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# Therapeutic Drug Monitoring of Antiepileptic Medications

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## 1. Introduction

Medications used to treat and prevent seizures (antiepileptic medications, AEMs) have been commonly managed by therapeutic drug monitoring (TDM) to optimize efficacy and avoid toxicity (Neels et al., 2004; Patsalos et al., 2008). TDM has been applied mostly to the first-generation AEMs that have been used clinically in the United States and Europe for several decades, namely carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone, and valproic acid. First-generation AEMs generally have significant inter-individual variability in their pharmacokinetics (absorption, distribution, metabolism, and excretion) and low therapeutic indices. Two randomized, controlled studies of AEM TDM showed that practitioners often apply information from TDM incorrectly (Fröscher et al., 1981; Januzzi et al., 2000). Consequently, improved education of medical practitioners on TDM is important for the future.

In the last twenty-five years, 14 new AEMs have entered the market in the United States and/or Europe (LaRoche & Helmers, 2004a,b; Patsalos, 1999). These drugs are sometimes characterized as second- or third-generation AEMs and include the following drugs: eslicarbazepine acetate, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, rufinamide, stiripentol, tiagabine, topiramate, vigabatrin and zonisamide. Eslicarbazepine acetate, lacosamide, rufinamide, and stiripentol have not yet been approved in the United States. In contrast to the first-generation AEMs, the newer agents generally (although not always) have wider therapeutic ranges and less adverse effects. This chapter focuses on TDM of AEMs in treatment of epilepsy, emphasizing whether the pharmacokinetics and clinical profile of the drug make TDM useful. AEMs are sometimes used to treat disorders other than epilepsy such as trigeminal neuralgia, fibromyalgia, and migraine headaches (Johannessen Landmark, 2008; LaRoche & Helmers, 2004a).

There are several main challenges in TDM of AEMs (Patsalos et al., 2008). First, there are no simple diagnostic or laboratory tests for seizure disorders. The electroencephalogram (EEG) is useful for diagnosis of seizure disorders but is too labor-intensive for long-term patient observation. Second, seizures often occur unpredictably, sometimes with long periods of time between episodes. Lastly, the toxicity of AEMs can resemble neurologic disease, sometimes leading to inappropriate escalations of medication therapy even when the dose is actually too high.

One of the most basic assumptions of TDM is that the concentration of drug being measured correlates with the concentration at the target site of action (e.g., brain tissue). TDM of AEMs

is usually performed on plasma or serum, or occasionally on some other body fluid such as saliva. TDM is difficult to apply when there are factors (e.g., irreversibility of action, drug tolerance) that lessen the correlation between clinical effect and serum/plasma concentration. AEMs with active metabolites also present a special challenge for TDM. For drugs with active metabolites (e.g., oxcarbazepine, primidone), TDM can include measurement of the concentrations of both parent drug and its metabolite(s) or just of the metabolite(s).

TDM of AEMs in saliva has not yet been widely applied (Liu & Delgado, 1999), but has been studied for ten drugs: carbamazepine (Ruiz et al., 2010; Tennison et al., 2004), gabapentin (Benetello et al., 1997; Berry et al., 2003), lamotrigine (Incecayir et al., 2007; Malone et al., 2006; Ryan et al., 2003), levetiracetam (Grim et al., 2003; Guo et al., 2007; Mecarelli et al., 2007), oxcarbazepine (Cardot et al., 1995), phenobarbital (Tennison et al., 2004), phenytoin (Tennison et al., 2004), topiramate (Miles et al., 2003), valproic acid (al Za'abi et al., 2003), and zonisamide (Kumagai et al., 1993). Of these ten drugs, gabapentin and valproic acid are clearly unsuited for salivary concentration analysis. Gabapentin shows low concentration in saliva versus plasma (salivary concentrations are only ~5-10% that of serum or plasma) and valproic acid has poor correlation between serum and salivary concentrations. Monitoring of salivary concentrations of AEMs has clear appeal in some patient populations, especially in the pediatric and geriatric populations. One study showed that salivary samples can be collected by the patient and mailed to a clinical laboratory without loss of sample integrity (Jones et al., 2005).

## 2. Application of TDM to AEMs

The most common reason to employ TDM for AEM therapy is that the drug shows unpredictable and/or variable pharmacokinetics, often related to differences in drug metabolism (Bialer, 2005; Perucca, 2006). Variability in pharmacokinetics may also occur due to alterations in drug absorption or distribution. Metabolism of AEMs may vary due to impaired organ function (typically kidney or liver), genetic factors, or drug-drug interactions. Many of the AEMs are metabolized by hepatic enzymes including cytochrome P450 (CYP) enzymes such as CYP3A4 and CYP2C9. A number of drugs are known to increase (induce) the expression of hepatic drug-metabolizing enzymes. Well-known inducers include carbamazepine, phenobarbital, phenytoin, rifampin (tuberculosis drug) and St. John's wort (herbal antidepressant) (Komoroski et al., 2004; Skolnick et al., 1976; Van Buren et al., 1984). In patients taking AEMs, the co-ingestion of liver enzyme inducers can lead to inappropriately low serum/plasma concentrations of the AEM if dose adjustments are not made. Some drugs may inhibit metabolism of AEMs, often by acting as antagonists of CYP enzyme activity, potentially leading to excessively high concentrations of drug unless the dose is reduced appropriately. Valproic acid inhibits multiple liver enzymes and has been well-documented to cause drug-drug interactions with other AEMs, which often requires careful TDM when valproic acid is used in multi-drug regimens to treat epilepsy (Neels et al., 2004). AEMs may be used in patients with some degree of renal impairment which can affect AEM pharmacokinetics by decreased clearance, or by removal of drug during dialysis procedures. In general, AEMs with low degrees of plasma protein binding are cleared more effectively by dialysis than AEMs that are highly protein bound (Lacerda et al., 2006).

