Pharmacokinetic-Based Design and Modification of Dosage Regimens

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PROLOGUE

An expected outcome of most clinical or applied pharmaco-kinetic courses offered in pharmacy schools is the design of dosage regimens for individual patients based on the drug kinetic and/or dynamic parameters in the patient. To achieve this outcome, specific methods are usually discussed for individual drugs such as aminoglycosides, digoxin, theophylline, and phenytoin among others.

In Pharmacy 211 (Clinical Pharmacokinetics), offered to PharmD students at Drake University College of Pharmacy, students first learn the principles of dosage regimen design and modification as a part of a module which covers general clinical pharmacokinetic concepts. The discussion of the individual drugs is then covered in a subsequent module. In the first module, students are provided with expected outcomes, specific objectives (posed as questions), reading assignments or handouts, computer simulation programs, and one or more problems designed to cover the outcomes/objectives for the topic. Students are expected to work on the problems before attending the class session(s) where the solutions to the problem(s) are discussed. At the completion of the session(s), computer programs are used by students for generation of practice problems and homework assignments. The material presented in this article (outcomes/objectives, reading handout, and example problems) for the topic of design and modification of dosage regimens is normally covered in four lecture hours.

Unless specifically referenced, the equations presented in the following sections may be found in most pharmacokinetics textbooks(1,2) and, therefore, are not referenced individually. A glossary of terms and abbreviations is provided in Appendix A.

EDUCATIONAL ENVIRONMENT

Pharmacy 211 (Clinical Pharmacokinetics) is a required three credit-hour course offered to students in the Spring semester of the first year of a track-in PharmD program. The course is offered as a single section, meeting twice a week, with an enrollment of 60 students in 1998. The author is responsible for the instruction in the first general module of the course, while clinical faculty have primary responsibility for the instruction in the second module dealing with individual drugs. Topics covered in the first general module include principles of therapeutic drug monitoring, sample collection and analysis, kinetic parameter estimation using population and patient-specific methods (*e.g.*, least square and Bayesian analysis), dosage regimen design and modification, and pharmacodynamic principles and their application.

The format of the module is based on an active learning strategy(3) which utilizes problems as the basis of instruction, instead of didactic lecturing. Additionally, learning is facilitated by the extensive use of computers both inside (by the instructor) and outside (by students) the classroom for simulation and generation of problems. The computer-generated problems(4) are based on the spreadsheet program EXCEL and provide students with unlimited number of practices for each topic. Additionally, the programs are used for generation and grading of homework assignments. The details of the problem-based, objective-driven format(3) and the computer-assisted learning strategy(4) are provided elsewhere.

EXPECTED OUTCOMES

- Design dosage regimens (maintenance dose, loading dose, and dosage interval) for individual patients based on the reported therapeutic range of the drug and the kinetics of the drug in the patient.
- Preict the effects of alterations in the kinetic parameters of drugs on their plasma concentration-time courses.
- Recommend modifications in dosage regimens based on the changes in the kinetic parameters of drugs.

SPECIFIC OBJECTIVES

- General Concepts
    1. What is the goal when a dosage regimen is designed?

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2. What are the necessary data to design a dosage regimen for a patient, and how are the data obtained?
3. How do alterations in volume of distribution (V), clearance (Cl), and elimination half life ($t_{1/2}$) affect the plasma profiles of drugs after single and multiple dose administrations?
4. Which kinetic parameter is important in determination of a loading dose?
5. Which kinetic parameter affects the estimation of maintenance dose or rate of infusion?

• Estimation of Dosage Regimens for Different Methods of Drug Administration
6. How can maintenance dose (D_M), dosage interval (τ), and loading dose (D_L) be estimated for drugs administered by multiple iv bolus or extravascular (*e.g.*, PO) dosing?
7. How can the infusion rate and D_L be estimated for drugs administered by constant iv infusion?
8. How does the dosage regimen need to be modified when the clearance of a drug changes?
9. How does the dosage regimen need to be modified when the volume of distribution of a drug changes?

