The learning tools used by this instructor in a pharmacokinetics course offered to entry level PharmD students are presented for the topic of relationship among pharmacokinetic parameters. These tools consist of specific outcomes/objectives, a reading handout, a practice problem as a focus of in-class discussion, several online web-based computer simulation modules, a take-home online assignment similar to the in-class practice problem, and an online in-class quiz. Except for the quiz questions, students are provided with all the tools in advance of the class sessions for this topic and are expected to attend the class prepared to discuss the practice problem. The class time is then devoted to the discussion of the problem and simulations by both the instructor and students, with minimal didactic lecturing. The students will take a quiz at the end of the class and submit the online assignment by midnight of the day the class is held.

**Keywords:** pharmacokinetics, clearance, volume of distribution, elimination half-life, elimination rate constant

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**INTRODUCTION**

Clearance (CL) and volume of distribution (V) are 2 major pharmacokinetic parameters that influence the shape of the plasma concentration-time profile of drugs after different routes of administration. The CL and V of drugs represent distinct processes in the body (elimination and distribution, respectively), which are independent of each other. However, a third parameter, elimination half-life ($t_{1/2}$) (or rate constant, k), is a reflection of the extent of both distribution and elimination, thus depending on both CL and V. There is a mathematical relationship among these 3 parameters, which allows estimation of the third parameter when the other 2 are known. However, the use of this equation without a complete understanding of the physiological relationship among these parameters and their interdependency may result in erroneous estimation of CL or V when there is a change in the kinetics of the drug. The materials presented in this article are learning tools that this instructor uses in a pharmacokinetics course to facilitate student learning of this concept. All the tools are designed based on the assumption of one-compartment linear kinetics.

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**EDUCATIONAL ENVIRONMENT**

Pharmacy 2340 (Clinical Pharmacokinetics) is a 3-credit-hour course that is offered during the fall semester of the second year of the PharmD program at Texas Tech. The class meets 2 times a week (75-minute sessions) for the entire semester. The course follows an introduction to pharmacokinetics taught within the Principles of Drug Action course during the spring semester of the first year. Pharmacy 2340 starts with compartmental analysis, develops into the physiological analysis, and ends up with clinical applications of pharmacokinetics. Throughout the entire course, the main emphasis is on the use of pharmacokinetic principles in the design and modification of dosage regimens. This course is followed by several pharmacotherapeutic courses in which clinical pharmacokinetics of specific drugs are integrated with pathophysiology, pharmacology, and pharmacotherapy of different diseases. The format of the course, which follows a quasi problem-based approach with heavy use of technology and active learning, has been discussed in a previous publication. Briefly, students are provided with detailed notes and examples about each topic well ahead of its discussion in class (usually 2 weeks, minimum of 1 week). In addition, for each topic, one or more practice problems covering all the desired outcomes are designed and distributed to students. The students are expected to work on these problems before attending the class, consulting the provided notes and examples. The class time is then centered on the solu-
tions to these problems and computer simulations, rather than on didactic teaching. All students have their own laptop computers and internet access during the session. During the last 10 minutes of each 75-minute session, the students take an online quiz related to the material covered in that session. Additionally, an online, interactive assignment, similar to the problem covered in class, is due at midnight of the same day the topic is covered in class. In 2003, a class of 78 students completed 28 quizzes, 18 assignments, and 5 examinations. The online interactive assignments, quizzes, and examinations have been developed by the instructor and described in detail before.2,3

The topic of “The Relationship Among Pharmacokinetic Parameters” is covered early in the course in one session following the coverage of the pharmacokinetics of intravenous (IV) and oral (PO) dosing and constant IV infusion.

OUTCOMES AND OBJECTIVES OF THE TOPIC

The desired outcomes and objectives of the session, which are posted online for students, are listed below.

Expected Outcomes

1. Understand the physiological (as opposed to mathematical) relationship among major kinetic parameters (volume of distribution, clearance, and half-life).
2. Predict the effects of alterations in major pharmacokinetic parameters (volume of distribution and clearance) or dose on the plasma concentration-time profiles of drugs after their administration through IV bolus, PO, and constant IV infusion methods.

