Antiepileptic Drugs

Therapeutic Drug Monitoring of the Newer Generation Drugs

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Antiepileptic drugs (AEDs) used to treat seizure disorders are today among the most common medications for which clinical laboratories perform therapeutic drug monitoring (TDM) (1, 2). The first-generation of AEDs—carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone, and valproic acid—were introduced by U.S. and European drug manufacturers several decades ago, and TDM quickly became part of using them in clinical practice. Generally speaking, these AEDs have complicated pharmacokinetics, including absorption, distribution, metabolism, and excretion, as well as narrow therapeutic ranges that cause significant differences in individuals' therapeutic dosages.

In the last 20 years, 14 more so-called newer generation AEDs entered the market: eslicarbazepine acetate, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, rufinamide, stiripentol, tiagabine, topiramate, vigabatrin, and zonisamide (3). Only eslicarbazepine acetate and stiripentol are not approved in the U.S., while all of the drugs are available in Europe. Compared to first-generation AEDs, the newer agents generally have wider therapeutic ranges and fewer serious adverse effects.

Despite the fact that evidence for the clinical benefit of monitoring blood levels of AEDs in patients is mostly anecdotal and retrospective, TDM today continues to be widely used in clinical practice. Only two randomized, controlled studies have been published, and neither showed clear clinical benefits (4, 5). Moreover, these two studies and others indicate that pre- and post-analytical errors occur frequently, particularly in timing blood draws and interpreting drug levels (1, 2).

This article will present an overview of the newer AEDs and why improved education on the proper use of TDM is an important goal for maximizing the safety and benefits of these drugs for patients.

Current Status of TDM for AEDs

TDM of AEDs is challenging because no simple diagnostic tests can assess the clinical efficacy of any of the drugs. Careful clinical observation and labor-intensive electroencephalograms (EEG) remain the mainstays of clinical assessment. Furthermore, seizures by nature occur irregularly and unpredictably, making diagnosis difficult.

The basic assumption of TDM is that the measured drug concentration correlates with the concentration at the target site of its action, usually an ion channel or neurotransmitter transporter in the brain, and therefore with the therapeutic effect. However, the correlation of drug concentration with clinical effect is reduced by factors such as irreversibility of drug action or an individual's tolerance of the drug. For example, TDM has limited utility for vigabatrin because it irreversibly binds to its molecular target.

Laboratories usually perform TDM on serum or plasma samples, and less commonly on cerebrospinal fluid or saliva. However, the popularity of saliva as a specimen for TDM of AEDs is growing. It is easy to collect and transport saliva (6), although it is not a viable specimen type for some AEDs (7). For drugs with active metabolites, TDM may also include measuring the concentration of metabolite alone or together with the parent drug. For example, TDM of oxcarbazepine often focuses on its active metabolite, 10-hydroxycarbazepine.

Commercially Available Immunoassays for Newer AEDs	
Anti-Epileptic Drug	**Immunoassay**
Eslicarbazepine	Not available
Felbamate	Not available
Gabapentin	ARK Diagnostics
Lacosamide	Not available
Lamotrigine	ARK Diagnostics; Thermo Scientific
Levetiracetam	ARK Diagnostics
Oxcarbazepine	Not available
Pregabalin	Not available
Rufinamide	Not available
Stiripentol	Not available
Tiagabine	Not available
Topiramate	ARK Diagnostics; Thermo Scientific
Vigabatrin	Not available

Zonisamide	ARK Diagnostics; Thermo Scientific

Clinical Need for TDM

Clinicians rely upon TDM for managing patients' AED therapy for multiple reasons. Perhaps the most common is that the patients exhibit significant inter-individual variability in their pharmacokinetic responses to most AEDs (1, 2). However, a few AEDs have predictable and consistent pharmacokinetics and generally require little or no TDM.

The major pharmacokinetic factor affecting a patient's therapeutic drug levels is how quickly the liver metabolizes the AED. It is well known that the cytochrome P450 (CYP) enzyme system plays a major role. Some drugs actually increase or induce liver metabolism by CYP enzymes, leading to quicker metabolism. Classic inducers include carbamazepine, phenobarbital, phenytoin, rifampin (a tuberculosis drug), and St. John's wort (an herbal antidepressant). These drugs may lower patients' blood levels below what is optimal unless the AED dose is increased.

