 1 has therefore been adapted to now show the effect that one hour of exercise would have on the concentration level of the drug in the blood.

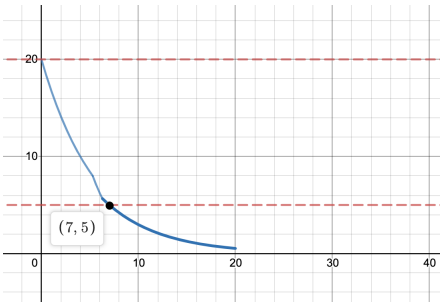

Figure 3: Model 1 including a 1 hour period of exercise.

The steeper section of the graph corresponds to the hour in which exercise was carried out. The graph is steeper because the half-life of the concentration is half of its original value during this period. The result of this exercise is that the drug reaches the minimum therapeutic concentration after 7 hours instead of 8 hours as it did in our initial version of Model 1. As such, whilst injection doses should remain the same, if exercise is is carried out for one hour, the following dose will need to be taken an hour earlier than normal.

3.4 Model 2

3.4.1 Assumptions for Model 2

As before, we list the assumptions specific to Model 2:

- The dose of the drug enters the bloodstream at a linear rate over time.
- It takes one hour for the whole dose to enter the system.
- Removal of the drug from the bloodstream begins as soon as the drug is injected (as with Model 1).

3.4.2 Drug Concentration as It Enters the Body

As stated in the assumptions, the drug enters the bloodstream at a linear rate and is subsequently removed. As such, the rate of change of the concentration of the drug in the blood can be given as a combination of the linear rate of increase of its concentration (as the drug is injected), and the exponential decrease in its concentration (as it is removed by the kidneys). The rate at which the drug leaves the blood is hence also affected by the concentration of the drug present in the blood at time t (as with Model 1). The iterative equation follows:

$$\frac{x_n - x_{n-1}}{\Delta t} = z \cdot t_n - x_{n-1} \cdot e^{-\frac{ln(2)}{4} \cdot t_n}, \tag{3.5}$$

where z is a constant of proportionality. Rearranging gives:

$$x_n = x_{n-1} + \Delta t(z \cdot t_n - x_{n-1} \cdot e^{-\frac{ln(2)}{4} \cdot t_n}). \tag{3.6}$$

Now, as we assume that the whole dose has entered the bloodstream after one hour, a dose that results in a concentration of $20mg/L$ would have a z value of $z = 50$.

Iterating this equation every minute gives the following data plot:

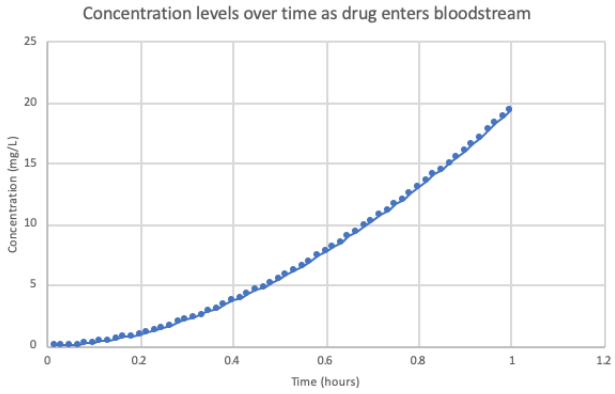

Figure 4: Concentration of the drug as it enters the bloodstream.

When the next injection is required (when the concentration reaches $5mg/L$), the increase in concentration of the drug in the bloodstream as time progresses will be modelled similarly. However, in this case, the initial concentration value will be $5mg/L$ rather than $0mg/L$.

3.4.3 Concentration of the Drug in the Blood After Injection

Once the whole dose has entered the body, the concentration over time behaves as it did in Model 1. We hence model it with the equation:

$$x = 20 \cdot e^{-\frac{ln(2)}{4}t}. \tag{3.7}$$

3.4.4 Injection Doses

Iterating equation (3.6) for the first and second injection as well as equation (3.7) for the time in between gives the following data plot:

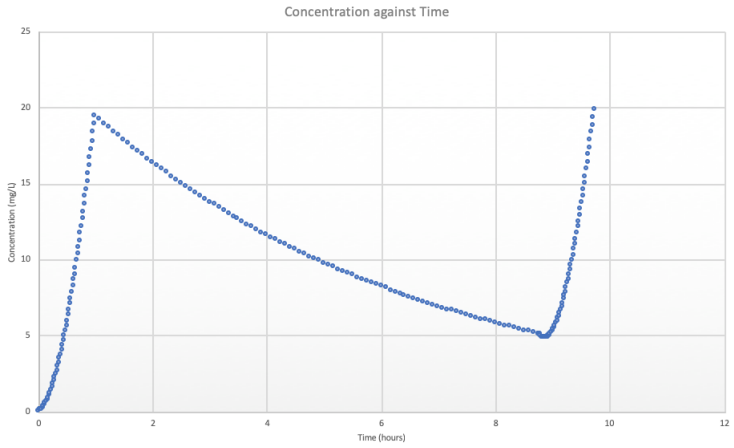

Figure 5: Concentration against time.