Special considerations apply to TDM of AEMs that are highly (> 90%) bound to serum proteins. For these AEMs, monitoring of unbound (free) concentrations may be clinically

useful (Dasgupta, 2007). Serum protein concentrations of drug can vary due to factors such as drug interactions, liver disease, pregnancy and old age. Co-administered medications (e.g., valproic acid) or endogenous substances can displace drugs from serum protein binding sites, increasing free drug concentrations. Uremia, typically secondary to renal failure, can also displace AEMs from serum protein binding sites. Free drug concentrations can be measured by preparing an ultrafiltrate of plasma (e.g., by centrifugation through a membrane) and then analyzing the concentration of drug. The main technical challenge is that free drug concentrations may be substantially lower than total drug concentrations in drugs that are highly bound to plasma proteins. Therefore, analytical methods to measure free drug concentrations need to have lower limits of quantitation than methods to measure total drug concentrations. Analytical methods used to measure total drug concentrations may have insufficient analytical sensitivity for free drug analysis (Dasgupta, 2007). A further practical challenge is that the ultrafiltration process needed for free drug analysis is not easily automated and adds processing time and effort to the clinical laboratory analysis.

The last common reason for TDM of AEMs is to assess compliance (adherence) to therapy such as in a patient who shows a lack of clinical response or the loss of efficacy in a therapy that was previously effective (Patsalos et al., 2008). Epilepsy therapy can occur over long periods of time even in the absence of seizures. Similar to other medications that may be taken chronically (e.g., anti-depressants, anti-hypertensives), patients may skip doses or stop taking the medication due to side effects, medication expense, or other factors.

## 3. Reference ranges for AEMs

Reference ranges for AEMs are challenging to establish. Ideally, TDM would guide physicians towards serum/plasma concentrations that optimally control seizures while avoiding or minimizing adverse effects. The 'reference range' of an AEM can be defined by a lower limit below which therapeutic effect is unlikely and an upper limit above which toxicity is likely (Patsalos et al., 2008). Reference ranges may vary with different types of seizures, or when AEMs are used for other purposes such as treatment of bipolar disorder or chronic pain. A special challenge occurs with defining reference ranges for the newer generation AEMs, which were generally studied in clinical trials as adjunctive therapy and not as monotherapy. Perucca has advocated the concept of 'individual therapeutic concentrations' (Perucca, 2000) wherein a patient is treated until good seizure control is achieved. The serum/plasma concentration at which good seizure control occurs serves as the patient's individual therapeutic concentration that can be used as the target concentration to maintain during chronic therapy. TDM for AEMs is especially important when there are factors that can alter AEM pharmacokinetics, e.g., pregnancy, impaired kidney or liver function, or concomitant therapy with hepatic enzyme-inducing or –inhibiting drugs.

With the background and theory on TDM above, each of the AEMs will be discussed in turn with regard to TDM. Table 1 summarizes the pharmacokinetic properties of the AEMs, while Table 2 presents a summary of the justifications of TDM for the AEMs. References for reference ranges used in Table 1 are as follows: carbamazepine, clonazepam, phenobarbital, phenytoin, primodone, valproic acid (Hardman et al., 1996), felbamate (Faught et al., 1993; Sachdeo et al., 1992), gabapentin (Lindberger et al., 2003), lacosamide (Kellinghaus, 2009), lamotrigine (Bartoli et al., 1997), levetiracetam (Leppik et

al., 2002), oxcarbazepine (10-hydroxycarbazepine metabolite) (Friis et al., 1993), pregabalin (Patsalos et al., 2008), stiripentol (Farwell et al., 1993), tiagabine (Uthman et al., 1998), topiramate (Johannessen et al., 2003), vigabatrin (Patsalos, 1999), and zonisamide (Glauser & Pippenger, 2000; Mimaki, 1998).

## 4. TDM of the first generation AEMs

The first generation AEMs are commonly managed by TDM, in large part due to complex and variable pharmacokinetics. In general, the first generation agents have narrow therapeutic indices, with high plasma concentrations frequently associated with central nervous system (CNS) and other adverse effects. Several of the first generation AEMs, especially phenytoin, have high degrees of binding to plasma proteins; consequently, free drug concentrations in plasma can be clinically useful in some patients (Dasgupta, 2007). Three of the first generation AEMs (carbamazepine, phenobarbital, and phenytoin) are strong inducers of liver drug-metabolizing enzymes, particularly of CYP3A4. CYP3A4 has very wide substrate specificity including for cyclosporine, tacrolimus, and theophylline, as well as endogenous compounds such as estradiol and vitamin D (Luo et al., 2004). The accelerated metabolism of ethinyl estradiol that can occur during therapy with CYP3A4 inducers can lead to ineffectiveness of estrogen-containing oral contraceptives and unintended pregnancy (Crawford, 2002). Chronic therapy with carbamazepine, phenobarbital, and phenytoin is also well-known to have the potential risk of osteomalacia secondary to vitamin D deficiency (Zhou et al., 2006).

### 4.1 Carbamazepine

Carbamazepine has complicated pharmacokinetics that favors use of TDM (Neels et al., 2004; Warner et al., 1998). Carbamazepine is generally well-absorbed following oral administration; however, absorption may be delayed considerably by large doses. The metabolism of carbamazepine is quite complex, with the main metabolite being carbmazepine 10,11-epoxide, a compound that shows similar anticonvulsant activity to carbamazepine. In chronic therapy, concentrations of the epoxide metabolite may reach plasma concentrations 50% that of the parent drug. As described above, carbamazepine is a strong inducer of liver drug-metabolizing enzymes, including the CYP3A4 enzyme that metabolizes carbamazepine itself. Thus, carbamazepine represents an example of a drug that shows 'autoinduction', namely that the metabolism of carbamazepine increases as the drug is used chronically (Pitlick & Levy, 1977). Auto-induction is usually complete by 2-3 weeks, although it can take longer in some individuals.

