Therapeutic drug monitoring (TDM) is commonly used to maintain “therapeutic” drug concentrations. Even in compliant patients, with “average” drug kinetics, TDM is useful to identify the causes of unwanted or unexpected responses, prevent unnecessary diagnostic testing, improve clinical outcomes, and even save lives. TDM has greatest promise in certain special populations who are: (a) prone to under- or overrespond to usual dosing regimens, (b) least able to tolerate, recognize, or communicate drug effects, or who are (c) intentionally or accidentally misdosed. TDM is especially useful in patients at the extremes of age, in adolescents, and in patients who are either taking multiple drugs or expressing unusual pharmacokinetics as a result of physiological, environmental, or genetic causes. Less-well-appreciated uses of TDM include prevention of dangerous underdosing of patients, investigation of adverse drug reactions, and identification of serious medication errors, even for a number of drugs that are not traditionally monitored. TDM can be useful for some drugs in any patient and for most drugs in some special populations.

Therapeutic drug monitoring (TDM) is the process of quantifying drug concentrations in patients and using these measurements to design individualized dosing regimens (dose, formulation, route, and frequency of administration) [1]. TDM is relatively new, but the potential for TDM to improve care is being increasingly recognized [2–7]. When performed correctly, TDM has been shown to efficiently maximize efficacy and minimize toxicity in many patient populations [8, 9]. TDM has become a routine method to maintain “therapeutic” concentrations of numerous drugs [10]. However, it requires drug concentrations to be interpreted for each specific patient’s complete clinical, pharmacokinetic, and pharmacodynamic information. Unfortunately, too many laboratories report (and laboratory certifying bodies accept) “numbers only”—i.e., concentration without complete and accurate medical and drug dosing information. When done poorly, as in a “numbers only” laboratory, TDM has not been effective [11] and can be dangerous [12].

For decades, clinicians have recognized that different patients given the same dose of a medication, even in an identical formulation, might have qualitatively or quantitatively different responses [1]. Not until reliable measurements of drug concentrations in bodily fluids became available, however, was it proven that many of these differences in dose/response relationships were the result of large interindividual differences in drug concentrations achieved in patients given identical doses. These dose/concentration differences were shown to be the result of wide interindividual variations in the absorption, distribution, and elimination of medications: pharmacokinetics (PK)1. These PK differences explained most of the interindividual differences in dose/response relationships. More recently, some differences in concentration/response relationships (pharmacodynamics; PD) have also been verified. Interindividual variations in PK and PD are especially important in “special populations,” who are more likely to either under- or overrespond to usual dosing regimens; who are least able to tolerate, recognize, or communicate drug effects; who have organ dysfunction; or who are intentionally or accidentally dosed incorrectly. I will here review some examples of special populations where TDM is useful to either predict or prevent toxicity or improve therapeutic outcomes. This review will not be exhaustive; rather I will concentrate on some of the more common or clinically most meaningful situations.

Important special populations where TDM is useful include patients at the extremes of age, patients with dosing problems, patients taking multiple medications, and patients who have unusual PK as a result of physiological, environmental, disease, or genetic factors [1].

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1 Nonstandard abbreviations: PK, pharmacokinetics; PD, pharmacodynamics; DLIS, digoxin-like immunoreactive substances; MEGX, monoethylglycinexylidide; and IV, intravenous.
PATIENTS AT THE EXTREMES OF AGE [13, 14]
Both the very young and the very old have characteristics that make them more likely to benefit from TDM [15]. PK and PD behavior [16] differ greatly in both populations, compared with “normal” adult populations. All PK processes are involved. Absorption may be altered by differences in gastroenterological physiology. Dosing uncertainty is a problem in both the very old and the very young as a result of erroneously measured, refused, vomited, repeated, or forgotten doses. Neither a 0.5-kg neonate nor a 50-kg 80-year-old woman is likely to have the same response to a dose that is ideal for a healthy 100-kg young man. Lack of suitable formulations is also responsible for dosing errors in both populations. A dosing error is also very easy when one is trying to administer to an infant 0.1 mg of morphine from a 50 g/L or even a 1 g/L morphine solution. Distribution of drugs is also altered in these populations because of differences in body composition. Even weight can change dramatically in these populations during a single course of therapy.

