

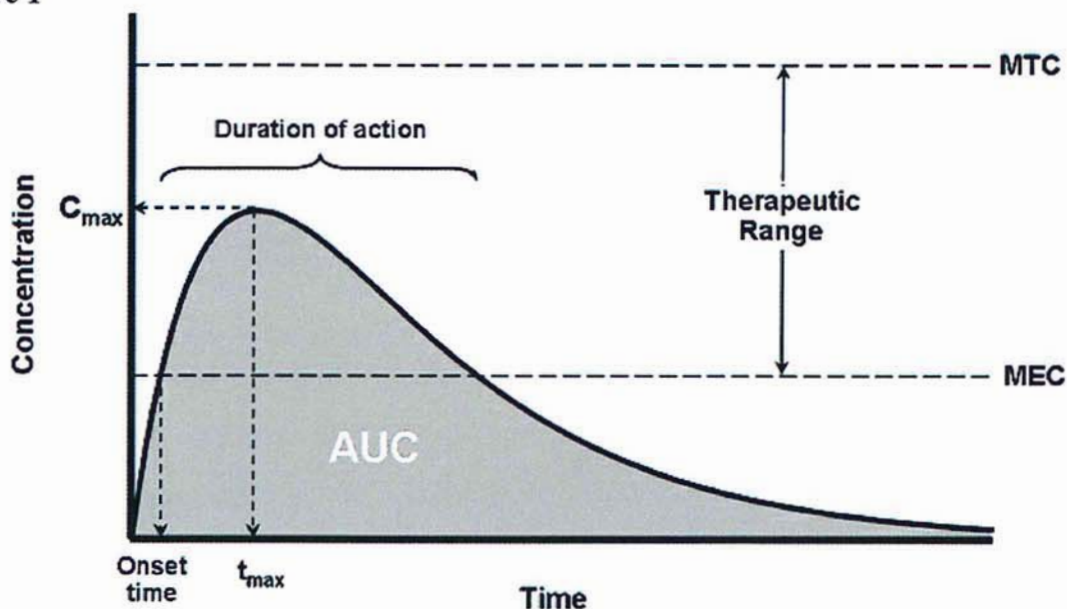
Graphing the Pharmacokinetic Profile

During my wisdom teeth removal surgery, I was administered an IV form of acetaminophen and was also prescribed an oral form of acetaminophen to use during my recovery. Since I am interested in pursuing a career in the medical profession, I wondered about how these forms differed with respect to how they interact with the body. This prompted me to think about how doctors graph these medications. I wondered about what the graphs of the IV and oral acetaminophen in the bloodstream would look like and how doctors might analyze them to determine what form of medication is most appropriate for any given patient.

The plasma concentration of acetaminophen, or any other drug, can be graphed in relation to time through what is called a concentration-time graph, a graph that is commonly used in the field of pharmacokinetics. A concentration-time graph of a drug can provide doctors insight into what is called a pharmacokinetic profile. By examining different properties of the curve, doctors can understand the specific characteristics of the drug that may make it appropriate or inappropriate for a patient with a certain condition.

Below is a model of a typical concentration-time curve after an oral administration of a drug:

Figure 1¹



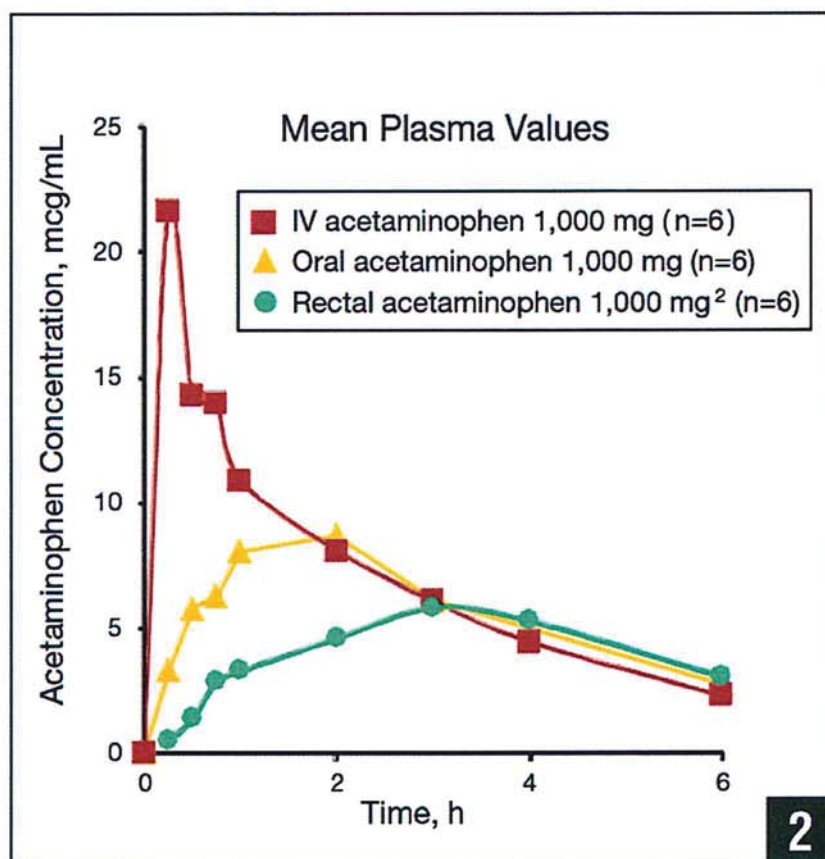
Although the graph may change slightly depending on the drug, the labeled items can be found in all concentration-time graphs. The following table provides an explanation of each characteristic and its respective significance.

