Monitoring the Levels of Antiepileptic Drugs forTherapeutic Purposes: An Overview of the Current Situation and Potential Future Advancements

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Abstract:

Antiepileptic drugs (AEDs) play a crucial role in treating epilepsy, with expected variability in their pharmacokinetics across diverse patient groups such as children, the elderly, pregnant individuals, and those undergoing polytherapy with potential drug interactions. Additionally, ensuring patient adherence is essential. Therapeutic drug monitoring (TDM) serves as a valuable tool for maintaining treatment quality. Given the prevalence of pharmacokinetic variability among AEDs, TDM enables a personalized approach to epilepsy care by allowing adjustments based on individual drug concentrations. Currently, there are 27 licensed AEDs, making them one of the most common medications subject to TDM. This review aims to provide an overview of the existing evidence on the application of AED TDM in both epilepsy and non-epilepsy conditions. The extensive pharmacokinetic variability of AEDs results in significant variations in serum concentrations among patients, making TDM beneficial for tailoring treatment to individual needs. Indications for TDM encompass scenarios where optimization of clinical outcomes is crucial. Future advancements may involve incorporating additional markers of toxicity and genetic variability to further enhance individualization and optimize AED treatment.

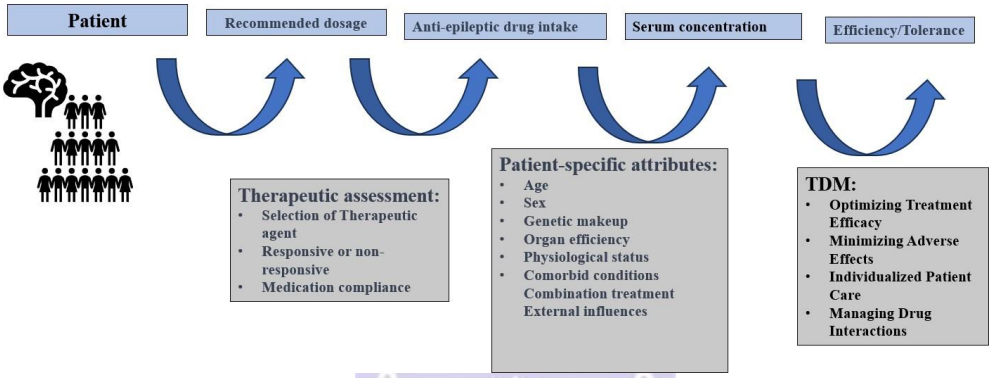
KEYWORDS: TDM, Antiepileptic, Toxicity

INTRODUCTION:

In the late 1960s, the monitoring of plasma, serum, or occasionally whole blood concentrations of the older antiepileptic medications phenobarbitone and phenytoin started to gain traction. Initially employed as a research technique, it appeared to hold potential for future applications in epilepsy management. Therapeutic drug monitoring (TDM) is defined as the measurement and clinical use of serum /plasma or saliva drug concentrations to adjust each patient's individual dosage and thus schedule to each patient's individual therapeutic requirements [(1—8)] Although few randomized studies have demonstrated a positive impact of TDM on the clinical outcome in epilepsy, evidence from non-randomized studies and everyday clinical experience indicates that the use of TDM for older as well as newer antiepileptic drugs (AEDs) may best be used to guide patient management, provided that serum concentrations are measured with a clear indication and with a clinical interpretation [(6)] . AED TDM has been used to manage pharmacological variability in and between patients for the last 50 years, and many drugs have
become available during that time, allowing continuous development of this field of research and evaluating its impact on clinical practice. TDM is relevant for all drugs where the serum concentration issupposed to reflect the concentration and pharmacological action at target in the brain. The only exception to this is vigabatrin, which is an irreversible inhibitor of the enzyme responsible for the degradation of GABA, GABA transaminase. This can result in a prolonged effect in the brain, even though the serum concentration of vigabatrin is declining or even zero. AEDs serve as the cornerstone oftreatment of patients with epilepsy. In the past few years, numerous new antiepileptic drugs (AEDs) have been brought into the market, bringing the total number of available AEDs internationally to 27 [(1)] .Across all these AEDs, there is significant variability in their pharmacological effects. Currently, it is easier to measure and potentially regulate pharmacokinetic variability, which pertains to how the body absorbs, distributes, metabolizes, and excretes the drugs [(3,4)] .

