# MATHETMATICAL MODELING OF PHARMACOKINETICS

Title analysis shown (45)
2 Comp. model good!

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# PHARMACOKINETICS

## INTRODUCTION

The term *pharmacokinetics* was introduced by Dost in 1953 to relate drug quantity and activity within the body to a mathematical model. Pharmacokinetics , by definition, is a study of drug absorption, distribution, metabolism, and excretion overtime. This also includes their relationships with these processes to the intensity and time source of pharmacologic effects of drugs and chemicals. Therefore, pharmecokinetics is of some importance to clinical medicine.

In this paper, I will discuss various models that are useful to pharmacokinetics. The first is the one compartmental model, the simplest model, which treats the body as a single kinetically homogeneous body. That is to say that the drug or chemical will only effect the body as a whole; the blood plasma. The second model is the multi-compartment model where it will be assumed that the drug or chemical in the first compartment will be in rapid equilibrium with a second; the equilibrium between blood plasma and tissue. The last issue that will be discussed is multidosing of single dose administration over a period of time.

## ONE COMPARTMENT MODEL

The one compartment model deals with the drug or chemical affecting a kinetically homogeneous body. This model is often used to describe a rapid intraveneous injection where the entire dose of the drug is administered to the blood stream. The drug is then distributed to the body tissues and/or eliminated.

"The one compartment model assumes that any changes that occur in the plasma levels of a drug reflects proportional changes in the tissues drug levels. However, this model does not assume that drug concentrations in each tissue are the same at any given point in time." [1]

The model can be represented by :

Dd Db Kel De
Drug Injection---------> Drug in Body----------->Elimination

Dd is the amount of drug administered.
Db is the amount of drug in the body.
De is the amount of drug eliminated or absorbed.
Kel is the elimination constant.

The role of elimination can be described as first order and being proportional to the amount of drug in the body (Db) at time, t.

$$\frac{db}{dt} \propto Db \quad \text{and} \quad \frac{dB}{dt} = -KelDB \quad \text{for } Kel > 0$$

Upon separation:

$\frac{dDb}{Db} = -Kel \ dt$

integrate both sides:

$\ln Db = -Kel(t) + Co$

$Db = Co\ e^{-(Kel)(t)}$

$D_b = D_{b\infty}\ e^{-(Kel)(t)}$

concentration! Why have we changed to concentrations?

$C_b = \frac{D_b}{V_b}$ where $V_b$ is the volume of blood

We can use the same equation to describe the concentration of drug in the blood plasma.

$D_b$ = (Volume)(Concentration)

$C_b = \frac{D_b}{V_b}$

(V is the apparent volume and does not effect the equation.)

$C_b = C_o\ e^{-(kel)(t)}$

$C_b(o) = C_o$

Where $C_B$ is the concentration in the body

and

where $C_o$ is the initial concentration of drug in the body.

We can then take the natural log of both sides to create a linear equation.

$\ln C_b = \ln C_o - Kel(t)$

log of.

this would be correct if log. graph paper plotted on

If plotted graphically, we can see that the slope of the equation is -Kel and that ln $C_o$ is the concentration intercept.The half life of the drug in the body can be found by setting Cb = 1 and Co = 2. (SEE FIGURE 1)

denoted $t_{1/2}$

$$\ln(1) = \ln(2) - Kel(t)$$

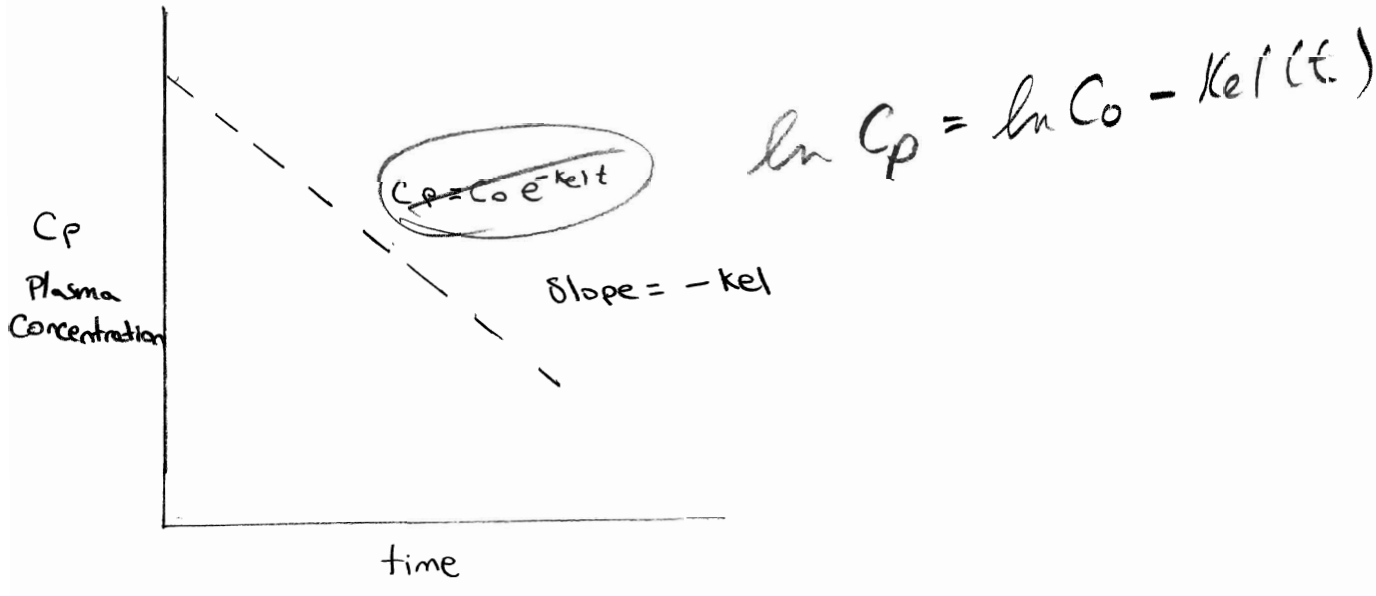
$$\ln\left(\frac{1}{2}\right) = -Kel(t)$$

