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Where next for antiepileptic therapeutic drug monitoring?

Kuda dalje sa terapijskim monitoringom antiepileptika?

Slobodan M. Janković

University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia

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Introduction

Therapeutic drug monitoring (TDM) is a clinical procedure of adjusting drug dose according to its measured concentrations in plasma or other biological fluid. It makes sense if the following conditions are met: there is a correlation between the plasma concentration and drug effect, concentrations in biological fluids vary significantly between the subjects (high inter-individual variability), the drug has a narrow therapeutic window, a suitable method of measuring drug concentrations exists, and the drug effect cannot be easily and precisely measured in clinical practice [1, 2]. However, in order to make an adjustment of the drug dose according to its plasma concentration, the therapeutic range of plasma concentrations should be known, based on the results of previous clinical trials. Some of the first and second generations of anticonvulsants fulfilled all these conditions, and the TDM of these drugs is currently conducted in clinical practice as a routine procedure: phenobarbital, phenytoin, carbamazepine and valproic acid. Classification of anticonvulsant drugs according to the generations (historical development) is usually made in the following way: the first generation drugs (phenobarbital, phenytoin, carbamazepine, ethosuximide and valproic acid), the second generation drugs (lamotrigine, topiramate, oxcarbazepine, tiagabine, pregabaline, vigabatrine, zonisamide, gabapentin, felbamate and levetiracetam) [3] and the third generation anticonvulsants (eslicarbazepine, lacosamide, perampanel, brivaracetam, rufinamide, retigabine and newer drugs) [4].

The true clinical impact of TDM in the patients with epilepsy was rarely investigated in clinical trials [5]. One of rare clinical trials published up to date [6] investigated the impact of TDM on the patients with newly diagnosed epilepsy (partial or idiopathic generalized nonabsence epilepsy) for carbamazepine, valproate, phenytoin and phenobarbital. TDM kept plasma concentrations within the therapeutic range in more patients than in the control group, but neither 12-month remission rate, fraction remaining seizure free since an initiation of treatment nor the time to the first seizure, or 12-month remission were significantly influenced by TDM. The adverse effects rate was also very similar in the TDM and the control group. The authors concluded that the TDM should be reserved for selected patients and special situations.

For many of the second and third generation anticonvulsants, therapeutic plasma range it is still either unknown or uncertain [7–10]. In such cirsumstances measuring the plasma concentration of a drug is only of an exploratory character, i.e., the precise recommendations about the amount of dose increase or decrease could not be given. However, the clinicians still can adjust the dose of an anticonvulsant in some particular patient, using both information about the measured plasma concentration and clinical presentation of patient.

Even for anticonvulsants with the well- established TDM, only the total drug concentration in plasma is measured routinely, which may mislead a prescriber. If hypoalbuminemia is present, the total drug plasma concentration could be within the therapeutic range, but free drug may be highly elevated and cause serious toxicity, as reported for valproate [11]. Measuring plasma concentrations of free fraction of anticonvulsants should become a standard, and the therapeutic ranges of free drug should be established if we want to increase the precision and usefulness of TDM.

These, and several other issues remain unresolved with the TDM of anticonvulsants. The aim of this review was to describe them in sufficient detail, offering basis for planning the further developments of TDM.

Correspondence to: Slobodan M. Janković, University of Kragujevac, Faculty of Medical Sciences, 34 000 Kragujevac, Serbia.
E-mail: slobodan.jankovic@medf.kg.ac.rs

Issues with therapeutic drug monitoring of phenobarbital, phenytoin, carbamazepine and valproic acid