Other drugs inhibit CYP enzyme metabolism of some AEDs. This inhibition can lead to excessively high drug concentrations unless the clinician reduces the patient's dose. Inter-individual differences may also result from: impaired organ function, typically kidney or liver; drug-drug or drug-food interactions; or genetic or pharmacogenetics factors. In renal failure patients, AEDs may be removed during dialysis procedures, especially those that only bind plasma proteins weakly. A number of factors also may alter serum protein concentrations including liver disease, advanced age, pregnancy, uremia, and other drugs (e.g., valproic acid) that also bind serum proteins.

Clinicians also rely upon TDM to assess patient compliance. Typically, they prescribe the drug for the patient for months or even years, despite the absence of seizures. Patients may skip doses or stop taking the medication altogether because they haven't had a seizure, or they may quit taking it due to adverse effects or the cost of the medication. Lastly, AED levels may also be useful in managing suspected toxicity due to inadvertent or intentional overdose.

The Reference Range Dilemma

Although the newer AEDS offer many benefits for patients, laboratories have struggled to establish reference ranges for TDM, primarily because many of the drugs are effective over a wide range of serum/plasma concentrations (1, 2, 8). Furthermore, some individuals show good clinical response at levels above or below the standard reference range. Reference ranges also vary with different types of seizures, as well as with whether the AED is taken as monotherapy or in combination with other AEDs.

A noted clinical pharmacologist, Emilio Perucca, MD, PhD, has promoted the concept of "individual therapeutic concentrations" for AEDs, wherein a patient is treated until good seizure control is achieved (8). In this model, the clinician assesses the AED's serum/plasma concentration at a clinical endpoint and uses it as the patient's individual therapeutic concentration. The frequency of TDM can be adjusted as needed when any changes occur that might alter the AED's pharmacokinetics.

Table 1 summarizes some of the pharmacokinetic properties of the newer AEDs, and Table 2 presents a summary of the factors that influence their clinical use and interpretation.

Click here for Tables 1 and 2, and Figure 1

Analytical Methods

Another reason that TDM of the newer AEDs has been challenging is that homogeneous immunoassays have only recently become available on standard chemistry analyzers. Early on, some clinical laboratories developed analytical methods using chromatography techniques, with or without mass spectrometry (MS) (9). Many laboratories, however, send out samples to reference laboratories.

Today, most reference laboratories employ high-performance liquid chromatography (HPLC) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) for measuring levels of newer-generation AEDs. Immunoassays are also commercially available for gabapentin, lamotrigine, levetiracetam, topiramate, and zonisamide, with assays for other AEDs in development. Table 3 summarizes the analytical methodologies used for measuring AED serum/plasma concentrations (9), as well as the viability of saliva as a specimen type (7).

Table 3

Analytical Methods for Therapeutic Drug Monitoring of Newer Antiepileptic Drugs

Generic Drug Name	Primary Analytical Methodology(ies)*	Viability of Saliva as a Specimen Type
Eslicarbazepine	HPLC	Unknown
Felbamate	GC, HPLC, LC-MS/MS	Unknown
Gabapentin	HPLC, LC-MS/MS, immunoassay	Limited, low concentrations in saliva
Lacosamide	HPLC, LC-MS/MS	Yes
Lamotrigine	HPLC, LC-MS/MS, immunoassay	Yes
Levetiracetam	GC, HPLC, LC-MS/MS, immunoassay	Yes
Oxcarbazepine	HPLC, LC-MS/MS	Yes
Pregabalin	HPLC, LC-MS/MS	Unknown

Rufinamide	HPLC, LC-MS/MS	Unknown
Stiripentol	HPLC	Unknown
Tiagabine	LC-MS/MS	Unknown
Topiramate	GC, HPLC, LC-MS/MS, immunoassay	Yes
Vigabatrin	HPLC	No
Zonisamide	HPLC, LC-MS/MS, immunoassay	Yes
* Abbreviations: GC, gas chromatography; HPLC, high-performance liquid chromatography; LC-MS/MS, liquid chromatography-tandem mass spectrometry.		

A Closer Look

The newer AEDs are a welcome addition to therapeutic options for treating epilepsy; however, the large number of drugs along with the variability in patients' responses presents a wide array of challenges for assessing their levels in patients. Laboratorians need to be aware of the key clinical and pharmacokinetic properties of these AEDs in order to optimize their TDM. Below is a brief review of each drug that summarizes key parameters.