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

$t_{1/2}$

The half life (T) describes the amount of time it takes for the concentration of drug in the body to reduce to half of its original concentration.

FIGURE 1



Example

ONE COMPARTMENT OPEN MODEL

A person is given an intravenous dose of an antibacterial drug, and blood samples were taken at various time intervals. The concentration of the drug (Cb) was determined in the plasma fraction of each blood sample and the following data was observed.

| Time (hr) | Cb ( g/ml) |
|---|---|
| 0.25 | 8.21 |
| 0.50 | 7.87 |
| 1.0 | 7.23 |
| 3.0 | 5.15 |
| 6.0 | 3.09 |
| 12.0 | 1.11 |
| 18.0 | 0.40 |

(Plotted on graph #1)

It was determined that the concentration of drug in the blood plasma can be found from :

(Comment on the strikingly linearity of the graph).

$$Cb = Co\ Exp(-kt)$$

Cb = blood concentration at time t

Co = intitial drug concentration

k = elimination constant

Co extrapolated from graph is found to be 8.4 g/ml

slope k = ( ln(3.09) − ln(0.40) ) / ( 6 − 18 )

= −0.17 (−0.17037...)

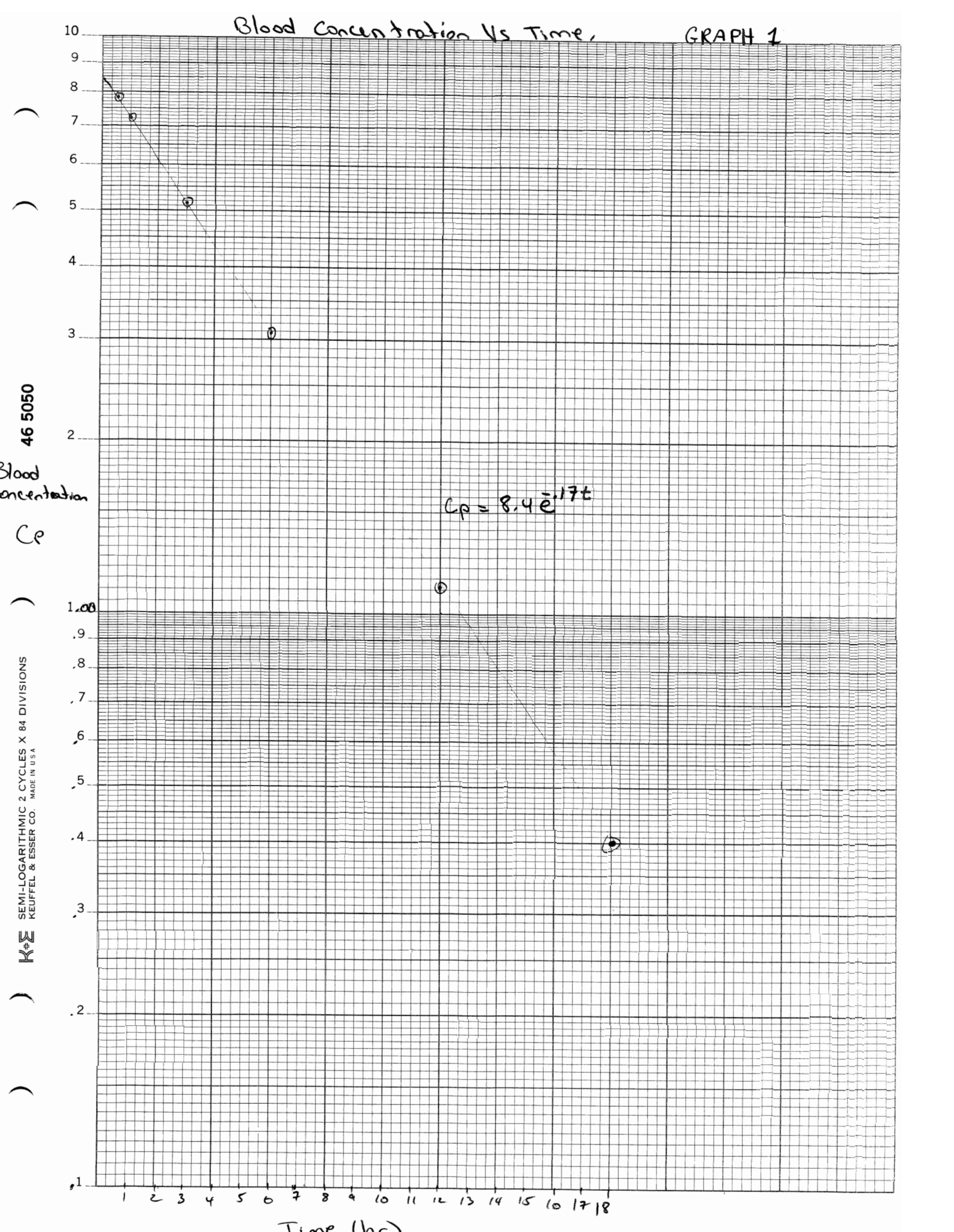
The equation for the curve is given by:

$$Cb = 8.4\ Exp(-0.17*t)$$

1p

Is there a reason why these two data points were used?

