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Short Commentary

Therapeutic Drug Monitoring: Is There Anything New?

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Abstract

Therapeutic drug monitoring (TDM) is a tool of healthcare professionals meaning measurement of drug concentrations in biological samples, which they use to individualize therapy. In this way, these measured concentrations are used in order to maintain them within a recommended target range, thereby optimizing individual dosage regimens. The aim of this paper is to outline the essence of TDM and to point out novelties in this area. It can be concluded that the concentration of the drug is not a substitute for the clinical assessment: hence, in clinical practice one should treat the individual patient and should not be guided exclusively by laboratory values. TDM enables dose individualization since drug concentrations may be biomarker for desired or adverse effects of drugs. However, the use of TDM or target concentration intervention as a new approach implies significantly more than just a measurement of drug concentration g in biological samples and a comparison with recommended values of the desired range.

Keywords: therapeutic drug monitoring, target concentration intervention, drug concentrations, sampling, indications, cost-effective, critical dose

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1 INTRODUCTION

Therapeutic drug monitoring (TDM) is a tool of healthcare professionals meaning measurement of drug concentrations in biological samples (e.g. whole blood, plasma, serum, urine, saliva, etc.)[1-4]. Measured concentrations of the drugs in the biological samples are used to individualize therapy when using the certain drugs. In this way, these measured concentrations are used in order to maintain them within a recommended target range, thereby optimizing individual dosage regimens[1,2,5].

Concentration of drug in biological samples is not determined routinely[1]. Moreover, the desired or adverse effects of certain drugs may correlate better with concentrations in biological samples than with a dose of drugs. Therefore, TDM is performed for certain drugs that meet the specified conditions. For example, when there is a large inter-subject variation between the dose and effect individualizing dosage of drugs is very

difficult[2]. This measurement of drug concentration is most important for drugs with a narrow target range. Similarly, intra-subject variations can occur over time, and TDM could be useful. Generally, the TDM involves measuring drug concentrations accompanied with the clinical interpretation of the results. The aim of TDM is using the appropriate concentrations of "critical dose" drugs to optimize clinical outcomes in patients[5].

At this moment when personalized medicine is placed in the forefront of patient treatment, its improved efficiency and safety can be ensured by adjusting the dose of the drug to the individual needs of each patient[6]. However, this requires the wide availability of medical devices for measuring drug concentrations as well as health personnel trained to work on these devices.

The aim of this paper is to outline the essence of TDM and to point out novelties in this area.

2 METHODS

The literature search was conducted during the September 2022. The literature search collected a comprehensive set of data regarding the TDM Databases (i.e., Web of Science, Scopus, PubMed, Google) were searched using the term "TDM", "target concentration intervention (TCI)", "drug concentrations", "sampling", "critical dose", "analytic techniques", and "cost-effective".

3 TDM

3.1 Prerequisites for TDM

When an effect of drugs is readily measured, the dose of a drug should be adjusted according to the clinical response[1]. For example, glucose concentrations in blood are monitored in diabetic patients using insulin products. On the other hand, when an effect of drugs is not easily measured, TDM is a more useful. The main criterion for TDM is that correlation between concentrations of drug and desired clinical effects or adverse effects exists[7]. Other criteria for TDM can be narrow target range (based on the recommended target concentration range), significant pharmacokinetic inter- and intra-individual variability, vulnerable populations such as children and pregnant women, polypharmacy with expected drug interactions etc. Table 1 shows the list of drugs for which TDM is most often performed[1,7,8]. The desired concentrations of the drug are attainable only by complete collaboration by a multidisciplinary TDM team, which it is comprised of clinicians, nurses, clinical pharmacologists and pharmacist-analysts[4,5,9-11].

3.2 What are the Indications for TDM?

Many drugs have a large margin of safety and due to this fact strict individualization of the dose is unnecessary. On the other hand, drugs with a narrow therapeutic window or critical dose (drugs which usage in comparatively small differences in dose and/or concentration lead to dose and/or concentration dependent, serious therapeutic failures and/or serious adverse drug reactions) require individualization of the dosage regimen[7,12].

Another situation is when methods for measuring the concentration of drugs in the blood are expensive, so TDM is done only for certain drugs in certain indications. Therefore, routine monitoring is not advocated for most drugs. Whenever there is a clinical test that is cheap, it is preferred. We perform TDM when we do not have an adequate clinical test and when the previously mentioned general conditions for measuring drug concentration in biological samples are met[2]. For example, the indications for TDM include[1]: (1) avoiding toxicity (nephrotoxicity and cardiotoxicity in the patients with renal transplantation who are exposed to high concentration of tacrolimus); (2) adequate dosing (dose adjustment after reaching a steady state); assessment of adequate loading dose (after starting treatment, as like for digoxin); and dose estimation due to individualization of the dose requirements; and (3) enabling surveillance (assessment of lithium compliance during the treatment of patients with bipolar disorder); and diagnosing failure in therapy (TDM can differentiate inadequate drug treatment, non-compliance and adverse drug effects which can mimic the underlying disease).