Early after introduction of TDM as a routine procedure in the patients prescribed with first generation anticonvulsants, the clinicans became aware of several issues that make difficulties when deciding about a dose adjustment after the plasma concentration of the drug is obtained [12]. First, they understood that the therapeutic ranges of plasma concentrations could not be applied to all patients, without taking into account a seizure type and frequency, yet the specific data were lacking to guide the prescriber. An importance of measuring an unbound fraction of drug within plasma was also perceived, as well as an influence of numerous factors which may change pharmacokinetics of anticonvulsants and make dose adjustments wrong if not considered in an individual patient (genetic polymorphisms, drug-drug and drug-food interactions, co-morbidities, noncompliance, or a special physiological states like pregnancy). It became clear that in order to choose the right dose regimen at least in some patients (sometimes wrongly classified as „therapy resistant"), it is necessary to make an objective estimate of long-term seizure frequency, adverse effects on motor and intelectual functions, quality of life, perhaps continuous electroencephalography (EEG) monitoring and measurement both of total and unbound anticonvulsant plasma concentrations. This led to an idea that an individual therapeutic threshold value (ITTV) should be searched for in a patient, or the minimum steady-state anticonvulsant concentration that, in that patient, results with the complete control of seizures and a lack of significant adverse drug reactions [13]. A clinician should prescribe the lowest dose of anticonvulsant that achieves through plasma concentrations above the ITTV; however, establishing the exact ITTV in a patient is difficult task to achieve in clinical practice, and a great majority of clinicians still relies on the population therapeutic range of plasma concentrations instead. Nevertheless, we should start a treatment of patient having the population therapeutic range in mind, but then, if possible, to adjust an interpretation of measured plasma concentrations to the individual characteristics of patient and the influences he/she was exposed to, as mentioned before.

Several studies showed that was not appropriate to consider only one range of steady-state plasma concentrations as therapeutic for certain anticonvulsant, since it depends on the type and the severity of epilepsy, measured by the seizure frequency before the treatment [14, 15]. In theory, if specific therapeutic ranges of cetrain anticonvulsant are established for each type of epilepsy and severity class, a prescriber would have a clear target steady-state concentrations to achieve in every patient, so the use of information about the measured plasma concentration for adjusting the dose regimen would be straightforward. Unfortunately, up to date, the well-designed and large enough studies have aimed to establish the type- and severity-dependent steady-state plasma therapeutic concentration ranges were not conducted, and we are left without this knowledge.

Phenytoin, carbamazepine and valproic acid were the first anticonvulsants for which an advantage of measuring unbound plasma concentration over the total plasma concentration was shown in clinical practice, especially in such situations when a patient had the low albumin levels [16]. However, a direct measurement of unbound drug is technically more difficult and demanding, and some clinicians revert to the calculation of adjusted phenytoin plasma concentration based on the measured total plasma concentration, albumin level and Sheiner-Tozer equation. Although relying on the fact that the adjusted plasma concentrations give better results than the total plasma concentrations when deciding about phenytoin dose, using the measured free (unbound) plasma concentration of phenytoin for dose adjustment remains the gold standard for TDM of this drug [17]; unfotrunately, we are far from achieving that standard in a majority of TDM units, even in the developed countries.

Therapeutic drug monitoring

TDM is only possibly useful for the second-generation anticonvulsant lamotrigine, since a correlation between plasma concentrations and effect was not proven unequivocally, and the therapeutic range was loosely defined [18, 19]. There is similar experience with topiramate, another second-generation drug, as its average plasma concentrations were not significantly different between the responders, non-responders and patients with toxic reactions [20, 21]. An unproven plasma concentration-effect correlation and wide, or the unreliable therapeutic range are common place for all other second-generation anticonvulsants, including tiagabine [22], pregabaline [23], vigabatrine [24], zonisamide [25], gabapentin [26], felbamate [27] and levetiracetam [25]. Vigabatrine is not significantly bound for plasma proteins and acts as an irreversible enzyme inhibitor of gamma-aminobutyric acid aminotransferase, so TDM of this drug is considered useless [24]; the additional obstacles for TDM use in the patients on levetiracetam therapy are very wide therapeutic range and minimum side effects [25]. Measuring free (protein unbound) plasma concentrations of second-generation anticonvulsants within the framework of TDM was not even attempted.

For a majority of the third generation anticonvulsants data about the clinical usefulness of TDM are missing [28], or only point to a large inter-individual variability, which is just one of the conditions that should be met (e.g., eslicarbazepine, lacosamide) [29, 30]. A reliable therapeutic range of plasma concentrations is not established for any of these drugs, although the assays for the measurement of plasma concentrations are developed and validated for many of the newest anticonvulsants, like perampanel [31], or rufinamide [32].

