An Aid to Optimize Drug Response - TDM.

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ABSTRACT

Therapeutic Drug Monitoring (TDM) is the measurement of specific drugs at intervals in order to maintain a relatively constant concentration of the medication in the blood stream. It refers not only to quantitative drug levels but also to the interpretation and the therapeutic application of those concentrations to patient care. Drugs that are monitored are those which have a narrow 'therapeutic window'. There is not such variation in the blood levels which is required to be effective than that which may cause serious toxic symptoms. Thus a steady state is required to be maintained.

Today, TDM allows more accurate titration of dosage and greater individualization of drug therapy. TDM often allows patients to be maintained on mono- rather than poly-drug therapy; thus TDM decreases the risk of adverse side effects. Only within the last few decades has a clear understanding of the relationship between drug's concentration within a biological system and its pharmacological activity become possible. Our investigators have established that by utilizing analytical TDM techniques, a minimum effective concentration (MEC) of a given drug in plasma is necessary to achieve that drug's therapeutic effect.

(Keywords: therapeutic index, drug analysis, drug toxicity)

INTRODUCTION

Therapeutic Drug Monitoring should not mean therapeutic drug measurement. It refers not only to quantification of drug levels but also to the interpretation and therapeutic application to the patient care.

It is essential that, not only the attending physician, but all health care professionals who are involved with the patient care, should understand the principles and techniques of therapeutic drug monitoring. Such understanding will enable the health professionals to assist, more effectively, the treating physician in interpretation of TDM results, thus optimizing the drug therapy.

Effective patient therapy, using TDM should answer the following points:

1. What is the current clinical status of the patient?
2. Therapeutic goals for that patient.
3. Therapeutic range for that particular drug for a particular diagnosis.
4. Was this patient on this drug prior to this analysis?
5. Is the patient receiving any other medication?
6. Did the patient receive a loading dose? How much and when?
7. What serum drug level is expected after the loading dose?
8. The half-life of that drug in relation to patient's age.
9. Has the patient reached steady state?
10. Does patient has any other clinical condition which might change the drug's clearance?

Principles of Therapeutic Drug Monitoring

Every drug acts to produce a change in some known physiological function or process. Any drug may increase, decrease, or stabilize physiological function of tissues, organs, and systems. The biological (or pharmacodynamic) effect achieved following administration of a drug is the sum of the processes by which that drug creates changes in some physiological or biochemical process.

A change in function due to a drug's activity may return the function or physiological process to normal, or, it may prevent deviation from the normal physiological state. If a drug eliminates or controls the progression of a given disease, the drug is said to have "therapeutic efficacy" for that disease.

The ultimate goal of all drug therapy is to abolish or prevent the development of an acute or chronic pathological state. Much more difficult to evaluate and treat, are the disease states with only occasional clinical manifestations (e.g., hypertension, asthma, cardiac arthythmia, epilepsies, etc.). Prior to the advent of TDM, clinicians were largely dependent upon trial and error to ascertain the appropriate drug dosage for a particular patient which would produce the therapeutic plasma concentration necessary to control these diseases.

A patient was administered a fixed quantity of drug and, if the desired effect was not achieved, the dosage was increased until clinical signs of toxicity appeared. At this point, the dosage was reduced. In case if the desired response did not occur, a second drug was introduced. If the response to the second drug was not forthcoming, the process was repeated until the desired effect was achieved or until all possible drug combinations were explored and exhausted. Unfortunately, trial and error therapy placed both the patient and the physician at the mercy of the kinetics of the drug in a particular individual.

Our current ability to monitor drugs and to correlate their plasma concentration with their therapeutic effects had still to wait for further developments of highly specific technologies. Furthermore, it is now accepted that there are optimal plasma concentration ranges within which therapeutic effects can be expected to occur in most patient receiving a particular drug. If plasma concentrations exceed the optimum therapeutic range, a minimum toxic concentration (MTC) is reached, at which undesirable side effects can be expected to develop clinically.

