6 General Approaches to Clinical Pharmacokinetic Monitoring

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CONTENTS

INTRODUCTION

Basic pharmacokinetics has focused on a detailed scientific study of what the body is doing to the drug to facilitate the following:

- Liberation of the drug from the dosage form
- Absorption of the compound into the systemic circulation
- Distribution to various sites of action
- Metabolism to active or inactive compounds
- Elimination from the body.

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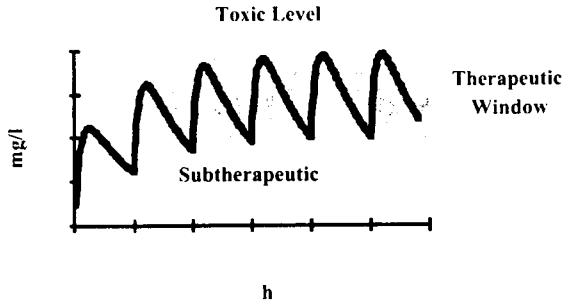

FIGURE 6.1 The therapeutic window.

Many medications being developed today must be used carefully because too much drug in the body may have toxic effects, or not enough drug can result in ineffective therapy because the threshold of the therapeutic response is not achieved. The application of basic pharmacokinetic knowledge to these medications that have this well-defined therapeutic window is referred to as therapeutic drug monitoring. Figure 6.1 illustrates this concept of a therapeutic window. Consequently, the area of pharmacokinetics that monitors therapeutic concentrations has evolved to another scientific subdiscipline of pharmacokinetics. Taking the basic pharmacokinetic information and combining that with a patient's actual physiological response to the medication is what clinical pharmacokinetics is all about. Gerhard Levy[1] has said, "Simply stated, clinical pharmacokinetics is a health science discipline that deals with the application of pharmacokinetics to optimize the pharmacotherapeutic management of individual patients." The terms *clinical pharmacokinetics*, *therapeutic drug monitoring* (TDM) and *applied pharmacokinetics* have all been used to describe the process of taking drug concentrations, basic pharmacokinetic principles, and the person's clinical response and combining them to optimize drug therapy for the patient. This is demonstrated in Figure 6.2.

Adjustment of drug dosage on the basis of individualized target drug concentrations can achieve better outcomes in therapy by preventing or minimizing adverse effects or reaching desired therapeutic outcomes more rapidly.[2-6] However, for this approach to be successful, there are three important things to consider: accurately determined drug concentrations, correctly selected pharmacokinetic equations, and

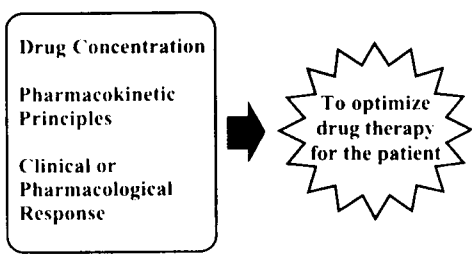

FIGURE 6.2 Clinical pharmacokinetics or TDM is applied pharmacokinetics.

a thorough understanding of the patient's medical conditions that can influence clinical and pharmacological response. They are all indicated in Figure 6.2.

DRUG CONCENTRATION

The clinical pharmacokineticist involved in making recommendations to adjust drug therapy must make sure that the blood level determinations that are being used to adjust therapy are properly collected and determined. Invalid starting information can result in inappropriate alterations in drug therapy. In general, blood level determinations are done when a medication has a narrow therapeutic index and monitoring levels of the drug in the sampling compartment can be helpful to keep the concentrations above the minimum threshold, and below any potential toxic levels.[7] If a compound has no documented toxicity in the range of typically used doses, there is no need to monitor levels.

Why Do We Measure Drug Levels?

There are usually three reasons for monitoring drug levels:

1. Determine the best possible safe dosing regimen. When therapy is initiated it may be beneficial to measure levels to help design a dosing regimen that will keep levels within the desired therapeutic window.
2. If the organ systems that determine the rate at which the drug leaves the body are changing, then it is advisable to measure drug levels to maintain the drug at optimal levels.
3. Outpatients who have been stabilized on a dosing regimen sometimes benefit from having levels checked to confirm patient compliance or aid in the identification of noncompliance.

