6 INTERPRETATION OF SERUM DRUG CONCENTRATIONS

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OBJECTIVES

After completing this chapter, the reader should be able to

- Justify the need for concentration monitoring of a drug based on its characteristics and the clinical situation
- Identify and justify information needed when requesting and reporting drug concentrations
- Describe and categorize factors that may contribute to interpatient variation in a therapeutic range of drug concentrations
- Explain the importance of documenting the time a sample is obtained relative to the last dose, as well as factors that can affect interpretation of a drug concentration, depending on when it was obtained
- Compare linear to nonlinear pharmacokinetic behavior with respect to how drug concentration measurements are used to make dosage regimen adjustments
- Describe how altered serum binding, active metabolites, or stereoselective pharmacokinetics can impact the interpretation of drug concentration measurements

The pharmacist is a key member in the therapeutic drug monitoring process. This chapter is designed to review the indications for drug concentration monitoring and to discuss how drug concentrations obtained from the clinical laboratory, specialized reference laboratory, or physician's office should be interpreted. General considerations for interpretation will be described, as well as unique considerations for drugs that commonly undergo therapeutic drug monitoring. Future directions of therapeutic drug monitoring will also be discussed.

This chapter is not intended to provide an in-depth review of pharmacokinetic dosing methods; nevertheless, knowledge of certain basic pharmacokinetic terms and concepts is expected. The general phrase *drug concentration* will be used throughout the chapter unless specific references to serum, plasma, whole blood, and saliva are more appropriate. The bibliography lists numerous texts about therapeutic drug monitoring and clinical pharmacokinetic principles with applications to clinical practice.

THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring is broadly defined as the use of drug concentrations to optimize drug therapy for individual patients.[1] Prior to using drug concentrations to guide therapy, physicians adjusted drug doses based on their interpretation of clinical response. In many cases, drug doses were increased until obvious signs of toxicity were observed (e.g., nystagmus for phenytoin or tinnitus for salicylates). The idea that intensity and duration of pharmacologic response depended on serum drug concentration was first reported by Marshall and then tested for the screening of antimalarials during World War II.[2,3] Koch-Weser, in a hallmark paper, described how steady-state serum concentrations of commonly used drugs can vary 10-fold among patients receiving the same dosage regimen.[4] He further described how serum concentrations predict intensity of therapeutic or toxic effects more accurately than dosage.

Starting in the 1960s, there was rapid improvement in analytical methods used for drug concentration measurements; extensive research correlating serum or plasma drug concentrations with clinical efficacy and toxicity quickly followed. In the 1970s, physicians, pharmacists, and laboratory technologists began forming specialized therapeutic drug monitoring or clinical pharmacokinetics services in hospitals. Today, with the emergence of immunoassays that require no specialized equipment, drug concentration measurements can be easily performed in physician offices.[5]

The increased availability and convenience of drug assay methods has led to a number of concerns. Is therapeutic drug monitoring being done simply because it is available, rather than because it is clinically necessary? There are numerous reports of suboptimal therapeutic drug monitoring practices that contribute to inappropriate decision making as well as wasted resources.[6-8] Questions are also being raised about whether therapeutic drug monitoring actually improves patient outcomes.[9,10] However, many clinicians claim that therapeutic drug monitoring is greatly underused and could, if appropriately used, further improve patient care and reduce healthcare costs.[11-13] Clearly, there is a need for more education of all healthcare professionals

involved in the therapeutic drug monitoring process to make its use more appropriate and cost-effective. Such education efforts have been shown to effectively reduce the numbers of inappropriate drug concentration requests.[14]

Goal and Indications for Drug Concentration Monitoring

The primary goal of therapeutic drug monitoring is to maximize the benefit of a drug to a patient in the shortest possible time with minimal risk of toxicity. The number of hospitalizations or office visits used to adjust therapies or manage and diagnose adverse drug reactions may therefore be reduced, resulting in cost savings.