INTRODUCTION

For a majority of drugs subject to pharmacokinetic monitoring, the goal is to design individualized dosage regimens in patients in order to keep the plasma concentrations of the drug within a preset minimum (C_{min}) and maximum (C_{max}) for multiple dosing regimens or at steady state (C_{ss}) for constant input regimens. For most drugs, the C_{min} and C_{max} values correspond to the minimum effective (MEC) and minimum toxic (MTC) concentrations. For example, the therapeutic range of digoxin for cardiac dysfunction is between 0.8 and 2 ng/mL[5]. This implies that the concentrations above 2 ng/mL are more likely to be associated with toxicity and concentrations below 0.8 ng/mL are more likely to produce little or no effect. Therefore, it is desired that a dosage regimen for digoxin would produce plasma concentrations within this therapeutic range.

For some drugs, the desired C_{max} and C_{min} may have other therapeutic significance. For instance, for aminoglycoside antibiotics such as gentamicin, the toxic effects are related to the trough or C_{min} levels in addition to some dependency on peak or C_{max} values[6]. Generally, for antibiotics, the desired C_{max} is a value several fold above the minimum inhibitory concentration of the drug for the responsible organism[7]. However, C_{min} is usually significantly lower than the minimum inhibitory concentration[7]. Nevertheless, irrespective of the pharmacodynamic significance of the C_{max} and C_{min} values, the goal of the design of dosage regimen in most cases is to achieve plasma concentrations within or at the target C_{max} and C_{min} boundaries.

DESIGN OF DOSAGE REGIMENS

The following sections center around drugs for which a plasma therapeutic range is reported and the goal is to design a dosage regimen to achieve plasma concentrations within this range. Additionally, although most of the concepts presented here apply to drugs following either one- or multicompartment distribution models, the focus is on drugs whose kinetics can reasonably be approximated by a one compartment model.

The required data to design a dosage regimen are the information about the kinetics of the drug in the patient and the reported therapeutic range of the drug. The kinetic parameters are derived from the plasma sample(s) taken from the patient (patient-specific values), adjustment of the reported average kinetic values for patient characteristics such as renal function (adjusted population values), or both the population and patient-specific data (Bayesian values)[8].

An Example Drug

In each of the following sections, the application of the methods is demonstrated using a hypothetical drug with the following characteristics: therapeutic range, 10-20 mg/L; V, 35 L; Cl, 3.2 L /h; oral bioavailability (F), 100 percent; and absorption half life, 1 hr.

IV Bolus Dosing

The process is explained below using the kinetic parameters of the example drug.
• Estimate a target average steady state concentration (C_{ave}^{∞}) from the MEC and MTC values. The following equation defines C_{ave}^{∞} the value based on the minimum (C_{min}^{∞}) and maximum (C_{max}^{∞}) steady state concentrations equal to MEC and MTC, respectively.

$$C_{ave}^{\infty} = \frac{C_{max}^{\infty} - C_{min}^{\infty}}{\ln \dfrac{C_{max}^{\infty}}{C_{min}^{\infty}}} = 14.4 \text{ mg/L}$$

Please note that C_{ave}^{∞} (14.4 mg/L) is slightly different from an algebraic average (15 mg/L) of C_{min}^{∞} (10 mg/L) and C_{max}^{∞} (20 mg/L). This is because the plasma concentrations of drugs with first order elimination decline exponentially instead of a simple linear decline.

• Estimate the dosing rate (dose/τ) necessary to achieve C_{ave}^{∞}. For this calculation, one also needs Cl and extent of systemic availability (F) of the drug:

$$C_{ave}^{\infty} = \frac{F \cdot (\text{Dose}/\tau)}{Cl}$$

or

$$\text{Dose}/\tau = \frac{Cl \cdot C_{ave}^{\infty}}{F}$$

For IV administration, F is equal to 1. Therefore,

$$\text{Does}/\tau = Cl \cdot C_{ave}^{\infty}$$

$$\text{Does}/\tau = 3.2 \text{ L/h} \times 14.4 \text{ mg/L} = 46 \text{ mg/h}$$

• Estimate the maximum allowable τ (τ_{max}). The rate of decline in the plasma concentration from C_{max}^{∞} to C_{min}^{∞} is governed by the drug elimination half life ($t_{1/2}$) or rate constant (K). Therefore, one can estimate how long it would take for the plasma concentration to decline from a maximum to a minimum. The therapeutic range boundaries (20 and 10 mg/L) may be set as the limits of C_{max}^{∞} and C_{min}^{∞} and the time which takes for the plasma concentration to decline from 20 to 10 mg/L may be

estimated from the following equation:

$$C_{min}^{\infty} = C_{max}^{\infty} \; e^{-k\tau_{max}}$$

The above equation can be rearranged to solve for τ_{max}:

$$\tau_{max} = \frac{\ln \dfrac{C_{max}^{\infty}}{C_{min}^{\infty}}}{K}$$

The $t_{1/2}$ and K of the example drug are 7.6 hr and 0.091 hr^{-1}, respectively (estimated from the Cl and V values). The τ_{max} may then be calculated:

$$\tau_{max} = \frac{\ln \dfrac{20}{10}}{0.091} = 7.6 \text{ hr}$$

- Choose a practical τ based on the calculated τ_{max}. The τ_{max} of 7.6 hr means that the longest interval that may be selected for the patient is 7.6 hr. Because the drug administration every 7.6 hr is not practical, a τ should be selected from one of the following more practical values: 4, 6, 8, 12, or 24 hr. Obviously, one would rather choose a longer τ if possible (for patient and staff convenience). However, a selected practical τ cannot be more than τ_{max} if the desired outcome is to keep the plasma concentrations between C_{max}^{∞} and C_{min}^{∞}. In this case, a τ of 6 hr appears to be the best choice.

- Estimate the dose. Knowing τ and the dosing rate (dose/τ), one can simply estimate the dose:

  Dose = Dosing Rate x Dosage Interval
  = 46 mg/h x 6 hr = 276 mg

If the dose is not practical or the available strengths would not allow the administration of the exact dose, one may round it to the nearest practical number. For instance, the above dose may be rounded to 280 mg.

- Re-estimate C_{ave}^{∞}, C_{max}^{∞}, and C_{min}^{∞} based on the selected τ and dose. If one would administer a dose of 350 mg (46 mg/hr x 7.6 hr), at exact intervals of 7.6 hr, the predicted C_{ave}^{∞}, C_{max}^{∞} and C_{min}^{∞} values would be the same as those targeted (14.4, 20, and 10 mg/L, respectively). However, in the above case, it was decided to administer 280 mg every 6 hr instead of 350 mg every 7.6 hr. Therefore, one may need to re-estimate these concentration values using the practical τ (6 hr) and dose (280 mg). Because the dosing rate is almost the same for practical (47 mg/hr) and exact (46 mg/hr) regimens, the predicted C_{ave}^{∞} (14.6 mg/L) would be very close to that targeted (14.4 mg/L):

$$C_{ave}^{\infty} = \frac{F \cdot (\text{Dose}/\tau)}{Cl} = \frac{280/6}{3.2} = 14.6 \text{ mg/L}$$

However, the fluctuation between the maximum and minimum concentrations would be less (lower C_{max}^{∞} and higher C_{min}^{∞}) for the practical regimen because the selected interval (6 hr) is shorter than that calculated (7.6 hr). To estimate C_{max}^{∞} and C_{min}^{∞} values with the practical regimen, first, the C_{max} and C_{min} after the first dose (C_{max}^{1st} and C_{min}^{1st} respectively) are estimated. Then, using
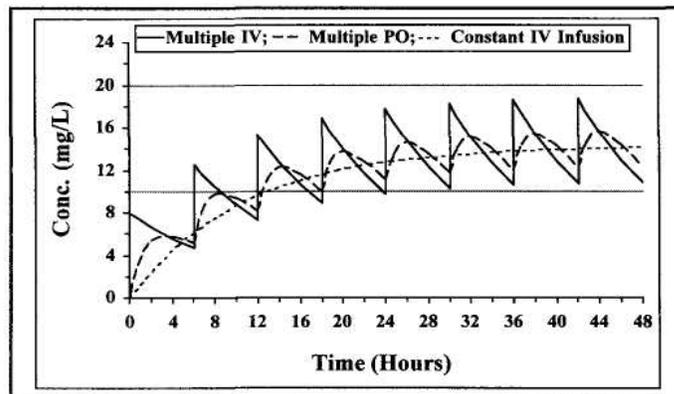

Fig. 1. Simulated plasma concentration-time courses of an example drug after the IV bolus and PO administration of 280-mg doses every 6 hr and after constant IV infusion of 46 mg/hr. The kinetics of the example drug are listed in the text.

the accumulation factor (R), the C_{max}^{∞} and C_{min}^{∞} values are predicted as demonstrated below.