MEC (minimum effective concentration)	The minimum concentration of medication in the bloodstream required for the drug to be effective.
MTC (minimum toxic concentration)	The minimum concentration of medication in the bloodstream expected to produce a toxic effect.
Therapeutic Range	The range (between MTC and MEC) of concentrations at which the drug is effective with minimal toxicity.
Duration of Action	The length of time that the drug is effective, meaning that the concentration level is above the MEC.
Onset Time	The time after administration at which the drug first reaches MEC and becomes effective.
C_{max}	The maximum plasma concentration the drug reaches.
t_{max}	The time after administration at which the drug reaches the maximum plasma concentration.
AUC (area under curve)	Reflects the actual body exposure to the drug after administration.

¹ Mehrotra, N, M Gupta, A Kovar, and B Meibohm. "The Role Of Pharmacokinetics And Pharmacodynamics In Phosphodiesterase-5 Inhibitor Therapy." *International Journal of Impotence Research* 19.3 (2006): 253-264. Print.

Concentration-time curves can be used to compare drugs in many ways. In *Figure 2*, you can see how the curves vary depending on the type of administration despite the fact that the dose is consistent.

Figure 2²



Although the curves have many differences, we will focus on the C_{\max} and AUC, as these are both measures of exposure. (This concept will be explored later in the paper.) We will also direct our focus to the IV acetaminophen and oral acetaminophen curves, as they are more commonly used than rectal acetaminophen.

By looking at the maximums of the graphs, we notice that IV acetaminophen has a significantly higher C_{\max} than oral acetaminophen, meaning that the peak plasma concentration is greater. Similarly, by looking at the overlap of the graphs, we can tell that the AUC of IV acetaminophen is greater than that of oral acetaminophen.

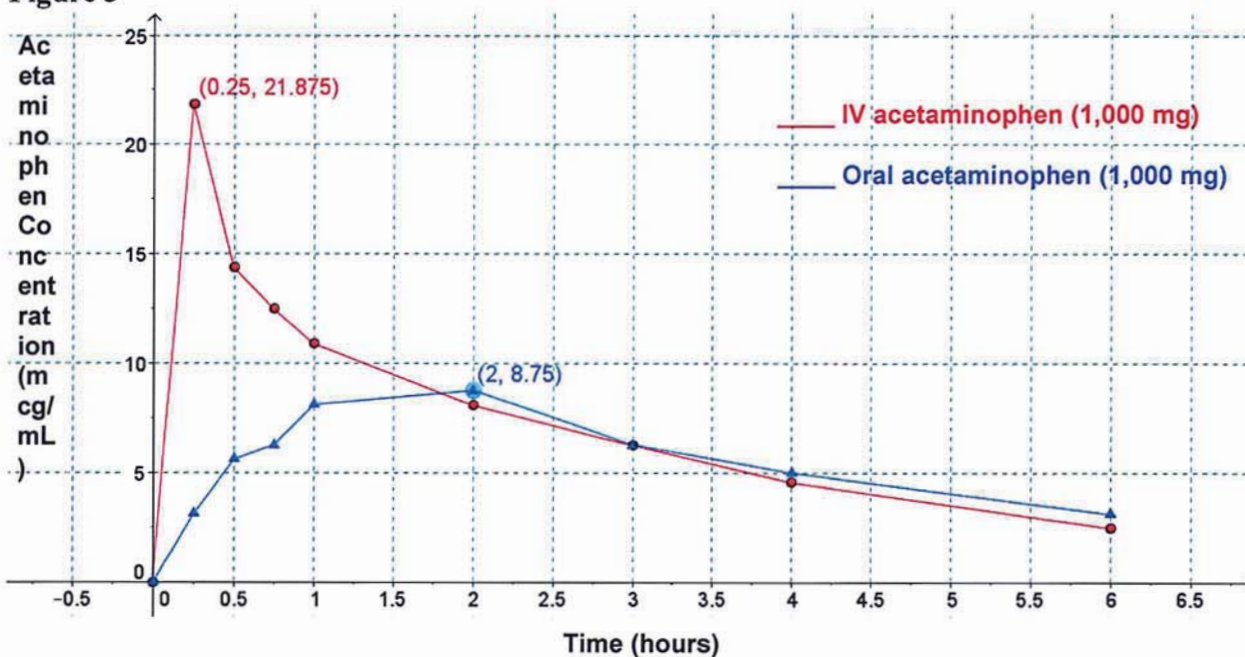
² Lachiewicz, Paul F. "The Role of Intravenous Acetaminophen in Multimodal Pain Protocols for Perioperative Orthopedic Patients." *Orthopedics* 36.2 (2013): 16. *Healio Orthopedics*. Web. 11 Nov. 2013.