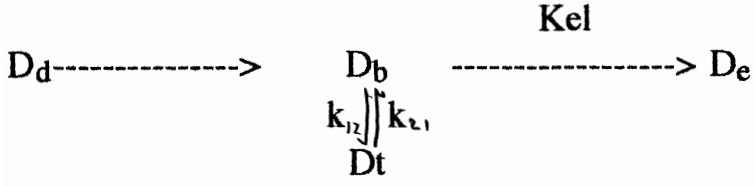
– least-squares fit?


Blood Concentration Vs Time, GRAPH 1
Cp = 8.4 e^-.17t
Blood Concentration
Cp
Time (hrs)
46 5050
SEMI-LOGARITHMIC 2 CYCLES X 84 DIVISIONS
KEUFFEL & ESSER CO. MADE IN U.S.A.

## MULTICOMPARTMENT MODEL

In the single compartment model, it is assumed that the drug in the blood is in complete and rapid equilibrium with the body tissues and that the plasma concentration is proportional to all the drug in the body. If the drug in the plasma is in slower equilibrium with a tissue, as in the case where the tissue has lower blood flow or does not have an affinity to the drug, a model containing two or more compartments is required. It will still be assumed that drug elimination and drug entering into and out of compartments will be first or der processes. The simplest of the multicompartment model is the 2 compartment model which can be represented by:

FIGURE 2




$D_d$ is the amount of drug administered.
$D_b$ is the amount of drug in the ~~body~~ blood
$D_e$ is the amount of drug eliminated

$D_t$ ?

The body is separated into two compartments : the central compartment(Db) which can be represented by the blood plasma and the tissue compartment(Dt). The exchange of drug between the central compartment and the tissue compartment occurs relatively slowly.

Again: why have we changed to concentrations?

$Ct = \frac{Dt}{Vt}$ $\quad$ $Cb = \frac{Db}{Vb}$

where

Where Vt is the volume of blood in the tissue and Vb is the volume of drug in the central compartment.

The rate of change of drug concentration in the blood and in the tissue is:

$\frac{dCt}{dt} = k_{12}Cb - k_{21}Ct$

one of these must be wrong!

$\frac{dCt}{dt} = k_{21}Ct - k_{12}Cb - Kel\ Cb$

(b)

Show details! (math. analysis).

$Cb = Co\left[\frac{k_{21} - a}{b - a}\right] e^{-at} + \left[\frac{k_{12} - b}{a - b}\right] e^{-bt}$

It would be helpful to have explicit formulas for a & b.

$Ct = Co\left[\frac{k_{21}}{b - a}\right] e^{-at} + \left[\frac{k_{12}}{a - b}\right] e^{-bt}$

$k = Kel$

$a + b = k_{12} + k_{21} + k$

$ab = k_2 k$

how?

explain!

Co is the initial concentration in the blood.
t is the time after administration of dose.
a and b are constants that depend solely on $k_{12}$, $k_{21}$, k.
b is the elimination phase constant.
a is the distributive phase constant.

according to next page

$a > b$.

$Cb = A e^{-at} + B e^{-bt}$

where $A = Co\ \frac{(a - k_{21})}{a - b}$

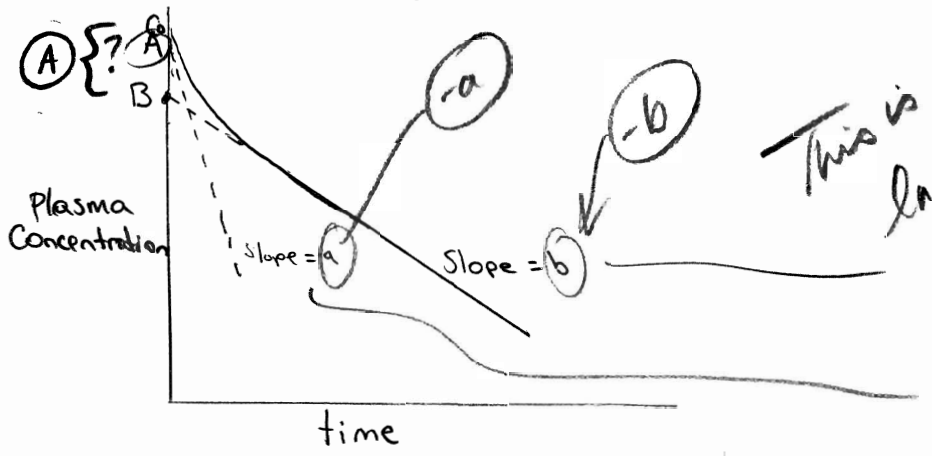
and

where $B = Co\ \frac{(k_{21} - b)}{a - b}$

When Cb is plotted graphically, it will resemble:

$Cb = A\,e^{-at} + B\,e^{-bt}$

FIGURE 3




This is again a ln Cb vs t plot.

this is relatively obvious although not explained well

this is not clear!