Apart from pharmacokinetic factors, environmental conditions, physiological differences among individuals, and genetic variations also contribute significantly to the wide range of serum concentrations observed for any given AED. This variability underscores the complexity of factors influencing the effectiveness and safety of AEDs in individuals with epilepsy.Also, aspects of adherence, if the drug is taken as prescribed, come into play in the

total evaluation ofthe AED treatment. The onset of epilepsy is predominantly in early life, it is a chronic condition that often lasts for years or the whole lifetime, and many patients require long-term therapy. The principal outcome in epilepsy is the absence of seizures. Two-thirds of patients achieve seizure control with monotherapy AEDs, and 20–30% require polytherapy [2,9,10] . Furthermore, even though there are now numerous available AEDs, the number of patients that are not responding to a first AED is 50%, and one-third is still regarded as being treatment resistant, many of which have several seizure types [11] . Indeed, the choice of the appropriate AED for different seizure types is of paramount as some AEDs are specifically effective in certain seizure types, for example, ethosuximide in absence seizures and stiripentol in Dravet syndrome [12,13] . Thus, in patients with refractory epilepsy with a challenging treatment and seizure occurrence, TDM may be a valuable tool to optimize and individualize AED treatment and to monitor treatment over time as shown in figure 1.



The aim of this review is to provide an updated overview of the current evidence of the use and implementation of TDM in epilepsy and other indications. Reasons for TDM will be highlighted, such as pharmacokinetic variability, drug interactions, adherence, and pharmacogenetic variations.

Figure 1: The diagram depicts the process from prescribing an antiepileptic drug to ensuring its proper use and monitoring serum concentrations. It considers patient-specific factors like adherence, variations in pharmacokinetics, pharmacodynamics, and pharmacogenetics.

METHOD OF ANALYSIS:

Originally, the quantification of plasma phenobarbitone and phenytoin concentrations relied on ultraviolet spectrophotometry, often involving preliminary derivatization of the drugs[14–17] However, these techniques were labor-intensive, occasionally lacked sensitivity, and were somewhat non-specific, depending on the efficiency of initial separation stages during drug extraction from plasma. Spectrophotometric methods were not widely adopted and were eventually superseded by chromatographic techniques, such as quantitative thin-layer chromatography (TLC) [18] gas-liquid chromatography (GLC) with derivatization, and later high-performance liquid chromatography (HPLC). These chromatographic methods provided specific and sensitive assays, sometimes enabling simultaneous measurement of drug metabolites.

While gas chromatographic-mass spectrometric and HPLC-mass spectrometric assays offered increased sensitivity and specificity, their adoption for routine use was limited due to the high cost of required instrumentation, mostly restricting them to research applications. HPLC methods persisted in laboratories with lower throughput and a requirement to measure various antiepileptic drugs. In contrast, busier service laboratories, able to allocate dedicated instruments for drug assays, predominantly favoredvarious immune-assays.

These immune-assays employed different techniques to quantify the in vitro product resulting from the reaction between the drug under examination and an antibody raised against it. Methods included radiation measurement, linked enzyme-catalyzed reactions liposome lysis [16] , fluorescence polarization [17] , nephelometric inhibition [18] , substrate-labeled fluorescence [17] , and electron spin resonance [18]) . Immune-assays were generally more cost-effective than HPLC, offering convenience and rapid results. Despite their high sensitivity, some antibodies used in these

assays, or specific antibody batches, might cross-react with drug metabolites, potentially yielding results divergent from more inherently specific methods. Such discrepancies could mislead prescribers, especially when inactive metabolites are measured alongside the drug, particularly if their relative proportions are atypical, as might happen with metabolite accumulation (e.g p-hydroxy phenytoin) in conditions like renal failure or due to pharmacokinetic interactions [19,20] .