However, a more accurate interpretation of the data would require further mathematical analysis. In order to adequately measure the exposure of each respective administration, we must more accurately calculate the C_{\max} and AUC of both graphs. We can begin by locating several approximate data points that each curve passes through. The values listed in the table are approximations from the graph in Figure 2. Although the values are approximated, the margin of error is acceptable for our purpose.

Table 1

Time (hours)	0	0.25	0.5	0.75	1	2	3	4	6
IV acetaminophen	0	21.875	14.375	12.5	10.938	8.125	6.25	4.575	2.5
oral acetaminophen	0	3.125	5.625	6.25	8.125	8.75	6.25	5	3.125

We can then plot these points on a graph:

Figure 3

The maximum points of each curve tell us the C_{\max} values for each respective administration of acetaminophen. Thus, the C_{\max} of IV acetaminophen is approximately 21.875, meaning that there is approximately 21.875 micrograms per milliliter (mcg/mL) in any given volume of blood plasma. Likewise, the C_{\max} value of oral acetaminophen is approximately 8.75, meaning that

there is approximately 8.75 mcg/mL in any given volume of blood plasma. The AUC of each graph can be calculated using different methods, and although the process is different, both will yield the same answer. One way to calculate the AUC is to divide the area under the curve into conventional geometric shapes. The area of each individual shape is added together to find the total area under the curve. We will first use this method to find the AUC of the oral acetaminophen curve.

Figure 4

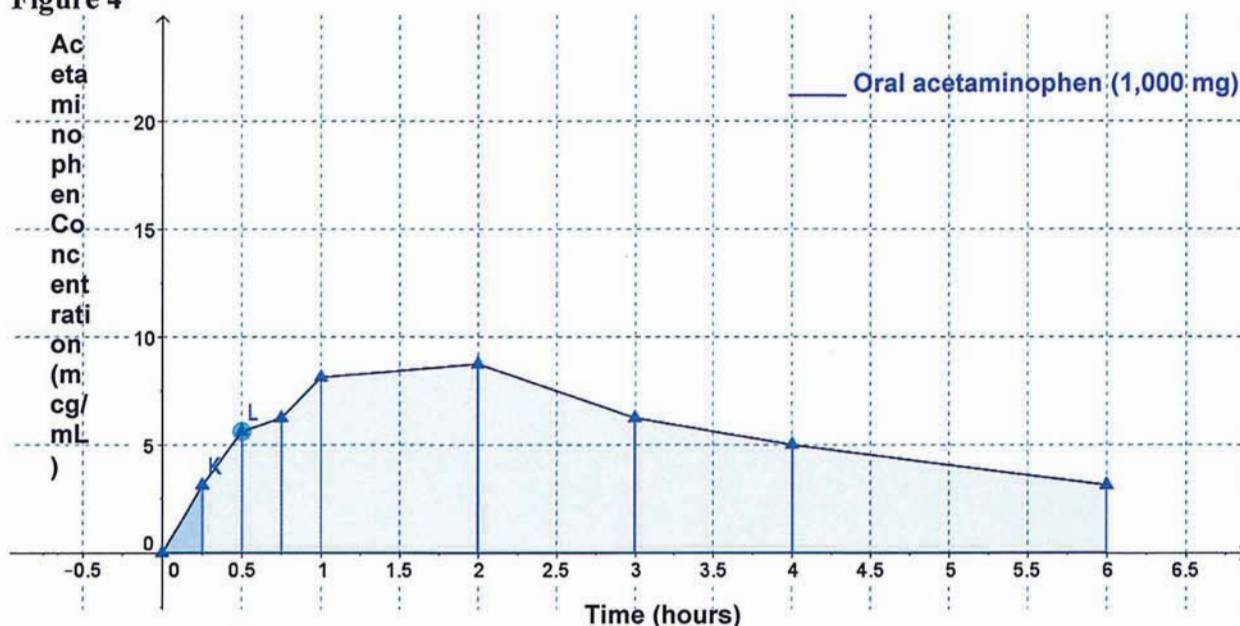


Figure 4 shows the graph of oral acetaminophen separated out into geometric shapes (primarily trapezoids), which are shaded in blue. We will first find the area of the triangle shaded in darker blue. The area of the triangle represents the area under the curve from $x = 0$ to $x = 0.25$. To calculate the area of this triangle, we will use the area of a triangle formula.

$$A = \frac{1}{2}(bh)$$

The base equals the x-coordinate of Point K. Therefore $b = 0.25$. The height equals the y-coordinate of Point K. Therefore $h = 3.125$. Using these values, we can calculate A .

$$A = \frac{1}{2}(0.25)(3.125) = 0.390625$$

We will use the same idea to find the area of the next shape; however, the method will differ slightly because the shape is a trapezoid rather than a triangle. The area of this trapezoid represents the area under the curve from $x = 0.25$ to $x = 0.5$. To calculate the area of this trapezoid, we will use the area of a trapezoid formula.

$$A = \frac{1}{2}(b_1 + b_2)h$$

b_1 equals the y-coordinate of Point K. Therefore, $b_1 = 3.125$. b_2 equals the y-coordinate of Point L. Therefore, $b_2 = 5.625$. h equals the distance between Points K and L on the x-axis (refer back to Figure 4). We can determine this by finding the difference between the x-coordinates of Points K and L. Therefore, $h = 0.5 - 0.25 = 0.25$. Using these values, we can calculate A .

$$A = \frac{1}{2}(3.125 + 5.625)0.25 = 1.09375$$

Using the same methods, we can find the area of the remaining trapezoids. Each of the following area values is an exact calculation.