Therefore, in many hospitals there are services (TDM or clinical pharmacokinetic services) which task is to evaluate the response of the patient to the recommended dosage regimen[7]. The main tasks of these services are: the selection of appropriate pharmacotherapy calculation of an adequate dose of the drug; evaluation of patient response; determination of needs for measuring drug concentrations; implementing an assay for measuring drug concentrations in biological samples; performance of pharmacokinetic evaluation of measured drug concentrations; readjusting dosage regimen, if necessary; implementation and validation of methods for measuring drug concentrations; procurement of new devices for measuring drug concentrations; monitoring serum drug concentrations associated with recommendation for patients etc.

On the other hand, situations when TDM should not be done are: when drugs with large therapeutic index is used; in the case of drugs where there is no correlation between the concentration in the biological sample and the clinical response, and when the efficacy or toxicity of therapy can be clinically estimated e.g. blood pressure[13].

As we have previously stated, TDM can also be performed in vulnerable patients, such as the pediatric

Table 1. List of Drugs for Which TDM is Often Used (Recommended Target Ranges are Subject of Change Depending on the Clinical State)

Therapeutic Group of Drugs	Name of Drug	Target Range
Immunosuppressive drugs	Tacrolimus	5-20μg/L (whole blood)
	Sirolimus	5-15μg/L (whole blood)
	Cyclosporine	50-125μg/L (serum or plasma) 150-400μg/L (whole blood)
	Mycophenolate mofetil	Cyclosporine-based regimen: ≥1.3mg/L Tacrolimus-based regimen: ≥1.9mg/L
	Everolimus	3-8ng/mL together with low doses of calcineurin inhibitors
	Sirolimus	3-8ng/mL together with low doses of calcineurin inhibitors
Antimanic agents	Lithium	Acute mania-0.8-1.2mmol/L Maintenance-0.4-1.0mmol/L
Cardiac glycosides	Digoxin	0.8-2μg/L and <0.01μg/L in refractory heart failure
Anticonvulsants*	Phenytoin	10-20mg/L
	Carbamazepine	5-12mg/L
	Lamotrigine	1.5-3mg/L
	Sodium valproate	50-100mg/L
Antibiotics	Vancomycin	Trough 10-20mg/L
	Gentamicin	5-10μg/mL
	Tobramycin	5-10μg/mL
	Amikacin	20-30μg/mL
Antiarrhythmics	Procainamide	4-10μg/mL
	Quinidine	1-4μg/mL
	Lidocaine	1-5μg/mL
Antiasthmatics	Theophylline	10-20μg/mL

Notes: *phenobarbital, ethosuximide, sometimes gabapentin, levetiracetam, topiramate, zonisamide, eslicarbazepine acetate, felbamate, lacosamide, oxcarbazepine, pregabalin, rufinamide, stiripentol, tiagabine, vigabatrin (other anticonvulsants for which TDM is recommended).

population, since TDM enables more precise drug administration, thereby reducing the risk of therapeutic failures or drug toxicity[14].

3.3 Samples and Sampling Time

Different conventional biological samples are use for TDM (whole blood, plasma, serum, urine, saliva, etc.). Dried blood spot (DBS) is something new in TDM[15]. The advantages of DBS sampling comparing to conventional methods are the minimally invasive procedure of a finger prick; home sampling by the patient; it is more convenient for TDM in infants and neonates; the small volume of sample, as well as the stability of the analytes and storage and transport of samples. Therefore, DBS sampling can be an alternative to conventional sampling. For example, concentrations in DBS were correlated with serum vedolizumab concentrations, allowing DBS to be used for intensive sampling to gain more insight in vedolizumab pharmacokinetics[16]. Similarly, adjustment of infliximab dosage interval can be facilitated by infliximab concentration measurement in DBS samples[17]. It has been shown that it is DBS that is a reliable method to measure this drug and can be used to predict infliximab trough concentrations.

On the other hand, unless TDM is being used to forecast a dose or there are concerns about toxicity, samples should be taken at steady state (3-5 half-lives after starting therapy)[1,18]. The concentration of the drug is most commonly measured in biological samples obtained immediately before the next dose, and since its minimum value is expected, it is so-called trough concentration of drug. The adequate timing of the blood sample collection is of decisive importance for TDM since drug concentration changes during the dosing interval[1]. However, samples can be collected at any point during the dosage interval when drugs with long half-lives are used (for example phenobarbitone). Detection of toxicity related to peak concentration of drugs can be detected by sampling at the time of specific symptoms, such as the case with lithium.