CONCENTRATION CAN BE OBSEREVED IN BODY FLUIDS:

Antiepileptic drug concentrations are typically assessed in plasma or serum, where their values are essentially the same. Although it is feasible to measure these concentrations in whole blood, variations may exist between red cells and plasma concentrations. For instance, the red cell to plasma concentration ratio is approximately 0.23:1 for phenytoin and 0.38:1 for carbamazepine [21,22] . The interpretation of whole blood drug concentration values may be influenced by red cell numbers. Limited data are available regarding the correlation between antiepileptic drug concentrations in whole blood andtheir biological effects.

Most antiepileptic drugs primarily act on or near neuronal surfaces, and their effects are determined by the drug concentration in the extracellular fluid around these sites. This extracellular fluid equilibrium with plasma water suggests that plasma unbound antiepileptic drug concentrations often offer a more accurate measure of potential pharmacological effects than whole plasma drug concentrations. Ideally, measuring unbound concentrations in plasma or serum is recommended, especially for drugs that bind to plasma proteins. In clinical practice, assessing plasma unbound antiepileptic drug concentration becomes necessary when altered plasma protein binding capacity is suspected due to physiological changes (particularly in late-stage pregnancy), diseases (mainly hepatic or renal disorders), malnutrition, or a known drug interaction involving competition for plasma protein binding sites. Although some drugs can displace antiepileptic drugs from binding sites in test tube situations, the negligible clinical consequence in the body is due to the redistribution and elimination of the displaced drug. Due to the inherent difficulties in dialysis procedures ,measurement of plasma unbound drug concentration often involves a preliminary ultrafiltration step which can introduce its own complications and errors [23,24,25] .

Antiepileptic drug levels can be assessed in cerebrospinal fluid (CSF) and tears, with the exception of gabapentin, demonstrating close approximation to unbound plasma concentrations[26,27,28]. Unfortunately, challenges in collection make these fluids unsuitable for routine monitoring. Saliva, on the other hand, poses fewer collection difficulties and allows for routine monitoring without invasive procedures [29] . Saliva's low protein concentration, compared to whole plasma, makes it practically equivalent to plasma water for drug concentration assessment. Unless pH differences affect the unbound nonionized drug fractions or hinder equilibration between fluids, saliva concentrations should mirror plasma concentrations. The pH difference is negligible for phenytoin and carbamazepine, while ethosuximide, being unbound in whole plasma, exhibits equal concentrations in saliva. Correction for pH differences in salivary phenobarbitone concentration can be achieved using the Henderson-Hasselbalch equation if saliva pH is measured post-collection [30,32] .However, valproate's entry into saliva is not solely through passive transport, and its salivary concentrations do not correlate with plasma levels [33,34] . Lack of correlation may stem from variations in saliva flow rate or the presence of recent drug traces in the mouth during collection, as seen with carbamazepine up to 2 hours after intake [35] .

DIFFERENCE IN THE PHARMACOKINETICS AMONG VARIOUS PATIENTS POPULATION:

During the transition from childhood to old age ,various physiological and pathological changes may occur , such as renal and liver function ,and other diseases can contribute to changes in the pharmacokinetic characteristics of AEDs .

INFANTS AND CHILDREN

In young children, rapid physiological changes during early development significantly impact the pharmacokinetics of antiepileptic drugs (AEDs). Clearance is generally high, leading to

low elimination half-lives, especially from 6 months to around 6 years of age. The volume of distribution also undergoes changes [36,37,38,39]. Consequently, infants and young children often require higher doses per kilogram of body weight compared to older children and adolescents. This variability complicates predicting optimal therapeutic doses, and therapeutic drug monitoring (TDM) becomes particularly valuable in these cases. In contrast, older children and adolescents exhibit pharmacokinetics similar to adult populations.

DURING PREGNANCY:

Pregnant women experience physiological alterations, including decreased absorption, altered distribution, reduced protein binding for highly bound drugs, increased metabolism due to enhanced enzyme capacity, and elevated excretion. These changes lead to increased serum concentration/dose ratios during pregnancy, returning to baseline post-partum. Various AEDs, such as lamotrigine, levetiracetam, oxcarbazepine, topiramate, zonisamide, and gabapentin, are affected, with valproate being contraindicated due to associated risks. Valproate's extensive pharmacokinetic variability in women suggests monitoring free, unbound concentrations for safe management [40,41,42] .