Correlation Between Drug Dose, Serum Concentration, and Clinical Response:

The rational for TDM is based on the demonstration that the intensity of the pharmacological action of many drugs correlates better with serum concentration than with dosage. Although for most drugs the dose administered corresponds to some extent with the intensity of the pharmacological effect, a significant variability in the dose-response relationship is observed among many patients due to many factors like patient compliance, correct medication, bio availability, distribution, metabolism, and elimination. In addition, the drug concentration at the receptor site is influenced by regional blood flow, binding to plasma proteins and the transport mechanism. The other responsible factors to alter the intensity of the pharmacological effect could be tissue response, interaction with after drugs disease state and the age of the patient.

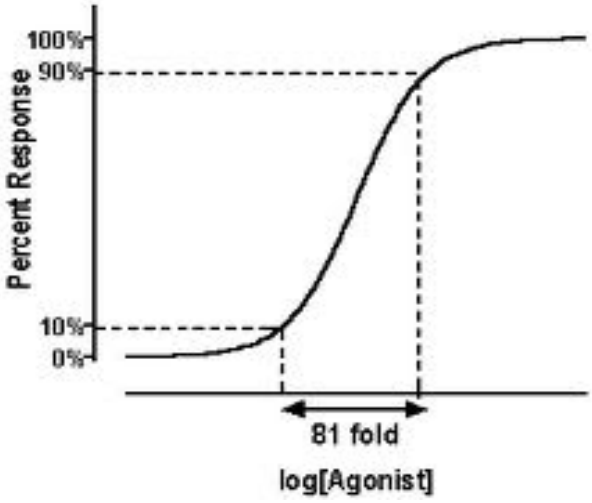

Figure 1: Dose–Response Curve after Repeated Oral Administration of a Drug.

WHEN DRUGS ARE TO BE MONITORED

Drug concentration monitoring is neither warranted nor feasible for all drugs, as with some drugs serum concentrations are not directly related to clinical response. Some drugs have a large therapeutic index, and precise dosage is therefore not required (e.g., cephalosporin). The

decision to monitor concentration of a drug may be based on the properties of the drug itself, the clinical status of the patient, or both. Serum concentration monitoring is principally of value in measuring the clinical effectiveness of a drug:

- When the receptor- drug interaction is reversible
- When the serum concentration of the drug is in equilibrium with its concentration at the site of action.
- When the effect of the drug does not lead to receptor tolerance.
- When a 'therapeutic range' can be defined for the serum concentrations of the drug.

Which Drugs Should be Monitored

Commonly, the drugs with narrow therapeutic index and/or High Toxicity ratings need to be measured. Following drug's measurement is of proved value.

1. Aminoglycoside antibiotics
2. Anticonvulsants
    - Phenytion
    - Phenobarb
    - Carbamazepine
3. Digoxin
4. Lithium
5. Theophyllin
6. Cyclosporine
7. Methotrexate
8. Vancomycin
9. Tricyclic antidepressants
10. Lignocaine
11. Procainamide
12. Thyroid Hormones, etc.

CLINICAL INDICATIONS FOR MEASURING DRUG CONCENTRATION

Drug concentration measurements are clinically indicated primarily for cases in which the expected therapeutic effect has not been observed, for cases in which patient compliance needs to be monitored or for cases of suspected over dose. In addition, the measurement of drug concentration is useful in establishing the optimum dose of a drug when no other parameter to measure the response is available. When drugs are prescribed as prophylaxis, an inadequate drug concentration may be detected before any clinical deterioration. This is of value in the use of anti-convulsants. Knowledge of drug concentration is also essential when symptoms resulting from toxicity and under treatment are similar, like, Tachycardia cannot be used in the diagnosis of theoplyllin overdose, since tachycardia may be present in patients with severe respiratory obstruction. Toxic doses of phenytion can cause seizures.