When Do We Draw Them?

Most Often at Steady State

Figure 6.1 illustrates that, if drug levels are measured before steady state is achieved, therapeutic adjustments could result in concentrations much higher than desired. Dosage adjustments can be made from non-steady-state levels, but the pharmacokineticist must make sure that the appropriate pharmacokinetic equations are chosen that include accumulation factors and that it is known how many doses have been given, and the timing of those doses. Many clinicians choose to wait until steady state is achieved before drug levels are measured to assess the current therapy so that simplified steady-state equations can be used.

Sometimes a Single Level

If the drug is given by a constant-rate infusion, or if the peak–trough fluctuation is minor, then it is sufficient to draw only a single steady-state level as shown in Figure 6.3.

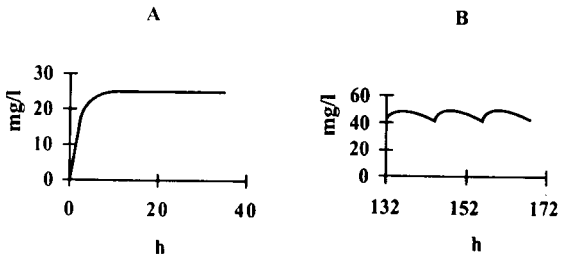

FIGURE 6.3 Plasma concentrations of constant rate infusion (A) and minimal peak–trough fluctuation (B).

Often a Peak and Trough

If the drug is given by extravascular administration or intermittent infusion and it demonstrates a significant difference in concentration before and after dosing, then generally a peak and a trough concentration will need to be measured. The semilog concentration vs. time plot of Figure 6.4 demonstrates this.

Optimal Sampling Times

Depending on the pharmacokinetic equations that are used to individualize therapy, the timing of samples may be very important.[8] The peak for an intravenous (IV) bolus dose would be obtained immediately after the dose is given. The peak concentration following an IV infusion of the drug will usually occur right after the infusion stops. If the concentration of the drug is plotted against time on a semilog plot and if the declining concentration following absorption or the infusion is not a straight line, then the drug exhibits a measurable distribution phase. If the drug demonstrates a significant distribution phase, as in Figure 6.4 and if the pharmacokinetic analysis will assume a one-exponential elimination, then the peak must be measured when distribution is complete.

Once distribution is complete, the slope of the log concentration vs. time curve from the measured peak down to the trough will be linear. A steady-state trough sample should be drawn immediately before the next dose is given after the peak

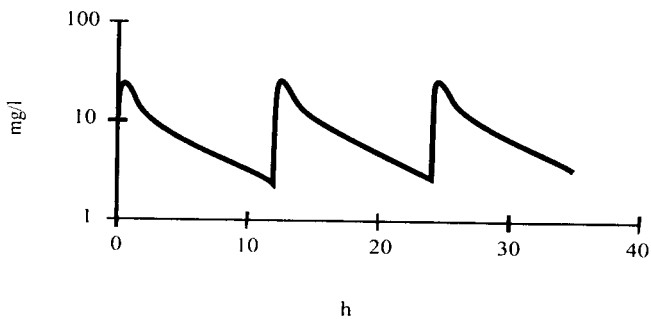

FIGURE 6.4 Often a peak and trough are necessary.

has been obtained. Generally, if the sample is drawn within 30 min of the dose being given, it can be treated as if it were drawn immediately before the dose was given. Ideally, the peak is measured and then the trough at the end of the dosing interval. Experience has shown that quite often those levels are done on two different nursing shifts. The more people involved in the collection of the blood samples, the greater the chance for error, like forgetting to draw the sample, drawing it at the wrong time, etc. Therefore, to be practical and to reduce errors, it is routine to draw a trough before a dose is given, then measure the peak at the appropriate time following the drug administration. Since the samples are being obtained at steady state, the trough obtained before a dose should be exactly the same as the trough following the peak. Therefore, that value is extrapolated to postdose trough and the pharmacokinetics can then be determined using this extrapolated value. Each drug that will be examined in subsequent chapters has optimal sampling times. Take note of these optimal sampling times. For example, gentamicin and tobramycin levels should be obtained at steady state immediately before a dose is given and 30 min after the intermittent infusion stops. Vancomycin levels should be obtained immediately before a dose is given and 60 min after the infusion stops.