Specific Objectives

1. What is the mathematical relationship among CL, V, and elimination t½ (or k)?
2. What is the physiological relationship among CL, V, and elimination t½ (or k)?
3. What are the effects of a change in the CL of a drug on its major kinetic parameters (V and t½) and plasma concentration-time course [concentration immediately after IV bolus injection (C0), maximum concentration after PO dosing (Cmax), steady-state concentration after IV infusion (CSS), time to reach CSS (TSS), and/or area under the plasma concentration-time curve (AUC)] after IV bolus, PO, or constant IV administration?
4. What are the effects of a change in the V of a drug on its major kinetic parameters (CL and t½) and plasma concentration time course (C0, Cmax, CSS, TSS, and/or AUC) after IV bolus, PO, or constant IV administration?
5. What are the effects of a change in the administered dose or infusion rate (R0) on the major kinetic parameters (CL, V, t½) and plasma concentration-time profile (C0, Cmax, CSS, TSS, and/or AUC) of drugs after IV bolus, PO, or constant IV administration?

READING HANDOUT

The following material is provided to students as a reading assignment that must be completed before attending the class session for the discussion of the topic. Additionally, other readings from suggested textbooks serve as optional reading assignments. The equations and a majority of introductory concepts presented in the reading handout may be found in most pharmacokinetics textbooks.4,5

Mathematical Relationship Among Pharmacokinetic Parameters

Clearance (CL), volume of distribution (V), and elimination rate constant (k) are important kinetic parameters that influence the plasma concentration-time courses of drugs after all routes of administration. The mathematical relationship among these 3 parameters is defined by the following equation:

\[ \text{CL} = k \cdot V \]  

If 2 of these parameters are known, the third can easily be estimated from the above equation. However, the use of equation 1 without an understanding of the underlying physiological relationship among these 3 parameters may result in erroneous conclusions. This is because the 3 parameters in the above equation are not equal. Whereas V and CL are independent parameters, k (or t½) is a parameter that is dependent on both V and CL. This is explained in more detail in the following section, and an example is provided.

Physiological Relationship Among Pharmacokinetic Parameters

Clearance of drugs in humans is dependent on certain physiological parameters of the subject and physicochemical properties of the drug. For a particular drug, clearance varies among different subjects because each subject may exhibit different physiological parameters.
For example, metabolic clearance of drugs by the liver is dependent on the hepatic blood flow, degree of protein binding of the drug in blood, and the intrinsic capability of the liver enzymes to metabolize the drug. If one or more of these parameters are changed in a patient because of disease states, interacting drugs, or environmental factors, the clearance of the drug in the patient may change. For instance, rifampin induces the liver enzymes responsible for the metabolism of warfarin. Therefore, in the presence of rifampin, the hepatic clearance of warfarin significantly increases.

The extent of distribution of drugs, however, is independent of their clearance. Therefore, a change in the clearance of a drug does not necessarily alter the drug distribution. Indeed, an increase in the clearance of warfarin because of enzyme induction by rifampin did not affect the volume of distribution of the drug. Similar to clearance, the distribution is dependent on certain physiologic parameters of the patient and physicochemical properties of the drug, such as tissue perfusion, permeability of tissues to drugs, plasma and tissue binding, and the volume of body water. Therefore, a change in any of these parameters resulting from interacting drugs, disease states, and/or age, may affect the volume of distribution of the drug independent of what may or may not happen to its clearance. For example, the volume of distribution of gentamicin is reduced in patients with sepsis who are dehydrated. However, the renal function and the clearance of gentamicin may be normal in these patients. Therefore, clearance and volume of distribution are independent of each other and one may change in the absence of a change in the other.

In some situations, it is possible that both major kinetic parameters (clearance and volume of distribution) change simultaneously. However, the changes in V and CL are independent of each other and because of the underlying mechanism(s) that affect both processes. Examples of such cases are given later in this note.

In contrast to CL and V, which signify certain physiological processes, the elimination half-life (or rate constant) does not represent any independent process by itself and is influenced by both the distribution and elimination processes. An increase in clearance (elimination efficiency) results in a reduction in the half-life (an increase in k). This is easy to understand because the more efficient the elimination pathway, the faster is the decline in the plasma concentrations. An increase in V, however, results in prolongation of half-life (a decrease in k). This is because an increased V results in a more extensive distribution into the tissues, where the drug is safe from elimination. However, because the distribution is a reversible process, as the drug gets eliminated from the blood and the blood concentrations decline, the drug in the tissue will redistribute to the blood, resulting in a more sustained blood level (increased \( t_{1/2} \) or reduced k).

