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Feature

Therapeutic Drug Monitoring (TDM)

Therapeutic drug monitoring (TDM) is the measurement of drugs and their active metabolites in patients receiving medications for the purpose of optimizing their therapeutic effect while minimizing adverse effects. The basic assumption of TDM is that the circulating concentration of a drug correlates better with pharmacological effect than does the dosage of the drug given to the patient. Therefore, there are a number of things to be considered in order for therapeutic drug monitoring to be effective and this article will briefly address some of these.

Before discussing the indications for therapeutic drug monitoring, it is essential to have an understanding of basic pharmacology. When a drug is administered to a patient, a number of things happen. First, the body must be able to take up the drug and distribute it to the target site of action. A change in the amount of drug or metabolite in various body compartments over time is determined by *pharmacokinetics*. Once at the target site the drug must produce the desired effect, usually through binding with specific receptors. The effect a drug has on the body is determined by *pharmacodynamics*.

Pharmacokinetics describes what happens when a drug is administered and is dependent on the extent and rate of Absorption, Distribution, Metabolism and Elimination (ADME). Typically, most drugs are administered orally and the amount absorbed (bioavailability) depends on a number of factors such as the formulation (fast acting vs. extended release), solubility and pK of the drug, co-administration of other drugs or food, and gastric emptying times. The drug is usually absorbed in the small intestine by passive diffusion. After the drug is absorbed it enters the hepatic portal system and is transported directly to the liver. In the liver the drug may be extensively metabolized by hepatic enzymes before reaching the general circulatory system. Once in circulation, the drug is distributed to various fluids and tissues. The volume of distribution (V_D) of a drug describes the extent of distribution and is dependent on the solubility of the drug, rate of perfusion of the tissue, and the extent of protein binding. Further metabolism of the drug may occur in the liver or specific tissues and finally the drug and metabolites are excreted, usually in the urine or feces.

Pharmacodynamics describes the physiological effect of the drug and metabolites. This includes the desired therapeutic effect of the drug as well as unwanted side-effects. Pharmacodynamic variability can arise from differences in drug-receptor interaction and receptor response.

Criteria for Therapeutic Drug Monitoring

1. Test Availability

Obviously, a test for the drug and active metabolites must exist in order to perform therapeutic drug monitoring. Most routine chemistry analyzers offer immunoassays for the more common therapeutic drugs. Some drugs require more specialized chromatographic techniques such as gas chromatography (GC) or liquid chromatography (LC). This type of equipment is not commonly found in most clinical laboratories. Therefore, monitoring for these drugs may require sending the sample to a reference laboratory for analysis. The turn-around time for these analyses must be quick enough to produce clinically meaningful results, especially if a change in dosage is required due to toxicity or adverse reaction.

2. Narrow Safety Margin

As mentioned above, the basic assumption for TDM is that the concentration of drug circulating in the bloodstream correlates well with the pharmacological effect of the drug. The drug concentration usually also correlates with the toxicity of the drug.

The therapeutic range often describes the minimum concentration required for effective therapy and the maximum concentration permissible, above which there is a potential for toxicity. If the therapeutic range (window) is large, then the drug is considered to be safer since a larger dose of drug is required to produce toxicity. Many of the newer antiepileptic drugs (e.g. Lamotrigine) and serotonin selective reuptake inhibitors (e.g. Paxil, Zoloft) have a wide therapeutic range and therefore do not require therapeutic drug monitoring. Dosages can be titrated upward until the desired therapeutic effect is reached and tapered if clinical signs of toxicity are noted.

Drugs such as aminoglycosides, digoxin, theophylline, and lithium have a narrow therapeutic range. This means that there is a very limited range of drug concentration that will produce a therapeutic effect. Below this range the drug will be ineffective or partially effective and above which it will be toxic. Therefore, a drug or other therapeutic agent with a narrow therapeutic range (i.e. with little difference between toxic and therapeutic doses) may have its dosage adjusted according to measurements of the actual blood levels.

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3. Compliance

Therapeutic drug monitoring can be considered in patients that do not show an apparent clinical response to a drug despite being on a seemingly adequate dosage. If the measured drug concentration appears consistent with the dosage of the drug, then the patient may be considered a non-responder to therapy. If the measured concentrations are very low or not detected then the patient is either "non-compliant" or is an unusually "fast metaboliser".

