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How Clinicians Use Therapeutic Drug Monitoring

ABSTRACT *Medical practitioners consult the laboratory to monitor drug levels to reduce toxicity, to manage cases of drug overdose, to determine how to compensate for the impact of drug interactions, to reduce pharmaceutical costs, and to evaluate patient compliance with treatment. In this article, we describe why therapeutic drug monitoring is used and what factors help determine proper dosage of a drug.*

This is the first article in a three-part series on therapeutic drug monitoring (TDM). Other articles discuss pharmacokinetics and pitfalls in TDM. On completion of this series, the reader will be able to explain the role of TDM in establishing a dosage; identify parameters needed to perform TDM; list preanalytic and analytic factors that contribute to accurate laboratory analysis of therapeutic drugs; list the factors that must be considered to time the collection of samples for TDM properly; and describe reasons for unexpected high and low TDM results.

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Therapeutic drug monitoring (TDM) has gained wide popularity among clinicians during the past two decades. Clinicians use the results to calculate a dosage tailored to the patient's needs. When clinicians determine the dosage, they use TDM only as a guide to treatment, not as the sole criterion. With TDM, a maximum therapeutic response with minimal side effects can be achieved.

TDM is used to evaluate serum drug levels. It is important to remember that TDM does not mean merely determining whether a serum level is above, within, or below a therapeutic range. It encompasses looking at a serum level in relation to the patient's clinical status, medication profile, and medical history to determine whether a change in the dosage is necessary. After all, clinicians treat patients—not serum levels.

Determining the Patient's Response to the Dosage

The most important parameters used to calculate the best dosage are half-life, volume of distribution, and clearance (see Glossary). If the half-life is known and first-order kinetics are assumed, the value of a serum level at any point in time after the drug is administered can be calculated. The clinician then can predict the time a level would become subtherapeutic. This would be the time to give the next dose.

The practitioner uses the volume of distribution (Vd) to calculate the dosage needed to clinically change the serum level.

Clearance is important because it is used to calculate the dose required to maintain a steady-state serum drug level.

The following scenario usually occurs in the clinical setting: An initial dose is based on a ratio of milligrams of the drug to the patient's body weight in kilograms. Steady-state serum drug levels then are obtained. These values are entered into computer-based software or a programmable calculator. Based on these levels, half-life, Vd, and clearance are derived. Using these parameters, a new dosage is calculated and is given to the patient only if the clinical situation warrants it. For example, if the serum levels are subtherapeutic and the patient's condition is worsening, an increase in dose would be indicated. Conversely, if the serum levels are subtherapeutic, but the patient's condition is improving, a change in dose would not be necessary.

Why Clinicians Order TDM

The practitioner uses TDM for a variety of reasons from diagnosis to treatment.

To Monitor or To Confirm Overdose

Therapeutic drug monitoring can assist the practitioner in identifying drug overdose and in tracking the progress of treatment administered to counteract the overdose. For example, acetaminophen is metabolized primarily to two nonreactive metabolites and one reactive (toxic) metabolite. In a patient who has overdosed on

acetaminophen, the pathways that convert the drug to the nonreactive metabolites become saturated, increasing production of the reactive metabolite. This reactive metabolite causes the liver toxicity associated with acetaminophen overdose. By obtaining a plasma acetaminophen level and knowing the time after ingestion, a clinician can refer to a nomogram[1] to evaluate the probability of liver toxicity.

To Determine the Dosage of a Medication

For the most part, medications exhibit either first-order (linear) kinetics or saturation (Michaelis-Menten or nonlinear) kinetics. Some medications, such as the anticonvulsant phenytoin, exhibit first-order kinetics at lower doses, but saturate the metabolic pathway at higher doses. Saturation kinetics occurs then, and the serum drug level is less predictable.

To Evaluate the Impact of the Patient's Social Habits and Disease States

Patients' social habits, such as smoking and drinking, and medical conditions can influence serum levels of medications. For example, smokers clear theophylline, a bronchodilator, faster than nonsmokers,[2] and thus have lower serum levels of this drug. Smokers therefore would require higher dosages of theophylline than nonsmokers. If they quit smoking, they eliminate this drug more slowly and become at risk for toxicity. Monitoring this drug has become more significant with the availability of nicotine patches and gums over the counter. Patients can stop smoking without their clinicians' knowledge.

Conversely, patients with congestive heart failure eliminate theophylline slowly[3] and therefore produce higher serum levels for this drug than the average patient. Patients with renal disease slowly eliminate drugs that are metabolized in the kidney. Thus their serum levels are high for such medications as vancomycin, aminoglycosides, and digoxin, which are eliminated predominantly by the kidney.