Eslicarbazepine Acetate. Approved in Europe, but not in the U.S., eslicarbazepine acetate is a pro-drug that is rapidly metabolized by liver esterases to form eslicarbazepine, the active metabolite that is the target of TDM. Overall, the drug has relatively predictable pharmacokinetics; therefore, TDM has a minimal role in eslicarbazepine therapy, except when it is taken by renal insufficiency patients who may have impaired drug clearance.

Felbamate. The Food and Drug Administration (FDA) approved felbamate for treating adults with partial seizures and children with Lennox-Gastaut Syndrome, a type of childhood epilepsy that is often refractory to standard AED therapy. By 1994, however, clinicians identified cases of aplastic anemia, some of which progressed to severe liver failure, that were associated with felbamate therapy. While the drug has remained on the market, FDA sought revised labeling and restricted its use.

Patients taking a typical dose of felbamate have serum/plasma concentrations of 30–60 mg/L, but children clear the drug 20–65% faster than adults. Overall, felbamate TDM has relatively modest utility, and unfortunately, toxicity cannot be easily predicted from laboratory studies. Given felbamate's potential adverse effects, laboratorians should advise clinicians to closely monitor blood counts and liver function of patients receiving this therapy.

Gabapentin. FDA originally approved gabapentin for treating epilepsy, but the drug has achieved far greater popularity as an adjunctive therapy for chronic pain. Gabapentin is not metabolized, shows little binding to serum proteins, and is cleared almost entirely by the kidneys. A wide range of serum/plasma concentrations, 2–20 mg/L, are associated with effective seizure control.

Other than optimizing dosing in renal insufficiency patients, TDM has overall low utility in gabapentin therapy. Saliva concentrations can be monitored, but they are only 5–10% of those in serum/plasma.

Lacosamide. This drug has predictable pharmacokinetics across all ages and is cleared almost equally by the liver and kidney. Clinically significant drug-drug interactions involving lacosamide are also uncommon. Lacosamide TDM has relatively low utility except in patients with severe liver and/or kidney failure.

Lamotrigine. Approved in the U.S., lamotrigine is widely used to treat partial seizures, as well as bipolar disorder. Several first-generation AEDs have been associated with severe birth defects, but lamotrigine has a solid safety record in pregnancy, making it the AED of choice to treat pregnant women experiencing seizures. Dermatologic reactions occur frequently, however, and patients should seek medical attention promptly if any skin reactions occur.

Lamotrigine's pharmacokinetics are well understood, but fairly complex. The drug exhibits: increased metabolism over time (auto-induction); drug-drug interactions with CYP enzyme inducers and inhibitors; and impaired clearance in renal failure. But lamotrigine's clearance is higher in children and markedly higher (~300%) in pregnancy.

Researchers have proposed a reference range of 3–14 mg/L for refractory epilepsy therapy; however, the incidence of toxic effects is significantly increased when serum/plasma concentrations are above 15 mg/L. Given the complicated pharmacokinetics and well-defined toxicity level, TDM plays a major role in lamotrigine therapy. In addition to serum/plasma, saliva is a viable specimen type for lamotrigine TDM.

Levetiracetam. A widely used newer AED, levetiracetam is available in both oral and intravenous formulations, with the intravenous form used for acute management in the hospital setting. The drug does not bind serum proteins, has predictable pharmacokinetics, and limited drug-drug interactions because it is not metabolized by the liver.

Laboratories that perform TDM of levetiracetam should separate serum or plasma from whole blood rapidly, as hydrolysis of levetiracetam can occur in the blood tube. Saliva is also a viable specimen type for levetiracetam. Researchers have proposed a therapeutic reference range of 12–46 mg/L, but laboratorians should be aware that samples drawn shortly after a dose of intravenous levetiracetam can appear to have very high drug levels. The main value of TDM for levetiracetam is adjusting dosage for pregnant patients and those with renal insufficiency.

Oxcarbazepine. Oxcarbazepine is structurally related to carbamazepine, but it has a lower incidence of adverse effects, such as agranulocytosis and drug-drug interactions. The drug is metabolized primarily to 10-hydroxycarbazepine, which accounts for much of the anti-seizure activity. For TDM, oxcarbazepine is treated like a pro-drug, with monitoring focused on 10-hydroxycarbazepine. Clearance is reduced in the elderly and in individuals with renal insufficiency, but increased in pregnant women and patients taking liver enzyme-inducing drugs.

Laboratories have observed that a wide range of serum concentrations, 3–35 mg/L, are clinically effective in seizure treatment, with toxic side effects more common at >35 mg/L. Overall, TDM is useful especially in renal insufficiency, pregnancy, and cases with suspected drug-drug interactions. Saliva is also a possible specimen type, although 10-hydroxycarbazepine has a shorter half-life in saliva compared to serum.