Figure 5

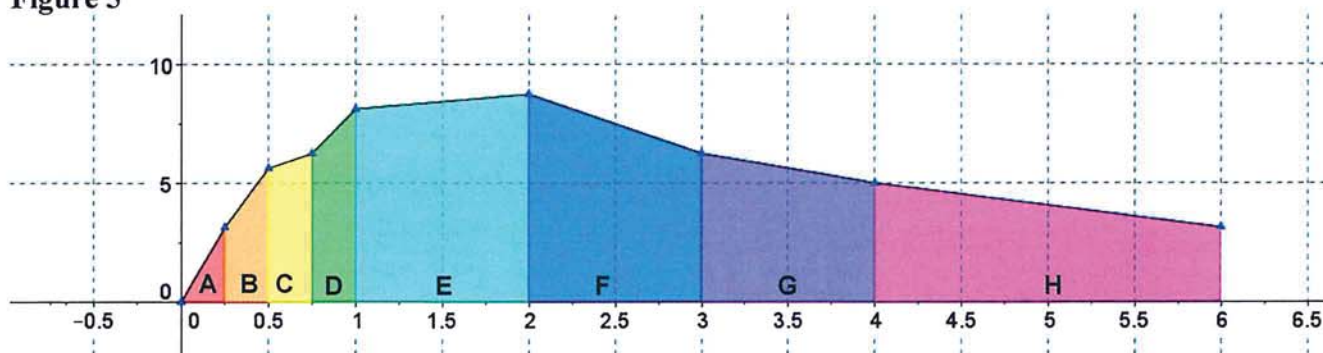


Table 2

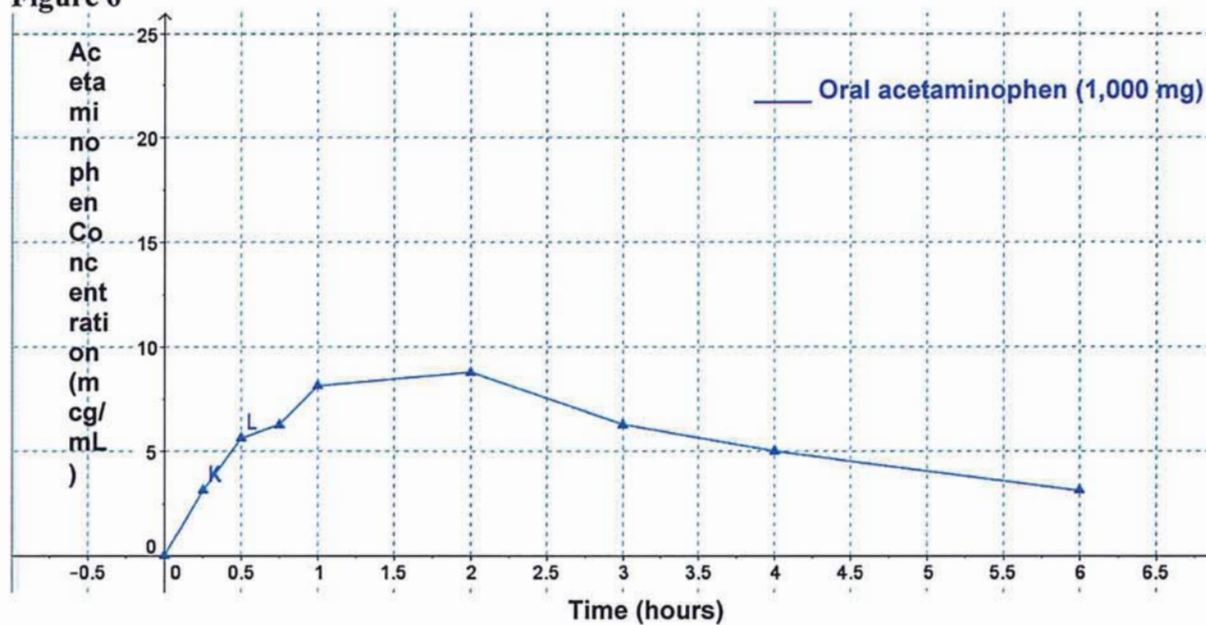
Shape	A	B	C	D	E	F	G	H
Area	0.390625	1.09375	1.484375	1.796875	8.4375	7.5	5.625	8.125

By adding the areas of each of the individual shapes together, we get the total AUC from $x = 0$ to $x = 6$.

$$A + B + C + D + E + F + G + H = 34.453125$$

We can also find the area of each shape through integration. To calculate the AUC using integrals, we will examine each segment of the curve. Each segment, such as segment KL, can be defined by a function that will be converted to an integral in order to find the area.