To Minimize Toxicity

Practitioners order medication levels to minimize or avoid adverse drug reactions in drugs that have a narrow therapeutic range. For a medication that has a narrow therapeutic range (sometimes called narrow therapeutic window), the amount of drug needed to benefit the patient approaches the toxic range. Drugs with a narrow therapeutic range include digoxin, lithium, aminoglycoside antibiotics (ie, gentamicin, tobramycin, netilmicin, and amikacin), phenytoin, and theophylline (Table).

Administering the total daily dosage of aminoglycosides as one dose a day improves patient outcomes and reduces toxicity. This technique pushes peak levels above the recommended therapeutic peak range and into the toxic range. Toxicity is avoided because the levels do not remain consistently higher than the therapeutic range. The recommendation for peak and trough concentrations for a once-daily dosage of gentamicin is 16 to 26 μg/mL, and for tobramycin, less than 1 μg/mL.[4]

Methotrexate is an antineoplastic drug used in the treatment of cancer. When given in high doses, methotrexate is driven into the tumor cells. Unfortunately, the toxicity methotrexate imparts to tumor cells also can affect normal cells. Leucovorin, an antidote for methotrexate toxicity, can selectively rescue normal cells by providing folinic acid to them. Leucovorin continues to be administered until the methotrexate level has fallen below toxic levels.[5] The monitoring of methotrexate levels has reduced the occurrence of toxicity and morbidity.[6,7]

Glossary

Bioavailability—the amount of a drug that is absorbed

Clearance—the rate (volume over time) at which a drug is cleared from the body

First-order kinetics—the metabolism of a drug in the body in which the serum drug level is proportional to the dose, eg, double the dose, double the serum drug level

Half-life—the time it takes a drug level to be reduced by 50%

Peak concentration—the serum drug level obtained after a drug has been administered; varies with the drug because it depends on the drug's distribution phase; from one half-hour to one hour

Pharmacokinetics—the study of how drugs are absorbed, metabolized, distributed, and eliminated

Saturation or Michaelis-Menten or nonlinear kinetics—the metabolism of a drug in the body in which the drug level is disproportional to the dose because all elimination sites have been taken up

Steady state—when the rate a drug is administered equals the rate at which it is eliminated

Trough concentrations—the serum concentration obtained before administering the next dose

Volume of distribution—the apparent volume a drug distributes in the human body

THERAPEUTIC RANGE *VS* TOXIC RANGE

Drug	Therapeutic Range*	Toxic Range	Signs of Toxicity
Digoxin[†,‡]	0.9–2 ng/mL	> 2 ng/mL	Arrhythmia, nausea and vomiting, altered color vision
Lithium[†,§]	0.6–1.4 mEq/L	1.2–1.5 mEq/L > 1.5 mEq/L > 3.0 mEq/L	Mild: Hand tremors, nausea, vomiting Moderate: Agitation, nystagmus (involuntary, rhythmic rapid eye movements) Severe: Seizures, respiratory complications
Gentamicin, Tobramycin, Netilmicin[†,‖]	Peak: 5–10 μg/mL Trough: < 2 μg/mL	Peak: > 12–14 μg/mL Trough: > 2 μg/mL	Kidneys Problems with hearing and balance
Amikacin[†,‖]	Peak: 20–30 μg/mL Trough: < 5 μg/mL	Peak: > 32–34 μg/mL Trough: > 8–10 μg/mL	Kidneys Problems with hearing and balance
Phenytoin[†,#]	10–20 μg/mL	> 20 μg/mL	Nausea, vomiting, headache, diarrhea, arrhythmias
Theophylline[†,**]	10–20 μg/mL	> 20 μg/mL	Nystagmus and gait disturbances

*The therapeutic range depends on the patient's medical condition.

† Bauer LA. Individualization of drug therapy: clinical pharmacokinetics and pharmacodynamics. In: Young LY, Koda-Kimble MA, eds. *Applied Therapeutics: The Clinical Use of Drugs.* 6th ed. Vancouver, Wash: Applied Therapeutics; 1995:15–31.

‡ Keys PW, Stafford RW. Digoxin: therapeutic use and serum concentration monitoring. In: Taylor WJ, Finn AL. *Individualizing Drug Therapy: Practical Applications of Drug Monitoring.* New York, NY: Gross, Townsend, Frank; 1981;3:1–21.

