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Monitoring Drug Concentration in Emergency Medicine

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Monitoring Drug Concentration in Emergency Medicine

Abstract

The careful monitoring of a drug's concentration in the body of a patient is of the utmost importance in modern medicine. Many of the lifesaving medications that are administered in an emergency medicine environment have a narrow window of efficacy. This effective concentration is in an ever-changing state, as the body processes and eliminates exogenous compounds that are introduced to maintain homeostasis. To ensure the proper treatment and/or management of ailments, special attention must be given to the concentration of a given drug in the body as time progresses. These changing concentrations can be evaluated and tracked using the mathematical tools that are taught in Calculus-themed courses.

In this paper, the steps required to accurately calculate the concentration of a given drug in a patient's body will be examined. We will arrive at a formula that can reliably be used to determine this concentration at a point in time.

Keywords

emergency medicine, drug's concentration, rate law for a first order reaction, Atropine, bradycardia

Problem Statement

How can calculus be used to accurately track the elimination of first order drugs to maintain a consistent window of effectiveness in a patient? Use the drug Atropine, an anti-cholinergic medication commonly used to treat dangerous levels of bradycardia (low heart rate), as an example.

Motivation

In the context of Emergency Medicine, giving a patient the correct dosage of life-saving medications is critically important. All drugs have a range of concentrations in which they are maximally effective, often known as the drug's "window of efficacy." When a drug falls out of this range via the process of metabolism, the potential positive effects of that compound can quickly dissipate. This becomes a massive problem when keeping in mind the numerous life-threatening ailments that may bring an individual to the Emergency Department. Over 95% of medications administered in the Emergency Department are of a first order variety (Sepia2, 2022), (RxList, 2021), meaning that the concentration of these drugs does not decrease at a stable rate, but rather that the rate of elimination is related to the overall concentration of the drug. To maintain adequate blood plasma levels of Atropine, our example drug, we must be able to calculate the rate at which it clears the body. If we were to assume that Atropine is metabolized at a consistent rate, then further doses would not be administered in a quick enough fashion, and the patient would begin to experience worsening symptoms of bradycardia (low heart rate). This can lead to death, and so it is vitally important that we use math to model the elimination rates of first order medications.

Mathematical Description and Solution Approach

The average rate of elimination (1) for a drug can be written as such: (Science Direct, 2021)

$$R = -\frac{\Delta[D]}{\Delta t} \tag{1}$$

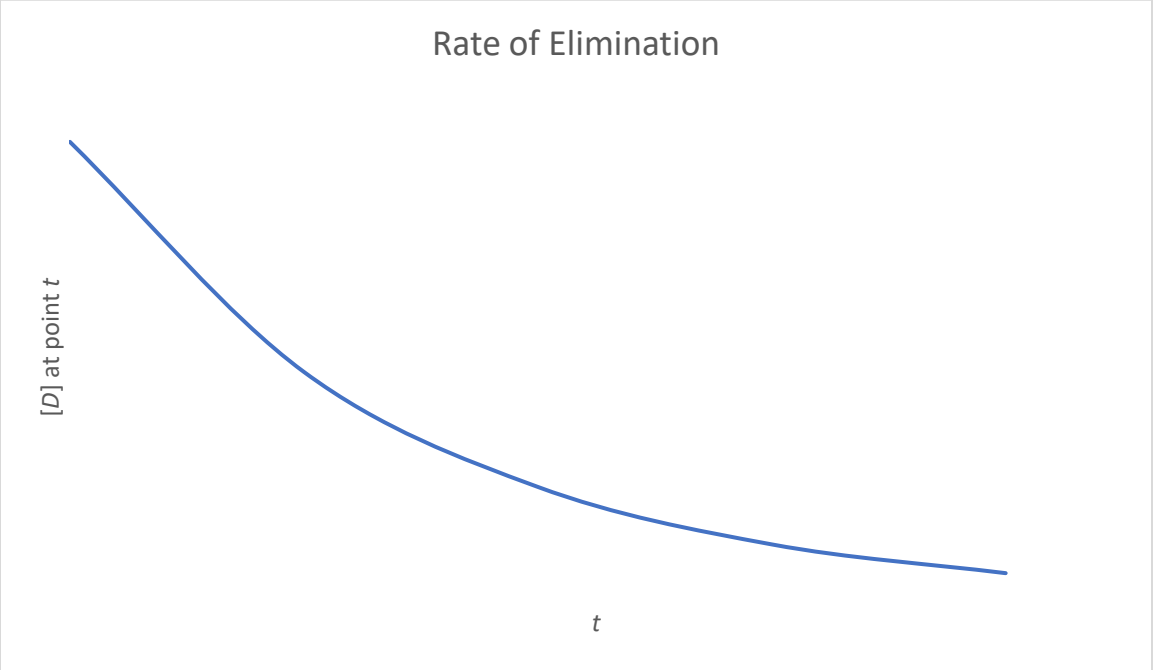
Where R = rate, $\Delta[D]$ = The change in concentration of drug, *D*, and Δt = The change in time. This equation is negative because it represents a diminishing quantity of the drug, *D*.