B can be found by extrapolation of $Cb = Be^{-bt}$ since as t increases $Ae^{-at} \to 0$ since a > b .

[note $Be^{-bt} \to 0$ as $t \to \infty$ also but more slowly since $a > b$]

$\ln Cb = \ln B - bt$

T can be found from b: $t_{1/2}$.

$\ln Cb = -bt + \ln B$

$\ln(1) = -bt + \ln(2)$ ?

$\ln\left(\frac{1}{2}\right) = -bt$

$\frac{\ln 2}{b} = T_{1/2}$

$C_b = Ae^{-at} + Be^{-bt}$

$C_b(0) = C_0 = A + B$

$A = C_0 - B$

Alternative

$\ln(Cb(t) - Be^{-bt}) = \ln A - at$

slope (-a)

intercept (ln A)

$\ln Cb(t) = \ln(Ae^{-at} + Be^{-bt})$

$\frac{d}{dt}(\ln Cb(t)) = \frac{-aAe^{-at} - bBe^{-bt}}{Ae^{-at} + Be^{-bt}}$

for small t $\frac{d}{dt}(\ln Cb(t)) \simeq \frac{-aAe^{-at}}{Ae^{-at}}$

$\simeq -a$

Example

TWO COMPARTMENT OPEN MODEL

A drug was administered by rapid I.V. injection into a patient. Blood samples were taken over 7 hours and assayed for intact drug. The results are tabulated below.

| time (hr) | Cb ( g/ml) | time (hr) | Cb ( g/ml) |
|---|---|---|---|
| 0.00 | 70.0 | 2.5 | 14.3 |
| 0.25 | 53.8 | 3.0 | 12.6 |
| 0.50 | 73.3 | 4.0 | 10.5 |
| 0.75 | 35.0 | 5.0 | 9.0 |
| 1.00 | 29.1 | 6.0 | 8.0 |
| 1.50 | 21.2 | 7.0 | 7.0 |
| 2.00 | 17.0 | | |

Plotted on semi logorithmic graph paper (graph #2) the slope b is determined.

slope b = ( ln(7) - ln(8) ) / ( 7 - 6 ) = - 0.134

The intersept B is found by extrapolation which is found to be 18.

Therefore

Cb = A Exp (-at) + 18 Exp(-0.134*t)

Taking t = 0

Co = A + 18

A = 70 - 18 = 52

A second line can be found subtracting the extrapolated line from the given data points.

should be explained more carefully

For time t = 1

29.1 − 18 Exp(−0.134*1) = 13.36

for time t = 2

17.0 − 18 Exp(−0.134*2) = 3.23

at $t=0$
$70 - 18\,Exp(-0.134*0)$
$= 70 - 18 = 52$

Now slope a can be determined.

slope a = ( ln(3.23) − ln(52) ) / ( 2 − 0 ) = −1.39

Therefore the equation for the curve is:

Cb = 52 Exp(−1.39*t) + 18 Exp(−0.139*t)

The values for $k_{12}$, $k_{21}$, and k can be found from the rate constants a and b, and from the y intercepts A and B.

Kel

k = ab( A + B ) / ( Ab + Ba )

$k_{12}$ = AB( b − a )^2 / ( A + B )*( Ab + Ba )

$k_{21}$ = ( Ab + Ba ) / ( A + B )

} Show some work.

OK

k = (1.39)(.134)(18 + 52) / (52*.134 + 18*1.39)

