RATIONAL USE OF DRUG CONCENTRATION MEASUREMENTS

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OUTLINE

For most medications, drug concentration monitoring is unnecessary. In contrast, a thorough efficacy and monitoring plan should be developed for every drug a patient receives. At a minimum, this plan should include the following information[1]:

- An understanding of the desired therapeutic outcome of drug therapy and a reasonable length of treatment for the patient
- The potential efficacy and safety of the drug versus other possible therapies for the patient
- Monitoring parameters (eg, laboratory tests, symptom relief, symptoms of toxicity) that will indicate optimum therapeutic outcomes or toxic/adverse reactions caused by the drug

The value of drug concentration monitoring in achieving desired therapeutic outcomes for drugs in which concentration monitoring is generally considered useful is often debated. Some clinicians suggest that concentration monitoring is excessive and, when concentrations are measured, they are frequently used inappropriately. Others consider it a routine part of outcome assessment for several important drugs with narrow therapeutic ranges.

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Drug concentration monitoring is used primarily "for monitoring drugs with narrow therapeutic ranges, drugs with marked pharmacokinetic variability, medications for which target concentrations are difficult to monitor, and drugs known to cause therapeutic and adverse effects" in which it can be assumed that there is a relationship between dose and drug concentration and "between concentration and therapeutic effects."[2]

Clinicians who consider using drug concentration monitoring should always ask themselves the following questions:

- Is the patient already responding as desired to the drug therapy?
- Is the patient having any toxicity that might be related to the drug therapy?
- Are the efficacy and toxicity of this drug better predicted by measuring drug concentrations or evaluating the clinical response?
- Would the results of a drug concentration measurement change the clinical management of the patient if not in the desired range?

Clinicians should carefully establish efficacy and safety goals of therapy and monitor whether they are being achieved, even when drug concentrations are used as an adjunct to regimen evaluation.

For drugs in which concentration monitoring is routinely used but the desired effect of the drug can be easily and quickly measured clinically, the value of measuring its concentration is limited or even potentially harmful if one spends time measuring concentrations at the expense of proper clinical assessment. When the signs and symptoms of benefit and toxicity can be assessed easily and quickly (within hours or, in some cases, days), appropriate dosage adjustments can usually be based on the clinical response of a patient rather than on drug concentrations. When drug concentration monitoring adds to the predictability of response over monitoring a patient clinically, several key issues should be considered before ordering a drug concentration measurement. **Figure 1-1** is a graphic representation of the decision-making process involved in considering those issues.

EVALUATING THE NEED FOR A DRUG CONCENTRATION MEASUREMENT

Drug Selection

Before considering the need for drug concentration monitoring, the first consideration for all drug therapy is appropriateness of the selected drug for obtaining the desired outcome in a specific patient. For instance, evidence suggests that the addition of aminoglycosides, which are routinely monitored with drug concentrations, to other safer antibiotics in patients with sepsis or febrile neutropenia doesn't improve a patient's outcome but does increase the chance of nephrotoxicity.[3,4] Clinicians should ask themselves whether there are potentially equally effective, less toxic, or less expensive alternatives that should be considered (eg, β-lactams alone instead of in combination with aminoglycosides for infections with susceptible organisms, valproic acid in nonpregnant patients instead of phenytoin for certain types of epilepsy, generic alternatives equally effective to a different drug available as brand name only). After it is deemed necessary to use a drug that may require drug concentration monitoring, it is important to determine if efficacy and toxicity are related to drug concentrations in a particular situation.

For example, intravenous vancomycin for the treatment of a systemic infection with methicillin-resistant *Staphylococcus aureus* may necessitate the use of concentration measurements, whereas its use orally for a patient with *Clostridioides difficile* colitis would not be warranted because of the limited absorption of oral vancomycin.