The rate law for a first order reaction (2) can be written as such: (Science Direct, 2021)

$$R = k[D]^1 \tag{2}$$

Where *R* = rate law, *k* = rate constant of a drug, and [*D*] = the concentration of drug, *D*. This equation is raised to the first power.

In a first order drug like Atropine, the drug concentration will decrease at an exponential rate such as depicted in this graph:



Because these equations both represent the rate of our reaction, we can set them equal to each other in such a fashion as this:

$$-\frac{\Delta[D]}{\Delta t} = k[D]^1$$

The equation on the left represents the average rate of elimination (1). We can, however, use calculus to arrive at an instantaneous rate of change. We start by setting up the equation to show the differential of [*D*] with respect to *t*, time.

$$-\frac{d[D]}{dt} = k[D]^1$$

We must now work the equation so that both [D] values are on the same side. We start by dividing both sides of the equation by [D] to remove it from the right side:

$$-\frac{d[D]}{(dt)[D]} = k$$

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Next, we will divide both sides by (-dt).

$$\frac{d[D]}{[D]} = -kdt$$

We will now integrate both sides to obtain the instantaneous rate of elimination. Because k is a constant, it can be pulled in front of the integral, leaving the overall equation to be represented as such:

$$\int \frac{d[D]}{[D]} = -k \int dt$$

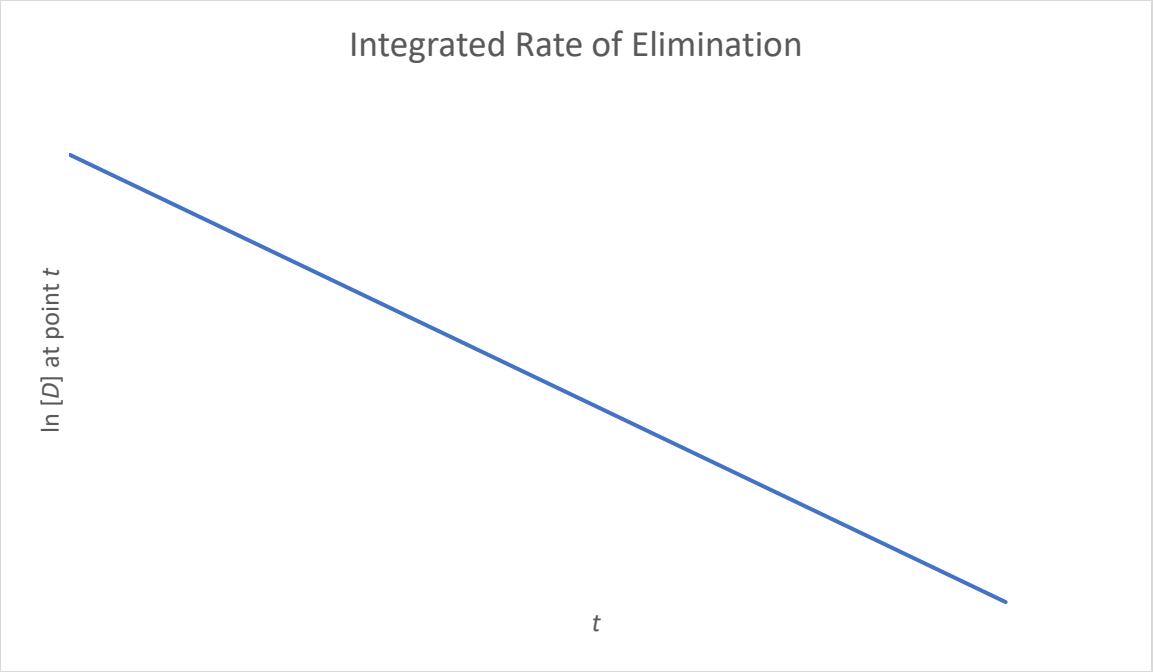
We must now set boundaries for this integration. With respect to the left side representing amount, we will be integrating from $[D]_0$, or the initial concentration of drug *D*, to $[D]_t$, or the concentration of drug *D* at some time, *t*. On the right side we will be integrating from zero, or initial time, to some time *t*. The equation will now look like this:

$$\int_{[D]_0}^{[D]_t} \frac{d[D]}{[D]} = -k \int_0^t dt$$

We will now integrate. The integral of $\frac{d[D]}{[D]}$ will become *ln [D]* evaluated at two points, $[D]_t$ and $[D]_0$. The integral of *dt* will become *t*, evaluated at two points, *t* and *zero*. We use the fundamental theorem of calculus to solve in this manner:

$$ln[D]_t - ln[D]_0 = -kt \qquad (3)$$

We now have the equation for the integrated rate law (3). This equation can be used to determine the value of [*D*] at any time *t*, given the initial concentration of [*D*] and the rate constant, *k*. The graph of this equation now shows a steady rate of declining drug concentration:



Based on properties that we know about the composition of functions and natural logs, we can now convert the equation (3) to solve for $[D]_t$ in the following manner:

$$ln[D]_t = \ln[[D]_0] - kt$$

Will become

$$[D]_t^{\ln [D]_t} = e^{ln[D]_0 - kt}$$

$$\rightarrow [D]_t = e^{ln[D]_0} \times e^{-kt}$$

$$\rightarrow [D]_t = [D]_0 \times e^{-kt} \quad (4)$$

This equation can now be quite easily used to determine plasma concentrations of IV atropine to always maintain an appropriate therapeutic dose. Some research allowed me to discover that the *k* value for Atropine elimination is 0.2776 per hour (Aguettant LTD, 2015). We can use this figure to calculate the half-life of Atropine. Let us assume that the beginning concentration of Atropine is 50 mg, and we are attempting to reach a value of 25 mg. (Note: this value of 50 mg is well above therapeutic levels, and only serves demonstration purposes).

If we plug in 2 hours to the value *t*, we will get this calculation:

$$50 \times e^{-(0.2776)(2)} = 28.6979$$

This value is slightly above 25 mg, so let us now substitute 3 hours for value *t*:

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$$50 \times e^{-(0.2776)(3)} = 21.7145$$

This value is slightly below 25 mg, so we can assume that the half life of Atropine lies between 2 and 3 hours. Let us run one last calculation with 2.5 hours as the value of *t*.

$$50 \times e^{-(0.2776)(2.5)} = 24.9786$$

We have arrived at a value remarkably close to 25 mg. This places the half-life of Atropine at approximately two and a half hours.

Furthermore, let us consider the equation for the absorption of a first order drug: (Science Direct, 2021)

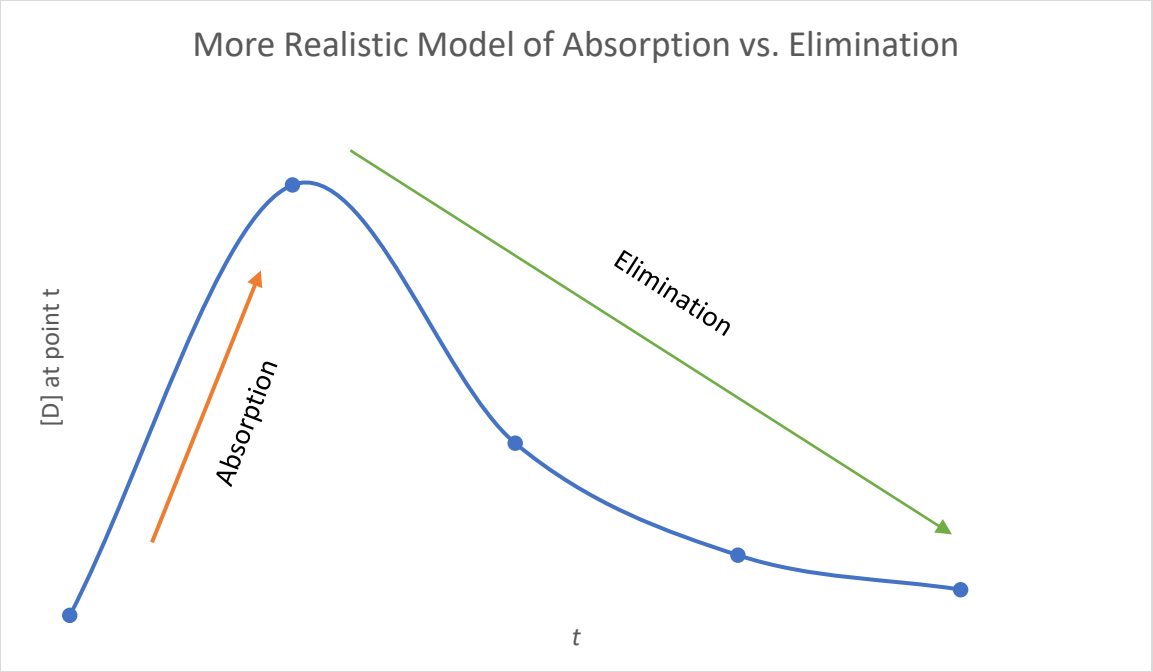
$$[D]_t = [D]_0 \times b \times e^{-k_a t} \quad (5)$$