How Are They Measured?

Normally, drug concentrations are obtained by venipuncture of venous blood. Arterial samples are much more difficult to obtain and in most cases arterial and venous concentrations of the drug are the same. Plasma is the fluid portion of whole blood that remains after the solid materials (red blood cells, white blood cells, and platelets) have been centrifuged off. Serum is the liquid that remains after blood has been allowed to clot. Thus, fibrin and the solid materials have been removed. Normally, serum and plasma concentrations of the drug are the same, because there is very little binding of most drugs to fibrin or other components of the blood clot.[9] Plasma samples are obtained by using an anticoagulant to prevent the blood from clotting. Heparin or a calcium-binding resin like EDTA, citrate, or fluoride can be used to prevent the clotting. However, some of these anticoagulants can interfere with the assay of some drugs. Consequently, as a general rule, drug concentrations are usually determined in serum.

There are many assay techniques that can be used to determine the drug concentrations that will be used to individualize drug therapy. Microbiological assays were one of the early assays used to determine the concentration of antibiotics. These assays tend a have a fairly high degree of error and they take a long time to achieve results (24 to 72 h). Radioimmunoassays tend to be able to detect reasonably low levels of compounds (sensitivity), but generally do not have high specificity (metabolites and other substances can easily interfere with the determination of the actual drug concentration). High-performance liquid chromatography (HPLC) has a reasonable sensitivity and specificity, tends to be inexpensive, and is generally very rapid, so it is a commonly used method of determining drug concentrations. Gas liquid chromatography (GLC) usually has a high specificity, is very sensitive, and is fast; however, it tends to be very expensive. Consequently, it is used frequently for research purposes, but not

often for routine clinical monitoring of drug concentrations. Probably the most frequently used assay method for therapeutic drug monitoring is an enzyme multiplied immunoassay. Generally these are prepared in kits that have a very reasonable sensitivity and specificity and they tend to be very inexpensive and very rapid.

It is also very important to take note of the units in which assay results are reported. When the concentration information is used in the pharmacokinetic equations, it is important that the proper concentration units be used to obtain the correct units for volume of distribution and half-life. Once again, as individual drugs are reviewed, take note of the preferred assay technique, the proper sampling matrix, and the units of concentration reported.

BASIC PHARMACOKINETIC PRINCIPLES

Applied pharmacokinetics involves predicting steady-state responses. The three main approaches to pharmacokinetic analysis involve the use of physiological models, traditional compartmental models, or a model-independent (linear systems) approach. Physiological compartmental models are very complex and very good for describing in detail what the body is doing to the drug. However, often it is difficult to develop strong predictive relationships for drug response in the clinical environment because often there is limited information about all of the model parameters for the patient. Model-independent, or noncompartmental approaches, are suitable in some cases, but often dynamic clinical data without an extensive sampling scheme cannot effectively predict pharmacokinetic behavior. Consequently, compartmental models alone or sometimes in conjunction with a Bayesian forecasting approach are often used to optimize therapy.

Approval of new drug applications is only finalized when there is a thorough understanding of the basic pharmacokinetics of a drug. Pharmacokinetic studies have been conducted in animals in preclinical trials and in humans at each subsequent stage of the drug development process. For each drug, this basis of scientific knowledge of what the body is doing to the drug should lead to a concrete plan as the best way to monitor and individualize drug therapy for this compound. Drugs that have a linear response to dose and are eliminated in a mono-exponential fashion can use simple one-compartment model equations to predict response to future therapy. Drugs that exhibit a biphasic decline in concentration when the log concentration is plotted against time will require a more complex two-compartment model. If either absorption or elimination are dependent upon a saturable process, then a nonlinear pharmacokinetic model will be necessary to try to describe the drug response. Sometimes it is possible to take a model-independent approach and determine those parameters that are useful to use the drug wisely. Occasionally, it is even possible to take other information about the patient and use that to help forecast the person's response. Therefore, the clinical pharmacokineticist must be able to select the appropriate pharmacokinetic model to use when taking drug concentrations and using them to individualize therapy. It is necessary to choose a kinetic model that is descriptive of the time course of drug concentration and its relationships to therapeutic effect.

