Math in Pharmacokinetics: How Biological Half Life is Calculated

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1. Introduction

Pharmacokinetics, the study of drug movement inside the body, is one of the major branches in pharmacology that heavily relies on mathematics. In principal, when a drug is injected into the patient, it undergoes two phases: absorption and elimination. During absorption phase, the drug concentration in blood plasma increases until it reaches a maximum point notated as ConcentrationMax. The drug concentration then decreases in various shapes depending on its type, molecular weight, and the difference between rate of absorption and rate of distribution of the drug [1]. Antibodies, for example, rapidly distributes into the peripheral tissues for a short period of time; its concentration then slowly declines in a linear trend because it redistributes into plasma and recycles via FcRn-mediated transcytosis.

Throughout decades of research, pharmacologists have developed a vast number of mathematical formulas to calculate certain traits of new drugs. One of the main studies is predicting how long the drug would stay inside the patient in vivo using 'elimination half life'. Half life, in definition, is how long a substance loses half of its quantity in the given environment. Similarly, elimination half life is the time it takes for the concentration of a drug to decrease by half inside the body. Half life is crucial for pharmacologists to understand various factors of the drug such as its biodistribution efficiency and to find the right dosing interval: the interval between drug administration to the patient.

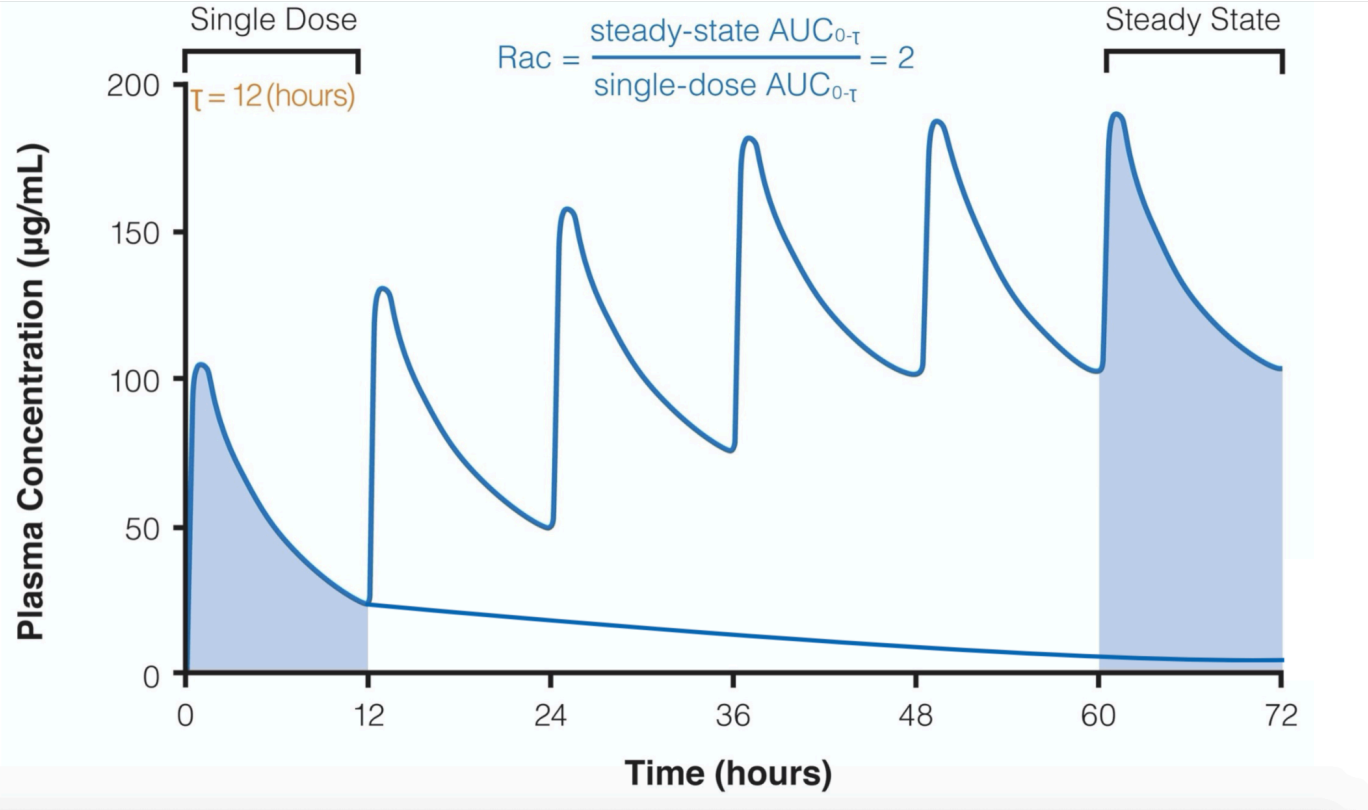
In this study, we will apply logistics and calculus so as to derive the theoretical half life of a hypothetical drug 'XCX'. This paper will provide a glimpse of how mathematics is combined with medicine, which would be very unique for pre-university students.