Pregabalin. Pharmaceutical researchers designed pregabalin to be a more potent analog of gabapentin. Similar to its predecessor, pregabalin is effective in treating chronic pain, and since its introduction, FDA approved a separate indication for treating fibromyalgia. Pregabalin has predictable pharmacokinetics with no reported drug-drug interactions and minimal binding to serum proteins; however, renal failure patients generally take lower dosages.

Within the reference range of 2.8–8.3 mg/L, patients experience beneficial anti-seizure effects. However, other than adjusting dosage for renal failure patients or assessing adherence to therapy, TDM has minimal benefit in pregabalin therapy.

Rufinamide. Approved in the U.S. for Lennox-Gastaut syndrome, rufinamide has very complicated metabolism pathways and a high potential for drug-drug interactions.

Serum/plasma levels within a broad reference range of 3–30 mg/L correlate well with seizure control. Monitoring serum levels can be especially helpful in patients taking concomitant liver enzyme inducers or who are receiving hemodialysis. Overall, TDM is quite useful for this drug.

Stiripentol. Approved in Europe in 2001, stiripentol has yet to be approved in the U.S. It has very complex pharmacokinetics, including non-linear elimination kinetics, high serum protein binding, and extensive metabolism by the liver, which resembles the classic AED phenytoin more than newer AEDs. The stiripentol reference range is not well-defined, but serum concentrations of 4–22 mg/L correlate with good management of seizures in children.

Monitoring the free-drug fraction of stiripentol would appear to be beneficial, but no methods have been reported to date. Overall, clinical use of the drug is limited, and therefore so is experience with TDM.

Tiagabine. The AED drug tiagabine is not widely prescribed in the U.S. or Europe. Its limited use has been attributed to a propensity to cause non-convulsive status epilepticus, a serious adverse effect (10). It shows significant binding to proteins (>96%), as well as variability in inter-individual metabolism by the liver. Although therapeutic levels of the drug are substantially lower than those for other newer generation AEDs, tiagabine has a broad reference range of 0.02–0.2 mg/L for its anti-seizure effect. Overall, TDM is very useful for tiagabine due to its complex and variable pharmacokinetics.

Topiramate. Approved for treating epilepsy in children and migraine headaches in adults, topiramate is metabolized in the liver and has the potential for drug-drug interactions. Researchers have proposed a reference range of 5–20 mg/L for epilepsy therapy. TDM of topiramate is valuable because individuals' metabolism is quite variable. Saliva is also a viable specimen type.

Vigabatrin. An irreversible inhibitor of GABA transaminase, vigabatrin breaks one of the principle assumptions of TDM, namely that the concentration in serum/plasma correlates with the concentration at the target site. This may be one reason why laboratories have observed a wide range, 0.8–36 mg/L, of trough serum/plasma concentrations found in patients successfully treated with the drug. Consequently, other than to assess patient compliance or to evaluate possible drug overdose, there is little benefit in monitoring vigabatrin.

Zonisamide. Metabolism of zonisamide is affected by drugs that induce or inhibit CYP enzyme activity. There is significant inter-individual variability in metabolism of the drug, especially in patients who are on concomitant therapy with other drugs that also affect expression of liver enzymes. Toxic side effects are uncommon at serum concentrations <30 mg/L, and researchers have proposed a reference range of 10–40 mg/L in serum/plasma for managing seizures. Saliva is also a viable specimen type for zonisamide TDM. Overall, TDM is useful for zonisamide.

The Take-Home Message

The past 20 years have seen the introduction of 14 newer AEDs for treatment of seizure disorders. Clinicians also prescribe the newer agents for "off-label" conditions, including bipolar disorder, chronic pain syndromes such as fibromyalgia and trigeminal neuralgia, or migraine headaches.

As use of these drugs increases, clinical laboratories will likely see more requests from clinicians to monitor patients' drug levels. Although physicians often order the tests to assess adherence to therapy, laboratorians should approach TDM for conditions other than seizure disorders cautiously, as it is not well-defined at present.

The availability of more automated immunoassays for measuring these drugs, as well as the expected development and introduction of more assays by manufacturers, will allow larger numbers of laboratories to perform in-house TDM of the newer AEDs. Laboratorians would do well to recognize this trend and evaluate new assays carefully so that they can best help clinicians understand the clinical utility of the results.

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