Clinical Response

The physiological processes that determine the rate at which a drug leaves that body have a profound effect on the dose and drug concentration vs. time profile. In addition, many genetic characteristics and environmental factors, including diet and concomitant use of other drugs, can all impact this relationship. Physiological variables such as age, gender, body composition, disease, and pregnancy also affect the disposition of drugs and therefore can modify the relationship between the dose and therapeutic response. The clinical pharmacokineticist must not only ensure appropriate drug concentrations have been obtained and that the correct pharmacokinetic equations have been chosen, but also must know enough about the patient's health and well-being that adjustments can be made to therapy based on anticipated clearance changes the patient may exhibit.

THERAPEUTIC DRUG MONITORING

Single-Drug Concentrations

Medications that exhibit a linear response or dose-independent response can have the therapy optimized by using a single blood level determination. If the drug is given by a constant-rate infusion or if it is an extravascular administration, the peak–trough fluctuations are minor, and the patient is at steady state, then a simple proportion can be used.

$$D_{new} = \frac{D_{current} \cdot C_{desired}}{C_{ss,\,measured}} \tag{6.1}$$

It is necessary to know the target, or desired, concentration and the current dose to make a modification in therapy. This approach can be used for lidocaine infusion, or for slow release theophylline, for digoxin, phenobarbital, and procainamide.

Peak and Trough Concentrations

Individualization of dosage for patients receiving intermittent infusions or extravascular administration and for which a peak and trough concentration is required will need three types of information. The therapeutic target concentrations: the desired peak and trough concentrations must be known. Also, the patient's steady-state volume of distribution will be required as an estimate of the extent of drug distribution. Last, an estimate of the person's rate of drug elimination is required. The target concentrations will be chosen based upon information known about the patient's current health and the treatment goals. The steady volume of distribution and the rate of elimination can be estimated prospectively from population estimates for the patient or they can be determined retrospectively from measured peak and trough drug levels. (See illustration in Figure 6.5.)

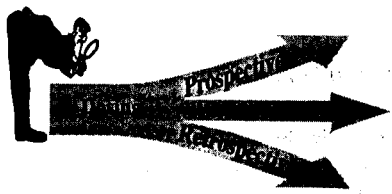

FIGURE 6.5 Therapeutic drug monitoring.

Prospective Population Estimates

An example of a population estimate for the steady-state volume of distribution of vancomycin may be 0.7 mg/kg of corrected body weight. Body weight, or perhaps body weight in conjunction with an estimate of the person's hydration status, is often used to estimate volume of distribution. If the drug is not lipophilic, then it will not distribute well into adipose tissue. Therefore, for this type of drug, an obese patient's actual body weight (ABW) is not a good estimate of steady volume of distribution. Because excess weight has significant interstitial fluid associated with it, one cannot exclude the excess weight and compute only lean body mass (LBW). As a result, a body weight correction is utilized if a person's actual body weight is more than 30% over his or her lean body weight.. The corrected body weight, or adjusted body weight that is used is 40% of the excess over lean body mass. Therefore, for hydrophilic drugs in obese patients, the dosing weight (DWT) or corrected body weight is

$$\text{DWT} = \text{LBW} + 0.4 \cdot (\text{ABW} - \text{LBW}) \tag{6.2}$$

The lean body weight or ideal body weight can be obtained from insurance tables or by using the following relationships:

$$\begin{aligned} \text{LBW} &= 50\text{ kg} + 2.3\text{ kg (for each inch over 5 ft)} && \text{for males} \\ &= 45.5\text{ kg} + 2.3\text{ kg (for each inch over 5 ft)} && \text{for females} \end{aligned} \tag{6.3}$$

The population estimate of rate of elimination may be a regression relationship based upon creatinine clearance (Cl_{cr}) or some other factor(s) that correlate well with the elimination of the drug. For example, an estimate of the elimination rate for vancomycin is $K_{el} = 0.000954 * Cl_{cr} + 0.0036$.[10] Measurement of creatinine clearance is usually unpleasant for patients and difficult to perform accurately, so often creatinine clearance is predicted. One of the commonly used methods of predicting Cl_{cr} is the Cockcroft and Gault method:[11]

$$Cl_{cr} = \frac{(140 - \text{Age}) \cdot \text{LBW}}{72 \cdot SrCr_{ss}} \cdot (0.85 + 0.15 \cdot \text{Sex}) \tag{6.4}$$

where Sex is 1 for a male and 0 for a female and $SrCr_{ss}$ is serum creatinine.