Where *b* represents the bioavailability of the drug, a value from 0 to 1, and *ka* represents the absorption constant of the drug. This equation will represent how much of a drug has been released into the body to be biologically active. This absorption will be much more rapid than the elimination, and we can use a composition of functions to evaluate the exact bioavailable concentration of a drug at any time.

Let f be $[D]_t = [D]_0 \times b \times e^{-k_a t}$, and let g be $[D]_t = [D]_0 \times e^{-kt}$. We can determine the amount of active drug by calculating (f-g) thusly:

$$[D]_t = ([D]_0 \times b \times e^{-k_a t}) - ([D]_0 \times e^{-kt}) \quad (6)$$

With the above equation, if we know the absorption and elimination rate factors for a given drug, and that drugs bioavailability value *b*, we can determine the exact concentration of the drug at any time *t*. The graph below depicts a more typical absorption and elimination curve that will be seen in first order drugs such as Atropine. Notice how the absorption phase is quick lived, very soon being overtaken by the elimination phase.



Discussion

I used the average rate of elimination (1) and rate law of first order reaction (2) formulas to arrive at an integrated rate law for a first order reaction (3). This new formula allows us to determine the instantaneous rate of concentration decrease in an exponentially decreasing formula. Apart from calculation purposes, this formula additionally allows for the production of a graph with a straight line that is easier to interpret. I found that the exponential formula (4) arrived at was incredibly easy to use, and far handier than adding the additional natural log functions that are found in the integrated rate law (3). I very much like the utility of equation (6) in that it allows us to take into consideration the absorption of the drug, even if this is a quick lived phase.

Conclusion

We have discovered that there is indeed a straightforward way to calculate the instantaneous rate of elimination of first order drugs, which comprise more than 95% of Emergency Medicine pharmaceuticals. With the exponential formula (4) and established k value of Atropine, we were able to arrive at a half-life of approximately 2.5 hours. This is important knowledge, not only to maintain a therapeutic window, but also to avoid possible negative interactions with other medications. If we know that Atropine loses its effectiveness after plasma levels of the medication fall below 85-90% (Aguettant LTD, 2015), (RxList, 2021), we can use the exponential formula (4) to calculate that this will take approximately 30 minutes:

$$50 \times e^{-(0.2776)(0.5)} = 43.52$$

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43.52/50 = 87%

With this knowledge, we know that additional doses of Atropine must be administered appropriately at intervals of approximately 30 minutes. We also know that long after the effects have worn off, Atropine still will be present in the body. With therapeutic effects rapidly vanishing after 30 minutes, Emergency Providers must keep in mind that even 2.5 hours later, there will still be half of the initial concentration of Atropine that is still present in the bloodstream. This is vital information that must be relayed to any other providers that may assume care of the patient. An Anesthesiologist, for example, must be aware of this drug's concentration in the patient's bloodstream in the event that sedation is required for an emergent surgical procedure.

NOMENCLATURE

Mg = Milligram, or 0.001 grams

R = Rate law

k = Rate constant of drug

$[D]$ = The concentration of drug D

$\Delta[D] =$ The change in concentration of drug D

$\Delta t =$ The change in time

$[D]_t$ = Concentration of drug, D, at time, t

$[D]_0$ = Initial concentration of drug D (where $t = 0$)

b = The bioavailability of the drug D (a value from 0 to 1)

ka = The absorption constant of the drug D

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