Therefore, the half-life is dependent on both the clearance and volume of distribution. A better way of presenting the relationship among these 3 parameters is:

\[
t_{1/2} = \frac{0.693V}{CL} \tag{2}
\]

or

\[
k = \frac{CL}{V} \tag{3}
\]

The above equations correctly imply the dependence of half-life (or k) on both V and CL. Whereas there is a direct relationship between V and \( t_{1/2} \), the opposite is true for the relationship between \( t_{1/2} \) and CL.

Example. The volume of distribution (V) and elimination rate constant (k) of an antibiotic in a patient with sepsis are 12 L and 0.60 hr\(^{-1}\), respectively. What is the clearance (CL) of the drug in the patient? During the course of therapy with the antibiotic and after appropriate hydration, V is increased to 18 L. What are the CL and k values at this point?

Using Equation 1, one may estimate CL at the beginning of therapy because the other 2 parameters (k and V) are known:

\[CL = k \cdot V = 0.6 \times 12 = 7.2 \text{ L/hr or 120 mL/min}\]

However, the use of Equation 1 to estimate CL when V is changed to 18 L could result in an erroneous value if there is a lack of understanding of the relationship among these 3 kinetic parameters:

\[CL = k \cdot V = 0.6 \times 18 = 10.8 \text{ L/hr or 180 mL/min}\]

The above calculation is incorrect because it assumes that when V is increased as a result of hydration, there is no change in the \( t_{1/2} \) (1.16 hr) or k (0.60 hr\(^{-1}\)) of the drug. Indeed, because \( t_{1/2} \) or k is dependent on the changes in CL or V, an increase in V by a factor of 1.5 (12 to 18 L) results in a similar increase (1.5 fold) in \( t_{1/2} \) (from 1.16 to 1.73 hr) or decrease in k (from 0.60 to 0.40 hr\(^{-1}\)) as predicted by Equations 2 and 3, respectively, without any inherent effect on CL:
Therefore, if one desires to use Equation 1 for estimation of CL in the presence of increased V, one has to first account for the change in k (from 0.60 to 0.40 hr\(^{-1}\)) due to an increased V:

\[
\frac{CL}{V} = \frac{7.2 \text{ L/hr}}{18 \text{ L}} = 0.40 \text{ hr}^{-1}
\]

Consequently, a change in V does not result in a change in CL by itself. However, as mentioned above, there are situations that may result in alteration of both parameters simultaneously.

The clinical consequences of overestimation of CL in the above example may be significant. This is because the maintenance doses of drugs are directly related to the estimated CL. Therefore, a 50% overestimation of CL in the above example may result in 50% overestimation of the maintenance dose and possible toxicity.

If the patient-specific plasma concentration-time data were available when V was increased in the above example, k and V could be directly obtained from these data. In these cases, the change in V would be reflected in the k obtained from the actual data. Therefore, estimation of CL from Equation 1 would result in a correct answer in such cases. However, the problem arises when one desires to predict changes in the kinetic parameters and drug plasma concentrations as a result of a change in CL and/or V in the absence of plasma concentration-time data (eg, above example). In these cases, understanding the relationship among CL, V, and \(t_{1/2}\) (or k) becomes crucial in accurate estimation of these kinetic parameters.

**Alterations in Clearance**

Clearance of drugs may be altered due to different disease states (eg, liver cirrhosis or renal dysfunction), aging (eg, reduced renal function in elderly), drug interactions (eg, reduction of hepatic clearance of theophylline due to coadministration of erythromycin), or environmental factors (eg, increase in the clearance of theophylline in cigarette smokers). As mentioned above, a change in CL does not necessarily affect V. However, the elimination \(t_{1/2}\) changes in inverse proportion to CL. This means an increase in CL would result in a proportional decrease in half-life and vice versa. In the following examples, the effects of an increase in the clearance on the plasma concentration-time profiles of drugs are demonstrated for different methods and/or routes of administration.

**IV bolus administration.** In order to determine the effect of a change in CL on the plasma concentration-time profile after IV bolus dosing, one can determine the following parameters in the presence of altered CL:

1. **Concentration at time 0** \(C_0\): This parameter is not dependent on clearance because there is no elimination at time 0. It only depends on the magnitude of the dose and the extent of drug distribution:

\[
C_0 = \frac{\text{Dose}}{V}
\]

Therefore, a change in CL would not affect \(C_0\).

2. **Half-life** \(t_{1/2}\): As mentioned above, \(t_{1/2}\) and CL are inversely related:

\[
\left(\frac{0.693V}{CL}\right)
\]

Therefore, an increase in CL would result in a proportional decrease in \(t_{1/2}\), while a decrease in CL prolongs \(t_{1/2}\).