Clearance of drugs (both metabolic and renal) is altered by age and disease-related changes, as well as by drug and diet interactions. In general, clearance is decreased at the extremes of age and may change significantly during a single course of therapy [17, 18]. PD differences also occur, as a result of changes in end-organ responsiveness, receptor function, protein binding, and agonist or antagonist concentrations. The ability to tolerate or communicate drug effects is also diminished at both extremes of age.

A number of unique, practical additional considerations are present in neonates [19]. Therapeutic ranges for some drugs are quite different; e.g., therapeutic theophylline concentrations are lower for neonates (5–15 mg/L) than for adults (10–20 mg/L). Moreover, time of drug administration is not simple to determine in neonates; it may take hours for a dose, even if administered into an intravenous line, to actually reach a neonate [20]. Assay interference from endogenous substances is also more common than in adults; e.g., digoxin-like immunoassay substances (DLIS) are much more of a problem in neonates [21]. Neonates may also show different ratios of parent drug to metabolites, the hydroxy metabolite of phenobarbital and its glucuronide conjugate being present in much higher concentrations in neonates than in older subjects. Metabolic pathways may differ qualitatively as well as quantitatively. Caffeine is present in significant quantities in neonates who are given theophylline—a result of the metabolism of theophylline. Protein binding can be quite different in neonates, producing very different therapeutic ranges for highly protein-bound drugs such as phenytoin. Drugs administered to the mother may enter a newborn’s system as a result of either placental transfer or ingestion from breast milk. Finally, concentrations of drugs given either by aerosol (e.g., aminoglycosides) or orally (e.g., digoxin or theophylline) can be artifically greatly increased because of skin contamination of skin puncture samples, as a result of aerosol deposition; or by finger to mouth (or even foot to mouth) transfer of orally administered drug to skin sampling sites. These are only some of the many individual factors that must be considered when doing TDM in this special population [18].

OVER- AND UNDERDOSE
Both intentional and accidental dosing errors are common in almost all populations. Over- and underdosing can occur in patients with either chronic or acute diseases [22, 23]. Some of these errors are the result of formulation or of age-related problems (see above), but many are common in all populations. Underdosing is common in adolescents, who want to deny their need to take medication. Underdosing can also be an attempt at self-harm. Neither the severity of disease nor the patient’s understanding predicts compliance [24]. Poor compliance is seen in patients with life-threatening asthma [25] and is also one of the most common causes of organ transplant rejection episodes in adolescents, for example [26].

Overdose is a form of overcompliance and can occur as a result of poor understanding, drug abuse (opioids or stimulants), or a desire to hasten or increase the magnitude of effects (acne or asthma medications). Suicide must also always be considered in adolescent compliance problems, both under- and overcompliance. Compliance problems are common but difficult to detect without TDM [27–29]. Because physicians have been shown to have a no-better-than-chance probability of predicting which patients will be compliant or not, one could argue that TDM is indicated, even if only to check on compliance, for any agent for which poor compliance could be dangerous. This would include many drugs for which no currently available commercial assays exist. Important examples include drugs for AIDS [30] and tuberculosis [31], where drug resistance (as a result of poor compliance) can have major economic and public health consequences.

MULTIPLE MEDICATIONS [32]
Patients receiving multiple medications also constitute a large “special population” [33]. TDM can be useful in these patients to detect important drug interactions that can alter absorption, clearance, or protein binding. The larger the number of drugs, the more probable a significant interaction. Indeed, patients receiving eight or more drugs (e.g., a surprisingly high percentage of hospitalized, chronically ill, or elderly patients) [34] have essentially a 100% chance of a significant drug–drug interaction. Patients on multiple drugs are also more likely to have altered and changing PK or PD characteristics.

ABNORMAL RESPONSES TO DOSAGE REGIMENS [35]
Many “normal” patients who reliably take an “average” dose of an acceptable formulation of an effective medication will have acceptable efficacy with minimal or no toxicity. These patients are likely to do well without TDM
when placed on textbook dosage regimens. Many patients, however, including many hospitalized patients, do not do well on standard dosage regimens. Some have toxic symptoms, others have inadequate efficacy, some have both. Several PK and PD causes of these suboptimal responses—e.g., unusual absorption, distribution, metabolism, elimination, or end organ responsiveness—can be identified with TDM. TDM results that are either excessive or low but consistent with clinical observations (i.e., lack of response associated with unexpectedly low concentrations, or very high concentrations associated with signs of toxicity) can provide extremely useful information. This is true both for drugs with a well-established therapeutic range and for many additional agents.