§ Fankhauser MP. Bipolar disorders. In: DiPiro JT, Talbert RL, Hayes PE, Yee GC, Matzke GR, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach.* 2nd ed. East Norwalk, Conn: Appleton & Lange; 1993;1044–1064.

‖ Zaske DE. Aminoglycosides. In: Evans WE, Schentag JJ, Jusko WJ, eds. *Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring.* 3rd ed. Vancouver, Wash: Applied Therapeutics; 1992:14.1–14.47.

Tozer TN, Winter ME. Phenytoin. In: Evans WE, Schentag JJ, Jusko WJ, eds. *Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring.* 3rd ed. Vancouver, Wash: Applied Therapeutics; 1992:25.1–25.44.

** Edwards DJ, Zarowitz BJ, Slaughter RL. Theophylline. In: Evans WE, Schentag JJ, Jusko WJ, eds. *Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring.* 3rd ed. Vancouver, Wash: Applied Therapeutics; 1992:13.1–13.38.

To Minimize Dosages

Practitioners may order the measurement of serum drug levels to give the patient just enough drug while maximizing the clinical outcome and avoiding toxicity. For example, aminoglycoside antibiotics concentrate in the urine. After 1 hour, urine concentrations can be 24 to 75 times greater than peak plasma concentrations.[8] To reduce the risk for adverse side effects, a lower dose is required to treat urinary tract infections than that required to treat pulmonary or blood infections.

To Save Money

Sveska and colleagues compared patients monitored by a TDM service with those who were not.[9] Length of drug therapy and length of hospital stay were significantly shorter for the patients monitored by the service.

Adjusting the dosage to the lowest amount clinically necessary can reduce drug expenditures.[10] Also, when pharmacists schedule the time at which samples must be drawn (in relation to the administration of the drug), the number of improperly drawn samples has been reduced,[11,12] decreasing unnecessary laboratory work.

To Monitor for Active Metabolites

Practitioners may monitor serum levels to assess the clinical impact of active metabolites, byproducts of the metabolism of an administered drug. Active metabolites cause a therapeutic effect similar to that of the administered drug, although its potency may be different. Procainamide, an antiarrhythmic, breaks down to N-acetylprocainamide (NAPA). This conversion depends on

an enzyme called N-acetyltransferase. Some individuals are fast acetylators, meaning they convert more procainamide to N-acetylprocainamide than slow acetylators.[13] An estimated 80% of Asians and 50% of blacks and whites are rapid acetylators. As such, they convert about 30% of a procainamide dose to N-acetylprocainamide, compared with 15% for slow acetylators. It is important, therefore, to monitor NAPA and procainamide levels concurrently.

To Explain How a Medication Failed

Patients do not always comply with the regimen prescribed to them. It has been estimated that $22 billion to $37 billion are spent as a result of this type of noncompliance.[14] Monitoring medication levels is a useful tool in tracking compliance. For example, a clinician evaluating a patient who takes phenytoin for seizures can use TDM to rule out noncompliance if the seizures continue. Establishing that the patient is not following the treatment plan might prevent the clinician from adding second-line drugs or unnecessarily increasing the dosage.

To Monitor Interactions Between Drugs

Through TDM, interactions between drugs can be identified and the dosage adjusted accordingly. For example, cimetidine, used to treat duodenal ulcers, inhibits the hepatic mixed-function oxidase system in which cytochrome P-450 has an important role. The P-450 system also metabolizes phenytoin and theophylline, whose levels increase when these drugs are combined with cimetidine.[15,16]

Phenobarbital is a hepatic enzyme-inducer that increases the metabolism and elimination of phenytoin and theophylline.[17] Phenobarbital, therefore, decreases serum levels of phenytoin and theophyline. Changes in the serum level of phenytoin or theophylline can be significant because these drugs have narrow therapeutic ranges.

Medications eliminated by the kidney also can interact with each other. Probenecid and penicillin are eliminated by active tubular secretion in the kidneys.[18] Penicillin levels are higher and last longer when probenecid is administered to the patient before penicillin.[19]

Interactions between drugs also affect oral absorption and protein binding of medications. Medications that decrease absorption of other medications include cholesterol-binding resins, which lower cholesterol. These drugs bind with fat-soluble vitamins, digoxin, and anticoagulants.[20] Medications that alter gastrointestinal pH can alter the absorption of medication. Antacids increase gastric pH altering disintegration, dissolution, solubility, and gastric emptying time. Absorption of weakly acid drugs (eg, digoxin and phenytoin) decreases with antacids, diminishing the pharmaceutic effect. In contrast, absorption of weakly basic drugs (eg, pseudoephedrine and levodopa) increases with antacids, possibly causing toxicity.[21]