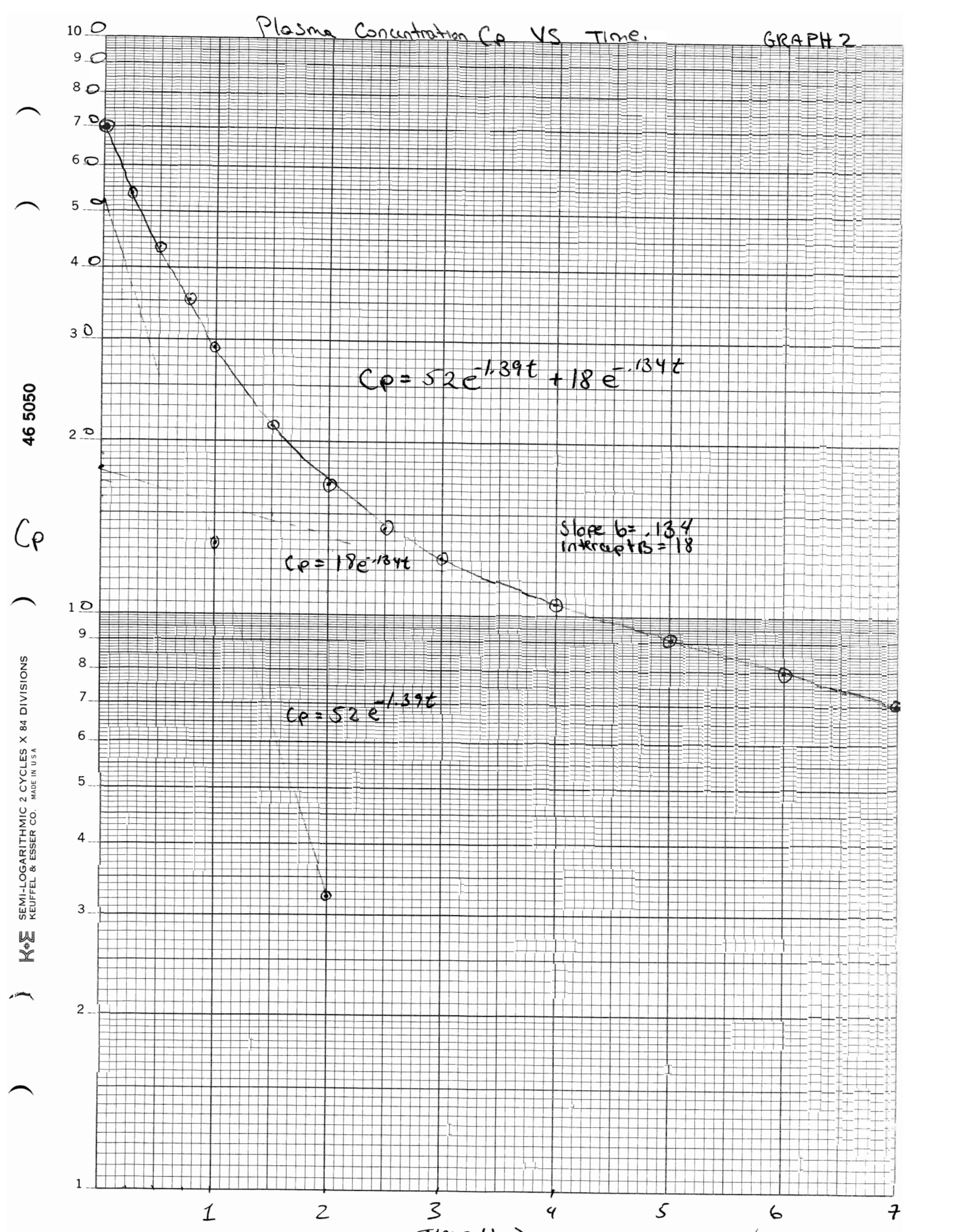
= 0.407/hr

$k_{12}$ = (52)(18)(.134 − 1.39)^2 / (70)(52*.134 + 18*1.39)

= 0.659/hr

$k_{21}$ = ( (52)(.134) + (18)(1.39) ) / (52 + 18)

= 0.456/hr


Plasma Concentration Cp VS Time.
GRAPH 2
$Cp = 52e^{-1.39t} + 18e^{-.134t}$
Slope b = .134
Intercept B = 18
$Cp = 18e^{-.134t}$
$Cp = 52e^{-1.39t}$
Cp
Time (hr)
46 5050
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## MULTIPLE DOSAGE

Often the concentration of a drug in a body must be at a certain level to work effectively. Multiple dosing is one of the methods used to increase the concentration of a drug in a body. An example of this type of drug would be an antibiotic which must maintain a correct plasma level without excessive fluctuation and drug accumulation.

For the one compartment multiple dose model, the prediction of blood plasma levels from time to time is found by using the characterisitcs of a single dose. With the knowledge of dose concentration and time interval between doses it is possible to predict the concentration of the drug in the blood at a later time.

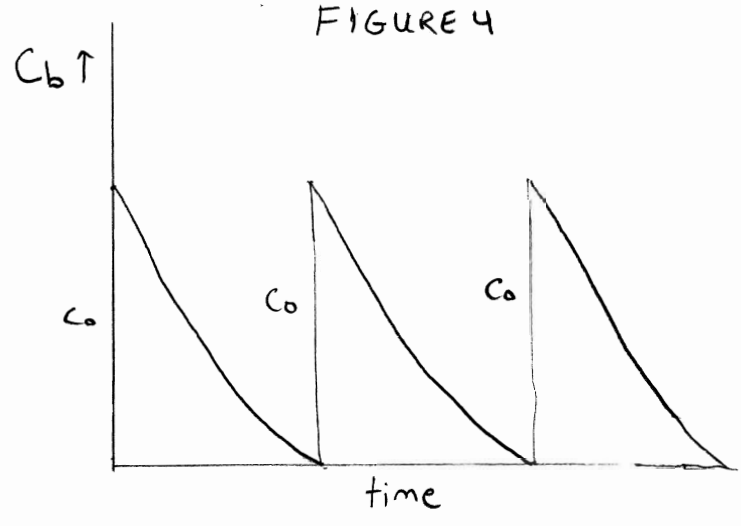
Going back to the one compartment model for a single dose, it can be seen that the concentration in the blood decreases with time(This model deals with what happens to the blood concentration if the drug is given at regular intervals.)

The single dose can be described by the equation:

$Cb = Co\, e^{-kt}$, $k > 0$ and k is the elimination constant

If the time interval is long enough to let concentration in the blood to drop to zero before administering another dose, it can be seen that the graph would resemble:

FIGURE 4




The height of each peak is the concentration of each dose.

If H is the highest safe level and L is the lowest effective level , the concentration of Co should be chosen to fall in between these two levels such that Co = H - L for a single dose.