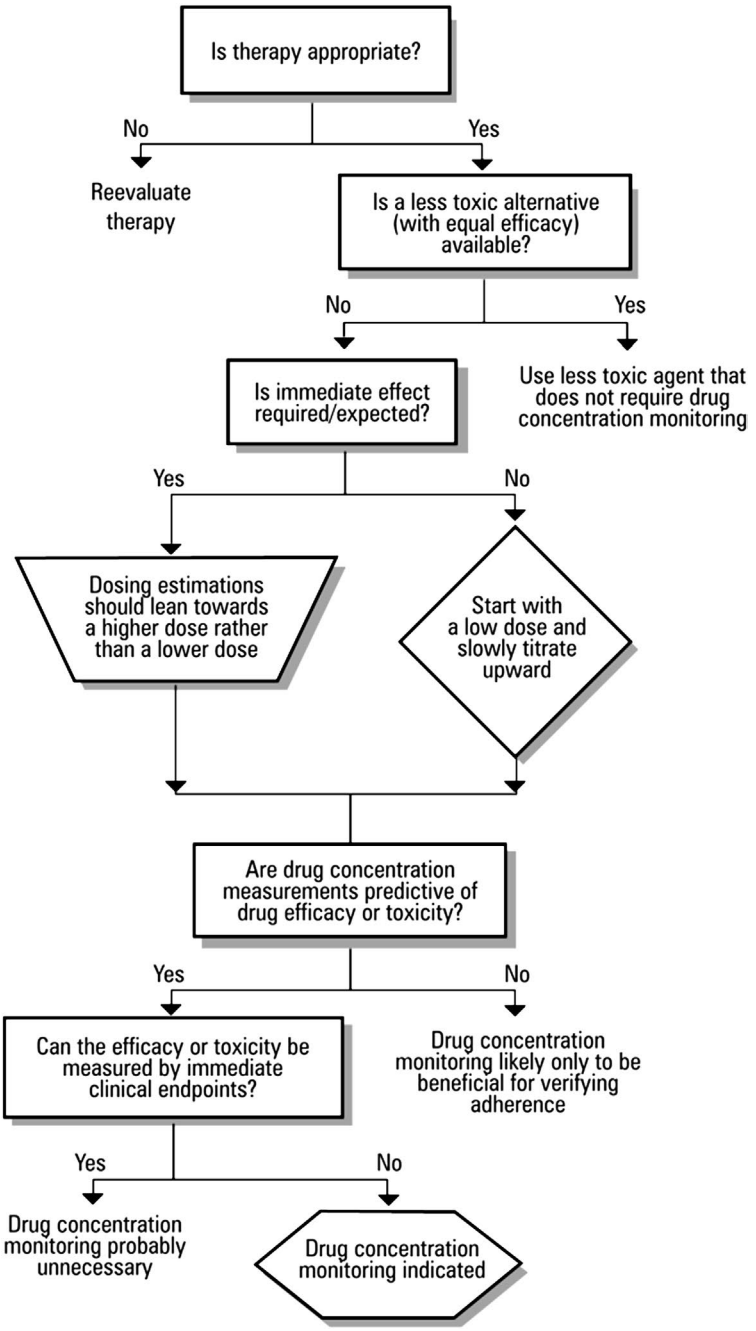

FIGURE 1-1. Decision-making process for using drug concentration measurements focused on efficacy and safety.

Efficacy Concerns

When therapeutic and toxic end points cannot be readily and quickly determined clinically, drug concentration measurements may be useful if research has shown them to be predictive of therapeutic or toxic effects. For instance, in a patient started on an antiepileptic medication for relatively infrequent seizures (every 2–3 months), improved seizure control may not become apparent

for several months. Ensuring that the patient's concentrations are in the generally accepted population therapeutic range may be the best and likely only approach to determining an appropriate dose and schedule.

Clinicians should always ask themselves whether patient outcomes are better predicted by an established "therapeutic range" or by an individual's clinical response. If a clinically important event occurs infrequently (eg, seizures or arrhythmias) or is life threatening, or if the beneficial effect of the drug may be delayed (eg, resolution of depression), the drug concentration found to be effective in similar patients can be used as an initial goal. However, depending on the drug used and the disease state treated, population-based therapeutic ranges may only be weak predictors of therapeutic success because the concentration–effect relationship varies between individuals. Dosage adjustments should be made based on the clinical response whenever possible, using drug concentrations as a guide.