Like other first generation AEMs, neurological side effects are common with high doses of carbamazepine, particularly when the plasma concentration exceeds 9 mg/L. Carbamazepine can also produce rare idiosyncratic adverse effects including severe dermatologic reactions such as Steven-Johnson Syndrome or toxic epidermal necrolysis. There is an association with severe skin reactions during carbamazepine therapy with the human leukocyte antigen (HLA) allele HLA-B*1502 which is common in patients with South Asian ancestry, particularly India (Alfirevic et al., 2006; Lonjou et al., 2006). Pharmacogenetic testing for this allele may be useful in patients of South Asian descent who are being considered for therapy with carbamazepine.

| Drug | Oral bioavailability | Serum protein binding | Time to peak conc. (hrs) | Serum half-life (hrs) | Reference range in serum (mg/L) |
|---|---|---|---|---|---|
| Carbamazepine | >70 | 75 | 4-8 | 10-20 | 4-10 |
| Clonazepam | >95 | 85 | 1-2 | 20-26 | 0.005-0.07 |
| Eslicarbazepine acetate | ≥80 | 30 | 1-4 | 20-24 | Not established |
| Ethosuximide | >90 | 0 | 2-4 | 30-50 | 40-100 |
| Felbamate | >90 | 25 | 2-6 | 16-22[a] | 30-60 |
| Gabapentin | <60 | 0 | 2-3 | 5-9 | 2-20 |
| Lacosamide | ≥95 | 15 | 0.5-4 | 12-13 | 5-10 |
| Lamotrigine | ≥95 | 55 | 1-3 | 15-35 [a, b] | 3-14 |
| Levetiracetam | ≥95 | 0 | 1 | 6-8 | 12-46 |
| Oxcarbazepine | 90 | 40 | 3-6 | 8-15 [a] | 3-35 |
| Phenobarbital | >95 | 50 | 4-12 | 90-110 | 10-25 |
| Phenytoin | 90 | >95 | 4-12 | 6-24 | 10-20 |
| Primidone | >90 | 20 | 2-4 | 10-20 | 8-12 |
| Pregabalin | ≥90 | 0 | 1-2 | 5-7 | 2.8-8.3 |
| Rufinamide | 85 | 30 | 5-6 | 8-12 [a] | Not established |
| Stiripentol | ≥90 | 99 | 1-2 | Variable | 4-22 |
| Tiagabine | ≥90 | 96 | 1-2 | 5-9 [a] | 0.02-0.2 |
| Topiramate | ≥80 | 15 | 2-4 | 20-30 | 5-20 |
| Valproic acid | >95 | >90 | 1-4 | 11-17 | 30-100 |
| Vigabatrin | ≥60 | 0 | 1-2 | 5-8 | 0.8-36 |
| Zonisamide | ≥65 | 50 | 2-5 | 50-70 [a] | 10-40 |

[a] Serum half-life significant decreased with concomitant therapy with liver enzyme inducers (rifampin, carbamazepine, phenobarbital, phenytoin, St. John's wort)
[b] Serum half-life significantly increased with concomitant therapy with valproic acid.

Table 1. Pharmacokinetic Parameters and Reference Ranges for the AEMs

TDM is frequently used in carbamazepine therapy due to the challenging pharmacokinetics. Monitoring of carbamazepine is usually achieved by a variety of marketed immunoassays that have high specificity for the parent drug and limited cross-reactivity with the metabolites (Warner et al., 1998). TDM sometimes also includes monitoring of the epoxide metabolite, which can contribute a substantial amount of the therapeutic effect. One challenge of monitoring the epoxide metabolite is that commercial immunoassays specific for this metabolite are not available, and thus a technology such as high-performance liquid chromatography (HPLC) is generally needed, which usually means the analysis is performed at reference laboratories.

### 4.2 Clonazepam

Clonazepam is a benzodiazepine used in treatment of epilepsy, as well as in a variety of other conditions such as anxiety or panic disorders, restless legs syndrome, and mania (Riss et al., 2008). Other benzodiazepines such as diazepam and lorazepam are used commonly for acute management of seizures but not as often for long-term management. In general,

benzodiazepines are limited by tolerance during chronic therapy. Clonazepam is extensively metabolized, with less than 1% of the administered dose recovered as parent drug. The main metabolite is 7-aminoclonazepam, which is therapeutically inactive.
TDM has a relatively limited role in clonazepam therapy (Warner et al., 1998). Plasma concentrations do not correlate all that tightly with therapeutic effect, with a wide range of concentations (5 to 70 ng/mL) associated with effective management of seizures. Higher plasma concentrations are associated with increased frequency of CNS side effects such as drowsiness or lethargy. Other than to establish an individual therapeutic concentration or to assess compliance with therapy or evaluate possible toxic effects, monitoring of clonazepam is generally of limited value.

### 4.3 Ethosuximide

Ethosuximide has excellent bioavailability and is not bound to any appreciable degree to plasma proteins (Brodie & Dichter, 1997; Perucca, 1996). Approximately 25% of the ingested drug is excreted unchanged. The remainder of the excretion is mostly to a hydroxyethyl metabolite, which is inactive with respect to anticonvulsant effect. Ethosuximide has a fairly wide therapeutic range with effective antiseizure activity commonly occurring with plasma concentrations of 40-100 mg/L. CNS and gastrointestinal side effects are more common with plasma concentrations exceeding 100 mg/L. TDM is commonly applied to ethosuximide therapy, although not as commonly as first generation AEMs such as carbamazepine, phenobarbital, and phenytoin that have more challenging pharmacokinetics (Warner et al., 1998).

### 4.4 Phenobarbital and primidone

Phenobarbital and primidone are structurally related compounds used in the management of epilepsy (Brodie & Dichter, 1997; Perucca, 1996). Primidone is converted to phenobarbital and phenylethylmalonamide (PEMA) by metabolism, with both metabolites contributing significant anticonvulsant activity. Phenobarbital and primidone show excellent absorption following oral dosing, although absorption of phenobarbital can be slow, especially with high doses. One of the striking pharmacokinetic features of phenobarbital is a long half-life, up to 100 hrs or more in adults and somewhat shorter (~80 hrs) in neonates.
TDM is commonly use for both phenobarbital and primidone (Warner et al., 1998). Plasma concentrations of 10-35 mg/L are generally recommended for phenobarbital management of seizures. Above 35 mg/L, CNS-related adverse effects are more frequent. TDM of primidone is complicated to interpret due to the formation of two active metabolites (phenobarbital and PEMA). Monitoring of primidone therapy often involves measurement of both primidone and phenobarbital plasma concentrations, both of which can be done with commercial immunoassays.

