THERAPEUTIC DRUG MONITORING (TDM)

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Abstract

Therapeutic drug monitoring specializes in the measurement of drug concentrations in biological fluids and may serve as a practical aid to clarify various conditions of unexpect response to chronic drug treatment. Briefly, its main purpose is to optimize and/or individualize dosage regimens to maintain efficient and safe drug therapy. This is acieved by maintaining serum/plasma drug concentrations within a target range (therapeutic range, therapeutic window), which is defined as the range of plasma drug concentrations that produce therapeutic effects with minimal risk of adverse responses/side or toxic effects. In this review, indications, practical applications as well as the clinical value and cost-effectiveness of therapeutic drug monitoring is discussed.

Key Words: Therapeutic drug monitoring, therapeutic range, therapeutic window, clinical pharmacology, clinical pharmacy

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Özet

Terapötik ilaç izlemi, kronik ilaç tedavisi sırasında öngörülemeyen veya beklenmeyen cevapların ortaya çıkma nedenlerini biyolojik sıvılarda ilaç konsantrasyonlarını saptamak suretiyle aydınlatmaya yardımcı bir uzmanlık alanıdır. Diğer bir deyişle, ilaç tedavisinin etkili ve güvenli bir şekilde sürdürülebilmesi için, serum / plazma ilaç konsantrasyonlarının belirli bir hedef aralıkta (terapötik aralık, terapötik pencere) kalmasını sağlayacak dozaj rejimlerinin optimize edilmesi ve / veya bireyselleştirilmesi amacını taşır. Terapötik aralık veya terapötik pencere, en düşük advers etki / yan veya toksik etki riski ile en uygun terapötik etkiyi sağlayan plazma ilaç konsantrasyonları aralığı olarak tanımlanır. Bu derlemede, klinik farmakoloji ve klinik eczacılığın önemli bir uygulama alanı olan terapötik ilaç izleminin endikasyonları ve pratik uygulamalarının yanı sıra, klinikteki değeri ile maliyet etkinliği tartışılmaktadır.

Anahtar Kelimeler: Terapötik ilaç izlemi, terapötik aralık, terapötik pencere, klinik farmakoloji, klinik eczacılık

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What is Therapeutic drug monitoring?

Therapeutic drug monitoring (TDM) is a branch of clinical pharmacology and clinical pharmacy that specializes in the measurement of drug concentrations in biological fluids, mostly serum, plasma or saliva. Although therapeutic drug monitoring may serve as a practical guide to clarify various conditions of unexpected response to chronic drug treatment, its main purpose is optimization and/or individualisation of dosage regimens and to achieve efficient and safe drug therapy by maintaining serum or plasma drug concentrations within a target range (therapeutic range, therapeutic window, Figure 1) (1).
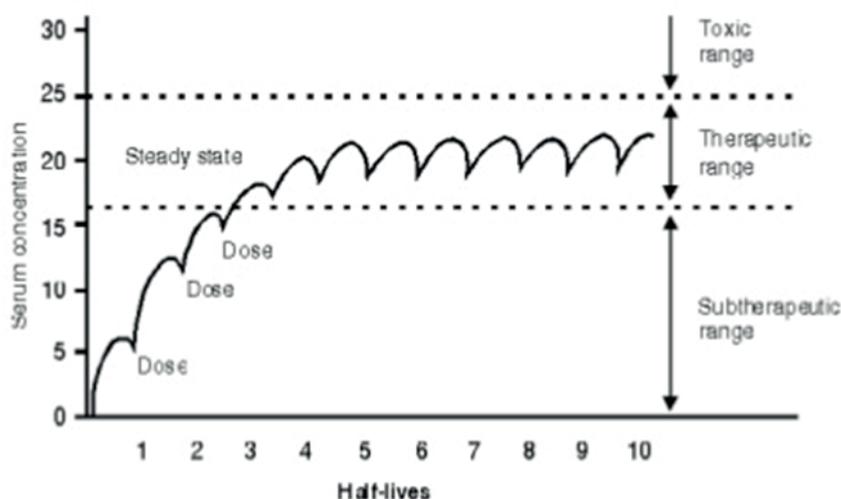

Figure 1: Therapeutic range at steady state

Therapeutic window is generally defined as the range (i.e. upper and lower reference values) of plasma drug concentrations that produce therapeutic effects with minimal risk of adverse responses/side or toxic effects in most of the patients. The main goal of TDM is to maintain plasma drug concentrations within a predetermined range to optimize treatment outcomes , since concentrations above reference values are generally linked to increased probability of increased side effects, whereas those below the reference values to ineffectiveness or unsatisfactory response.