3.4 Interpretation of the Results

Drug concentrations need to be interpreted in the context of the individual patient without rigid

adherence to a target range[1]. For example, if a patient immunosuppressive drug concentration is just below the target concentration, without any signs of acute graft rejection, correction of the dose is not necessary. Most drug assays measure total drug concentration in biological samples (bound and unbound drug), but only the unbound drug interacts with its receptor to produce a response. The unbound fraction may be affected by factors such as serum albumin concentrations, displacement by an interacting drug and by renal failure.

Large number of factors such as genetic variation, duration of the disease, drug indication, toxicity mimicry, severity of disease, cardiac, hepatic and renal function, drug-drug interactions, drug-food interactions, physiological conditions, comorbidities, age, gender, body mass index, pregnancy, personal lifestyle factors, smoking, alcohol abuse, analytical methods, analytical instruments, metabolites, collection timing, collection tube factors, handling/processing of samples, etc. may change the pharmacokinetics and/or pharmacodynamics of the drug, therefore requiring dosing regimen individualization[7,19]. Generally, the manufacturer's instructions are used for the starting drug dose at the beginning of the therapy[7]. The drug dose is then adjusted appropriately, as a result of TDM use. Therefore, one of the most important elements of TDM is the provision of accurate and clinically relevant intervals of the desired therapeutic range[19].

3.5 Measuring and Monitoring

Drug concentrations should be measured in a mass or molar units within a clinically useful time frame (time that is shorter than the dosing interval) in laboratories with appropriately trained staff[18]. There are differences in target range recommendations between laboratories, countries and associations; therefore target ranges should accompany results in order to assist clinicians in achieving safe and effective prescribing. The TDM also promotes the principles of rational prescribing of drugs, as well as individualized or personalized therapy.

3.6 Most Often Used TDM Assays

For concentration drug measurements a variety of analytic techniques are available, such as mass spectrometry (MS), immunoassay, chemiluminescent immunoassay, chemiluminescent microparticle immunoassay, enzyme immunoassay, fluorescence polarization immunoassay, particle-enhanced turbidimetric inhibition immunoassay, radio-immunoassay, and other methods[7,19]. The method chosen to determine the concentration of the desired drug may depend on a large number of factors: physicochemical characteristics of the drug, target drug concentration, volume and nature of the biologic specimen, available instrumentation, cost of each assay, and analytical skills of the laboratory personnel.

Over the last two decades, liquid chromatography-tandem MS (LC-MS/MS) has become the gold standard for measuring drug concentrations in biological samples in most laboratories around the world[20]. LC-MS/MS offers analytical specificity superior to that of immunoassays or conventional high performance/pressure liquid chromatography for low molecular weight analytes. LC-MS/MS is nowadays the standard method in most laboratories for measuring concentrations of drugs in biological samples. On the other hand, this device is quite expensive, so it is not available to many laboratories in everyday practice.

The most modern approach to measuring the concentrations of the drug in the blood includes a portable, palm-sized transmission-localized surface plasmon resonance setup[6]. This tool is comprised of off-the-shelf components and coupled with DNA-based aptamers specific to the one drug. Its uncomplicated construction and compact size, together with the remarkable performances, represent a leap forward toward effective point-of-care devices for TDM.

3.7 TDM Limitations

Some of the obstacles for TDM are the limited number of drugs amenable to TDM, limited accessibility to many laboratories as well as high cost of analyses[7,18]. The validity of suggested target ranges is also a large problem. Active metabolites may contribute to the therapeutic response but are not routinely measured, too. Moreover, many drugs are biotransformed into compounds that are pharmacologically active. When evaluating the therapeutic effect of such drugs, the relative contributions of all active substances present in the biological sample must be integrated[21].

The most common sources of pitfalls and errors during the TDM are: inadequate compliance, incorrect time of drug administration, inadequate dose of the drug, incorrect sampling time, and lab assay error[13].

Although implementation of TDM is considered expensive, financial resources spent on used methods will likely to be regained by positive outcomes, such as decreased number or duration of hospitalizations, and thus it is a marker for health-economic evaluations[22,23]. A pharmcoeconomic analysis of the impact of TDM in epileptic patients showed that patients undergoing TDM had much more effective seizure control, fewer adverse events, lower costs imposed to the patient, lower number of hospitalizations per seizure, and greater chances of remission[24]. Generally, studies have confirmed the pharmacoeconomic cost-effectiveness of TDM in the patients who are using theophylline, digoxin, antiepileptic drugs, lithium, and immunosuppressive drugs[25-28].