Figure 6



In Figure 6, examine the segment that begins at the origin and ends at Point K. Let the origin $(0, 0)$ be point 1. Let Point K $(0.25, 3.125)$ be point 2. To determine the function that describes this line segment, we must first find the slope. To find the slope, we calculate the difference in y-values divided by the difference in x-values:

$$m = \frac{y_2 - y_1}{x_2 - x_1}$$

Thus:

$$m = \frac{(3.125 - 0)}{(0.25 - 0)} = \frac{3.125}{0.25} = 12.5$$

When can then use point-slope form to find the constant:

$$\begin{aligned} y - y_1 &= m(x - x_1) \\ y - 3.125 &= 12.5(x - 0.25) \end{aligned}$$

Therefore:

$$y = 12.5x \text{ when } 0 \leq x \leq 0.25$$

This makes sense, as the line passes through the origin.

We can then use this function to find the integral. It is important to note that this function defines only the segment between 0 and 0.25.

$$\begin{aligned} & \int_0^{0.25} 12.5x \, dx \\ &= \left[\frac{12.5x^2}{2} \right]_0^{0.25} = [6.25x^2]_0^{0.25} \end{aligned}$$

Thus:

$$[6.25(0.25)^2] - [6.25(0)^2] = 0.390625$$

This area matches our calculation using geometric methods (page 5).

We can use integrals to find the area under the curve for the next segment as well. First, we must find the function that defines segment KL (*Figure 6*). Let Point K (0.25, 3.125) be point 1. Let Point L (0.5, 5.625) be point 2. To determine the function that describes this line segment, we again must first find the slope.

$$\begin{aligned} m &= \frac{y_2 - y_1}{x_2 - x_1} \\ m &= \frac{(5.625 - 3.125)}{(0.5 - 0.25)} = \frac{2.5}{0.25} = 10 \end{aligned}$$

We can then use point-slope form to find the constant:

$$\begin{aligned} y - y_1 &= m(x - x_1) \\ y - 5.625 &= 10(x - 0.5) \end{aligned}$$

Therefore:

$$y = 10x + 0.625$$

We can then use this function to find the integral. Again, it is important to note that this function defines only the segment between 0.25 and 0.5

$$\begin{aligned} & \int_{0.25}^{0.5} 10x + 0.625 \, dx \\ &= \left[\left(\frac{10x^2}{2} \right) + \left(\frac{0.625x^1}{1} \right) \right]_{0.25}^{0.5} = [5x^2 + 0.625x]_{0.25}^{0.5} \end{aligned}$$

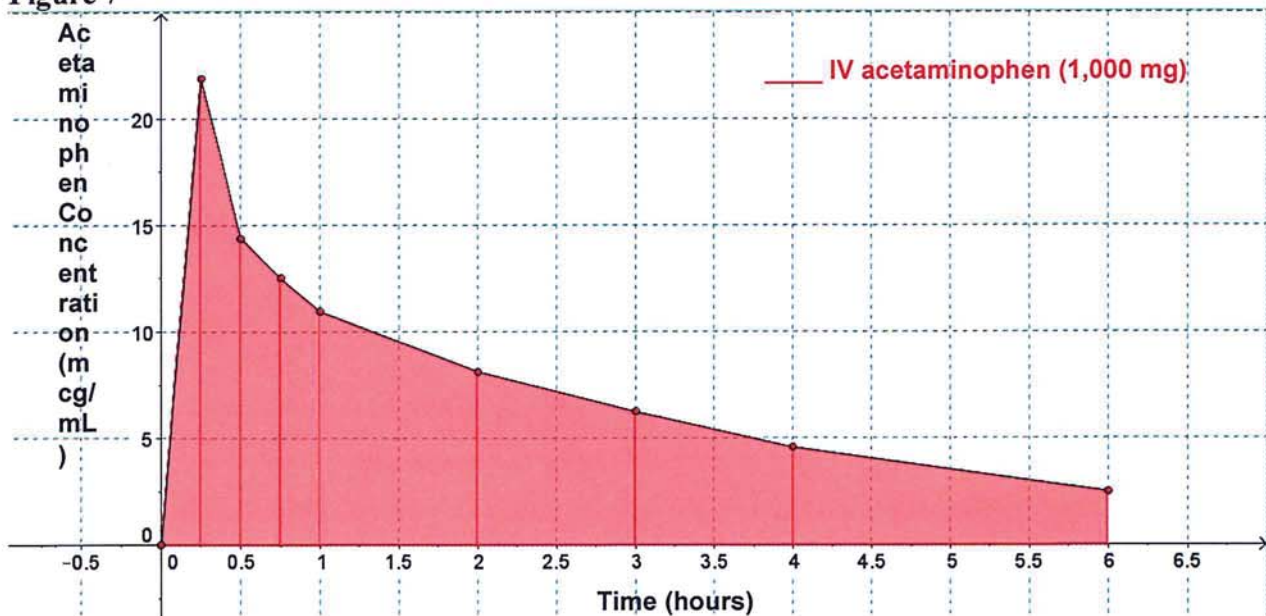
Thus:

$$[(5(0.5)^2) + (0.625(0.5))] - [(5(0.25)^2) + (0.625(0.25))] = 1.09375$$

This area matches our calculation using geometric methods (page 6). We can use this same method to determine the area under the curve for the remaining segments. By adding these individual areas together, we can determine the area under the curve for the entire curve, even though it cannot be defined by the same function. (Refer to Figure 5, Table 2 on page 6). This value, 34.453125 mcg/mL* h, represents the patients exposure to the drug.