It is clear that the use of TDM for the first-generation anticonvulsants could be improved and enlarged, and also many of second and third-generation anticonvulsants have true potential to become drugs where routine use of TDM is mandatory. However, there are several obstacles to achieve this ideal situation, and both the technological developments and substantial workforce along with the financial investments are necessary to overcome the obstacles. Without at-

tempting to be systematic, the obstacles and ways to remove them could be listed as following: unknown seizure type and severity-specific therapeutic ranges of plasma steady-state concentrations of almost all anticonvulsants; a lack of simple, rapid and inexpensive methods for measuring plasma concentrations of free drug (unbound for plasma proteins); lack of noninvasive methods for measuring steady-state concentrations of anticonvulsants which correlate well with therapeutic and toxic effects; a lack of evidence that TDM for each particular anticonvulsant is improving the relevant outcomes of treatment, as the seizure control and quality of life, as well as the decreasing adverse events rate and overall treatments costs.

Seizure type and severity-specific therapeutic ranges

The only reliable way to establish a seizure type and the severity-specific therapeutic range of steady-state plasma concentrations of an anticonvulsant is to conduct a properly designed and adequately powered clinical trial which would include the patients with various seizure types and severity of epilepsy. Some of the researchers in their clinical trials analyzed the effects of anticonvulsants in the various subgroups according to the seizure type and noted different effects with the same plasma concentrations [33], but the attempts were rarely made to establish therapeutic ranges, usually because the subgroup analyses were underpowered, but also because the statistically significant concentration-dose relationshipis sometimes nonlinear [34]. However, an indirect proof that there must be the seizure type – the specific therapeutic ranges are dosing recommendations of topiramate and many other anticonvulsants in their Summaries of product characteristics, which are dependent on a seizure type [35]. Recently, a comprehensive systematic review was made (810 full-text articles reviewed, and data extracted from 163) with an aim to establish a therapeutic index for anticonvulsants based on the published clinical data for five anticonvulsants, but it was possible only for phenytoin, phenobarbital and valproate, regardless of the seizure type or severity [36]. This situation could be improved, at least partially and for new anticonvulsants, if the guidelines for clinical trials include recommendation that one of the study outcomes should be establishing the seizure type (and if possible severity and the specific therapeutic range (or index) of plasma concentrations. Another way is more sophisticated use of observational data for antiepileptics where TDM has already been already done in clinical practice, through pooling the data from different studies and use of statistical techniques to eliminate a bias.

Measuring plasma concentrations of free drug

Measuring concentrations of free (unbound drug) *in vitro* is usnally performed by one of the following methods: equilibrium dialysis, ultrafiltration and the Hummel and Dreyer method for the gel permeation chromatography. However, when measuring the free drug in plasma, only the equilibrium dialysis and ultrafiltration are used, because the gel permeation chromatography has high measurement „noise" due to the abundance of the small-size molecules in plasma [37]. Perhaps the most suitable for use in clinical practice is the ultrafiltration method. Although up to date, enough simple, rapid and inexpensive method for measuring the free plasma concentration of anticonvulsants was not developed for the routine TDM, it should not be too far away, since something similar was already developed for measuring the free plasma concentrations of ten beta lactam antibiotics in the critically ill patients [38].