Historical Background of Therapeutic Drug Monitoring

In the 1960s, several pharmacokinetic publications appeared in the literature linking mathematical theories to drug treatment outcomes and TDM was introduced as a new aspect of clinical practice. One of the milestones was the study published by Buchthal (2) demonstrating a certain concentration-effect relationship in epileptic patients treated with phenytoin. Buchthal was able to demonstrate that only 6 out of 24 patients with serum phenytoin levels <10mg/L (25%) were seizure-free, in contrast, 21 of 27 patients with serum phenytoin levels >10 mg/L (77%) were seizure-free. Soon thereafter, Kutt (1964) and Lund (1974) have determined the toxicity threshold for pheytoin as follows (3, 4):
• Nystagmus in all patients with serum phenytoin >20 mg/L

• Ataxia starting in patients with serum phenytoin >30mg/L
• Ataxia in all patients with serum phenytoin >40 mg/L
Similar studies with other drugs led to the emergence of "clinical pharmacokinetics" as a discipline and increased awareness of drug dose- concentration-response relationships. In 1970s, therapeutic drug monitoring focused mainly on side effects and/or toxic drug reactions and it was shown clearly that by maintaining plasma levels within predetermined upper and lower reference values of the therapeutic window, the incidence of toxicity certain to drugs such as digoxin, phenytoin, lithium, and theophylline could be reduced (5-7, 8).

Today, indications for TDM include monitoring of patient compliance, drug efficacy, drug-drug interactions, interindividual variation in drug response, side/toxic effects, as well as therapy cessation (9,10).

If a given dose of a drug produces the same plasma concentration in all patients, i.e. in absence of interindividual pharmacokinetic variability, there would be no need to measure the plasma concentration for most drugs. However, patients vary considerably in the extent to which they absorb, distribute, and eliminate drugs, which may lead to clinically relevant variability in pharmacokinetic characteristics. It is possible to reduce pharmacokinetic variability by optimizing the dosage or dosage interval of the drug to maintain plasma drug concentrations within a predetermined "target therapeutic window".

Up to ten-fold variation in steady-state plasma drug levels have been found among patients treated with the same dose of important drugs such as phenytoin, warfarin and digoxin. Reasons for such variations are differences between drug formulations, genetic variation, underlying disease, environmental effects, pharmacokinetic and/or pharmacodynamic variability and drug-drug interactions(11). Measuring plasma concentration of a drug may help the clinician to clarify unexpected response to drugs and/ or to achieve maximum therapeutic effect with minimal toxicity risk.

There are two major sources of interindividual variability to drug response, i.e. variations in the relationship between a given dose and the plasma concentration attained with this dose (pharmacokinetic variability) and the relationship between drug concentration at the receptor site and the response produced (pharmacodynamic variability). Major sources of pharmacokinetic variability are the patient' s compliance to drug treatment, physiologic factors such as age, gender, pregnancy, disease states (hepatic, renal, cardiovascular, respiratory), drug interactions, environmental factors and genetic polymorphisms affecting drug metabolism.

For plasma concentration measurements to be useful, a drug should satisfy following criteria (10):

- Difficulty in interpreting clinical evidence

- A good relation between the plasma drug concentration and the therapeutic or toxic effect, or both

- A low toxic:therapeutic ratio

- The drug is not metabolised to clinically important active metabolites

Main characteristics of drugs for which therapeutic drug monitoring is suitable or required are:

- Clinically relevant pharmacokinetic variability

- Concentration related therapeutic and adverse effects

- Narrow therapeutic index

- Defined target therapeutic concentration range

- Therapeutic effect difficult to monitor

If the clinical effect of a certain drug can be readily measured (e.g. heart rate, blood pressure), it is better to adjust the dose on the basis of clinical response and therapeutic drug monitoring is not necessary.

Therapeutic drug monitoring is used in two major situations:

- For drugs used ***prophylactically*** to maintain the *absence* of a condition such as seizures, cardiac arrhythmias, depressive or manic episodes, asthma relapses or organ rejection. For these drugs, it is impossible to monitor a response. Thus, the physician can select a dosage that will produce a certain 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.

- To avoid serious toxicity of drugs with a narrow therapeutic range (e.g. digoxine, aminoglycosides, vancomycine, etc.) at the beginning of treatment, during changes in dosage regimens and during cessation of treatment.