3. **Area under the plasma (blood) concentration-time curve** (AUC): This parameter is directly dependent on the extent of input (dose) and inversely related to the output (elimination or CL), as described by the equation:

\[
\text{AUC} = \frac{\text{Dose}}{CL}
\]

Therefore, an increase in CL would result in a proportional decrease in AUC, while a decrease in CL increases AUC.

Therefore, for example, if the CL of a drug is increased by a factor of 2, \(C_0\) remains the same, \(t_{1/2}\) decreases by a factor of 2, and AUC declines by a factor of 2 as demonstrated in Figure 1.

**Oral administration.** Similar to the IV bolus injection, an increase in CL results in a shortening of \(t_{1/2}\) after PO dosing (Figure 2):

\[
\left(\frac{0.693V}{CL}\right)
\]

Additionally, the AUC will decline proportionally, assuming that the fraction of the dose reaching the systemic circulation (F) does not change:

\[
\text{AUC} = \frac{F \cdot \text{Dose}}{CL}
\]

There are situations where a change in CL is also
associated with a change in F. These situations are discussed in detail under “Clearance Concepts” in this course. However, for the purpose of this paper, we will assume that a change in CL does not affect F. In contrast to the IV bolus case, in which the maximum concentration (Cmax) was not dependent on CL, the maximum concentration after the oral dose (Cmax) is somewhat affected by CL. This is because, depending on the speed of oral absorption, Cmax occurs some time (Tmax) after the oral dose. Therefore, during the time that plasma concentration is rising, the elimination process is also occurring, resulting in lowering Cmax compared with C0 after the IV administration of the same dose. Consequently, the effect of an increase in CL on Cmax (Figure 2) is dependent on Tmax; the shorter the Tmax, the lesser is the effects of a change in CL on the magnitude of Cmax.

Constant IV infusion. A change in CL would inversely impact both the magnitude of the steady state (CSS) and the half-life (Figure 3). Additionally, a change in the half-life, because of a change in clearance, would affect the time to reach steady state (TSS). For example, a twofold increase in CL causes a twofold decrease in CSS:

\[ CSS = \frac{P_0}{CL} \]

and half-life:

\[ t_{1/2} = \frac{0.693V}{CL} \].

Because TSS is dependent on the half-life (eg, 94% of steady state is achieved after 4 t1/2’s), the decrease in t1/2 will be reflected in a proportional decrease in TSS (Figure 3).

Alterations in Volume of Distribution

Volume of distribution of drugs may be altered due to different disease states (eg, reduced V of aminoglycosides in sepsis), aging (eg, increased V of phenobarbital in neonates), or drug interactions (eg, reduction of V of digoxin due to co-administration with quinidine). As mentioned above, a change in V does not necessarily affect CL. However, the elimination t1/2 changes in direct proportion to V. In the following examples, the effects of an increase in the volume of distribution on the plasma concentration-time profiles of drugs are demonstrated for different methods and/or routes of administration.

IV bolus administration. In order to determine the effect of a change in V on the IV plasma concentration-time profile, one can determine the following parameters in the presence of altered V:

- Concentration at time zero (C0): As mentioned above, C0 is dependent on dose and V

\[ C_0 = \frac{Dose}{V} \].

Therefore, a change in V would inversely affect C0.

- Half-life (t1/2): As mentioned above, t1/2 and V are directly related.

- Area under the plasma (blood) concentration-time curve (AUC): This parameter is not affected by V and is related only to CL and the avail-

![Figure 1. The effects of a two-fold increase in the clearance of a drug on its plasma concentration-time profile after the intravenous bolus administration of the drug. The kinetic parameters used for simulation are CL of 1.16 L/h and V of 10 L for the “Normal CL” scenario. CL was increased to 2.32 L/h for the “Increased CL” scenario.](image1)

![Figure 2. The effects of a two-fold increase in the clearance of a drug on its plasma concentration-time profile after the oral administration of the drug. The kinetic parameters used for simulation are CL of 1.16 L/h, V of 10 L, absorption rate constant of 1 hr⁻¹, and F of 1 for the “Normal CL” scenario. CL was increased to 2.32 L/h for the “Increased CL” scenario.](image2)
able dose in the systemic circulation. As demonstrated by Equation 4, a change in V would affect the plasma concentrations (C) at any time point (t), thus affecting the plasma concentration-time profile of the drug:

\[ C = \frac{Dose}{V} e^{-\frac{CL}{V}t} \]  

(4)

However, the overall AUC remains unchanged (see below for explanation).

