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THERAPEUTIC DRUG MONITORING: WHEN TO DO IT

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Abstract:

Therapeutic drug monitoring of concentrations of drugs in body fluids, usually plasma, can be used during treatment and for diagnostic purposes. The timing and collection of sample specimens plays an important role to measure the drug concentration and it provides appropriate therapeutic judgment. For selected drugs therapeutic drug monitoring aims to enhance drug efficacy, reduce toxicity or assist with diagnosis.

Therapeutic drug monitoring (TDM) is the use of drug concentration measurements in body fluids as an aid to the management of drug therapy for the cure, alleviation or prevention of disease.

Keywords: *Drug therapymonitoring, Timing of Sample collection, adverse effects*

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INTRODUCTION:

Timing of the plasma sample ('when to do it')

- Unless therapeutic drug monitoring is being used to forecast a dose or there are concerns about toxicity, samples should be taken at steady state (4-5 half-lives after starting therapy) [2,3].
- At steady state, plasma concentration is usually Proportional to receptor concentration. Some drugs, such as perhexiline, which has a very long half-life in patients who are 'poor metabolisers, should be monitored before steady state is achieved to preventtoxicity developing after the first few doses. Another example where early monitoring may be useful is after phenytoin loading, where measurement of the plasma concentration can give a preliminary indication of adequate dosing.
- The timing of the collection of the sample is important as the drug concentration changes during the dosing interval. The least variable point in the dosing interval is just before the next dose is due. This pre-dose or trough concentration is what is usually measured. For drugs with long half-lives such as phenobarbitone and amiodarone, samples can be collected at any point in the dosage interval [4].

Table 1: Indications for measuring plasma drug concentrations [(5)]:

1.Monitoring compliance
2.Individualizing therapy [during early therapy & during dosage changes]
3.Diagnosing under treatment
4.Avoiding toxicity
5.Diagnosing toxicity
6.Monitoring and detecting drug interactions
7. Guiding withdrawal of therapy.

Timing of blood samples [6]:

1. **Aminoglycoside antibiotics**
   Intravenous: Peak- 5 min after the end of the infusion; trough-just before the next dose.
   Intramuscular: Peak-1 h after the injection; trough-just before thenext dose
2. **Cyclosporin:**
   Just before the next dose; measure at the same time of day on each occasion (for example, before the morning dose)
3. **Digoxin:**
   At least 6 hours after the last dose (it is before to give a single daily dose in the evening).
4. **Lithium**- Exactly 12 hours after the last dose.
5. **Phenytoin**: Timing is not important.
6. **Theophylline:**
   During an infusion: 4-6 hrs after starting the infusion; stop infusion for 15 min before taking the sample.
   Oral: just before the next dose; measure at the same time of day on each occasion.

Table 2: Types of samples required:

Drug	Type of Sample
Digoxin, Phenytoin, Theophylline	Plasma or Serum
Aminoglycoside antibiotics, Lithium	Serum
Cyclosporin	Whole blood or Plasma (Consult your laboratory)

- Correct sample timing should also take into account absorption and distribution. For example, digoxin monitoring should notbe performed within six hours of a dose, because it will still be undergoing distribution and so plasma concentrations will be erroneously high. Occasionally, sampling at the time of specific symptoms may detect toxicity related to peak concentrations of, for example, carbamazepine and lithium.
- For once-daily dosing of aminoglycosides, the timing of the blood sample is determined by the method of monitoring. For example, it is collected 6-14 hours post-dose when a nomogram is used, or twice within the dosing interval to calculate the area under the concentration-time curve [(7-8)].
- When aminoglycosides are prescribed in multiple daily doses to treat, for example, enterococcal endocarditis, then trough samples are measured to minimize toxicity and assess whether concentrations are adequate for efficacy.

There are several circumstances in which plasma drug concentration measurement may be helpful, although each indication does not applyequally to each drug.

COMPLIANCE:

In the article on compliance we discussed the ways in which compliance may be monitored. Measuring the plasma concentration may be helpful as a low

measurement reflects either poor recent compliance or under treatment. Poor compliance is implicated if the patient is taking a dose which is unlikely to be associated with such a low concentration or if previous measurements suggest that the plasma concentration should be higher for the given dose.

INDIVIDUALISING THERAPY:
When starting drug therapy it may be useful to measure the plasma concentration in order to tailor the dosage to the individual. This applies to all drugs, although it is most important for lithium, cyclosporine, and the amino glycoside antibiotics. If for any reason at a later stage the dosage regimen has to be altered (for example, in patients with renal failure) plasma concentration measurement may again be helpful.

DIAGNOSING UNDERTREATMENT:
Undertreatment of an established conditionmay often be diagnosed on observing a poor clinical response. However,when the drug is being used as prophylaxis you cannot observe the response
and may have to settle for giving a dosage that will produce a target plasma concentration. This applies particularly to lithium in preventing manic-depressive attacks, to phenytoin in preventing fits after neurosurgery or trauma, and to cyclosporine in preventing transplant rejection.

AVOIDING TOXICITY:
In all cases measurement during the early stages of treatment allows you to avoid plasma concentrations likely to be associated with toxicity.

DIAGNOSING TOXICITY:
In many cases drug toxicity can be diagnosed clinically. For example, it is usually easy to recognize acute phenytoin toxicity, and measuring the plasma concentration may not be necessary forthe diagnosis, although it may be helpful in adjusting the dosage subsequently. On the other hand, digoxin toxicity may mimic some of the effects of heart disease, and measuring the plasma concentration in cases in which toxicity is suspected may be helpful in confirming the diagnosis. Similarly, nephrotoxicity due to aminoglycoside antibiotics is hard to distinguish clinically from that caused by a severe generalised infection, andthe plasma concentration may help to distinguish the two.

DRUG INTERACTIONS:
If a potentially interacting drug is added measurement of the plasma concentration may guide subsequent changes in dosage. For example, when giving a thiazide diuretic to a patient taking lithium, measurement of the plasma lithium concentration will help to avoid toxicity. This also applies to theophylline when erythromycin is added. Conversely, measurement of the whole blood cyclosporin concentrationwill helps to avoid under treatment if rifampicin is added.

STOPPING TREATMENT:
Measurement of the plasma drug concentration may guide when to stop treatment in two circumstances.
(1) When the plasma concentration is below the therapeutic range in a well patient. For example, if the plasma digoxin concentration is below the therapeutic range in a patient whose clinical condition is satisfactory then withdrawal of digoxin is unlikely to lead to clinical deterioration. Note that this use of the plasma concentration measurement depends on the concept that there is a lower end to the therapeutic range. This is not always the case-while it is probably true for digoxin it is not true for other drugs, particularly phenytoin.

(2) When the plasma concentration is high without therapeutic benefit. For example, if there is no response to lithium and the serum concentration is at the upper end of the therapeutic range increased dosage is unlikely to be beneficial and the risk of toxicity is high. Withdrawal of lithium and the use of different treatment would be justified.

CONCLUSION:
The use of TDM requires a combined approach encompassing pharmaceutical, pharmacokinetic, and pharmacodynamic techniques and analyses. The appropriate use of TDM requires more than a simple measurement of patient blood drug concentration and a comparison to a target range. Rather, TDM plays an important role in the development of safe and effective therapeutic medications and individualization of these medications. Additionally, TDM can help to identify problems with medication compliance among noncompliant patient cases. When interpreting drug concentration measurements, factors that need to be considered include the sampling time in relation to the dose, the dosage history, the patient's response, and the desired clinical targets. This information can be used to identify the most appropriate dosage regimen to achieve the optimal response with minimal toxicity [9,10].

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