FIGURE 5

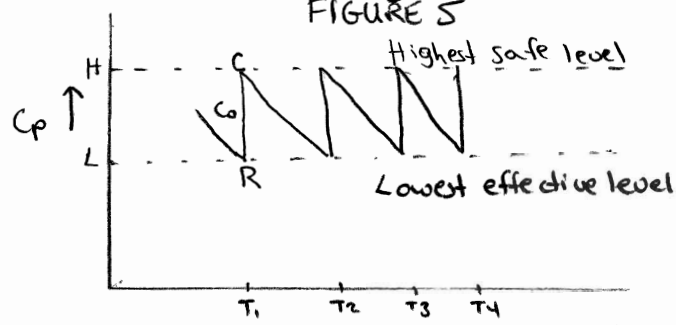



diagram is not completely realistic !

The level at which the next dose is administered is the residual level.

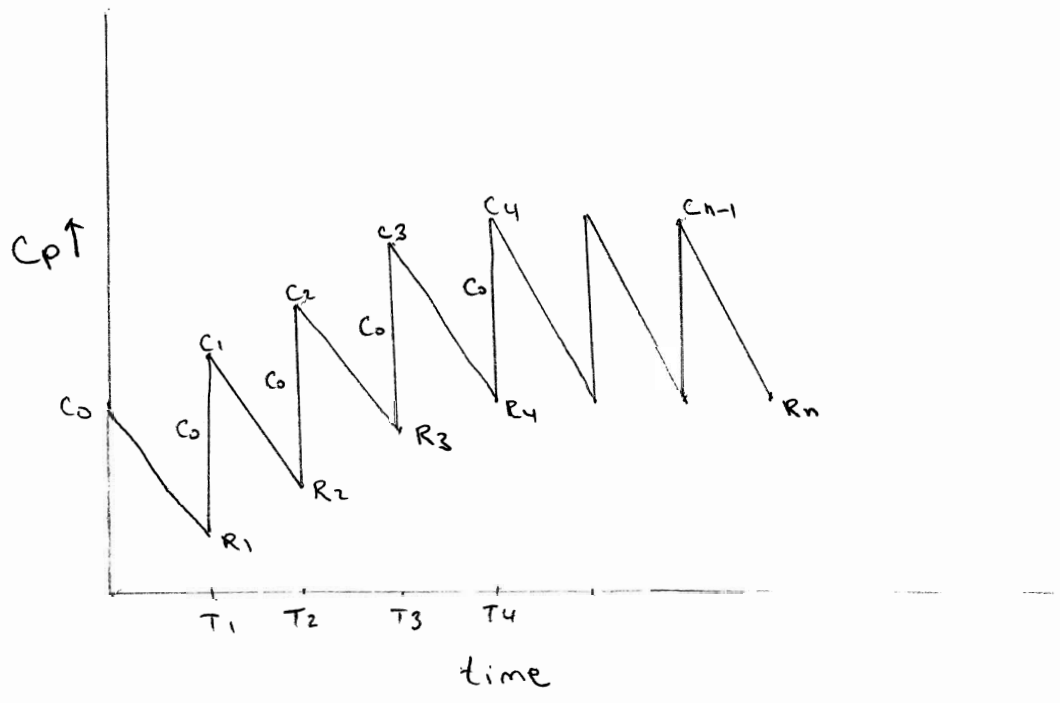
## DRUG ACCUMULATION (REPEATED DOSES)

Taking a look at what happens to Cb after administration of a drug, it can be seen that the concentration of the blood will jump by Co, and after a certain fixed time T, Cb will have fallen to a new level. The first residual $R1 = Co\ e^{-kT}$, this level is what remains in the blood after time T.

At time T1, a following dose is administered and Cb will be $C1 = Co + Coe^{-kT}$. After time T, R2 becomes $Co(Co + Coe^{-kT})e^{-kT}$

This type of accumulation is determined after each dose. This can be seen by the figure below.

FIGURE 6




Table

$C_0 = C_0$

$C_1 = C_0 + C_0 e^{-kT}$

$C_2 = C_0 + (C_0 + C_0 e^{-kT}) e^{-kT}$

$C_{n-1} = C_0 + C_0 e^{-kT} + \dots + C_0 e^{-(n-1)kT}$

$R_1 = C_0 e^{-kT}$

$R_2 = (C_0 + C_0 e^{-kT}) e^{-kT}$

$R_3 = (C_0 + C_0 e^{-kT} + C_0 e^{-2kT}) e^{-kT}$

$R_n = C_0 e^{-kT} + C_0 e^{-2kT} + \dots + C_0 e^{-nkT}$

From the table we can see that:

$$Rn = Co\ Exp(-kT) + Co\ Exp(-2kT) + \ldots + CoExp(-nkT)$$

$$= Co\ Exp(-kT) * ( 1 + Exp(-kT) + \ldots + Exp(-(n-1)kT) )$$

sum of a finite geometric series

Knowing the equality

$$1 + r + r^2 + \ldots + r^{(n-1)} = ( 1 - r^n ) / ( 1 - r )$$

The equation for the residual concentration after n doses can be written as :

$$Rn = Co\ Exp(-kT) * ( 1 - Exp(-nkT) ) / ( 1 - Exp(-kT) )$$ ✓

The residual gives the blood concentration before the next dose is administered.