Generally, TDM applied at the beginning of drug treatment may enable clinicians to avoid toxic plasma levels. In the majority of cases, drug toxicity can be diagnosed clinically, e.g., it is relatively easy to recognize acute phenytoin toxicity, and TDM may not be necessary for diagnosis of phenytoin toxicity. However, TDM certainly is a helpful guide in adjusting phenytoin dosage subsequently. On the other hand, digoxin toxicity may mimic certain symptoms of heart disease, therefore, measuring digoxin plasma level in patients in which toxicity is suspected may be necessary in confirming toxicity. In addition, digitalis sensitivity may be detected by means of TDM, in patients with toxicity associated with digoxin plasma concentrations below 2.0 ng/mL (12).

When the characteristics of drugs for which therapeutic drug monitoring is suitable or required are not met, the regular/periodic use of TDM is hard to justify. However, in some circumstances (e.g. in monitoring compliance or undertreatment), TDM may sometimes be applied for drugs which fulfil some but not all of the criteria, including anticonvulsants such as carbamazepine and ethosuximide, antiarrhythmic drugs, tricyclic antidepressants and methotrexate. Indications for plasma drug concentration measurements and drugs which should be monitored are shown at Table 1 and Table 2.

Table 1. Indications for plasma drug concentration measurements

➢ Monitoring compliance
➢ Individualizing therapy ✓ during early therapy ✓ during dosage changes ✓ during cessation of therapy
➢ Diagnosing undertreatment
➢ Avoiding toxicity
➢ Monitoring and detecting drug interactions

Table 2: Drugs which should be monitored (13,14)

Drug	*Therapeutic range mg/L*
Digoxin	0.5 - 2.1[1]
Amiodarone	1.0 - 2.5
Lignocaine	2.0 - 5.0
Quinidine	2.0 - 5.0
Flecainide	0.2 - 0.9
Mexilitine	0.5 - 2.5
Salicylate	150 - 300
Perhexiline	0.15 - 0.6
Theophylline	10 - 20
Phenytoin	10 - 20
Carbamazepine	5.0 - 12
Sodium valproate	50 - 100
Phenobarbitone	15 - 40
Ethosuximide	50-100
Lamotrigine	1-4
Gentamicin, tobramycin,	trough <2[2]; peak >5
Amikacin	trough <5[2]; peak >15
Vancomycin	trough <10; peak 20 - 40
Lithium	0.6 - 1.2[3]
Cyclosporin	50-125[1] (serum or plasma)
Tacrolimus	5-20[1](whole blood)
Sirolimus	5-15[1] (whole blood)
(1) microgram/L (2) for 8-hourly dosing (3) mmol/L	

Accurate drug concentrations are attainable only by a TDM team comprised of clinicians, nurses, and pharmacists. Collaboration and communication among TDM team members is necessary to ensure best practices in TDM.

Attention must be paid to the timing of blood sampling, the type of blood sample, the measurement technique, and the interpretation of results. The blood sample should be obtained at the correct time after dosing; the timing of sampling is mostly responsible for misinterpretation of the results. An appropriate pharmacokinetic evaluation requires the acquisition of properly timed blood specimens (13). To interpret a blood plasma concentration properly, the TDM team must be informed as to when a plasma sample was obtained in relation to the last dose administered and when the drug regimen was initiated. If a plasma sample is obtained before distribution phase of the drug is completed, for example with digoxin, the plasma concentration will be higher than predicted on the basis of dose and response. Peak plasma concentrations are helpful in evaluating the dose of antibiotics used to treat severe, life-threatening infections. In cases of slow or delayed absorption, plasma samples should be drawn at trough or just before the next dose (Css min; minimal steady state concentration, through levels) when determining routine drug plasma concentrations. Trough levels are less likely to be influenced by absorption and distribution problems (15). Usually blood samples are collected at the end of the dosage interval (trough level). For antibiotics administered intravenously, peak concentrations are also measured at 30 min following infusion cessation. For aminoglycoside antibiotics, both peak and trough concentrations are important measurements.

If a patient is on a repeated dosage, blood samples should be collected after a "steady state" drug level is reached, for example, after at least 5 half-lives at the current dosage regimen. However, drugs with long half-lives (e.g. amiodarone and perhexiline) should be monitored before steady state is achieved to ensure that patients with impaired metabolism or renal excretion are not at risk of developing toxicity. If the drug has been administered by bolus injection, samples should be taken at least 1 h post-dosage to avoid overlapping the distribution phase. If drug toxicity is suspected, the plasma concentrations should be monitored as soon as possible.