Noninvasive methods for measuring steady-state concentrations of anticonvulsants

Measuring the concentrations of anticonvulsants in saliva was long ago seen as potentially a very suitable method for TDM, as it is noninvasive and easy to repeat as many times as necessary from the point of view of patients, who certainly would be much more compliant with a such method than with TDM based on the blood samples (injection phobia is highly prevalent in every social milieu) [39]. Besides, the physicans always prefere painless methods, if available [40]. It was early proven for the first-generation anticonvulsants that the intra-individual variability of measured concentrations in saliva was small enough to be acceptable for TDM purposes [41], and later significant correlation was found between total plasma concentrations and concentrations in saliva [41] when anticonvulsants were used in a monotherapy, or a combination, but not after the polytherapy. In general, concentrations of anticonvulsants in saliva make 10%–40% of plasma concentrations, what is enough for routine TDM [40]. It was recently shown that the valproate concentrations in saliva correlate well with concentrations of free valproate in plasma [42], which is promising because the free drug in plasma is considered to be active, and as mentioned earlier, in good correlation with the therapeutic effect. However, more recent studies showed that the salivary valproate concentration was not reliable to be used for TDM, while the following anticonvulsants could be measured in saliva and steady-state values used for TDM: carbamazepine, ethosuximide, clobazam, gabapentin, lamotrigine, lacosamide, levetiracetam, oxcarbazepine, phenytoin, phenobarbital, primidone, topiramate, and zonisamide [43]. Although possible, TDM based on salivary concentrations is far from the routine use – much remain to be done on establishing a therapeutic range in saliva for the abovementioned anticonvulsants, including specially designed clinical studies (both clinical trials and observational studies) for each drug separately.

Therapeutic drug monitoring and treatment outcome

Ultimate goal of TDM is to improve treatment outcomes of anticonvulsants and minimize occurrence of adverse effects. However, the achievement of that goal was surprisingly rarely proven in clinical studies even with the first-generation anticonvulsants. It was demonstrated for some anticonvulsants that TDM resulted in the decreased seizure frequency [44], or that the complete seizure control was

achieved in some patients previously considered a therapy resistant [45]. TDM is also very useful to discover the non-compliant patients [46] and a relationship with the decreased frequency of adverse effects, which was shown in a few studies [47]. A decrease in the overall treatment costs with the use of TDM was not shown, but several studies pointed to a generation of unnecessary costs if TDM was improperly used (taking blood samples out of the steady-state, misinterpretation of results, etc.) [48]. The effects of TDM on quality of life of patients with epilepsy were not investigated, either. There were some studies, too, which failed to find any connection between TDM and treatment outcomes, or adverse effects [49]. Considering the scarcity and incompleteness of published data, there is an obvious need for new clinical trials, or observational studies which would explore a relation between the TDM of anticonvulsants and the treatment outcomes (including costs and quality of life) / adverse effects, both for the old and new drugs that fulfill the criteria for TDM.

Availability of point of care of therapeutic drug monitoring tools

Although the intense development of point of care (POC) tests were introduced in the past for TDM of anticonvulsants, their use did not widespread because there was not enough patients to justify the costs at that time and the quality assurance was questionable [50]. However, rapid technological advances in nanosciences and biosensors created an opportunity for the development of reliable and less expensive point-of-care tests for measuring concentration of anticonvulsants in the blood, or saliva and obtaining immediate results [51, 52]. This advancement would be useful especially in the evaluation of possible toxicity of an anticonvulsant, as it is when we need the information about drug concentration as soon as possible. Another possible prospect of POC tests is that the establishment of individual therapeutic threshold value could become feasible for more patients than it was case until now (mesurements could be done at the patient's home, during weekends and holidays, and when the staff trained for venepunction is not available). With POCs, we could capture the concentrations of anticonvulsants immediately after, or before a seizure event, and also when a patient is changing diet, or has the drugs unrelated to epilepsy prescribed. All these advantages should help us to tailor a better anticonvulsant therapy for an individual patient, and hopefully, improve therapeutic outcomes.

Conclusion

Despite a relatively long history of TDM use within the framework of epilepsy treatment, we are using only small part of possibilities it offers, in the first place because of lack of specific knowledge. In order to use full capacity of TDM in the future for maximum benefit of patients with epilepsy, we need to establish the seizure type and severity-specific therapeutic ranges for those anticonvulsants where TDM has clinical significance, as well as to prove the positive effects of TDM on a wide spectrum of treatment outcomes. The development of non-invasive TDM methods, the point-of-care tests and reliable methods for routine measurement of free drug concentrations in plasma are also the areas where progress could empower TDM of anticonvulsants and bring new qualities. However, we should acknowledge that for many years, the TDM has been successfully used for adjusting doses of the first-generation anticonvulsants, provided that important confounding factors were taken into account, like hypoalbuminemia, hypervolemia, acid-base disequilibrium, and others.

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