For many patients, there are likely specific threshold concentrations (assuming the drug will be effective or toxic at some point) above which a desired effect is achieved and another at which toxicities start to be seen. Even for drugs with fairly well-established therapeutic ranges, it is best to think of the range as a "gray area" in which the likelihood of toxicity increases as the concentration increases and the likelihood of poor response increases as concentration decreases. For example, some patients may have signs of toxicity in the therapeutic range, other patients may not show signs of toxicity with concentrations somewhat above the therapeutic range, and most patients will have toxicities with concentrations well above the range.

Some clinicians have recommended measuring the drug concentration associated with therapeutic success or toxicity to serve as a benchmark for subsequent therapy. Subsequent failure of therapy or toxicity could be evaluated based on whether concentrations have fallen below or above this established benchmark, respectively. This approach assumes that the threshold for efficacy or toxicity does not change with time. Because physiologic and pathophysiologic conditions can change with time, this assumption may not be valid in all cases.

Toxicity Concerns

When a patient exhibits signs or symptoms of toxicity, a practitioner should first determine if the dosage could likely be decreased or stopped empirically without loss of benefit. If a patient is at risk for toxicity or develops toxicity that is likely caused by a drug rather than other potentially confounding aspects of the patient's diseases or other drug therapies, the dose should be empirically decreased or the drug stopped. If that cannot be done because of concerns over the loss of therapeutic benefit or inability to differentiate potential causes, a drug concentration measurement may help to determine if the drug is the likely cause. This situation is only appropriate if drug concentrations have been shown to predict toxicity.

Drug concentration measurements may also be useful in patients who develop dysfunction in the primary organ of clearance for the drug (eg, liver or kidney), in patients in whom an interacting drug was started or stopped after the patient was stabilized on the initial drug, or in patients with the potential for pharmacogenomic changes in drug elimination.[5] Measurements are not required if empirical reduction or increase in the drug dosage is possible.

Adherence Issues

Lack of adherence to medication regimens is a frequently occurring problem. When a patient is suspected of not adhering to his or her medication regimen, drug concentration monitoring may be a useful tool, along with evaluation of pharmacy records or the medication administration record, to help establish whether adherence is an issue. However, if nonadherence is suspected, clinicians need to first explore possible reasons, such as a patient exhibiting intelligent nonadherence because he or she is not getting the desired effect or is having side effects. It is also possible that a patient cannot afford to purchase the medication, which is an issue that would be addressed in another manner.

APPROACHES TO DOSING WITH LIMITED NEED FOR DRUG CONCENTRATION MEASUREMENTS

Immediate Effect Required or Expected

If a patient requires treatment for an immediate life-threatening illness, the initial dosage should be selected based on avoidance of underdosing, not overdosing. The largest dose usually associated with efficacy and acceptable toxicities should be chosen to ensure the greatest chance of a positive outcome. When concentrations are not measured, concern for toxicity, if it occurs acutely, may be assessed clinically (if possible) and evaluated on the basis of the benefits versus risks of continued therapy at the selected dosage.

For drugs such as the aminoglycosides, vancomycin, and phenytoin that may be used for life-threatening illness, severe toxicity usually does not develop until after at least a few days of therapy (eg, renal/ototoxicity from aminoglycosides/vancomycin) or the acute toxicities are minor (eg, nystagmus, or ataxia with phenytoin). The acute treatment of life-threatening infections with aminoglycosides or vancomycin should be accomplished with dosages known to produce effective clinical results, whereas concerns over possible toxicity should be relevant but secondary. The initial dosage selected for a life-threatening infection does not have to be the dosage used for continued therapy. Dosage adjustment can be guided by drug concentration measurements, when appropriate, based on all other considerations. However, before clinicians routinely measure concentrations for a particular drug or class of drugs, they should review the available evidence for the therapeutic range. Despite widespread use, the evidence may not be persuasive when looked at in a systematic and critical way.[6,7]

Immediate Effect Not Required or Expected

For most conditions treated with medications, an immediate response is not needed. In these cases, the dosing can be approached in one of two ways.