n = Number of doses administered

T = Length of time between doses

k = elimination constant

Co = concentration of each dose

We can then find the limiting value for the drug by determining Rn as n increases to infinity.

$$R = \lim Rn = Co\ Exp(-kT) / (1 - Exp(-kT) )$$ ✓

$$= Co / ( Exp(kT) - 1 )$$ ✓

Since R is the limiting value, it can be said that

R = L when n goes to infinity

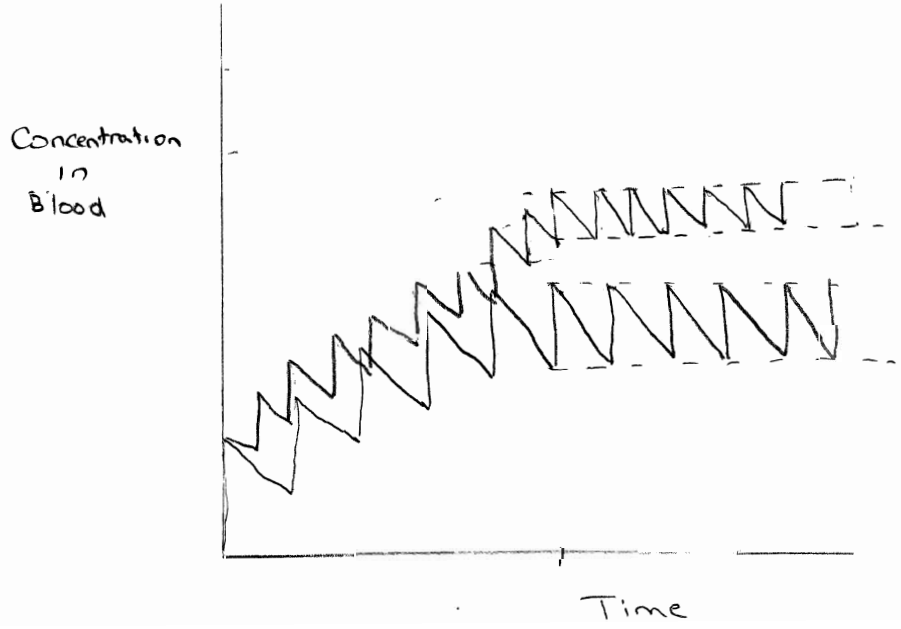
Therefore:

Co = H − R ——— obviously Co must be less than H-L & R ≥ L so Co must be less than H-R (not equal to it!

If we look at R = Co / ( Exp (kT) - 1 ) . The equation show that the accumulation measured with R is dependant on the elimination constant and the dose interval, and is independant of the dose concentration. It can then be assumed that if an intravenous drug is given repeatedly, the time required to reach a steady state is dependant on the half life of the drug, and is independant of the drug concentration, length of dose interval, and number of doses.

For example, if a drug dose interval is altered, the time required to reach a steady state is the same for the altered and unaltered condition. Howerver the level of the steady state will change proportionally.

FIGURE 7



To determine the time interval between drug doses for a fixed concentration that must meet High and Low specifications, the equation for the limiting value is used.

$R = Co / ( Exp(kT) - 1 )$

Let $Co = H - L$ ——— not possible $Co < H-L$.

$L = R$

Then

$L = ( H - L ) / ( Exp(kT) - 1 )$

$( Exp(kT) - 1 ) = ( H - L ) / L$

$= ( H/L ) - 1$

$Exp(kT) = H/L$

$kT = ln(H/L)$

$$T = ln(H/L) / k$$

T = length of time interval

H = highest safe concentration level

L = lowest effective concentration level

k = elimination constant

Example of muliple dosing (A)

ONE COMPRTMENT OPEN MODEL

It can be seen that the characteristic of the drug concentration in the blood plasma is given by the equation:

Cb = 8.4 Exp(-.17*t)

It is possible to find the concentration of a drug in the blood by determining the residual level at each dose interval.

Rn = Co Exp(-kT) * ( 1 - Exp(-nkT) ) / ( 1 - Exp(-kT) )

If we wanted to find the curve of the blood plasma concentration of a patient who received 6 doses of 8.4 g/ml every 4 hours.

R1 = 8.4 Exp(-.17*4) = 4.26

C1 = 8.4 + 4.26 = 12.66

R2 = 8.4 Exp(-.17*4)*(1-Exp(-2(.17)(4))/(1-Exp(.17(4))

= 6.42

C2 = 8.4 + 6.42 = 14.62

R3 = 7.51 C3 = 8.4 + 7.51 = 15.91

R4 = 8.07 C4 = 8.4 + 8.07 = 16.47

R5 = 8.35 C5 = 8.4 + 8.35 = 16.75

R6 = 8.48 C6 = 8.4 + 8.48 = 16.88

(Plotted on graph #3)

As the number of doses approaches infinity, the residual level will equal 8.63 g/ml.

Therefore L = 8.63 g/ml

and H = Co + L = 8.4 + 8.63 = 17.03 g/ml

Find the time between interval of drug dose such that the patients blood concentration has a low limit of 15 g/ml.