From the above graph, the maximum time that the drug is in the therapeutic range is approximately 8.4 hours.
Considering the linear component of the drug entering the bloodstream, if none of the drug was removed upon entering the blood then the concentration of the drug would be $50mg/L$. As such, an injection that would result in a $50mg/L$ concentration in the blood is consequently reduced to a $20mg/L$ concentration when the removal of the drug by the kidney is taken into account.
As in section 3.2.3, and based on the initial data given, a $25.23mg$ injection gives a $1mg/L$ concentration. Thus, to achieve a concentration of $20mg/L$, a dose of $1261.5mg$ is required in the first injection.
After concentration levels reduce to $5mg/L$, a dose of $1198.4mg/L$ is required to maintain concentration levels within the therapeutic range.

4 Results

Here we state an example dose regimen for each model.

4.1 Model 1

- Injection 1 - $504.63mg$ at 10PM.
- Injection 2 - $378.45mg$ at 6AM (8 hours later).
- Injection 3 - $378.45mg$ at 2PM (8 hours later).
- Injection 4 - $378.45mg$ at 10PM (8 hours later).
- Continue with $378.45mg$ dose injections every 8 hours.

4.2 Model 1 Adaptation

Here we assume the patient exercises for 1 hour after the second injection.

- Injection 1 - 504.63mg at 10PM.
- Injection 2 - 378.45mg at 6AM (8 hours later).
- Injection 3 - 378.45mg at 1PM (7 hours later).
- Injection 4 - 378.45mg at 9PM (8 hours later).
- Injection 5 - 378.45mg at 5AM (8 hours later).
- Continue with 378.45mg dose injections every 8 hours. If exercise is carried out for 1 hour, the next injection must be taken an hour earlier than previously planned. All subsequent injections after this, however, should be separated by 8 hours.

As exercising shortens the time for which a standard dose of the drug is effective, it would be easier if the patient exercised as little as possible whilst undergoing the treatment.

4.3 Model 2

- Injection 1 - 1261.5mg at 9:30PM.
- Injection 2 - 1198.4mg at 6:24AM (8.4 hours later).
- Injection 3 - 1198.4mg at 2:48PM (8.4 hours later).
- Injection 4 - 1198.4mg at 11:12PM (8.4 hours later).
- Continue with 1198.4mg dose injections every 8.4 hours.

5 Discussion

Our model attempts to deal with the changes in the patient's everyday life that affect the rate of removal of the drug from the bloodstream, such as the effect of undergoing exercise considered in the adaption of Model 1. However, in reality there is a much larger array of activities both essential and non-essential to a patient's daily life that are likely to affect how quickly the drug is removed. This includes eating, drinking, and the consumption of other drugs like alcohol. The assumptions that eating, drinking and sleeping do not affect the rate of drug removal are unlikely to be accurate, especially if alcohol is consumed. Any activity that raises the heart rate is also likely to affect the rate of drug removal for the same reason as mentioned in the adaption of Model 1. It is also impossible to predict when a raise in heart rate could occur, so for the impact of such conditions to be limited to a period of 1 hour in the patient's day is unrealistic.
Furthermore, the assumption that the heart rate doubles whilst the patient exercises also may not be accurate. The heart rate is unlikely to be at a constant value for the duration of exercise and it won't necessarily return to its resting rate instantly when the period of exercise ends as we have assumed.
The age of the patient would also need to be considered. As a patient gets older, the rate at which their kidneys filter blood will decrease as their body becomes less efficient.

Finally, our models only consider the single patient given in the problem statement. As different patients will have different volumes of blood, the dosage of an injection would need to vary for each individual case.

6 Conclusions

In conclusion, there are two main models that can be used to predict the concentration of the drug in the bloodstream over time.
Model 1 gives that there is a maximum of 8 hours in which the concentration of the drug remains within the therapeutic range. An initial injection of $504.63mg$ is required, followed by subsequent injections of $378.45mg$ every 8 hours.
Model 2, however, gives a slightly longer maximum time between injections of approximately 8.4 hours. As a consequence of this a much higher initial dose of $1261.5mg$ is required, followed by subsequent injections of $1198.4mg$ every 8.4 hours.

References

[1] AQA Biology *9-1 GCSE Combined Science: Biology AQA Higher Complete Revision Practice (CGP GCSE Combined Science 9-1 Revision)*

[2] Physics A formula book, *https://www.ocr.org.uk/Images/363796-units-h156-and-h556-data-formulae-and-relationships-booklet.pdf* Page 8

[3] Physics A formula book, *https://www.ocr.org.uk/Images/363796-units-h156-and-h556-data-formulae-and-relationships-booklet.pdf* Page 8