2. Results

XCX was injected into the patient via IV administration, meaning that the drug was delivered inside the bloodstream. The dosing interval was 12 hours, and the drug dose concentration was controlled so that every new dose would increase the concentration of drug inside blood plasma by 100μg/mL. The drug accumulation in the bloodstream was measured by collecting a blood sample from the patient, followed

by centrifugation and isolation of plasma from red blood cells. The amount of drug was then analyzed from the isolated plasma. The drug concentration in plasma was graphed in plasma concentration vs. time graph (Graph 1).

Graph 1: Accumulation of 'XCX' in Plasma after Multiple IV Infusion. Time measured in hours, and plasma concentration measured in micrograms per milliliter (µg/mL). Figure modified from Gidal, B. E., Clark, A. M., Anders, B., & Gilliam, F. (2017). The application of half-life in clinical decision making: Comparison of the pharmacokinetics of extended-release topiramate (USL255) and immediate-release topiramate. Epilepsy Research, 129, 26–32. https://doi.org/10.1016/j.eplepsyres.2016.10.020



3. Discussion

Graphical Analysis

a) Identifying single dose and steady state

In order to calculate the half life of XCX, two different regions must be identified: single dose and steady state. Single dose means the very first curve in the graph caused by the first injection of the drug inside the bloodstream. Steady state is when the line of the graph reaches a certain point and starts to create a pattern in the change of drug concentration.

As labeled in the graph above, the single dose was between the time interval [0, 12], inclusive. The graph repeats a similar curvature for every 12 hours, which is the dosing interval for the drug. However, despite

the repetitions, the overall drug concentration increases in a logistic manner until the sixth dose between the time interval [60, 72], inclusive. By then, despite the fluctuation, both maximum and minimum drug concentration remains constant as visually seen above. Thus, the single dose region is [0, 12] while and steady state is [60, 72].

b) Calculating Area under Curve

Two different area under curve (AUC) were calculated from single dose and steady state that were identified as previously explained.

For the single dose, the AUC was calculated as the total area that represents the presence of the drug that was injected for the first time. In pharmacokinetics, this area is calculated in integral form as follows:

$$AUC_{\infty} = \int_0^{\infty} C dt \tag{1}$$

where AUC∞ the AUC for single dose and C represents the function in the concentration-time graph. The extension of the decreasing curvature varies depending on the drug type and the site of measurement. Calculated, AUC∞ ~ 1500.

For the steady state, the AUC was calculated only between the time interval [60, 72]. This is because the cycle of drug concentration does not change unlike single dose. The integral formula is calculated as follows:

$$AUC_t = \int_t^{t+T} C dt \tag{2}$$

where AUCt symbolizes the AUC for steady state and C is function as previously identified. t (in hours) represents the starting time of the steady state, which is 60. T (in hours) is the dosing interval, which is 12 as explained in the Results section. Calculated, AUC_t ~ 3000.

Derivation of Half Life

a) Calculating Drug Accumulation Index

Drug Accumulation Index (RAC) is a constant the reflects the extent of drug accumulation. The constant varies depending on the drug type and the dosing interval. It is calculated in two different ways. In the first method, RAC is the ratio of drug concentration at steady state over drug concentration after the single dose:

$$RAC = \frac{AUC_t}{AUC_{\infty}}$$

(3)

In the second method, RAC is derived with an equation as follows:

$$RAC = \frac{1}{1 - e^{-K_E T}} \tag{4}$$

where K_E (in hours) is the Elimination Half Life and T (in hours) is the dosing interval.

Since equations (3) and (4) are equivalent to each other, K_E was easily derived because the remaining variables are identified: $AUC_t \sim 3000$, $AUC\infty \sim 1500$, and $T = 12$.

Combining RHS of equations (3) and (4) and simplifying them,

$$\frac{AUC_t}{AUC_\infty} = \frac{1}{1 - e^{-K_E T}}$$

$$\frac{3000}{1500} \sim \frac{1}{1 - e^{-K_E \cdot 12}}$$

After a bit of calculations,

$$K_E \sim -\frac{ln\left(\frac{1}{2}\right)}{12}$$

$$\sim 0.05776$$

Therefore, the biological half life of the drug 'XCX' is nearly 0.06 hours.

5. Conclusion

Through this theoretical experiment and calculations, we have created a new mathematical module to mathematically calculate the biological half life of a medicinal substance. Through this procedure, the half life of any macromolecules can be simply calculated without constrictions on its molecular weight, types, and electrostatic surface potential. Regardless, this paper briefly overviews the general utilization of mathematics into pharmacology.

6. References

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