Unfortunately, TDM is too often not considered for medications for which assays have been developed but are either not readily commercially available or for which a therapeutic range has not been established or is said not to exist. Often this is because of lack of training, underutilization of noncommercial but available analytical resources, or biased information provided by pharmaceutical marketing materials. Few healthcare workers are adequately trained to properly utilize TDM results, even for drugs that are routinely monitored. For example, a lack of well-defined therapeutic ranges or of readily available assays is unfortunately often quoted in marketing materials for new drugs and antibiotics. Yet, it can take decades for the potential value of TDM of a new drug to become obvious, and antibiotic TDM may be useful even if only to monitor compliance [36].

Investigation to identify the causes of unusually high or low concentrations can be very useful for many drugs, whether or not a therapeutic range has been identified [1]. Properly interpreted, the TDM results can identify clinically important problems such as over- or undercompliance, medication errors, and several physiological, environmental, genetic, or disease-related conditions. Physiological causes include organ dysfunction (see below), hormonal, or age-related changes. Environmental influences include exposure to chemicals or foods that alter drug metabolism. Tobacco smoke is a potent inducer of drug-metabolizing enzymes, whereas grapefruit juice can substantially inhibit drug metabolism. Medications and environmental toxins such as cadmium can decrease renal function.

Genetic differences in drug metabolism are also an important cause of unusual drug effects or TDM results [37]. Drugs metabolized by the cytochrome P450 enzyme gene superfamily can have large interindividual differences in concentrations as well as unusual, toxic, or therapeutic responses. Measurement of drug and metabolite concentrations in patients with abnormal blood pressure responses when given a certain antihypertensive drug was responsible for the ultimate identification of genetically determined cytochrome P450 polymorphism. Genetic metabolic differences can cause a >30-fold difference in metabolic rate between slow and rapid metabolizers of certain psychotropic, antihypertensive, and anticonvulsant medications.

These metabolic differences can have several important therapeutic implications. For example, there may be a total lack of response to codeine because of inadequate metabolism of codeine to morphine. Differences in isoniazid metabolism are associated with clinically meaningful differences in toxicity as well as altered antituberculosis efficacy and toxicity. Decreases in benzodiazepine efficacy can be the result of either genetically determined, rapid, presystemic metabolism or induction of metabolism by certain drugs. Concurrent use of rifampicin, for example, can almost abolish the effectiveness of midazolam.

PATIENTS WITH ABNORMAL ORGAN FUNCTION
Tests of organ function (renal or hepatic) are commonly used to predict which patients are at greater risk of unusual PK behavior. The opposite is less common: using TDM results to effectively monitor organ function. Use of the rate of formation of monoethylglycinexylidide (MEGX), a metabolite of lidocaine, is being increasingly recognized as an effective method to assess hepatic metabolic function. While debatable perhaps, MEGX concentrations after a dose of lidocaine have been claimed to predict both the need for hepatic transplants and donor organ survival better than do traditional liver function tests. MEGX testing may even be less expensive. Less-well-recognized is the fact that xanthine clearance is also an excellent way to assess hepatic metabolic function and that aminoglycoside clearance may be both more accurate and less expensive than other tests of renal excretory function.

AVOIDING UNDERDOSING
If properly done, TDM can be used to avoid underdosing patients. For many serious conditions, use of less than maximally effective doses is much more toxic (i.e., dangerous) than is overdosing. For example, mortality is greatly increased by underdosing of aminoglycosides in patients with serious infections. Timely TDM testing is imperative to assure rapid institution of maximally effective aminoglycoside doses in septic patients. Similar comments apply to patient populations who are at greater risk of underdosing because of PK differences. Cystic fibrosis patients (e.g.) have both larger volumes of distribution and more rapid clearance of many drugs than unaffected subjects. These and other populations need both higher and more-frequent doses.