IN ELDERLY POPULATION WITH HEPATIC AND RENAL DISEASE :

In the elderly and individuals with hepatic or renal impairment, AED clearance is reduced by 30–50%, and sometimes up to 90%. Physiological changes affect absorption, distribution, and metabolic capacity, leading to altered characteristics of AEDs. Polypharmacy is common in the elderly, complicating pharmacodynamic sensitivity and requiring cautious interpretation of TDM results [43]. Hepatic diseases may impact AED clearance, while renal function is crucial for AEDs eliminated via renal excretion. TDM is recommended for patients with hepatic and renal diseases, with a focus on free, unbound concentrations for highly bound AEDs due to unpredictable changes in protein binding and clearance. Overall, the extensive pharmacokinetic variability of AEDs emphasizes the importance of TDM in optimizing treatment.

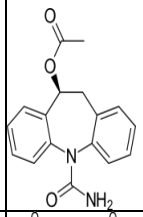
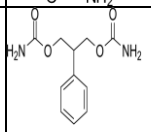
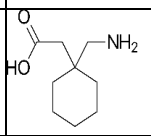
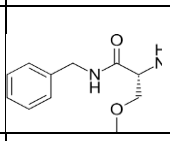
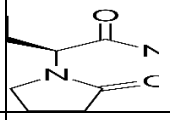
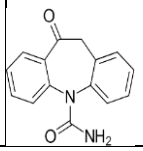
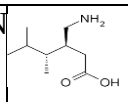
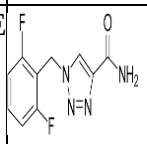
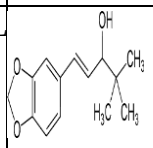
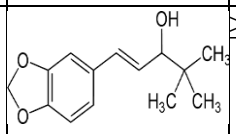
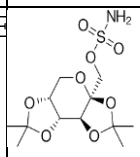
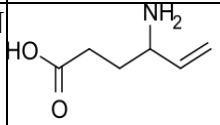
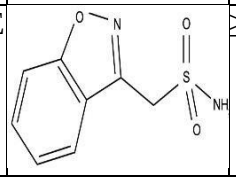
THE NEWER GENERATION OF AEDS :

In the last twenty years, 14 new AEDs have entered the market in the United States and/or Europe [44,45]. Among the antiepileptic drugs (AEDs), notable ones include eslicarbazepine acetate, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, rufinamide, stiripentol, tiagabine, topiramate, vigabatrin, and zonisamide. Notably, eslicarbazepine acetate, lacosamide, rufinamide, and stiripentol are currently not approved in the United States. These newer AEDs are often categorized as second or third-generation drugs. Compared to the older AEDs, the newer agents tend to have broader therapeutic ranges and fewer severe adverse effects.

Beyond epilepsy treatment, some of these newer AEDs find application in addressing other conditions such as bipolar disorder, chronic pain syndromes like fibromyalgia and trigeminal neuralgia, or migraine headaches [46] . This manuscript delves into the therapeutic drug monitoring (TDM) of these contemporary AEDs in epilepsy treatment, with a focus on assessing the utility of TDM based on the drug's pharmacokinetics and clinical effects.

Table 1- Showing patient-specific parameters, including drug chemical structure, oral bioavailability,half-life with and without enzyme inducers, time to peak concentration, and serum reference range, facilitates a comprehensive approach to optimizing antiepileptic drug prescription and monitoring.