$$C_{max}^{1st} = \frac{\text{Dose}}{V} = \frac{280 \text{mg}}{35 \text{L}} = 8.0 \text{ mg/L}$$

$$C_{min}^{1st} = C_{max}^{1st} \cdot e^{-K\tau} = 8e^{-0.091 \times 6} = 4.6 \text{ mg/L}$$

$$R = \frac{1}{1 - e^{-K\tau}} = \frac{1}{1 - e^{-0.091 \times 6}} = 2.4$$

$$C_{max}^{\infty} = C_{max}^{1st} \cdot R = 8.0 \times 2.4 = 19 \text{ mg/L}$$

$$C_{min}^{\infty} = C_{min}^{1st} \cdot R = 4.6 \times 2.4 = 11 \text{ mg/L}$$

Therefore, the dosage regimen of 280 mg every 6 hr would be expected to result in C_{min}^{∞}, C_{max}^{∞}, and C_{ave}^{∞} values of 11, 19, and 15 mg/L respectively (Figure 1). All of these concentrations are within the therapeutic range of 10 and 20 mg/L.

- Estimate a loading dose (D_L), if needed. In some cases, administration of a loading dose may be necessary, particularly if the half life of the drug is long and the immediate achievement of therapeutic concentrations is important. In these cases, D_L may be estimated by either of the following two methods using the maintenance dose (D_M) and accumulation factor (R) or from the V and C_{max}^{∞} values:

$$D_L = D_M \cdot R = 280 \text{ mg} \times 2.4 = 670 \text{ mg}$$

or

$$D_L = C_{max}^{\infty} \cdot V = 19 \text{ mg/L} \times 35 \text{ L} = 670 \text{ mg}$$

As mentioned above, the dose should be adjusted based on the available strengths and/or salts of the drug.

Extra vascular Dosing

The estimation of dose and τ after extravascular dosing (*e.g.*, oral administration) is more complicated than that after IV bolus doses because the rate and extent (F) of extravascular availability would also be important factors in addition to other kinetic parameters. One extreme case for

extravascular dosing is when the absorption is so fast that it can be assumed as instantaneous for practical purposes. This case would be similar to IV bolus administration with F of 1. Because of the complexity of calculations involving absorption rate constant, in practice, the absorption of most immediate release formulations is assumed to be instantaneous. Therefore, the equations used for IV bolus dosing can also be used for design of extravascular dosage regimens with reasonable accuracy. In fact, the actual fluctuation in the plasma samples after extravascular dosing would be less than that estimated using instantaneous absorption or IV administration (Figure 1). This is because in reality, absorption takes place over a certain period of time resulting in lower C_{max}^{∞} values than those estimated from an instantaneous absorption. Also, the gradual absorption of the drug from the site of administration (*e.g.*, gastrointestinal tract) results in higher C_{min}^{∞} values after extravascular dosing, compared with IV administration of the same dose (Figure 1). Generally, slower absorption profiles would result in less fluctuation.

In another extreme, the profiles after controlled release formulations (*e.g.*, zero-order absorption) would result in almost constant concentrations at steady state with minimal fluctuation, a situation similar to constant IV infusion. In these cases, the constant infusion equations may be used for the prediction of dosage regimens of controlled release products.

Constant IV Infusion

This is the simplest case, as one deals with the infusion rate constant (R_0) only (no need to estimate τ). The following procedure may be used for this process:

- Estimate R_0 based on the desired steady state concentration (C_{ss}) and the drug clearance:

$R_0 = Cl \, C_{ss}$

The desired C_{ss} is normally a concentration within the MEC and MTC values. Using the example drug and assuming a desired C_{ss} of 14.4 mg/L, the following R_0 may be calculated (Figure 1):

$R_0 = 3.2$ L/h x 14.4 mg/L = 46 mg/h

- Estimate a loading dose based on the C_{ss} and V of the drug:

$D_L = C_{ss} \cdot V = 14.4$ mg/L x 35L = 500 mg

Administration of D_L should produce a concentration of 14 mg/L which is maintained by simultaneous start of the infusion at a rate of 46 mg/L.

Intermittent IV Infusion

Aminoglycosides and some other antibiotics such as vancomycin are usually administered via multiple short (30-60 min) IV infusions at regular intervals[6]. The principles discussed above need to be slightly modified in order to be applicable to dosing of these antibiotics. For example, for these antibiotics, it is desired to design a dosage regimen to have a C_{max}^{∞} value above the MIC of the drug and a C_{min}^{∞} value at or below a concentration associated with toxicity. The approach for selection of a dosage interval is, therefore, slightly different from that used above for the design of dosage regimens to produce concentrations within a therapeutic range (MEC and MTC). The specific methods for these drugs are not discussed here.