Most children past the neonatal period are also at risk of underdosing because of more-rapid clearance in early childhood. Children may require much more frequent doses, as well as greater doses per kilogram of body weight and per day to maintain therapeutic concentrations (e.g., of phenytoin) than do much larger, “normal” adults. Other patients with increased clearance include genetically rapid metabolizers, smokers, and patients receiving enzyme-inducing drugs such as rifampicin.

Paradoxically, patients with slow metabolism may also
be underdosed if given drugs that must be metabolized to be effective, e.g., terfenadine and codeine. Patients receiving enteral feedings are at risk of underdosing of anticonvulsant medications because the tube-feeding solutions may interfere with drug absorption. Renal patients are also often underdosed because of confusion between their need for lower maintenance doses (because of low renal clearance) and their need for greater than usual loading doses to achieve therapeutic concentrations (because of their larger volumes of distribution). A septic, anephric patient may need 4 or 5 mg/kg as an initial gentamicin dose rather than the 2.5 mg/kg given to a “normal” patient, and much more than the 1–2 mg/kg dose recommended by many pocket guides or even renal consultants. In fact, much of the improved efficacy of once-per-day aminoglycoside dosing may plausibly be the more rapid attainment of effective initial concentrations than is achieved by routinely prescribed doses.

**Nontraditional TDM**

TDM is being increasingly recognized as a useful tool for the use of several drugs that have no accepted “therapeutic ranges” or lack readily available assays. The use of area-under-the-curve measurement of anticancer drugs [38–42] is an example of nontraditional TDM. The “therapeutic ranges” for most anticancer drugs have not been well established and, although assays have been well described for many of these drugs, the assays are not widely available. Nonetheless, TDM of anticancer drugs has been clearly shown to both decrease cancer chemotherapy toxicity and increase survival, in comparison with the rigid one-dose-fits-all, protocol-driven, traditional approach to cancer chemotherapy. Measurement of drug concentrations has also been used to document poor compliance or poor absorption of numerous drugs, with or without a well-defined therapeutic range.

The antihistamine terfenadine (Seldane) is another example of the usefulness of nontraditional TDM. There is no therapeutic range for terfenadine, and assays for it are not readily available. The measurement of parent drug and metabolites, however, explained why substantial adverse effects could occur when drugs that blocked terfenadine metabolism were coadministered with it. This is an excellent example of how TDM can explain rare, “idiosyncratic,” adverse drug reactions.

**Medication Errors**

TDM can be useful to detect over- and underdosings that result from physician, pharmacist, nurse, or pharmaceutical medication errors. Identification of such errors can result in correction of important system errors and thereby avoid repeat problems. An example was the discovery at my institution that multiple unfilled aminoglycoside syringes had been sent to the floors as a result of a pharmacy compounding error. This was discovered through an investigation of TDM results that were below what was predicted on the basis of previous TDM results.

Another investigation of unexpectedly low aminoglycoside concentrations in newborns led to the discovery that the first aminoglycoside dose was being delayed for many hours in as many as 25% of premature infants transported to this hospital. This was happening because the first dose that was given by injection into the patient’s intravenous (IV) tubing at an outside hospital was being discarded, in accordance with a policy to change the IV tubing upon a new patient’s arrival. The policy had been made without realizing that a drug put into an IV line can take hours to be delivered to a newborn, i.e., when flow rates are slow.

A final example was the potentially lethal substitution of calcium vials for aminophylline vials, detected as a result of investigation of a theophylline concentration that was too low compared with previous results. Our TDM service has also detected a variety of other medication errors—e.g., errors in dosage calculations (especially 10-fold errors), mistakes in packaging, IV pump programing, and drug administration—by the proper interpretation and investigation of TDM results. Often this interpretation and investigation of a TDM result was the only indication that a problem existed, or the only way that the cause of the problem could have been detected. Almost always the error would have been missed if the result had been reported only as a “number.”

Many of these medication errors had major system implications. Correction of these errors had a major impact on future patient safety and outcomes. Patients in these categories also constitute a large, important “special” population.

Proper PK and PD interpretation of TDM results is both clinically and intellectually rewarding, and TDM is used routinely in several well-known special populations. The TDM approach may, however, be even more useful in other, not as commonly appreciated, special populations.

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