$H = Co + L$

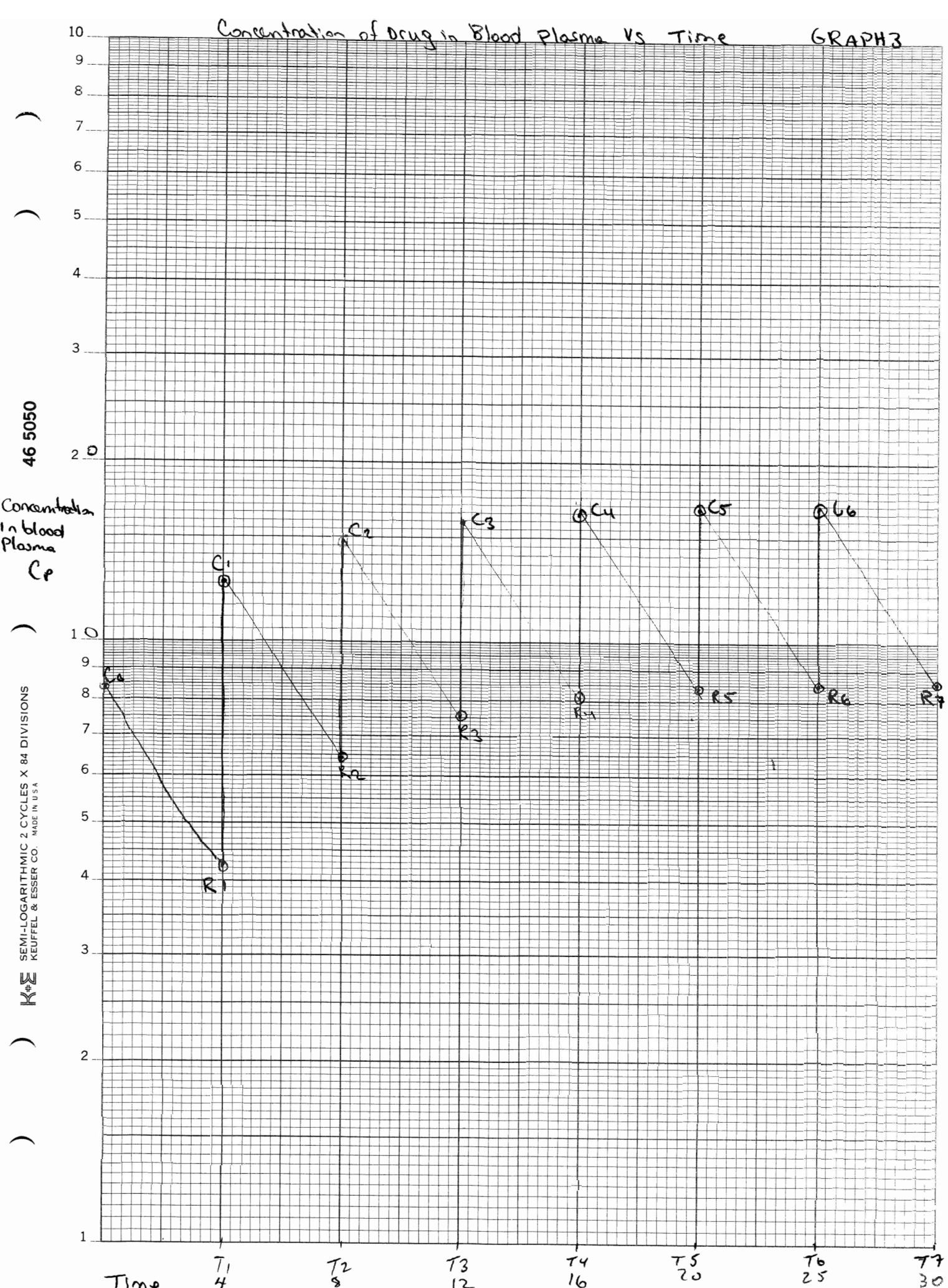
$= 8.4 + 15 = 23.4$

The length of time between drug doses can be determined from:

$T = \ln(H/L) / k$

$= \ln(23.4/15) / .17 = 2.61$ hrs

The dose of 8.4 g/ml is administered ever 2.61 hrs to raise the concentration in the blood to specified levels.


Concentration of Drug in Blood Plasma Vs Time
GRAPH3
46 5050
Concentration in blood Plasma Cp
10
9
8
7
6
5
4
3
2
1
C0
C1
C2
C3
C4
C5
C6
R1
R2
R3
R4
R5
R6
R7
T1 4
T2 8
T3 12
T4 16
T5 20
T6 25
T7 30
Time
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Though the models that were discussed are the simple cases, they can be improved apon to make the models more realistic to the workings of the body. An example of this would be to include elimination of the drug from places other than the central compartment. A multi compartment model can be created to determine the concentration of drug in the tissue compartments as well as in the blood for oral drugs instead of intravenous drugs, this would have more of a cascade affect. A model can also determine the multi dosing effect on body tissue as well blood plasma for multi compartments. There are many improvements that can be done on the examples that were given, and they all have some importance to clinical medicine.

meaning?

## END NOTES

1. Pharmacokinetics, Gibaldi, Milo. p. 1.

Example 1. Applied Biopharmaceutics and Pharmacokinetics, Shargel, Leon. p. 47. Question 2.

Example 2. Ibid., p. 64. Question 1.

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