### 4.5 Phenytoin

Phenytoin is likely the AEM for which TDM is applied most frequently (Warner et al., 1998). Phenytoin has very challenging pharmacokinetic properties. While absorption of the drug following ingestion is high, time to peak concentrations are variable (3-12 hrs) depending on dosage and intake relative to meals. Phenytoin is extensively bound to plasma proteins, and clinically significant increased free fractions are observed in neonates, patients with

hypoalbuminemia, and in patients with uremia due to renal failure (Dasgupta, 2007). Phenytoin has complex metabolism, with saturation of hepatic enzymes at therapeutic plasma concentrations, leading to zero-order (saturation) elimination kinetics. Two of the enzymes that catalyze the metabolism of phenytoin, CYP2C9 and CYP2C19, show pharmacogenetic variation, with individuals with lower catalytic acvitity (poor metabolizers) at risk for developing supra-therapeutic concentrations (Ninomiya et al., 2000). Phenytoin's unusual pharmacokinetic profile makes maintaining patients at therapeutic plasma concentrations a tricky and time-consuming goal that depends on recurrent TDM. Unfortunately, TDM cannot currently predict some of the annoying and occasionally serious adverse effects of phenytoin such as dermatologic reactions, hirsutism, and gingival overgrowth (Perucca, 1996). The latter two reactions occur unpredictably with chronic phenytoin therapy.

### 4.6 Valproic acid

Valproic acid has overall excellent bioavailability, although absorption can be delayed considerably with higher doses or when the drug is ingested with meals (Brodie & Dichter, 1997; Perucca, 1996). Valproic acid is approximately 90% bound to plasma proteins. Although measurement of free valproic acid concentrations in plasma is usually not needed for TDM, patients with hypoalbuminemia are at higher risk of having supra-therapeutic free concentrations. Valproic acid is extensively metabolized, with some of the metabolites having some anticonvulsant activity. Valproic acid is an inhibitor of multiple CYP enzymes and as such can cause drug-drug interactions, including with other AEMs such as carbamazepine, felbamate, lamotrigine, phenobarbital, phenytoin, and stiripentol (Besag & Berry, 2006). Valproic acid can cause hepatitis (with elevations of enzymes such as alanine aminotransferase), in some cases manifesting as fulminant liver failure. Consequently, many physicians periodically monitor hepatic enzymes and also instruct patients to seek medical attention with any signs or symptoms of liver damage such as abdominal pain or jaundice.

Valproic acid has a therapeutic range of 30-100 mg/L. CNS side effects are more common when plasma concentrations exceed 100 mg/L although some patients may have plasma concentrations of 150 mg/L or higher without adverse effects. Given the wide range of plasma concentrations associated with successful therapy, TDM can be especially valuable in valproic acid therapy in establishing an individual therapeutic concentration (Warner et al., 1998).

## 5. TDM of the new generation AEMs

### 5.1 Eslicarbazepine

Eslicarbazepine acetate [(S)-licarbazepine acetate] is a pro-drug that is rapidly and nearly completely metabolized to eslicarbazepine by liver esterases (Falcao et al., 2007; Maia et al., 2005). TDM focuses on eslicarbazepine and not on the minor metabolites oxcarbazepine (also used as an AEM) and (R)-licarbazepine. Unlike carbamazepine, eslicarbazepine does not exhibit auto-induction in metabolism, has low (~30%) binding to serum proteins, and overall has a low potential for drug-drug interactions (Almeida et al., 2010; Bialer et al., 2009). Eslicarbazepine has an elimination half-life of 20-24 hr during chronic administration

(Almeida et al., 2005). Mild to moderation hepatic failure has minimal impact on the pharmacokinetics of eslicarbazepine (Almeida et al., 2008). The main route of elimination of eslicarbazepine and other minor metabolites of eslicarbazepine acetate is via the kidneys, with moderate or severe renal failure significantly reducing the clearance of eslicarbazepine. Hemodialysis effectively removes eslicarbazepine and other metabolites of eslicarbazepine acetate (Maia et al., 2008).

Overall, TDM has a minor role in the therapeutic use of eslicarbazepine given the relatively predictable pharmacokinetics of the drug. TDM for eslicarbazepine may be useful in patients with renal failure. An enantioselective high-performance liquid chromatography-ultraviolet (HPLC-UV) method has been developed for the specific monitoring of eslicarbazepine and its metabolites (Alves et al., 2007).

### 5.2 Felbamate

Felbamate is approved in the United States for the treatment of partial seizures in adults and for Lennox-Gastaut Syndrome, a type of childhood epilepsy that is often refractory to AEM therapy (Bourgeois, 1997; Pellock et al., 2006). The use of felbamate has been limited due to the risks of aplastic anemia and severe liver failure, which led to revised labeling and restricted use of felbamate (Pellock et al., 2006). It is suspected that one or more metabolites of felbamate mediate the rare but serious adverse effects (Shumaker et al., 1990). Approximately 50% of the parent drug is metabolized by the liver to inactive metabolites (Shumaker et al., 1990; Thompson et al., 1999). Inducers of hepatic metabolism increase the metabolism of felbamate (Sachdeo et al., 1993; Wagner et al., 1991), while valproic acid inhibits the metabolism (Ward et al., 1991).

A clear reference range has not been established for felbamate, but seizure control usually occurs with serum/plasma concentrations of 30-60 mg/L (Faught et al., 1993; Sachdeo et al., 1992). Children clear felbamate approximately 20-65% faster than adults (Perucca, 2006). TDM may be helpful in felbamate therapy given the variable metabolism across individuals. Close monitoring of liver function and blood counts are advised during felbamate therapy, with the goal to discontinue therapy if any signs of bone marrow or liver damage appear.