For most drugs, the blood sample can be drawn into a heparinized tube or allowed to clot, and there are no important restrictions on storage before measurement. For lithium and aminoglycosides, however, the blood samples should be allowed to clot, and should be separated within 1 h. For cyclosporine, it is important to consult the local laboratory for details on the proper sampling technique and post-dosage timing. The laboratory must ensure that the assay used is as reliable, specific, validated and that quality control is undertaken. Laboratories performing TDM are using analytical methods ranging from radioimmunoassay to high-performance liquid chromatography (HPLC) procedures. Currently the majority of drug assays performed are variants of commercially available immunobinding assay procedures (16). The most commonly used procedures are fluorescence polarization immunoassay (FPIA), enzyme immunoassay (EMIT), and enzyme-linked immunosorbant assay (ELISA) (17, 18). These assays are specific; however, in certain cases, metabolites or other drug-like substances are also recognized by the antibody, resulting in cross-reactivity with metabolites, or in either a falsely elevated or decreased assayed drug concentration (19- 23).

For appropriate clinical interpretation of the results obtained with TDM, information such as dosage regimen, time of blood sampling, and accuracy, precision, sensitivity, and specificity of each assay sould be documented and assessed regularly. Wherever possible, the assay performance should be evaluated using an external quality assurance program. The assay results should be available quickly, preferably within 24 h of receiving the sample, as rapid dosing decisions must be made (24). The clinician should take into account not only the concentration but also other clinical

features such as the patient's condition that may affect the relationship between concentration and clinical effects (10). Patient demographic characteristics are critically important so that the contributions of age, disease state, ethnicity, and other variables to inter-individual variation in pharmacokinetics and pharmacodynamics can be considered.

Value and Cost-effectiveness of therapeutic drug monitoring

Concerns among health care authorities, hospital administrators, government, third party health insurers, clinicians and the public about rising health care costs, pharmacoeconomic principles is now being applied also to TDM, debating its cost-effectiveness.

It has been argued that no good evidence demonstrates that targeting plasma concentrations improves the therapeutic outcome (25, 26), and that the therapeutic value of plasma monitoring must be tested (27), however, these arguments ignore the fact that a stronger relationship exists between plasma concentration and effect than between dose and effect (11).
Some others argue that sometimes the plasma concentration itself is being treated rather than the patient itself (28), and that monitoring is useless in cases where, for example, the sampling time is inappropriate or information on administered drug dose, dosage history, patient response, and the desired clinical targets (29).

Efficient control of procedures such as assuring appropriate indications for ordering serum drug levels, correct timing of sample collections, communication of results to the clinician, monitoring clinician responses to treatment recommendations, patient response to the treatment and and cost savings associated with a TDM service are necessary for cost-effectiveness of TDM. Procedures may be implemented to assess whether requests for drug assays are warranted before the assays are actually performed, thereby ensuring the rational utilization of resources. This is often time consuming for clinicians, but it may prevent expensive tests that do not assist either immediate or long-term patient management (11).

A pharmcoeconomic analysis of the impact of TDM in adult patients with generalized tonic-clonic epilepsy showed that patients undergoing TDM had much more effective seizure control, fewer adverse events, better earning capacity, lower costs to the patient, savings from lower hospitalizations per seizure, and greater chances of remission (30). A meta-analysis showed that TDM does appear to be beneficial for patients taking theophylline or digoxin (31). Although several studies have reported high cost-effectiveness of dose individualization using TDM (32-35), plasma level monitoring of aminoglycosids is an important aid to reduce the incidence of aminoglycosid toxicity, to optimize the peak:MIC as an efficacy parameter.

Current immunosuppressants exhibit large inter- and intra-individual pharmacokinetic variability and it has been shown that blood concentration is a better predictor of clinical efficacy than dose (36). The International Federation of Clinical Chemistry /International Association of Therapeutic Drug Monitoring and Clinical Toxicology working group published important guidelines and recommendations for cyclosporine, silorimus, and tacrolimus monitoring (37).

On the other hand, although TDM is considered as the standard of care for antiepileptic drugs, digoxin, psychiatrics, and immunosuppressant drugs, formal cost-effectiveness data is lacking (38).

There is no justification for TDM without a definite purpose. Routine measurement of the plasma drug concentration without clear justification is as irresponsible as obtaining no measurement at all.

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