Pharmacodynamic-Based Dosage Regimen Design

Traditionally, drug information provided by pharmaceutical companies (such as package inserts and *Physicians' Desk Reference)* has contained information about the pharmacokinetics of drugs and the therapeutic range (if available). Consistent with this information, the focus of design of dosage regimens has been the use of pharmacokinetic data. However, recently, very specific pharmacodynamic information such as maximum effect (E_{max}) and the plasma concentration producing half of E_{max} (EC_{50}) are beginning to appear in these sources. Therefore, it is possible to design dosage regimens for these drugs to achieve certain effects rather than certain concentrations. For example, the so-called E_{max} model equation(9), relating E_{max}, EC_{50}, and the plasma concentration (C) producing a certain effect (E) may be used to translate the desired upper (E_{UPPER}) and lower (E_{LOWER}) effects (goal of therapy) to C_{max}^{∞} and C_{min}^{∞} values:

$$E = \frac{E_{max} \cdot C}{EC_{50} + C}$$

$$C = \frac{EC_{50} \cdot E}{E_{max} - E}$$

$$C_{max}^{\infty} = \frac{EC_{50} \cdot E_{UPPER}}{E_{max} - E_{UPPER}}$$

$$C_{min}^{\infty} = \frac{EC_{50} \cdot E_{LOWER}}{E_{max} - E_{LOWER}}$$

The estimated C_{max}^{∞} and C_{min}^{∞} values then can be used for the design of multiple dosing regimens as explained above. Similarly, for the constant IV infusion, a target effect may be converted to a C_{ss} value and a constant infusion rate be estimated as explained before.

As specific pharmacodynamic information becomes available for more drugs, it is expected that pharmacodynamic-based design of dosage regimens will become more routine in clinical practice.

ALTERATIONS IN THE KINETICS OF DRUGS

After a dosage regimen is designed and administered to a patient, it is necessary to verify the achievement of the desired concentration(s) by obtaining plasma samples at appropriate times (e.g., peaks and troughs at steady state) and adjusting the dosage regimen, if necessary. For example, the kinetic data estimated from the collected plasma samples may be different from those obtained from the population data which were used for the initial design of dosage regimens, resulting in a plasma concentration-time profile different than that anticipated. Hence, the newly estimated kinetic data should be used for re-estimation of a new dosage regimen.

Additionally, the kinetics of a drug in a patient may change during the course of therapy because of alterations in the pathophysiologic conditions of the patient and/or administration of interacting drugs. For example, gentamicin may reduce the renal function of the patient (a toxicity of gentamicin) and, therefore, reduce its own renal clearance during the course of therapy(6). Alternatively, other medi

cations added to the patient's therapy may interact at different kinetic levels with the drug, resulting in a change in one or more of the kinetic parameters. Therefore, it is necessary to understand what consequences these kinetic alterations may have on the plasma concentration-time profiles and whether or not a change in the dosage regimen is necessary as a result of these alterations. To be able to address these issues, one needs to understand the relationship among pharmacokinetic parameters.

Relationship Among Pharmacokinetic Parameters

Before discussing a modification of dosage regimens, it is necessary to realize how the three major kinetic parameters (V, Cl, and $t_{1/2}$ or K) are related to each other. This is important because these kinetic parameters determine the shape of the plasma concentration-time profiles and, therefore, affect the fluctuation between the C_{max}^{∞} and C_{min}^{∞} values. The mathematical relationship among these three parameters is demonstrated below:

$$Cl = K \cdot V$$

If two of these parameters are known, the third can easily be estimated from the above equation. However, the use of the above equation without an understanding of the underlying physiological relationship among these three parameters may result in erroneous conclusions. This is because V and Cl are independent parameters, while the elimination half life (or rate constant) is a composite parameter dependent on both V and Cl(2) as described below.

Clearance is a measure of the efficiency of the organ(s) of elimination and is dependent on certain physiologic parameters in the organ (*e.g.*, organ blood flow and drug intrinsic clearance and free fraction in the blood)(2). For instance, for a drug eliminated by renal excretion, clearance is dependent on how well the kidneys can excrete the drug in urine. Therefore, in the elderly with reduced renal function, the clearance of renally excreted drugs would be reduced.