Using either the geometric method or integration, we can find the approximate AUC for the IV acetaminophen curve:

Figure 7

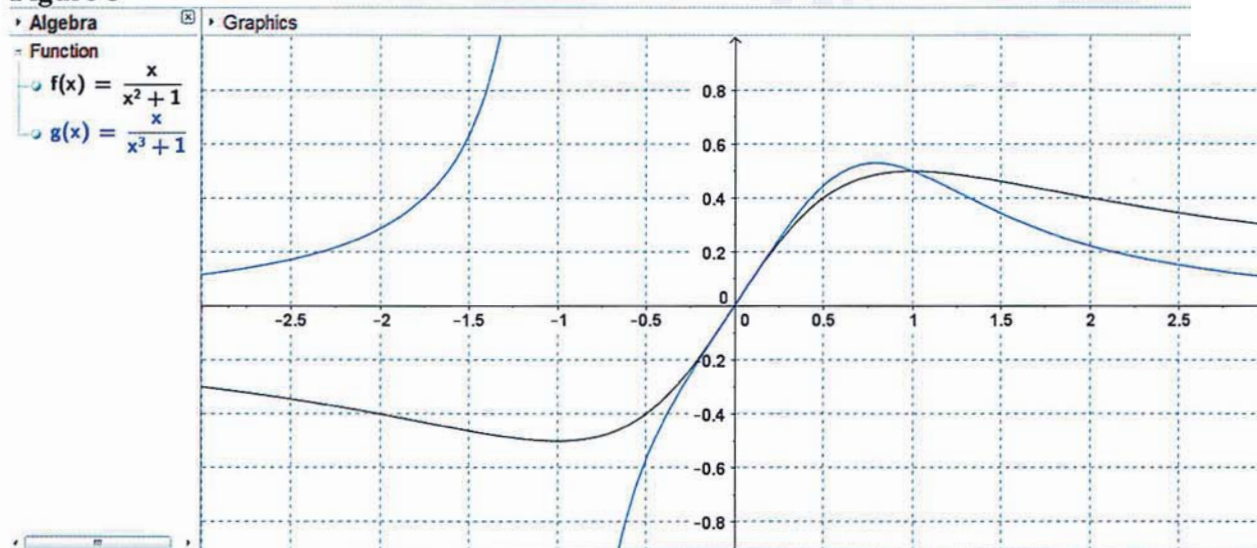


$$\begin{aligned} AUC &= 2.734375 + 4.53125 + 3.359375 + 2.92975 + 9.5315 + 7.1875 + 5.4125 + 7.075 \\ &= 42.76125 \end{aligned}$$

Therefore, the AUC of the IV acetaminophen curve, 42.76125 mcg/mL* h, is greater than that of the oral acetaminophen curve, 34.453125 mcg/mL* h. Essentially, this means that although the dose (1,000 mg) was the same for both administrations, the patient exposure is greater for the IV acetaminophen. However, it is important to note that these values were both approximations. While the curves describe the relative trend of the data, the curves would really be more gradual.

I wanted to find a function that would more accurately represent the true concentration-time curve for oral and IV acetaminophen. I remembered a couple graphs that I saw in class that may be parent functions of the data, shown here using Geogebra.

Figure 8



While the two functions pictured in *Figure 8* exist for the domain $(-\infty, \infty)$, the functions that describe the data in my problem would be limited to $[0, \infty)$ because the x-axis is time. With this, the most important aspect of both of these functions is the relationship between the numerator and denominator. To achieve the shape of a typical concentration-time curve, the numerator increases more rapidly than the denominator when $x < 1$. When $x > 1$, the denominator becomes increasingly larger than the numerator. For this reason, the function has an asymptote at $y = 0$. While it is not apparent in the window of the graph above, both functions would eventually approach $y = 0$ as x approaches ∞ . Relative to these principles, the two functions in *Figure 8* are similar. The differences in the denominators cause slightly different troughs. Because the function that describes the data in my problem passes through the origin, we can eliminate both vertical and horizontal translations. We know, then, that the functions for our data would be a variation of the following format, which involves vertical and horizontal dilations:

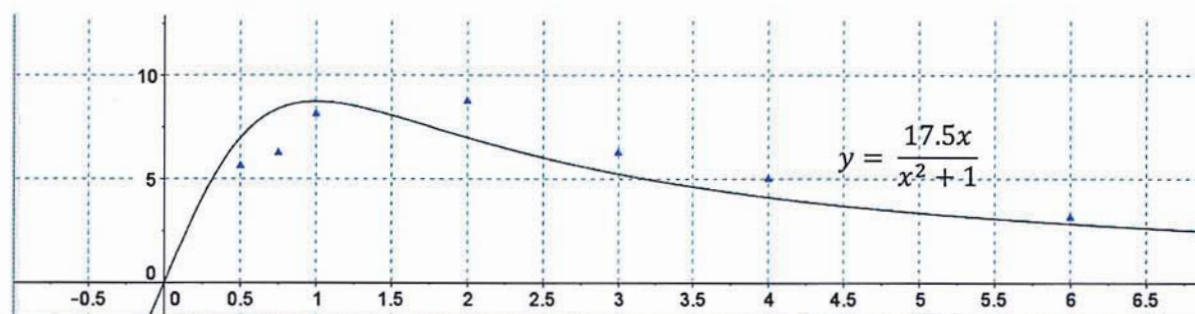
$$y = \frac{a(bx)}{(bx)^2 + 1}$$

In this format, a signifies the vertical dilation. A vertical dilation stretches/compresses the original function, $y = \frac{x}{x^2+1}$, vertically by a scale factor of a . Similarly, b signifies the horizontal dilation. A horizontal dilation stretches/compresses the original function horizontally by a scale factor of $\frac{1}{b}$.

By modifying the original function using vertical and horizontal dilations, we can create a function that more accurately represents the true concentration-time curve for oral and IV acetaminophen. Let's consider the oral acetaminophen graph first:

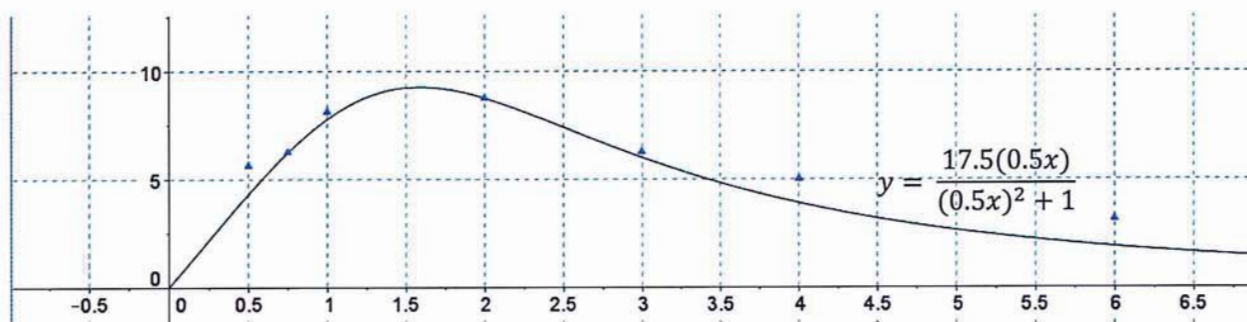
To determine the vertical dilation, I considered the maximum values. In the parent function $y = \frac{x}{x^2+1}$, the maximum is 0.5. The maximum for the data for oral acetaminophen was 8.75. $\frac{8.75}{0.5} = 17.5$. Therefore, a vertical dilation by a factor of 17.5 would yield a curve that has the same maximum:

Figure 9



Although the curve has the correct maximum, it does not occur at the correct x -value. The maximum of the parent function occurs at $x = 1$, which the maximum of our data occurs at $x = 2 \cdot \frac{1}{2} = 0.5$. Therefore, a horizontal dilation by a factor of 0.5 would yield a curve that passes through our maximum at the correct x -value:

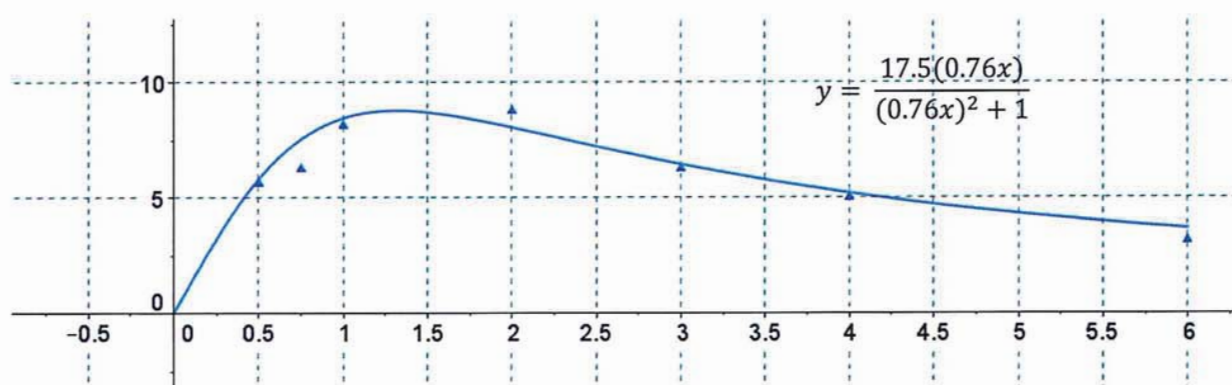
Figure 10



This function more accurately represents the data. However, the graph decreases too quickly following the maximum.