This equation estimates Cl_{cr} in ml/min, which is a patient-specific value. This is what would be used in the prospective equation to estimate the elimination rate. Some of the other methods of estimating creatinine clearance compute an estimate that is normalized to a standard body surface area, usually 1.73 m^2. These estimates would need to be un-normalized to estimate a patient-specific elimination rate. To normalize a Cl_{cr} estimate:

$$\text{NormCl}_{cr} = Cl_{cr} \cdot \frac{1.73}{\text{BSA}} \tag{6.5}$$

The body surface area (BSA) can be determined using a person's weight in kilograms and height in centimeters according to the following relationship, which has been shown to be useful for children and adults by Haycock and co-workers:[12]

$$\text{BSA} = \text{Wt}^{0.5378} \cdot \text{Ht}^{0.3964} \cdot 0.024265 \tag{6.6}$$

Population estimates of steady-state volume of distribution, elimination rate, and target concentrations are listed for each drug in subsequent chapters.

Retrospective Determinations

The measured peak and trough concentration can be plotted on a graph with the slope being the rate of elimination and the extrapolated intercept is the initial concentration. They are used to determine an estimate of the steady-state volume of distribution. However, the following equations, which Sawchuk and Zaske[13] originally published, can be easily used to obtain the same information with greater reliability.

- Calculate the elimination rate constant:

$$k_l = \frac{\ln C_1 - \ln C_2}{t_2 - t_1} = \frac{\ln C_{pk} - \ln C_{tr}}{t_{tr} - t_{pk}} = \frac{\ln(C_{pk}/C_{tr})}{\tau - t_{inf} - t_{pi}} \tag{6.7}$$

Here t_{pk} is the time the peak was measured relative to the start of the infusion and t_{tr} is the elapsed time of the trough relative to the start of the infusion that preceded the peak. τ is the length of the dosing interval, t_{inf} is the length of the infusion, and t_{pi} is the time from when the infusion stopped to when the peak is measured. All times are in hours.

- Calculate C_0:

$$C_0 = \frac{C_{pk}}{e^{-k_{el}(t_{pk} - t_{inf})}} \tag{6.8}$$

This is an extrapolation of the linear portion of the curve back to when the infusion stopped and is an approximation of the concentration at the end of the infusion. This corresponds to the maximum steady-state concentration.

- Calculate the half-life:

$$t_{1/2} = \frac{\ln 2}{k_{el}} \tag{6.9}$$

- Calculate the steady-state volume of distribution:

$$V_{ss} = \frac{R_0}{k_{el}} \cdot \frac{1 - e^{-k_{el} t_{inf}}}{(C_0 - C_{tr} \cdot e^{-k_{el} t_{inf}})} \tag{6.10}$$

Please note that R_0 is the zero-order rate of input, the infusion rate. It is the dose (in mg) divided by the length of the infusion (in hours). A very frequent error is to use the dose, but fail to divide by the length of infusion. Remember C_0 is not the measured peak; rather, it is the value extrapolated back to when the infusion stopped. In the denominator another frequent mistake is made when the trough concentration (C_{tr}) is subtracted from C_0 before the multiplication. The trough must be multiplied by the exponential term ($e^{-k_{el} t_{inf}}$) before it is subtracted from C_0.

- Calculate the dosing interval:

$$\tau = \frac{\ln(C_{Max,\,desired} / C_{Min,\,desired})}{k_{el}} + t_{inf} \tag{6.11}$$

Remember to select a practical dosing interval. Every 6, 8, 12, 24, 36, or 48 h would all be practical intervals.