The extent of distribution of drugs, however, is independent of their clearance. Distribution is dependent on certain physiologic parameters such as perfusion and permeability of tissues to drugs and the level of binding proteins in the blood and tissues(2). Therefore, a reduction in the renal clearance of a drug in the elderly does not necessarily mean that the volume of distribution of the drug will also be different in this population. In other words, clearance and volume of distribution are independent of each other(2).

On the other hand, the elimination half life is dependent on both V and Cl(2). An increase in Cl (elimination efficiency) results in a reduction in $t_{1/2}$ (or an increase in K). This is easy to understand since a more efficient elimination pathway would result in a faster decline in the plasma concentrations. An increase in V, however, results in prolongation of $t_{1/2}$. This is because the drug is distributed more extensively into the tissues (where it is safe from elimination) at first. However, because the distribution is a reversible process, as the drug gets eliminated and plasma concentrations decline, the drug in the tissue will return to plasma, resulting in a more sustained level in plasma (increased half life). Therefore, the half life is dependent on both the clearance and volume of distribution, and a more appropriate presentation of the relationship among these three parameters is:

$$t_{1/2} = \frac{0.693V}{Cl}$$

or

$$K = \frac{Cl}{V}$$

For example, if the volume of distribution changes, the half life (or rate constant) changes proportionally while clearance remains the same. To demonstrate this point, consider the following scenario. The volume of distribution and elimination rate constant of a drug in a patient are 35 L and 0.091 hr^{-1}, respectively. While under treatment with this drug, the patient receives a second drug which increases the drug V to 70 L. What is the clearance of the drug in the absence and presence of the interacting drug?

The mathematical relationship $Cl = K \cdot V$ may be used to estimate Cl in the absence of drug interaction:

$$Cl = 0.091 \times 35 = 3.2 \text{ L/hr}$$

Clearance is independent of V changes. Therefore, when V is increased to 70 L due to a drug interaction, Cl remains the same (3.2 L/hr). However, the above equation without an understanding of this fundamental concept may be misleading. This is because one may erroneously conclude from the equation $Cl = K \cdot V$ that doubling V would result in doubling Cl. This conclusion, however, is not valid as a two-fold increase in V would result in a two-fold decrease in K without any effect on Cl.

Effects of Clearance, Volume of Distribution, and Plasma Half Life on the Magnitude of Dose, Dosage Interval, and/or Dosing Rate

Clearance. Among the primary kinetic parameters, Cl determines the magnitude of dosing rate (Dose/ τ) or infusion rate (R_0) to achieve a certain average concentration at steady state (C_{ave}^{∞} or C_{ss}).

$$C_{ave}^{\infty} = \frac{F(Dose/\tau)}{Cl}$$

$$Dose/\tau = \frac{Cl \cdot C_{ave}^{\infty}}{F} \text{ or } Dose = \frac{Cl \cdot C_{ave}^{\infty} \cdot \tau}{F}$$

(For multiple Extravascular and IV doses)

and

$$R_0 = Cl \cdot C_{ss} \text{ (For constant IV infusion)}$$

The above relationships indicate that when the clearance of a drug is altered because of a drug interaction and/or disease state, C_{ave}^{∞} or C_{ss} would change inversely relative to the change in Cl. For example, the clearance of theophylline decreases by > 50 percent because of some drug interactions (*e.g.*, enoxacin(10)) or disease states (*e.g.*, hepatic cirrhosis(11)), resulting in higher C_{ave}^{∞} or C_{ss} values if the usual doses of theophylline are administered.