Therefore, for example, if the V of a drug is increased by a factor of 2, C0 declines by a factor of 2, t\(\frac{1}{2}\) increases by a factor of 2, and AUC remains the same as demonstrated in Figure 4.

The lack of effect of V on AUC is perhaps one of the hardest concepts to understand because one knows that a change in V causes a change in C0 and concentrations at any other time after the drug injection (Equation 4). Therefore, the question becomes why changes in plasma concentrations do not lead to a change in the AUC. The answer is that an increase in V, for example, causes a proportional decrease in C0, because the dose is distributed into a larger volume, while simultaneously causing a decline in the slope of the log of plasma concentration-time profile, because of a decrease in k or an increase in t\(\frac{1}{2}\) (Figure 4). Therefore, an increase in V causes a decrease in C (lower AUC) at early time points, whereas C values at later points are higher (higher AUC), compared with the C values observed with normal V (Figure 4). Consequently, there is no net change in the total AUC.

**Oral administration.** As demonstrated in Figure 5, the effects of an increased V on t\(\frac{1}{2}\) and AUC values after PO administration are similar to those after the IV bolus injection (lower C\(_{\text{max}}\), longer t\(\frac{1}{2}\), and similar AUC).

**Constant IV infusion.** A change in V would inversely alter the plasma concentrations of the drug at any time before reaching the plateau (Figure 6). However, the magnitude of the steady state (C\(_{\text{ss}}\)) is not affected by a change in V; C\(_{\text{ss}}\) is dependent only on the infusion rate and CL:

\[ C_{ss} = \frac{R_0}{CL} \]

Additionally, because the half-life responds in a direct manner to a change in V, T\(_{ss}\) is also affected by situations that result in altered V. For example, an increase in V would result in lower C before reaching steady-state and a longer T\(_{ss}\) without changing C\(_{ss}\) (Figure 6).

**Simultaneous Alterations in Clearance and Volume of Distribution**

As mentioned above, in some situations both major kinetic parameters (clearance and volume of distribution) change simultaneously. For example, acute trauma causes an increase in the plasma levels of \(\alpha_1\)-acid glycoprotein, which is responsible for binding to many basic drugs in plasma, resulting in a reduction in the free fraction of these drugs in blood. A reduction in the free fraction of the drug could potentially reduce both its extent of distribution (V) and elimination (CL), as reported for morphine. However, the degree by which the V or CL...
is affected depends on whether the drug is considered as having a high or low V or CL in normal subjects. This issue is the subject of detailed discussions later in the course when the physiological determinants of CL and V are discussed.

The CL and V may also be altered in opposite directions. For example, liver diseases, such as cirrhosis, simultaneously reduce the CL and increase the V of a number of drugs such as diazepam.10 This is because of multiple pathophysiological effects of liver diseases, including reductions in the metabolic activity of hepatocytes (responsible for the metabolism of drugs) and synthesis of albumin (responsible for the binding of many drugs in blood). Nevertheless, depending on the situation, the CL and V of a drug may change in the same or opposite directions. As stated above, the net result of changes in the CL and V on the half-life is dependent on the magnitude and direction of changes in both CL and V.

**Alterations in Dose**

In first order (or linear) pharmacokinetics, the major kinetic parameters (CL, V, and \( t_{1/2} \)) are dose- and route-independent, ie, they remain the same no matter what dose is administered or whether the drug is administered orally or intravenously. Furthermore, linear pharmacokinetics means that the plasma concentrations of drugs are linearly related to their dose at all the points after the drug administration, regardless of the route of administration. Therefore, \( C_0 \), \( C_{\text{max}} \), or \( C_{\text{SS}} \) will change in direct proportion to the changes in the administered dose (or infusion rate) as demonstrated in Figure 7. Because the concentrations at any time change, the AUC will also be proportional to the administered dose.