### 5.3 Gabapentin

Gabapentin was originally approved in the United States for the treatment in epilepsy but is currently used more often for the management of chronic pain (LaRoche & Helmers, 2004b; McLean, 1995). Gabapentin is rapidly absorbed by the *L*-amino acid transport system (Vollmer et al., 1988), and a study published in 1998 showed possible saturability of this system, with a decrease in bioavailability at doses of 4,800 mg/day of gabapentin as compared to lower doses (Gidal et al., 1998). However, a later study showed linear absorption up to 4,800 mg/day (Berry et al., 2003). Gabapentin does not distribute much into saliva, precluding the utility of salivary gabapentin concentrations for TDM (Berry et al., 2003). Gabapentin is not metabolized to any appreciable degree and has low binding to serum proteins (Vollmer et al., 1988). The bulk of excretion is via the kidneys, with the half-life increasing in patients with renal failure. Hemodialysis effectively clears gabapentin (Hung et al., 2008; Wong et al., 1995).

Gabapentin does not have a clear reference range (Armijo et al., 2004), although effective control of seizures generally requires concentrations of 2 mg/L or higher (Sivenius et al.,

1991). An approximate reference range of 2-20 mg/L for management of seizure disorders has been proposed (Lindberger et al., 2003). TDM is not usually necessary for gabapentin therapy other than to adjust dosing in patients with impaired kidney function or to assess adherance to therapy (Patsalos et al., 2008)

### 5.4 Lacosamide

Lacosamide is a novel functionalized amino acid that enhances inactivation of voltage-gated sodium channels (Curia et al., 2009; Perucca et al., 2008b). Lacosamide was approved in Europe in 2008 for partial-onset seizures in patients 16 years and older (Chung et al., 2010). Lacosamide has high bioavailability (~100%) and serum protein binding (Ben-Menachem et al., 2007; Luszczki, 2009). Approximately 60% of the parent drug is metabolized, mainly by CYP2C19 to an inactive metabolite. The remaining 40% is excreted unchanged by the kidneys. The low plasma protein binding of lacosamide suggests that the drug should be cleared effectively by dialysis, although data on this has not yet been published (Lacerda et al., 2006). The half-life of lacosamide is approximately 12 hours. Drug-drug interactions involving lacosamide appear to be uncommon (Beydoun et al., 2009; Johannessen Landmark & Patsalos, 2010). The predictable pharmacokinetics of lacosamide, along with lack of clinically significant drug-drug interactions, suggests a limited role for TDM in managing lacosamide pharmacotherapy. Consequently, TDM of lacosamide has limited benefit except in patients with severe liver and/or kidney failure, or to assess compliance with therapy (Cross & Curran, 2009; Thomas et al., 2006).

### 5.5 Lamotrigine

Lamotrigine has been approved by the United States Food and Drug Administration (FDA) for treatment of partial seizures and bipolar disorder (Neels et al., 2004; Patsalos et al., 2008). The major adverse effect of lamotrigine is dermatologic reaction, including severe Stevens-Johnson and toxic epidermal necrolysis syndromes (Knowles et al., 1999). Harm from skin reactions have been reduced by the clinical practice of cautiously escalating dose and promptly ceasing therapy if potential skin reactions appear. One of the major advantages of lamotrigine is a solid safety record in pregnancy, which contrasts with the teratogenic effects of first-generation AEMs such as carbamazepine, phenytoin, and valproic acid (Sabers & Tomson, 2009; Tomson & Battino, 2007).

Lamotrigine is quickly and completely absorbed from the gastrointestinal tract and is only ~50% bound to serum proteins. Lamotrigine distributes into saliva, and salivary lamotrigine concentrations correlate well with those in serum, allowing for saliva to serve as an alternative sample for TDM (Ryan et al., 2003; Tsiropoulos et al., 2000). Lamotrigine is extensively metabolized, principally by glucuronidation to form an inactive metabolite (Hussein & Posner, 1997; Rambeck & Wolf, 1993). Similar to carbamazepine, lamotrigine shows the phenomenon of autoinduction during chronic therapy. Autoinduction is usually complete within two weeks, with a ~20% reduction in steady-state serum/plasma concentrations if the dose is not increased (Hussein & Posner, 1997). Classic liver enzyme inducers significantly increase the metabolism of lamotrigine, reducing the serum half-life from 15-35 hr to approximatley 8-20 hr (Hussein & Posner, 1997; Rambeck & Wolf, 1993). Ethinyl estradiol-containing oral contraceptives also significantly increase the clearance of lamotrigine (Reimers et al., 2007; Sabers et al., 2001; Sabers et al., 2003). Valproic acid inhibits the metabolism of lamotrigine and can increase the serum half-life to up to 60 hr (Biton,

2006; Ramsay et al., 1991). Severe renal failure increases the serum half-life to ~50 hr in patients. Hemodialysis effectively clears lamotrigine (Fillastre et al., 1993). The clearance of lamotrigine is higher in children (Bartoli et al., 1997; Perucca, 2006) and much higher (~300%) in pregnancy (Perucca, 2006). A reference range of 3-14 mg/L has been advocated for refractory epilepsy therapy (Morris et al., 1998). The risk of toxicity increases significantly when serum/plasma concentrations exceed 15 mg/L (Besag et al., 1998; Morris et al., 1998).

TDM of lamotrigine is useful for several main reasons. First, the drug shows significant interindividual variation in liver metabolism, which can be affected by concomitant medications. Second, the clearance of lamotrigine varies across development and particularly increases during pregnancy (Pennell et al., 2008). Lastly, there is a fairly clear concentration (> 15 mg/L) above which adverse effects become more frequent (Bartoli et al., 1997; Biton, 2006; Rambeck & Wolf, 1993).