- Calculate the new infusion rate:

$$R_0 = C_{Max,\,desired} \cdot k_{el} \cdot V_{ss} \cdot \frac{(1 - e^{-k_{el} \tau})}{(1 - e^{-k_{el} t_{inf}})} \tag{6.12}$$

This equation determines an infusion rate in mg/h. To compute a dose to be ordered for the patient, take R_0 times the length of infusion that will be used. Then, select a practical dose. For example, vancomycin is often rounded to the nearest 250 mg to allow for the most economical preparation of the dose to be delivered to the patient.

- Calculate the new peak using the practical dosing interval and the practical dose that have just been determined.

$$C_{ss,\,pk} = \frac{R_0}{V_{ss} \cdot k_{el}} \cdot \frac{(1 - e^{-k_{el} t_{inf}})}{(1 - e^{-k_{el} \tau})} \tag{6.13}$$

- Calculate the new trough.

$$C_{ss,\,tr} = C_{ss,\,pk} \cdot e^{-k_{el}(\tau - t_{inf})} \tag{6.14}$$

This approach to dosing patients retrospectively will allow the clinical pharmacokineticist to optimize therapy by maintaining concentrations within certain therapeutic guidelines.

SUMMARY

Properly collected drug concentrations can be very useful to optimize drug therapy for those agents that have a narrow therapeutic window. Prospectively and retrospectively monitoring therapeutic drug concentrations can improve patient care and reduce hospital costs.[2-7] The prospective and retrospective dosing relationships can be incorporated into spreadsheets that can be used in handheld personal computers at the patient's bedside. They can also be programmed into programmable calculators that are also useful for bedside consultations.

REFERENCES

1. Levy, G., An orientation to clinical pharmacokinetics, in *Clinical Pharmacokinetics — A Symposium*, Levy, G., Ed., American Pharmacology Association, Washington, D.C., 1974, 1–9.
2. Whiting, B. et al., Clinical pharmacokinetics: a comprehensive system for therapeutic drug monitoring and prescribing, *Br. Med. J. (Clin. Res. Ed.)*, 288(6416):541–545, 1984.
3. Mungall, D. et al., Individualizing theophylline therapy: the impact of clinical pharmacokinetics on patient outcomes, *Ther. Drug Monit.*, 5(1):95–101, 1983.
4. Ried, L. D., McKenna, D. A., and Horn, J. R., Meta-analysis of research on the effect of clinical pharmacokinetics services on therapeutic drug monitoring, *Am. J. Hosp. Pharm.*, 46(5):945–951, 1989.
5. Ried, L. D., Horn, J. R., and McKenna, D. A., Therapeutic drug monitoring reduces toxic drug reactions: a meta-analysis, *Ther. Drug Monit.*, 12(1):72–78, 1990.
6. Schumacher, G. E. and Barr, J. T., Making serum drug levels more meaningful, *Ther. Drug Monit.*, 11(5):580–584, 1989.
7. Schumacher, G. E. and Barr, J. T., Using population-based serum drug concentration cutoff values to predict toxicity: test performance and limitations compared with Bayesian interpretation, *Clin. Pharm.*, 9(10):788–796, 1990.
8. Schumacher, G. E., Choosing optimal sampling times for therapeutic drug monitoring, *Clin. Pharm.*, 4(1):84–92, 1985.
9. Sadee, W. and Beelen, G. C. M., *Drug Level Monitoring*, John Wiley & Sons, New York, 1980.
10. Matzke, G. R. et al., Pharmacokinetics of vancomycin in patients with various degrees of renal function, *Antimicrob. Agents Chemother.*, 25(4):433–437, 1984.
11. Cockcroft, D. W. and Gault, M. H., Prediction of creatinine clearance from serum creatinine, *Nephron*, 16(1):31–41, 1976.

12. Haycock, G. B., Schwartz, G. J., and Wisotsky, D. H., Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults, *J. Pediatr.*, 93(1):62–66, 1978.
13. Sawchuk, R. J. and Zaske, D. E., Pharmacokinetics of dosing regimens which utilize multiple intravenous infusions: gentamicin in burn patients, *J. Pharmacokinet. Biopharm.*, 4(2):183–195, 1976.