I chose to adjust the horizontal dilation in order to effectively stretch the curve more horizontally. After substituting various values, I determined that a horizontal dilation by a factor of $\frac{1}{0.76}$ produced the closest line of best fit. Although the maximum is slightly lower, the new graph better represents the amount of the drug that would be in the blood after more than 3 hours. This information is important to determine when the next dose should be administered.

Figure 11



Using a calculator, you can use integration to find the AUC of this regression curve.

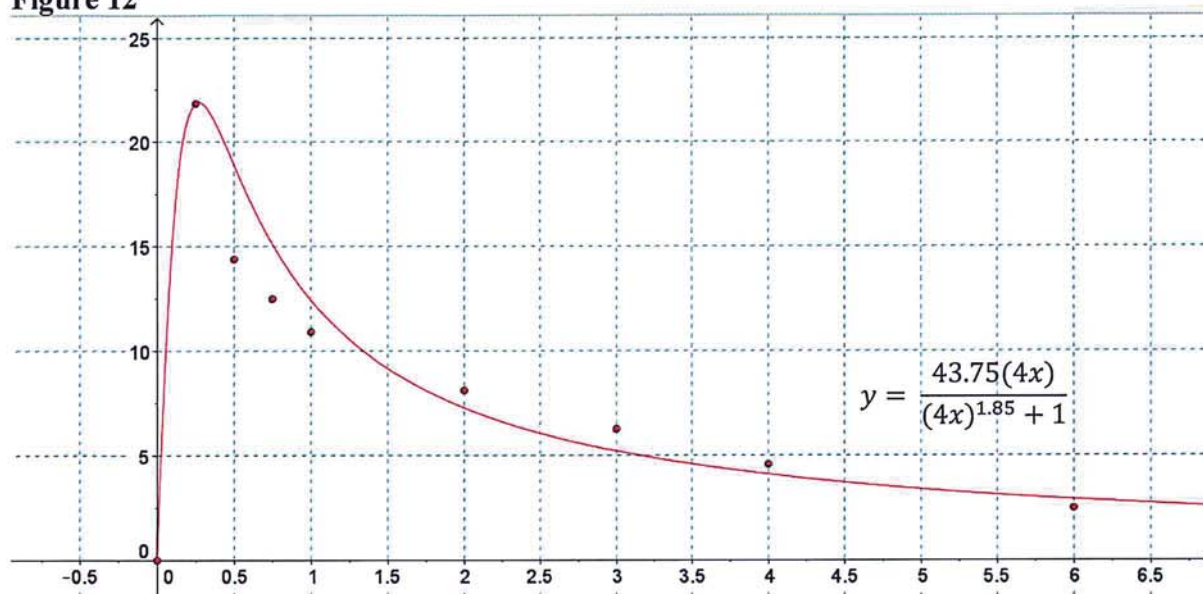
$$\int_0^6 \frac{17.5(0.76x)}{(0.76x)^2 + 1} dx$$

$$AUC \cong 37.3108791902$$

Compared to the AUC calculated from the line graph, 34.453125, this value is slightly greater. Although it is still an approximation and does not exactly represent the data, it is a more accurate value and provides a better pharmacokinetic profile of the drug.

I used a similar method to find the line of best fit and AUC for the IV acetaminophen curve:

Figure 12



$$\int_0^6 \frac{43.75(4x)}{(4x)^{1.85} + 1}$$

$$AUC = 43.76922217$$

Compared to the AUC calculated from the line graph, 42.76125, this value is just slightly greater. Again, although it is still an approximation and does not exactly represent the data, it is probably a more accurate value and provides a better pharmacokinetic profile of the drug.

Now that we have calculated C_{\max} values and AUC for both curves, we can consider their significance. As I mentioned earlier in the paper, both C_{\max} and AUC are measures of exposure in the sense that they both determine toxicity. However, the relative importance of each of these measurements can vary depending on the drug. For acetaminophen specifically, the C_{\max} is very predictive of liver damage. Thus, doctors pay special attention to the C_{\max} values. Because the IV

acetaminophen has a higher C_{\max} than oral acetaminophen (though it is still below the minimum toxic dose), it may not be ideal for patients with pre-existing liver conditions.

IV acetaminophen and oral acetaminophen are both commonly used for medical treatment. The IV form is generally better for patients who require fast effects and/or can't absorb the oral form. This is the reason why I was administered an IV form of acetaminophen during my wisdom teeth removal surgery. Unless the patient requires an IV form, the oral form of acetaminophen is generally given because the kinetics do not impact its therapeutic properties. Therefore, the oral form is a more convenient way for patients to receive the same therapeutic effect. This is the reason why I was given the oral form of acetaminophen for my recovery.

The pharmacokinetic principles behind this investigation can be applied to other drugs. This method of analysis is useful for doctors to prescribe the best medication, but also for patients to better understand how the drug they are taking interacts with their body. It was both interesting and exciting to see how algebra, geometry, and calculus can be applied to a practical scenario. I look forward to using my new knowledge in my career as a nurse!

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