To Monitor Drug Interactions With Food

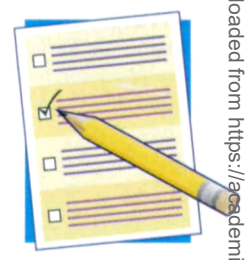
Food can delay or reduce the absorption of medication. For the most part, a delay is not clinically significant unless a rapid response from the drug is required. Reducing a drug's absorption, however, can be clinically significant. Food reduces the bioavailability of theophylline sprinkle, a form of theophylline intended to be dispersed on the patient's food, by 50%.[22] Monitoring serum levels would identify a reduction in absorption, which can be compensated by increasing the dosage.

What Happens to Medication in the Body

The laboratory professional and the clinician should understand the kinetic principles of the drug being monitored. It makes a difference whether a drug follows first-order kinetics or saturation kinetics. To double the steady-state serum level of a drug that follows first-order kinetics, the dose must be doubled. Saturation kinetics occurs when enzymes used to eliminate or metabolize drugs are fully occupied, causing the serum concentration to rise disproportionately to the dosage. Doubling the dosage of a drug that follows saturation kinetics may result in more than double the serum concentration.

Theophylline is a medication that follows first-order kinetics. At therapeutic concentrations and higher, phenytoin follows saturation kinetics. It is fairly easy to calculate the dosage of theophylline after obtaining a steady-state level. In contrast, it is more difficult to establish a dosage for phenytoin, which needs to be followed more closely.

Accurate sample and administration times are very important to TDM. Invalid sampling and administration times yield false pharmacokinetic calculations causing dosages to be adjusted improperly. A falsely elevated peak level will be obtained if serum is drawn immediately after the drug is administered because the drug has not



Test Your Knowledge

Look for the CE Update exam on Therapeutic Drug Monitoring (705) in the October issue of *Laboratory Medicine*. Participants will earn 3 CMLE credit hours.

passed the distribution phase. A falsely elevated peak level will result in a lower calculated volume of distribution, causing in turn the practitioner to calculate a dosage that is too low. To draw a peak aminoglycoside level, wait 30 minutes after the infusion is completed. The dosage also can be miscalculated if the draw time is not noted correctly.

A coordinated effort among the practitioner, the nurse administering the drug, and phlebotomist drawing the sample contributes to the accurate reporting of sampling and administering times. In our experience, documentation sheets and reminder stickers can be useful tools.

Conclusions

Therapeutic drug monitoring will continue to be an important tool in health care. Successful TDM programs require a coordinated effort among physicians, clinical pharmacists, and laboratory personnel. Therapeutic drug monitoring can reduce overall health care costs and improve patient outcomes.

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Internet Resources

Here are some Internet sites that offer more information on topics discussed in this issue of Laboratory Medicine.

Clinical Research

Association of Clinical Research Professionals Home Page
http://www.acrpnet.org

Health of Elderly Patients

"Information for Older Persons, Their Families, and People Interested in Aging," sponsored by Department of Health and Human Services' Administration on Aging
http://www.AoA.DHHS.GOV/aoa/pages/info.html

HELLP Syndrome

Case Study in Gynecologic Pathology from the University of Pittsburgh Medical Center's Department of Pathology: "Complications of Pregnancy"
http://www.pathology.pitt.edu/cases/case75.html

Pap Smear

Cervical Cancer: Screening and Prevention of Invasive Disease by Mitchel S. Hoffman, MD, and Dennis Cavanagh, MD, Gynecologic Oncology Program at H. Lee Moffitt Cancer Center & Research Institute published in the *Cancer Control Journal* (November/December 1995)
http://daisy.moffitt.usf.edu/cancjrnl/v2n6/article3.html

National Cancer Institute Cancer WEB's "Screening for Cervical Cancer"
http://www.graylab.ac.uk/cancernet/304728.html

Therapeutic Drug Monitoring

University of Oklahoma's College of Pharmacy's "A First Course in Pharmacokinetics and Biopharmaceutics"
http://157.142.72.143/gaps/pkbio/pkbio.html

Pocket Guide to Diagnostic Tests: Chapter 4—Therapeutic Drug Monitoring: Principles and Test Interpretation (Appleton & Lange, 1992) (site sponsored by the University of California–San Francisco's Division of General Internal Medicine)
http://dgim-www.ucsf.edu/People/Publications/Detmer/GDT-Ch4.html

These sites are offered for reader information only. A site's presence on this list does not constitute an endorsement by the ASCP.