DRUG	CHEMIC AL STRUCTURE	ORAL BIOAVAILA BILITY %	HAIF LIFE IN ABSENCE OF CONCOMMITANT ENZYME INDUCERS[a]	HAIF LIFE IN PRESENCE OF CONCOMMITANT ENZYME INDUCERS [a]	TIME T OPEAK CONCENTR ATION (h)	REFERE NCE RANGE IN SERUM (mg/L) [f]

ESLICARBAZEPINE ACETATE		≥ 80	20—24	20—24	1--4	Not established
FELBAMATE		>90	16—22	10--18	2—6	30—60
GABAPENTIN		<60	5—9	5—9	2—3	2—20
LACOSAMIDE		≥ 95	12 –13	12—13	0.5 –4	5—10
LEVETIRACETAM		≥ 95	6—8	6—8	1	12—46
OXCARBAZEPINE [c]		90	8—15	7—12	3—6	3—35
PREGABALIN		≥ 95	5—7	5—7	1—2	2—8.3
RUFINAMIDE		85	8—12	≤ 8	5—6	Not established
STIRIPENTAL		≥ 95	Variable	Variable	1—2	4—22
TIAGABINE [d]		≥ 90	5—9	2—4	1—2	0.02—0.2
TOPIRAMATE		≥ 80	20--30	10—15	2—4	5—20
VIGABATRIN		≥ 60	5—8	5—8	1—2	0.8—36
ZONISAMIDE		≥ 65	50—70	25—35	2—5	10—40

[a] Enzyme inducers include carbamazepine ,phenobarbitone ,phenytoin ,rifampicin and St. John's wort .

[b] Half -life increases to 30 –90 h during concomitant therapy with valproic acid (enzyme inhibitor)
[c] All parameters refer tom the active metabolite 10 - hydroxycarbazepine
[d] Monitoring of free drug may be useful for these drugs
[f] References for reference ranges
[Source : Matthew et al ' Therapeutic Drug Monitoring of the Newer Anti-Epileptic Medications'Pharmaceutical (Basel) .2010 Jun ;3(6) 1909—1935.]

Over the past two decades, 14 new antiepileptic drugs (AEDs) have been introduced in the United States and/or Europe, including eslicarbazepine acetate, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, rufinamide, stiripentol, tiagabine, topiramate, vigabatrin, and zonisamide. It's worth noting that eslicarbazepine acetate, lacosamide, rufinamide, and stiripentol have not yet received approval in the United States. These newer AEDs are sometimes classified as second- or third-generation drugs. Compared to the older AEDs, the newer ones often exhibit broader therapeutic ranges and fewer serious adverse effects. Additionally, some of the newer AEDs find applications beyond epilepsy treatment, being used for conditions such as bipolar disorder, chronic pain syndromes (e.g., fibromyalgia, trigeminal neuralgia), or migraine headaches. This article specifically focuses on Therapeutic Drug Monitoring (TDM) of the newer AEDs in epilepsy treatment, highlighting whether thedrug's pharmacokinetics and clinical effects justify the use of TDM.

A NOVAL MEDICATION THAT NECESSITATES SUPERVISION:

Monitoring the plasma concentrations of recently introduced antiepileptic drugs, such as lamotrigine, gabapentin, topiramate, oxcarbazepine, tiagabine, and remacemide, may be theoretically justified. Vigabatrin may be an exception. However, the practicality of monitoring felbamate remains uncertain due to its limited use. Currently, these drugs are predominantly used in combination therapy for refractory seizure disorders, making it challenging to establish clear correlations between plasma concentrations and clinical effects. Monitoring these drugs in monotherapy for recent-onset epilepsy is crucial for determining therapeutic and toxic concentration ranges. Without this knowledge, interpreting plasma concentration values, even though therapeutic ranges are occasionally provided, is challenging. Remacemide monitoring can be complex due to its racemate nature with biologically active enantiomers and metabolites [47] .

CONCLUSIONS AND FUTURE PROSPECTS :

Looking ahead, exploring saliva as a non-invasive medium for monitoring antiepileptic drug concentrations, especially in children or for frequent monitoring needs, is promising. This approach could enable patients to collect saliva strategically at home, such as after a seizure or during intermittent symptoms. Future advancements in analytical methodology may simplify, expedite, and reduce the cost of plasma antiepileptic drug monitoring. While existing methods are reasonably efficient, addressing the lack of high-quality plasma drug concentration-biological effect correlation data and enhancing prescribers' pharmacokinetic awareness and clinical expertise are essential for optimal use of available methods.

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