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REVIEW ARTICLE

An Updated Overview on Therapeutic Drug Monitoring of Recent Antiepileptic Drugs

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Abstract Given the distinctive characteristics of both epilepsy and antiepileptic drugs (AEDs), therapeutic drug monitoring (TDM) can make a significant contribution to the field of epilepsy. The measurement and interpretation of serum drug concentrations can be of benefit in the treatment of uncontrollable seizures and in cases of clinical toxicity; it can aid in the individualization of therapy and in adjusting for variable or nonlinear pharmacokinetics; and can be useful in special populations such as pregnancy. This review examines the potential for TDM of newer AEDs such as eslicarbazepine acetate, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, perampanel, pregabalin, rufinamide, retigabine, stiripentol, tiagabine, topiramate, vigabatrin, and zonisamide. We describe the relationships between serum drug concentration, clinical effect, and adverse drug reactions for each AED as well as the different analytical methods used for serum drug quantification. We discuss retrospective studies and prospective data on the serum drug concentration–efficacy of these drugs and present the pharmacokinetic parameters, oral bioavailability, reference concentration range, and active metabolites of newer AEDs. Limited data are available for recent AEDs, and we discuss the connection between drug concentrations in terms of clinical efficacy and nonresponse. Although we do not propose routine TDM, serum drug measurement can play a beneficial role in patient management and treatment individualization. Standardized studies designed to assess, in particular, concentration–efficacy–toxicity relationships for recent AEDs are urgently required.

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Key Points

Seizures occur sporadically, so antiepileptic drug therapy is generally experiential and prophylactic.

Therapeutic drug monitoring can help establish an individual's optimal serum/plasma concentration range and benchmark the serum concentrations at which seizures are restrained or at which antiepileptic drug-specific adverse effects occur.

Therapeutic drug monitoring enables more decisive and effective optimization of therapy and disease management.

1 Introduction

The fundamental objective of therapeutic drug monitoring (TDM) for antiepileptic drugs (AEDs) is the prevention of seizures and the minimization of negative effects on general well-being, including cognition, mood, and endocrine function. The International League Against Epilepsy (ILAE) determines seizure type on the basis of clinical outcomes and electroencephalograms. Around 34 AEDs have been prescribed to manage seizures over the last century. Many enzyme-inducing AEDs are cytochrome P450 (CYP) mixed function oxidase, glucuronyl transferase, or epoxy hydrolysis enzyme inducers. First-

△ Adis

generation 'old' AEDs such as carbamazepine, phenobarbital, and phenytoin are enzyme inducers. Table 1 lists the pharmacokinetic parameters of the newer or 'second-generation' AEDs (e.g., lamotrigine, gabapentin), the newest or 'third-generation' AEDs (e.g., retigabine, perampanel), and the newest orphan drugs (e.g., rufinamide, stiripentol).

1.1 Factors Influencing the Selection of Antiepileptic Drugs

The selection of AEDs for a particular seizure type depends on drug-specific (e.g., adverse effects, toxicity, drug interactions), patient-specific (e.g., sex, age, use of contraception, genetics), and country-specific (e.g., availability, cost) variables [1].

1.2 Therapeutic Drug Monitoring or Target Concentration Interpretation

The aim of TDM is to contribute a 'reference concentration range' that laboratories can cite and clinicians can use as a benchmark. The 'therapeutic concentration range' of an individual patient is the range that achieves the best possible response and should be selected on the basis of symptoms and associated risks. The flaw of this strategy is that, in a few patients, optimal benefit will only be attained above minimum toxic concentrations, with associated risks of adverse reactions. Serum drug concentrations (SDC) achieved over months or years can provide invaluable information regarding the clinical scenario for each patient to enable interpretation of a change in response [2, 3]. Serum samples collected within a few hours of a sudden seizure can provide information that may lead to clinical reasons or a definite cause of the seizure [4]. SDC measurement can distinguish between highly variable concentrations as a result of poor compliance and low concentrations because of erratic absorption, rapid metabolism, or drug interactions. The ability to discriminate between insufficient seizure control as a result of inadequate dosing or drug overload is invaluable [4]. Polypharmacy can also lead to complex intoxication despite concentrations being within the therapeutic window [5]. SDC is particularly relevant in pediatric and psychiatric patients in whom clinical assessment can be difficult. It is also useful for dosage adjustment in complex epilepsy that may need multiple drug therapy. The reference concentration range may not always be 'therapeutic', 'effective', or 'target', so the reporting method should be factual, with a statement such as 'the SDC lies between/above/below the reference range'. Clinical judgment should not be based solely on SDC, because adverse drug reactions can occur even at low concentrations.