Drug concentration measurements should not be performed unless the result will affect some future action or decision. Monitoring should not be done simply because the opportunity presents itself; it should be used discriminatingly to answer clinically relevant questions and resolve or anticipate problems in drug therapy management.[15] The clinician should always ask, "Will this drug concentration value provide more information to me than sound clinical judgment alone?"[9] The following are examples of clinical situations and the clinical questions that drug concentration measurements might be able to answer:

- **Therapeutic confirmation**—A patient is on a regimen that appears to offer maximum benefit with acceptable side effects. *Question: What is the drug concentration associated with a therapeutic effect in this patient for future reference?*
- **Dosage optimization**—A patient has a condition in which clinical response is not easily measured and has been initiated on a standard regimen of a drug. There is modest improvement and no symptoms of toxicity are evident. *Question: Can I increase the dose rate to further enhance effect? If so, by how much?*
- **Confirmation of suspected toxicity**—A patient is experiencing certain signs and symptoms that could be related to the drug. *Question: Are these signs and symptoms most likely related to a dose rate that is too high? Can I reduce the daily dose, and, if so, by how much?*
- **Avoidance of inefficacy or toxicity**—A patient is initiated on a standard regimen of an antibiotic that is known to be poorly absorbed in a small percentage of patients. Sustained subtherapeutic concentrations of this drug can lead to drug resistance. *Question: Will a higher daily dose be needed in this patient?* A patient has been satisfactorily treated on a dosage regimen of Drug A. The patient experiences a change in health or physiologic status or a second drug, suspected to interact with Drug A, is added. *Question: Will a dosage regimen adjustment be needed to avoid inefficacy or toxicity?*
- **Distinguishing nonadherence from treatment failure**—A patient has not responded to usual doses and noncompliance is a possibility. *Question: Is this a treatment failure, or does the patient need counseling on adherence?*

Characteristics of Ideal Drugs for Therapeutic Drug Monitoring

Not all drugs are good candidates for therapeutic drug monitoring, no matter how appropriate the indication seems to be. Those for which drug concentration monitoring will be most useful have the following characteristics[16]:

- **Readily available assays**—Methods for drug concentration measurement must be thoroughly evaluated for sensitivity, specificity, accuracy, and precision and be available to the clinician at a cost to justify the information to be gained. Chromatographic methods are most likely used in laboratory settings and are considered in many cases to be the reference methods. Increased interest in methods for use in ambulatory settings, however, has led to the development of immunoassay systems purported to be fast, reliable, and cost-effective.[5,18-21]
- **Lack of easily observable, safe, or desirable clinical endpoint**—Clinically, there is no immediate, easily monitored, and predictable clinical parameter to guide dosage titration. For example, waiting for arrhythmias or seizures to occur or resume may be an unsafe and undesirable approach to dosing antiarrhythmics and antiepileptics.
- **Dangerous toxicity or lack of effectiveness**—Toxicity or lack of effectiveness of the drug presents a danger to the patient. For example, serum concentrations of the antifungal drug, flucytosine, are not routinely monitored. However, specialized monitoring may be done to ensure that concentrations are below 100 mg/L to avoid gastrointestinal side effects, blood dyscrasias, and hepatotoxicity. As another example, specialized monitoring of the protease inhibitors (PIs) may be done to ensure adequate concentrations because rapid emergence of antiviral resistance is observed with sustained exposure to subtherapeutic concentrations.
- **Unpredictable dose–response relationship**—There is an unpredictable dose–response relationship, such that a dose rate producing therapeutic benefit in one patient may cause toxicity in another patient. This would be true for drugs that have significant interpatient variation in pharmacokinetic parameters, drugs with nonlinear elimination behavior, and drugs with pharmacokinetic parameters that are affected by concomitant administration of other drugs. For example, patients given the same daily dose of phenytoin can demonstrate a wide range of serum concentrations and responses.
- **Narrow therapeutic range**—The drug concentrations associated with therapeutic effect overlap considerably with the concentrations associated with toxic effects, such that the zone for therapeutic benefit without toxicity is very narrow. For example, the therapeutic range of total serum concentrations of phenytoin is widely accepted to be 10–20 mg/L for most patients; the upper limit of the range is only twice the lower limit.