### 5.6 Levetiracetam

Levetiracetam is a novel anticonvulsant structurally unrelated to other AEMs (Klitgaard, 2001; Leppik, 2001). Following oral administration, levetiracetam is rapidly and nearly completely absorbed, with the rate of oral absorption slowed by co-ingestion with food (Fay et al., 2005; Patsalos, 2000). Levetiracetam distribute extensively into saliva, with salivary concentrations usually being slightly higher than serum concentrations in patients receiving chronic therapy (Lins et al., 2007). Salivary and serum levetiracetam concentrations correlate well with one another, making saliva an alternative sample to perform TDM (Grim et al., 2003; Mecarelli et al., 2007).

Levetiracetam shows low binding to serum proteins and has linear pharmacokinetics. Nearly 100% of the absorbed drug is ultimately excreted by the kidneys (Patsalos, 2004), with approximately two-thirds as the parent drug and one-thirds as a metabolite that is formed by hydrolysis in the blood (Patsalos et al., 2006). There is very little, if any, metabolism of levetiracetam by the liver and, consequently low probability of significant drug-drug interactions (Johannessen Landmark and Patsalos, 2010). Given the low plasma protein binding, levetiracetam is likely efficiently cleared by hemodialysis (Lacerda et al., 2006). The serum half-life of levetiracetam is shorter in adult (6-8 hr) compared to neonates (16-18 hr) (Patsalos et al., 2008). Clearance of levetiracetam increases significantly in pregnancy, with an approximately 60% decrease in serum concentrations (Tomson and Battino, 2007).

A reference range of 12-46 mg/L has been proposed based on a study of 470 patients in a specialty epilepsy clinic (Leppik et al., 2002). Other than to assess compliance or investigate potential toxicity, the main value of TDM for levetiracetam is in adjusting dosage for renal insufficiency (Patsalos, 2000, 2004; Patsalos et al., 2008; Radtke, 2001). In collecting samples for drug monitoring, serum or plasma should be separated from whole blood rapidly, as *in vitro* hydrolysis of levetiracetam can occur in the blood tube and thus lead to artifactually low concentrations (Patsalos et al., 2006).

### 5.7 Oxcarbazepine

Oxcarbazepine has a chemical structure related to carbamazepine but causes less induction of liver enzymes. Oxcarbazepine is rapidly and completely absorbed and

metabolized to its monohydroxy derivative 10-hydroxycarbazepine (Larkin et al., 1991; Lloyd et al., 1994; May et al., 2003). 10-Hydroxycarbazepine is further metabolized, primarily by glucuronidation. The clearance of 10-hydroxycarbazepine is reduced in renal insufficiency (Rouan et al., 1994) and in the elderly (Perucca, 2006). The clearance of 10-hydroxycarbazepine is increased in pregnancy (Christensen et al., 2006; Mazzucchelli et al., 2006) and in patients taking liver enzyme-inducing drugs (May et al., 2003). Children require higher doses of oxcarbazepine per body weight than adults (Battino et al., 1995). 10-Hydroxycarbazepine and oxcarbazepine have similar potencies for anticonvulsant activity; however, 10-hydroxycarbazepine generally accumulates to higher concentrations in serum and thus accounts for the majority of the antiseizure activity (Lloyd et al., 1994).

Consequently, TDM for oxcarbazepine generally focuses on measurement of serum/plasma concentrations of the monohydroxy metabolite (Patsalos et al., 2008). Although 10-hydroxycarbazepine distributes into saliva, there are dose-dependent variations in the correlation between 10-hydroxycarbazepine saliva and serum concentrations that limit the utility of saliva as an alternative specimen for TDM of oxcarbazepine (Cardot et al., 1995; Kristensen et al., 1983; Miles et al., 2004). In clinical research studies, a wide range of 10-hydroxycarbazepine serum concentrations (3-35 mg/L) were observed to be clinically effective in seizure treatment (Friis et al., 1993), with toxic side effects being more common at serum/plasma concentrations of 35 mg/L or higher (Striano et al., 2006). TDM for oxcarbazepine is justified when changes are expected that might alter 10-hydroxycarbazepine clearance including pregnancy, concomitant use of liver enzyme-inducing drugs, or renal insufficiency.

### 5.8 Pregabalin

Pregabalin was originally designed to be a more potent analog of gabapentin (Selak, 2001) and shares many clinical similarities to gabapentin, including widespread use to manage conditions other than epilepsy such as neuropathic pain and fibromyalgia (Acharya et al., 2005; LaRoche & Helmers, 2004a). Pregabalin has very advantageous pharmacokinetics including high bioavailability, low binding to plasma proteins, minimal metabolism, and no significant drug-drug interactions (Busch et al., 1998). The majority of the absorbed dose (~98%) is excreted unchanged in the urine. Clearance of pregabalin approximates glomerular filtration rate (Corrigan et al., 2001), and dosing of pregabalin may need adjustment in patients with impaired renal function (Randinitis et al., 2003). Pregabalin is effectively cleared by hemodialysis (Yoo et al., 2009). An approximate reference range of 2.8-8.3 mg/L has been proposed for the use of pregabalin in managing seizures (Patsalos et al., 2008). The favorable pharmacokinetics of pregabalin generally obviates the need for TDM, other than to adjust dosing during renal failure or to assess compliance. If monitoring is performed, the short half-life of pregabalin (4.6-5.8 hr) (Bockbrader et al., 2000) necessitates that care must be taken in the timing of blood draws for TDM.

### 5.9 Rufinamide

Rufinamide is a novel anticonvulsant approved for use in Europe in January 2007 and in the United States in December 2008 for Lennox-Gastaut syndrome (Hakimian et al., 2007; Heaney & Walker, 2007; Wheless & Vazquez, 2010; Wisniewski, 2010). Rufinamide is well-

absorbed (80-90%) following oral administration (Perucca et al., 2008a). The peak exposure to rufinamide may increase significantly when taken with food as compared to an empty stomach. Consequently, patients are often counseled to take rufinamide in the same temporal relation to meals. Rufinamide is extensively metabolized, primarily by carboxyesterases, with only trace amounts of the parent drug excreted in feces or urine. The primary metabolite is inactive and mainly excreted by the kidneys.