To illustrate the significance of a change in Cl, assume that an interacting drug added to the regimen of the patient receiving the example drug (Cl of 3.2 L/hr) results in a two-
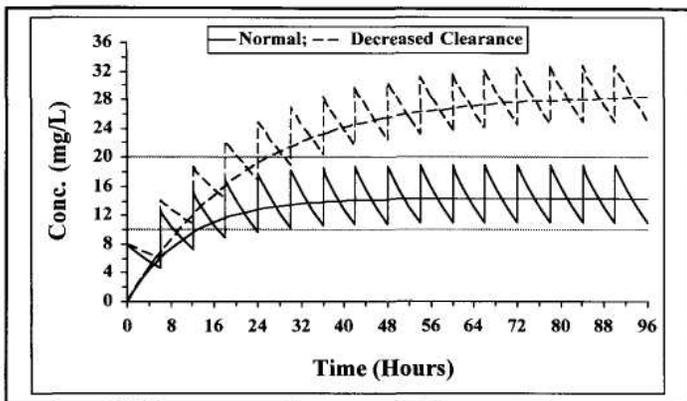
Fig. 2. Simulated plasma concentration-time courses of an example drug after IV multiple bolus and constant infusion dosing in the absence and presence of a drug interaction resulting in a two-fold reduction in drug clearance.
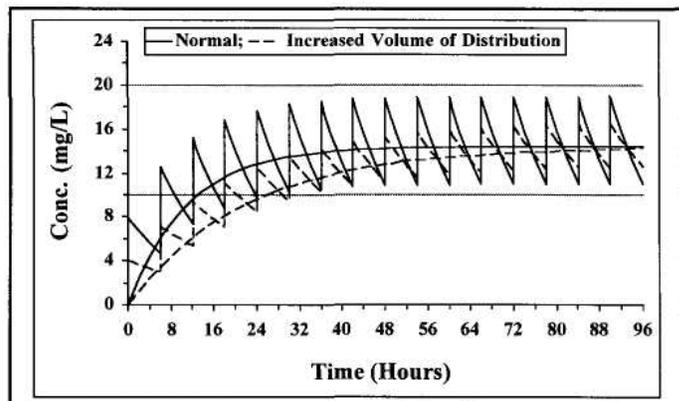

Fig. 3. Simulated plasma concentration-time courses of an example drug after IV multiple bolus and constant infusion dosing in the absence and presence of a drug interaction resulting in a two-fold increase in drug volume of distribution.

fold reduction in the drug Cl (to 1.6 L/hr). Administration of the same dose of the example drug (280 mg every 6 hr or 46 mg/hr as constant IV infusion) would be expected to result in C_{ave}^{∞} or C_{ss} value of 29 mg/L (instead of ~14.5 mg/mL) which is above the upper limit of the desired plasma concentration for this drug (20 mg/L) (Figure 2). In addition to an increase in C_{ave}^{∞} or C_{ss}, a two-fold decrease in Cl would result in the following changes in the kinetics of the drug (Figure 2):

- The drug half life in the above case would be expected to increase by a factor of 2 (15 hr instead of 7.6 hr).
- The time to reach steady state would be expected to double because of a two-fold increase in the half life.
- The fluctuation in the plasma concentrations after multiple dosing would be reduced in the presence of reduced Cl.

The modification necessary in the presence of the interacting drug is a decrease in the dosing rate or infusion rate (23 mg/hr instead of 46 mg/hr) which is proportional to the decrease in Cl (two-fold). For the multiple dosing method, the modification could be in the form of a reduction in the dose (140 mg every 6 hr), a longer interval (280 mg every 12 hr) or both (180 mg every 8 hr), keeping the dosing rate the same (~23 mg/hr) for all three scenarios and half of that in the absence of the drug interaction (~46 mg/hr). In choosing among the options for multiple dosing method, the fluctuation between the maximum and minimum concentrations relative to the therapeutic range, convenience to the patient and nursing staff, and cost should be considered.

Volume of Distribution. The drug V influences the magnitude of loading dose (D_L) because it relates the drug plasma concentration to the amount of drug in the body:

$$D_L = C_{ss}(\text{or } C_{max}) \bullet V$$

However, as demonstrated in the clearance section, the dosing rate (maintenance dose) of the drug is only dependent on Cl and not V. On the other hand, the loading dose is not affected by a change in Cl as demonstrated in the above equation. To clarify these concepts, assume that a drug interaction results in a two-fold increase in the V of the example drug (from 35 L to 70 L). The C_{ave}^{∞} or C_{ss} values of the drug in the presence of this interaction would not be different from those in the absence of the drug interaction

(Figure 3). Therefore, the dosing rate of the drug need not be altered. However, it should be noted that an increase in V results in a proportional increase in half life (from 7.6 to 15 hr), a proportional increase in the time to reach steady state, and a decrease in the plasma concentration fluctuation (Figure 3).

Although the dosing rate should be the same when V is increased, the reduced fluctuation may allow administration of larger doses at longer intervals (*e.g.*, 560 mg every 12 hr) for multiple dosing method. Additionally, because of the larger V, the loading dose should be increased. For example, for constant IV infusion, the loading dose should be increased from 500 mg (14.4 mg/L x 35 L) in the absence of drug interaction to 1000 mg (14.4 mg/L x 70 L) in the presence of drug interaction.