**Alterations in Other Kinetic Parameters**

In additions to the changes in CL and/or V, other kinetic parameters such as the extent (F) and rate (absorption rate constant) of drug entry into the systemic circulation will affect the plasma concentration-time courses of drugs after extravascular dosing (eg, oral). These changes are discussed in detail under the topic of “Bioavailability and Bioequivalence” in this course. However, for completeness they are briefly mentioned here. Whereas a change in F is analogous to a change in dose described above (Figure 7, middle panel), an altered absorption rate constant will result in a direct change in \( C_{\text{max}} \), inverse change in \( T_{\text{max}} \), and no effect on AUC. For example, an increase in the absorption rate constant (ie, faster absorption) will result in a higher \( C_{\text{max}} \), lower \( T_{\text{max}} \), and no change in AUC. The lack of change of AUC is because this parameter is dependent only on the available dose (F x Dose) and CL:

\[
\text{AUC} = \frac{F \cdot \text{Dose}}{\text{CL}}.
\]

Therefore, the rate of absorption does not affect AUC under linear kinetics.

**Multiple Dose Administration**

In terms of mode of administration, the focus of this handout has been IV and PO single dose administration...
and constant IV infusion. However, the interrelationship among CL, V, and t½ (or k), and the effects of alterations in CL or V on the plasma concentration-time courses after multiple dosing, are similar to those after the single dose administration. This topic is covered in more detail during 2 sessions on the Kinetics of Multiple Dosing.

Practice Problem and Simulations
As mentioned under Educational Environment section, the focus of the class session is the discussion of a practice problem (Appendix 1), which covers all the desired outcomes and objectives. Additionally, for this topic, the author has developed a series of online modules that simulate the effects of alterations in the kinetic parameters and/or dosage regimen parameters on the other kinetic parameters and the plasma concentration-time profiles. As for kinetic parameters, the modules are designed in a way that students can alter CL and/or V but not t½ or k; the latter of which is calculated by the program. Therefore, if students want to see a change in t½ or k, they must first change CL and/or V. This emphasizes the major point of this session, that t½ or k is dependent on CL and V.

REFERENCES

Figure 7. The effects of a two-fold increase in the dose or infusion rate of a drug on its plasma concentration-time profile after intravenous bolus (top), oral (middle), and constant intravenous infusion (bottom) administration of the drug. The kinetic parameters used for simulation are CL of 1.16 L/h, V of 10 L, absorption rate constant of 1 hr⁻¹, and F of 1. The dose or infusion rate constant was doubled for the “Increased Dose” or “Increased Infusion Rate” scenarios. TSS indicates the time to reach 94% of steady state (ie, 4 t½’s).
Appendix 1. Practice Problem

The volume of distribution and elimination rate constant of a drug are 23 L and 0.14 hr\(^{-1}\), respectively.

(1) What is the clearance of the drug?
   The drug is administered along with valproic acid, which increases the volume of distribution of the drug by a factor of 2 to 46 L.

(2) What is the clearance of the drug in the presence of valproic acid?
(3) What are the elimination rate constant and half-life of the drug in the presence of valproic acid?
(4) What is the effect of valproic acid on the plasma concentration of the drug at time zero \((C_0)\) (assume an IV bolus dose of 230 mg is administered in the presence and absence of valproic acid)?
(5) What is the effect of valproic acid on the plasma AUC of the drug?
(6) Please draw, on a semilogarithmic graph, the plasma concentration-time profiles of the drug (from zero to 24 hr) in the presence and absence of valproic acid.

(7) How does a two-fold increase in the volume of distribution affect the plasma concentration-time profiles of the drug after PO dosing and constant IV infusion?
   It is reported that phenobarbital induces the metabolism of the drug, thereby, increasing its clearance by a factor of two to 6.4 L/hr.

(8) What is the volume of distribution of drug in the presence of phenobarbital?
(9) What is the half-life of the drug in the presence of phenobarbital?
(10) What is the effect of phenobarbital on the plasma concentration of the drug at time zero \((C_0)\) (assume a dose of 230 mg is administered in the presence and absence of phenobarbital)?
(11) What is the effect of phenobarbital on the plasma AUC of the drug?
(12) Please draw, on a semilogarithmic graph, the plasma concentration-time profiles of the drug (from zero to 24 hr) in the presence and absence of phenobarbital.

(13) How does a two-fold increase in the clearance affect the plasma concentration-time profiles of the drug after PO dosing and constant IV infusion?
   The drug is administered alone but its dose is reduced by a factor of two to 115 mg.

(14) What is the effect of a reduced dose on the drug's kinetic parameters \((V, CL, and t_{1/2})\) and \(C_0\) and AUC?

(15) Please draw, on a semilogarithmic graph, the plasma concentration-time profiles of the drug (from zero to 24 hr) after the IV bolus administration of doses of 230 mg and 115 mg.

(16) How does a two-fold decrease in the dose affect the plasma concentration-time profiles of the drug after PO dosing and constant IV infusion?