Titrating the Dose Up

In conditions that do not require an immediate response, it may be possible to gradually titrate the dose up to the usual recommended starting dose, with the understanding that the medicines that can extend or improve a patient's quality of life can also produce a number of side effects. A strategy using one-quarter to one-half the usual starting dose could minimize side effects by identifying the lowest effective dose. This strategy may also provide cost savings to a patient. Such a dose titration approach likely requires more time for a clinician to monitor patient outcomes as well as more time for clinician–patient discussion because a patient often needs to be made aware of how to monitor for efficacy and toxicity. A patient should be told that the dose titration process takes time and that an immediate effect is not expected or necessary based on selection of this approach. The patient should understand that the time spent in determining the appropriate dose may prevent unnecessary adverse effects and reduce drug product expense.

Taking this approach may be justified from the perspective that many clinical trials begin with fairly aggressive doses to establish efficacy. Studies are often not conducted on lower doses until after the product has been on the market for a considerable length of time.[8]

As an example, if the usual dose of a drug is approximately 300 mg twice daily, one could start with a 100-mg product twice daily for 1 week and evaluate for any important clinical changes associated with the drug. If there is limited or no response after 1 week, the dose should be increased to 200 mg twice daily with evaluation again in 1 week. If response has been limited, increase the dose to 300 mg twice daily. If there is little or no response at this dose, it may be unlikely that there will be any response from further increases for most patients and the drug can just be stopped,

assuming that the patient has adhered to the recommended regimen, there were no identifiable problems with absorption, and the patient was not on a drug that enhanced the metabolism of the drug being used. If one wishes to increase the dose further, measuring concentrations may be useful if a therapeutic range has been previously established, for no other reason than to justify doses greater than those typically used. If the concentration comes back and is not consistent with estimates, other reasons for uncharacteristic drug concentrations should be considered (see Introduction). In a similar fashion, low doses of some of the antiepileptic medications could be given initially when these agents are being used for the treatment of chronic neuropathic pain, and the dose could be titrated up slowly over a period of a few days to a week. This approach also decreases a clinician's need to worry about potential drug interactions that impact the anticonvulsant's pharmacokinetic parameters, because one is starting with a low dose. However, clinicians need to keep in mind that even low-dose anticonvulsants may still have a clinically important impact on other drugs a patient is receiving. It should be noted that if patients are unable to titrate the dose themselves, a titration approach may require additional visits to a clinician, and the costs of the extra visits would need to be weighed against the potential use of a drug concentration.

Titrating the Dose Down

A second approach that may be used to determine the lowest effective dose is to begin therapy with the product monograph recommended dose (empirically adjusted on the basis of kidney and/or liver function and drug–disease interactions), assess response, and gradually reduce the dose according to the response of the patient (weighing beneficial and toxic effects). The advantage of this approach is that an effect will likely be seen more quickly than by titrating upward. However, titrating down may not lead to finding the lowest effective dose because clinicians and patients may be unwilling to decrease the dose once benefits are achieved. It is important to remember that higher-than-necessary doses increase the chance of adverse effects, may increase the frequency of dosing, and may thereby compromise adherence and increase the cost of therapy. Even in the face of drug efficacy without signs of toxicity, there may be value in tapering to the lowest effective dose over time to determine if the correct diagnosis was made, if the disease state is fluctuating, or if nondrug factors, such as lifestyle changes, have made a difference.

The approaches of titrating up or down apply to many medical conditions for which clinical end points are frequent and easily measurable (eg, asthma and hypertension). However, when the clinical end points are infrequent (eg, seizures) or life threatening (eg, arrhythmias), this approach may be of less value.

CONCLUSION

As with all laboratory tests, drug concentration monitoring should only be considered as a tool to supplement proper clinical assessment of patient response. Appropriate drug selection (based on the best available evidence) and proper initial dosage selection, along with the clinical monitoring of response, are the most crucial components of pharmacotherapy.

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