Half Life. As discussed above, the half life may change as a result of a change in V and/or Cl. Generally, a change in the half life affects the time to reach steady state and the shape of the plasma concentration-time courses (Figures 2 and 3). However, as discussed under clearance and volume of distribution sections, a change in the half life does not necessarily affect C_{ave}^{∞} but it will affect the C_{max}^{∞} and C_{min}^{∞} values (the degree of fluctuation).

Practice Problems

Examples of practice problems provided to students for the design and modification of dosage regimens are presented in Appendices B and C, respectively. As mentioned earlier, the in-class discussion of the topics centered around these problems.

CONCLUSIONS

Pharmacokinetic principles may be used to design dosage regimens for individual patients in order to achieve therapeutic plasma concentrations of drugs. The requirements for such designs are the estimated kinetic data of the drug in the patient and a known relationship between the plasma concentrations of the drug and the pharmacologic and/or toxic effects in the form of a therapeutic range. Additionally, an understanding of the relationship among major pharmacokinetic parameters would allow modification of dosage regimens when the kinetics of the drug are altered because of a drug interaction and/or disease states.

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APPENDIX A. GLOSSARY OF TERMS AND ABBREVIATIONS

V	Volume of distribution
Cl	Clearance
$t_{1/2}$	Plasma half life
D_M	Maintenance dose
τ	Dosage interval
D_L	Loading dose
C_{ss}	Steady-state drug concentration after constant IV infusion
MEC	Minimum effective concentration
MTC	Minimum toxic concentration
F	Oral bioavailability
C_{ave}^{∞}	Average steady-state concentration after multiple dosing
C_{min}^{∞}	Minimum steady-state concentration after multiple dosing
C_{max}^{∞}	Maximum steady-state concentration after multiple dosing
τ_{max}	Maximum allowable dosage interval
K	Elimination rate constant
C_{max}^{1st}	Maximum plasma concentration after the first dose
C_{min}^{1st}	Minimum plasma concentration after the first dose
R	Accumulation factor
R_0	Infusion rate constant
E_{max}	Maximum effect possible
EC_{50}	Plasma concentration producing half of E_{max}
E_{UPPER}	Desired maximum effect after multiple dosing
E_{LOWER}	Desired minimum effect after multiple dosing

APPENDIX B. AN EXAMPLE PROBLEM FOR DOSAGE REGIMEN DESIGN

A population study on the kinetics of a new drug indicates that the clearance (Cl) of the drug is related to creatinine clearance (Cl_{CR}) by the following equation:

$$Cl \, (mL/min/kg) = 0.5 + 1.44 \, Cl_{CR} \, (mL/min/kg)$$

Additionally, the average volume of distribution is 1.6 L/kg and the therapeutic range of the drug is between 6-10 mg/L. Please estimate the following in a 70-kg patient with Cl_{CR} of 50 mL/min.

I.   Adjusted kinetic parameters (Cl, V, and $t_{1/2}$).
II. Design a dosage regimen (dose, dosage interval, and loading dose) for IV bolus administration.
III. What are the predicted maximum, minimum, and average steady state concentrations based on your recommendation in II?
IV. The extent of oral availability (F) of an immediate release formulation of the drug is 0.8. Design a PO dosage regimen for the patient. What are the predicted maximum, minimum, and average steady state concentrations assuming instantaneous absorption?

APPENDIX C. AN EXAMPLE PROBLEM FOR DOSAGE REGIMEN MODIFICATION

The volume of distribution (V) and clearance (Cl) of a cardiac drug are 40 L and 2.31 L/h, respectively. The therapeutic range of the drug is between 2 and 5 mg/L.

I.   Please determine a dosage regimen (dose, dosage interval, and loading dose) for this drug to be administered via IV bolus method.
II. What are the predicted maximum, minimum, and average plasma concentrations at steady state using your recommendation in I?
•   After a month of therapy, the patient receives a second drug which results in doubling the Cl of the cardiac drug.
III. What are the V and $t_{1/2}$ of the drug in the presence of the interacting drug?
IV. What would happen to the average, minimum, and maximum steady-state plasma concentrations of the drug?
V.   How would you change the dosage regimen (dose and/or dosage interval) of this drug, if any?
VI. If the plasma concentrations of the drug are allowed to decline to zero before the administration of a new dosage regimen, what loading dose should be administered? How does this value differ from that calculated in I in the absence of the interacting drug?