Hepatic enzyme inducers such as carbamazepine and rifampin increase the excretion of rufinamide (Perucca et al., 2008a). Impaired renal function has minimal effect on clearance of rufinamde; however, increased doses of rufinamide are often needed in patients receiving hemodialysis due to removal of the drug by the dialysis procedure. Although reference ranges for rufinamide have not been well-defined yet, serum/plasma concentrations generally correlate with seizure control, allowing for determination of an individual therapeutic concentration that can be monitored over the course of chronic therapy (Luszczki, 2009; Perucca et al., 2008a; Wheless & Vazquez, 2010) TDM for rufinamide can be especially helpful in patients receiving hemodialysis or who are also taking liver enzyme inducers.

### 5.10 Stiripentol

Stiripentol is an AEM that was originally approved in Europe in 2001 but is currently infrequently used. Stiripentol is rapidly absorbed following oral administration but has overall low bioavailability, in large part due to extensive first-pass metabolism by the liver. The hepatic metabolism of stiripentol is very complex, with at least 5 different metabolic pathways generating over a dozen metabolites. The dosing of stiripentol is further complicated by zero-order (saturation) elimination kinetics, with a marked decrease in clearance with increased dosage (Levy et al., 1983). Stiripentol is also highly (>99%) protein bound and prone to drug interactions that can alter the free fraction (Lacerda et al., 2006). A well-defined reference range for stiripentol has not been established, although one study showed that serum concentrations of 4-22 mg/L correlate with control of absence seizures in children (Farwell et al., 1993).

The complex pharmacokinetics of stiripentol (extensive hepatic metabolism, high binding to plasma protein, and saturation kinetics) resemble that of phenytoin (Luszczki, 2009). Measurement of the free drug fraction of stiripentol may be clinically useful; however, methods to measure free fractions have not yet been reported. When used in combination AEM therapies, stiripentol may cause drug-drug interactions by inhibiting the metabolism of carbamazepine, clobazam, phenobarbital, phenytoin, and valproic (Levy et al., 1984; Tran et al., 1997; Tran et al., 1996).

### 5.11 Tiagabine

Tiagabine is currently approved in the United States and Europe but is used infrequently due to a propensity to cause non-convulsive status epilepticus (Eckardt & Steinhoff, 1998; Kellinghaus et al., 2002; Schapel & Chadwick, 1996). Tiagabine is rapidly absorbed with high bioavailability but, unlike many of the other newer AEMs, is highly bound to proteins (> 96%) (Gustavson & Mengel, 1995). Co-therapy with valproic acid can increase the free concentrations of tiagabine by displacing tiagabine from serum protein binding sites (Patsalos et al., 2002). The hepatic metabolism of tiagabine is complex and extensive

with less than 1% of the absorbed parent drug excreted unchanged (Gustavson & Mengel, 1995). The metabolism of tiagabine can be altered by concomitant therapy with liver enzyme inhibitors or inducers. The serum half-life is typically 5-9 hr for patients on tiagabine monotherapy. The half-life is reduced to 2-4 hr in patients receiving enzyme inducers (So et al., 1995). The serum half-life increases to 12-16 h in severe liver failure (Lau et al., 1997). Children have higher clearance than adults (Gustavson et al., 1997). Renal dysfunction does not significantly impact the pharmacokinetics of tiagabine (Cato et al., 1998).

The inter-individual variation in hepatic metabolism makes tiagabine a candidate for TDM. Further, the extensive binding of tiagabine to plasma proteins further suggests that measurement of free drug concentrations may be clinically useful (Dasgupta, 2007). However, a clear relationship between tiagabine serum/plasma concentration and therapeutic efficacy has not yet been established, with a broad reference range of 20-200 ng/mL proposed (Patsalos et al., 2008; Uthman et al., 1998). For measurement of free drug concentrations, analytical sensitivity is an issue, with some assays having insufficiently low limits of sensitivity to measure clinically relevant free drug concentrations (Williams et al., 2003). Consequently, such analysis is only performed at specialized reference laboratories.

### 5.12 Topiramate

Topiramate has approval for treatment of epilepsy of children and adults, and also for the treatment of migraine headaches (LaRoche & Helmers, 2004a). Topiramate has high bioavailability (~80%) and low binding to serum proteins (Easterling et al., 1988). Salivary topiramate concentrations correlate well with those in serum (with salivary concentrations being roughly 0.9 that in serum), which makes saliva an alternative specimen type for TDM (Jones et al., 2005; Miles et al., 2003). Approximately 50% of the absorbed dose is metabolized by the liver. Hepatic enzyme inducers can decrease the serum half-life of topiramate from 20-30 hr to approximately 12 hr (Britzi et al., 2005; Sachdeo et al., 1996). Children generally eliminate topiramate faster than adults (Perucca, 2006; Rosenfeld et al., 1999). A reference range of 5-20 mg/L has been proposed for topiramate for epilepsy therapy (Johannessen et al., 2003). TDM of topiramate is most useful due to variability in metabolism.