Table 2. The Principles of Therapeutic Drug Monitoring (TDM) and Target Concentration Interventions (TCI) on the Example of Measuring the Concentration of Vancomycin

Target Concentration Interventions	Therapeutic Drug Monitoring
The TCI approach focuses on adjusting dose to achieve a stated, discrete target with the aid of an explicit calculation method to determine the dose to achieve the target	The TDM strategy focuses on drug maintenance within a therapeutic window, with dose adjustments only considered if the measurement of exposure (area under the curve, AUC or concentration) is outside the therapeutic window
TCI requires that the output of the interpretation of the method should propose the next dose and a dosing interval, which is expected to achieve the target response	TDM does not recommend a dose
TCI contains the intervention component within itself	TDM does not contain the intervention component

The total cost of TDM is determined by costs of equipment, personnel, supply and overhead expenditures[29]. Cost-benefit analysis of gentamicin dosage regimens conducted in burn patients showed cost-benefit ratio of 8.7 to 1, with decreased mortality and increased economic productivity. Literature data showed that the usage of TDM offered substantial benefits, such as fewer adverse effects and shorter overall hospital stay.

For example, it was shown that simply constructed calculation based on the several parameters (such as gender of the transplant recipients, proton pump inhibitor use, corticosteroid dose applied and measured drug concentration of immunosuppressive drug) may help in optimization of tacrolimus daily dosing in patients with renal transplantation. On the other hand, this calculator, as well as TDM as a whole, could lead to cost savings for the health care system[30].

4 TCI

TDM as well as new approach TCIs are used in the daily practice of healthcare workers for optimized and individualized drug treatment[31]. It is considered that TCI should bring more clinical benefit due to precision of the approach and the ability to predict the dose required by individuals more precisely and timely[32]. Both TCI and TDM can be considered as approaches to concentration controlled dosing of individual patients[33]. The distinguishing principles of the TDM and TCI approaches continue today but the clinical importance of understanding why TCI is superior to TDM is still not widely recognized. However, the principles and clinical trial results show that the TDM approach is often ineffective or inferior in comparison to TCI, and the benefits of TCI arise from its better understanding and application.

The principles of TCI are as follows: (1) Definition and use a target to guide the dose required for optimal treatment; (2) Usage of pharmacological principles to predict the dose required to achieve the target; and (3) application of an intervention method for using individual patient measurement of response in order to recommend the next dose to achieve the target[33]. For example, the TCI and TDM approaches have both been used to guide vancomycin dosing (Table 2).

Literature evidence indicates that TCI compared to TDM has significantly better outcomes concerning patients[33]. The main practical challenge for TCI use is entering essential information into a its dosing tool. On the other hand, the dosing decision workflow considering TDM approach is simple and based on comparing the measured concentrations with the values within the therapeutic window. TDM dose changes are based just on measured drug concentrations, not taking into account the dosing history or patient characteristics, such as someone's weight or renal function. Therefore, this leads to the inferior dose individualization and outcomes in TDM approach. On the other hand, digitalization of healthcare records and integration with clinical decision supports TCI. Since TCI is becoming easier to use, it has advantages for everyday clinical practice.

Speaking about the differences between two concepts, there are attempts in determination of the target concentration that is optimal concerning TCI, as a result of the balance between effectiveness and adverse effects of drug[34]. According to TCI methodology, by reaching response or its lacking after the treatment is started, the adequate target concentration can be chosen[32]. In achieving this, modern pharmacokinetic/pharmacodynamic concepts are used, which have proven to be successful. On the other hand, some authors consider that TDM has not enough adequate perspective, since therapeutic range of drug concentrations chosen initially provides a limited perspective[35]. However, if all necessary information about the patient and his/her disease is provided for an experienced TDM team, and modern equipment is available to them, their interpretation of measured drug concentrations should lead to final rational therapeutic decision. Which concept will be implemented, mostly depends on the capabilities of the healthcare institution itself that provides this service to the patient.

5 CONCLUSION

It can be concluded that the concentration of the drug

is not a substitute for the clinical assessment. Therefore, in clinical practice one should treat the individual patient and should not be guided exclusively by laboratory values. TDM is helpful with dose individualization since drug concentrations may be biomarker for desired or adverse effects of drugs. However, the use of TDM or new approach TCI implies significantly more than just a measurement of drug concentrations in biological samples and a comparison with recommended values of the desired range. All available information about the patient and the disease should be provided to TDM team, and their interpretation of observed concentration should lead to final rational therapeutic decision and personalized pharmacotherapy. However, TCI have to be taken into consideration as an alternative, since it becomes more user-friendly and it gains more and more benefits for daily clinical use.

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Conflicts of Interest
The authors declared that they had no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contribution
Both authors participated equally in the creation of the idea, the methodology of the work, the writing of the draft version and the final revision of the work.

Abbreviation List
DBS, Dried blood spot
LC-MS/MS, Liquid chromatography-tandem mass spectrometry
MS, Mass spectrometry
TCI, Target concentration intervention
TDM, Therapeutic drug monitoring

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