Plasma drug levels should be monitored when:

- A drug has a narrow, well defined therapeutic range.
- Noncompliance is suspected.
- The desired therapeutic effect is not achieved.
- Symptoms of toxicity are observed.
- There are large inter-individual variations in drug utilization or metabolism.
- Drug utilization is altered as a consequence of secondary disease or an altered physiological state.
- There is a question of bioavailability of the drug formulation administered to the patient (generic vs. brand name).
- Drug interactions are suspected.
- There is need for a medico-legal verification of treatment

CLINICAL ADVANTAGES OF TDM

TDM provides a number of advantages for any given patient because it allows the physician to gain a better understanding of the pharmacological status of an individual. Such information can be utilized to optimize the patient's therapeutic regimen. Some advantages are:

1. Non- compliance can be identified.
2. Drugs within appropriate bioavailability can be identified.
3. Individual variations in drug utilization can be observed.
4. Altered drug utilization as consequence of disease can be identified.
5. Paradoxical drug intoxication can be prevented.
6. An altered physiological state can be compensated.

SAMPLING AND FREQUENCY

For most drugs either serum or plasma samples are used to determine circulating levels of the drug. However, in cases of cyclosporine whole blood is preferred because of temperature dependant redistribution of the drug between red cells and plasma after collection.

Accurate and precise timing, both in administering the drug and obtaining blood sample, are of paramount importance. It is imperative to know the length of time that has elapsed since the last dose. With long term therapy the blood samples should be taken at steady state. As a good practice, samples should be taken after drug dosing has continued for 4-5 half-lives, a time when over 90% of the steady state concentration has normally reached.

After intravenous infusion of a drug, blood samples should be taken after 1-2 hours of infusion. In cases of drugs like phenytion or Phenobarbital, timing of blood sampling is not important since fluctuations between peak and trough concentrations at steady state are relatively small. In cases of aminoglycosides, both peak and trough values have been commonly monitored to avoid under-dosing.

How often drug levels need to be monitored depends on the clinical situation of the patient, the clinicians experience about steady state.

PRACTICAL GUIDELINES FOR PHYSICIANS

Since, wide individual variability exists in patient utilization of drugs as a direct consequence of genetic factors, multiple drug therapies, age and weight, it is extremely difficult and dangerous to generalize the relationship between plasma concentration and drug dose without proper clinical information.

The importance of individualized drug therapy is particularly significant in children who utilize drugs at a faster rate than adults. Conversely, geriatric patients generally utilize drugs at a slower rate than adults.

In order to accurately interpret information about the pharmacological status of the patient, the following information should be supplied to the laboratory:

- Patient age, weight, height, sex and race.
- List of all the drugs which the patient is receiving.
- Total daily dose of all drugs
- Time the last dose of the drug was administered.
- Time the TDM specimen was drawn.
- Clinical status of the patient.

TDM SPECIMEN OPTIMIZATION

For appropriate interpretation of the results, the specimen optimization is necessary and following guidelines should adhered to:

1. Routine TDM specimens should always be drawn at a trough (i.e., immediately prior to the next dose).
2. Patient should be at steady state.

3. After dosage adjustments, allow five half lives for the patient to reach new steady state values.

4. Samples drawn during IV infusion should be obtained ideally from the opposite limb.

5. When indicated, peak levels are drawn 15-30 minutes after IV drug administration.

6. If samples are drawn from an IV line, the line must be thoroughly flushed before obtaining a specimen for analysis.

7. For drugs with slow distribution phases, allow sufficient time for complete distribution (e.g., Digoxin specimens should be drawn at least 12 hours after the last oral dose).

CONCLUSION

Doctors can never assume that a drug will produce the desired effect in a patient. The value of measuring the plasma concentration of some important drugs, will allow the doctor to tailor the treatment to the patient, monitor the compliance, diagnose under treatment or toxicity, and detect drug interactions. The onus is always on doctors to follow the patient's progress and to monitor the response to a drug.

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