### 5.13 Vigabatrin

Vigabatrin is an irreversible inhibitor of GABA transaminase, an enzyme that catalyzes the elimination of GABA (Rey et al., 1992; Schechter, 1989). Vigabatrin has high bioavailability (60-80%), low binding to serum proteins and is primarily excreted unchanged in the urine (Durham et al., 1993; Rey et al., 1992). Dose reductions of vigabatrin are generally needed in patients with renal failure (Rey et al., 1992). Clearance of vigabatrin increased during hemodialysis (Jacqz-Aigrain et al., 1997). The irreversible action of vigabatrin on its molecular target is likely the reason a wide range of serum/plasma concentrations (0.8-36 mg/L) of vigabatrin are associated with successful treatment with with vigabatrin. Other than to assess compliance or possible drug overdose, there is little value in monitoring vigabatrin plasma/serum concentrations (Patsalos, 1999).

| Drug | Need for TDM | Factors Favoring TDM | Limitations of TDM |
|---|---|---|---|
| Carbamazepine | Frequent | Auto-induction of metabolism; drug-drug interactions; high serum protein binding | Free drug concentrations needed for some patients |
| Clonazepam | Uncommon | Distinguish tolerance from inadequate dosing | Wide reference range; low toxicity incidence |
| Eslicarbazepine acetate | Intermediate | Decreased clearance with chronic dosing and liver failure | Generally predictable pharmacokinetics |
| Ethosuximide | Intermediate | Complex metabolism | Wide reference range, variable toxicity range |
| Felbamate | Intermediate | Variable metabolism, potential for severe toxicity | Uncertain reference range |
| Gabapentin | Uncommon | Decreased clearance with renal failure | Wide reference range; low toxicity incidence |
| Lacosamide | Uncommon | | Predictable dosing |
| Lamotrigine | Frequent | Variable metabolism; significant drug-drug interactions | |
| Levetiracetam | Intermediate | Decreased clearance with renal failure | Wide reference range, low toxicity incidence |
| Oxcarbazepine | Intermediate to Frequent | Variable metabolism, well-defined toxic range | |
| Phenobarbital | Frequent | Drug-drug interactions, long half-life | Tolerance to drug can complicate TDM |
| Phenytoin | Frequent | Variable absorption; high serum protein binding; drug-drug interactions; zero-order kinetics | Free drug concentrations needed in some populations |
| Primidone | Intermediate | Long half-life of metabolites, potential for toxicity | Need to monitor phenobarbital as well |
| Pregabalin | Uncommon | Decreased clearance with renal failure | Wide reference range, low toxicity incidence |
| Rufinamide | Intermediate to Frequent | Variable absorption; drug-drug interactions; decreased clearance with renal failure | Uncertain reference range |
| Stiripentol | Frequent | Extensive first-pass metabolism, high serum protein binding, zero-order kinetics | |
| Tiagabine | Intermediate | High serum protein binding | Uncertain reference range |
| Topiramate | Intermediate | Variable metabolism | |
| Valproic acid | Frequent | Well-established therapeutic range | Limited correlation of plasma concentration and efficacy |
| Vigabatrin | Uncommon | | Irreversible action |
| Zonisamide | Frequent | Variable metabolism, well-define toxic range | |

Table 2. Summary of Justifications of TDM of AEMs

### 5.14 Zonisamide

Zonisamide is approved in the United States for adjunctive treatment of partial seizures but is also used 'off-label' for bipolar disorder and migraine headaches (Leppik, 1999; Mimaki, 1998). After oral administration, zonisamide is rapidly absorbed and is only approximately 50% bound to serum proteins. Zonisamide is extensively metabolized by acetylation, oxidation, and other enzymatic pathways (Buchanan et al., 1996). CYP3A4 is responsible for some of the metabolism of zonisamide. Consequently, the metabolism of zonisamide can be significantly affected by CYP inducers and inhibitors. The elimination half-life of zonisamide is approximately 50-70 hr for patients receiving zonisamide as monotherapy but decreases to 25-35 hr in patients concomitantly taking enzyme inducers such as carbamazepine or phenobarbital. On the other hand, liver enzyme inhibitors such as ketoconazole and valproic acid may prolong zonisamide half-life (Perucca & Bialer, 1996). Zonisamide is cleared effectively by hemodialysis (Ijiri et al., 2004). In general, children require higher doses by weight than adults (Perucca, 2006). A serum/plasma reference range of 10-40 mg/L has been proposed for seizure management (Glauser & Pippenger, 2000; Mimaki, 1998). Toxic side effects are uncommon at serum concentrations below 30 mg/L (Miura, 1993). The main reason to perform TDM for zonisamde is inter-individual variability in metabolism, particularly in patients concomitantly taking CYP enzyme inducers or inhibitors.

## 6. Conclusion

TDM has traditionally been applied to the first generation AEMs such as carbamazepine, phenobarbital, phenytoin, and valproic acid, mainly due to the challenging pharmacokinetics of this group of drugs. The newer generation AEMs generally have more favorable pharmacokinetics and fewer adverse effects. The strongest evidence for routine TDM for the new generation AEMs are for lamotrigine, oxcarbazepine (10-hydroxycarbazepine metabolite), stiripentol, tiagabine, and zonisamide. For other AEMs, TDM may have value in adjusting dosing for organ failure or to assess compliance with therapy. Future research is needed to better delineate reference ranges and to establish the benefit of TDM in clinical practice.

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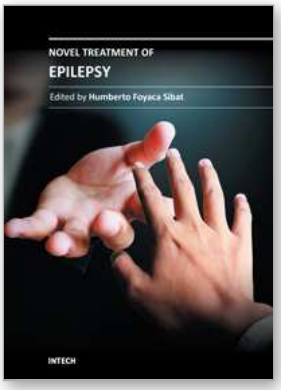


**Novel Treatment of Epilepsy**

Edited by Prof. Humberto Foyaca-Sibat

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Epilepsy continues to be a major health problem throughout the planet, affecting millions of people, mainly in developing countries where parasitic zoonoses are more common and cysticercosis, as a leading cause, is endemic. There is epidemiological evidence for an increasing prevalence of epilepsy throughout the world, and evidence of increasing morbidity and mortality in many countries as a consequence of higher incidence of infectious diseases, head injury and stroke. We decided to edit this book because we identified another way to approach this problem, covering aspects of the treatment of epilepsy based on the most recent technological results â€œin vitroâ€ from developed countries, and the basic treatment of epilepsy at the primary care level in rural areas of South Africa. Therefore, apart from the classic issues that cannot be missing in any book about epilepsy, we introduced novel aspects related with epilepsy and neurocysticercosis, as a leading cause of epilepsy in developing countries. Many experts from the field of epilepsy worked hard on this publication to provide valuable updated information about the treatment of epilepsy and other related problems.

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