4. High pharmacokinetic variability

Inter-individual variation in drug absorption, metabolism, and excretion can produce

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a poor correlation between drug concentration and dosage. Pharmacokinetic variability between patients can arise from multiple factors:

- Age – large pharmacokinetic differences between neonates, children, adults and geriatric individuals
- Gender – differences due to body fat composition
- Pregnancy – for example, plasma drug levels of phenytoin and phenobarbitone tend to be reduced during pregnancy
- Drug-drug interactions – co-administration of drugs which inhibit metabolism may lead to higher than expected concentrations and toxicity while co-administration of drugs that induce metabolic enzymes may reduce concentrations and lead to ineffectiveness
- Genetic polymorphisms in drug metabolizing enzymes (pharmacogenetics) – certain individuals may have polymorphic enzymes which are inactive or partially active resulting in delayed clearance while others may have multiple gene copies encoding for the enzyme resulting in "fast" or "rapid" metabolism of the drug
- Malabsorption – increased microfloral colonization, accelerated GI transit, delayed gastric emptying, bowel surgery may influence the amount of drug absorbed
- Liver disease – decreased metabolism
- Kidney disease – decreased renal clearance
- Cardiovascular disease – decreased perfusion

Therapeutic drug monitoring may be useful in establishing the initial individualized dosage for a given patient in the above situations. Once the dosage is established however, there may be no more need for continued TDM as long as the patient's clinical condition remains the same.

5. Therapeutic effect difficult to monitor

If there is an obvious clinical effect of a medication then TDM is usually not necessary. For example, drugs that lower blood pressure can be monitored directly by measuring blood pressure. Anticoagulants are more effectively monitored by measuring INR. If there is no clear physiological response to monitor and a drug is being used prophylactically, e.g. anticonvulsants, antiarrhythmics, depression, asthma, or organ rejection, then TDM may be warranted. Seizure activity in a patient taking anticonvulsants may indicate low drug concentrations or toxicity. The decision to increase or decrease the dose is most efficiently made on the basis of the serum concentration.

An important part of therapeutic drug monitoring is the timing of the blood collection. When a drug is administered, the blood concentration increases until it reaches a peak and then the concentration begins to fall.

Considerations for TDM

1. Sample type

Serum or plasma samples are usually collected for TDM. Serum separator tubes should be avoided since lipophilic drugs can dissolve in the gel barrier.

The use of oral fluid (saliva) for drug monitoring has received a great deal of attention. Measuring drugs in oral fluid is appealing because samples can be obtained non-invasively. There are however a number of limitations to using oral fluid. The concentration of a drug in saliva is proportional to the concentration of the unbound drug rather than to the total of bound and unbound drug, usually measured in a plasma sample. Intuitively, this should be preferred since the free unbound fraction of the drug should represent the active amount of drug in the body. While most drugs passively diffuse into the oral fluid, some drugs are actively secreted. Some drugs may reduce production and flow of saliva and stimulation of saliva flow may alter pH and hence diffusion of the drug.

2. Timing of Sample

An important part of therapeutic drug monitoring is the timing of the blood collection. When a drug is administered, the blood concentration increases until it reaches a peak and then the concentration begins to fall. The lowest concentration (trough) is usually just before the next dose. The time required for the serum concentration of a drug to decrease by 50% is called the half-life of the drug. When a drug is administered in intervals approximately equal to its half-life, a steady state concentration will be achieved after 4-5 half-lives. For drugs with a long half-life, there is little difference between the steady state peak and trough concentrations. For drugs with a short half-life, the differences between the peak and trough concentrations can be significant and both are usually measured (i.e. aminoglycosides).

Drugs that are given intravenously require time to redistribute into the different body compartments. In general, intravenous medications can be sampled 30-60 minutes post administration. Digoxin however requires 6 hours for redistribution to occur.

3. Interpretation

Drug concentration determinations must always be interpreted in the context of the clinical situation. For example, a concentration of digoxin that would normally be therapeutic could be toxic if the patient also has hypokalemia.

Conclusion

Therapeutic drug monitoring may be useful for establishing initial dosing and monitoring certain medications. TDM cannot compensate for errors in diagnosis, poor choice of drug, errors in dispensing and dosages, errors in sample timing, non-compliance, etc. However, when used in combination with good clinical observation, it can lead to optimal drug therapy. ❖