2 Newest Orphan Antiepileptic Drugs

2.1 Rufinamide

Rufinamide is a well-tolerated and effective treatment for drug-resistant epilepsies and is also used as a second-line adjuvant for routine neurologic practice [6]. A recently published clinical report [7] also indicated that rufinamide was successful in the treatment of super-refractory tonic-status epilepticus. Rufinamide was granted orphan drug status by the European Medicines Agency (EMA) and the US FDA in 2004 for the treatment of Lennox–Gastaut syndrome (LGS). Mean serum drug concentration was found to be 10 ± 6.5 mg/l in children aged <12 years, 10.6 ± 7.0 mg/l in adolescents aged 12–17.9 years, and 15.9 ± 8.5 mg/l in adults aged ≥18 years [8]. Approximately 85 % of the metabolites are eliminated via the kidneys, with an average half-life of 8 h. Metabolism is induced by enzyme inducers such as carbamazepine and rifampin [8]. Impaired renal function does not affect clearance, so patients undergoing hemodialysis may require larger doses. Rufinamide exhibits dose-dependent gastrointestinal (GI) absorption with good bioavailability ($\approx$85 %) and high peak plasma drug concentration (C_{max}) especially when administered with food [9]. Therefore, patients should be adequately counselled to ensure they understand the need to follow the strict dosage regimen with respect to meals. Serum rufinamide concentration was high ($\approx$22 %) when co-administered with valproic acid (VPA). Reductions in seizure frequency have been found to be dose dependent. Mean concentration was 10 ± 6.5 mg/l in children aged <12 years, 10.6 ± 7.0 mg/l in those aged 12–17.9 years, and 15.9 ± 8.5 mg/l in patients aged ≥18 years [10]. Patients receiving a dose of 40 mg/kg were found to have a serum concentration range of 0–45 µg/ml, indicating considerable pharmacokinetic variability. Therefore, TDM may be beneficial in clinical practice, albeit no reference range is available. Adverse reactions such as dizziness, fatigue, nausea, vomiting, diplopia, and somnolence have also been found to increase with concentration [8]. Enzyme-inducing AEDs such as oxcarbazepine, and particularly methsuximide, have been demonstrated to decrease the serum concentration of rufinamide [11]. TDM for rufinamide correlates well with seizure control and therefore can be helpful in treatment individualization [12]. Monitoring is useful for patients receiving enzyme inducers or those who are concurrently undergoing hemodialysis. Information regarding the pharmacokinetics of rufinamide in pregnancy and patients with hepatic impairment is inadequate. Drug interactions data are comparable to those for (PER) perampanel. A current report suggests a reference range of 126–168 µmol/l

Table 1 Pharmacokinetic parameters of current antiepileptic medications

Drug	Oral bioavailability (%)	Reference concentration range (mg/l)	t_{max} (h)	Time to steady state (days)	$t_{1/2}$ (h)	Protein binding (%)	Volume of distribution (l/kg)	Active metabolite	Need for TDM	References
Rufinamide	≥85	5–30	5–6	2	8–12	30	07–1.1	No	Intermediate to frequent	[11, 12]
Stiripentol	≥90	4–22	1–2	1–2	4.5–13	99	Variable	No	Frequent	[15, 16, 21]
Perampanel	100	a	05–1.5	14–21	70–110	96	77	No	a	[23, 24]
Retigabine	60	a	0.5–2	1–2	8	80	6.2	No	a	[12, 35]
Eslicarbazepine acetate	≥80	10–35	1–4	4–5	20–40	35	2.7	Yes	Intermediate	[38, 43]
Vigabatrin	≥60	0.8–36	1–2	1–2	5–8	0	0.8	No	Intermediate	[55]
Lacosamide	≥95	5–10	05–4	2–4	12–13	15	0.6	No	Uncommon	[60]
Pregabalin	≥90	2–5	1–2	1–2	5–7	0	0.5	No	Intermediate	[73, 82]
Zonisamide	≥65	10–40	2–5	9–12	50–70	50	1.45	No	Frequent	[96]
Levetiracetam	≥95	12–46	1	1–2	6–8	0	0.5–0.7	No	Intermediate	[100, 104]
Tiagabine	≥90	0.02–0.2	0.5–2	1–2	5–9	96	1–1.3	No	Frequent	[109, 112]
Topiramate	≥80	5–20	2–4	4–5	20–30	15	0.6–0.8	No	Intermediate	[121, 130]
Lamotrigine	≥95	2.5–15	1–3	3–6	15–35	55	1–1.4	No	Frequent	[143, 144]
Felbamate	>90	30–60	2–6	3–4	16–22	25	0.8	No	Intermediate	[157, 159]
Gabapentin	<60	2–20	2–3	1–2	5–9	0	0.6–0.8	No	Uncommon	[170]

$T_{1/2}$ elimination half-life, *TDM* therapeutic drug monitoring, t_{max} time to reach maximum plasma concentration following drug administration

a Not yet established

(30–40 mg/l) in LGS, which presumably would be lower for other seizure types [7]. High-performance liquid chromatography (HPLC) [13] and liquid chromatography–mass spectrometry (LC–MS) [14] can be used to determine plasma/serum concentrations.

2.2 Stiripentol

Stiripentol (STP) has been granted orphan drug status by EMEA for PGTCS in 2001 and approved additionally for the treatment of severe myoclonic epilepsy in infancy (SMEI) or Dravet's syndrome [15, 16]. Stiripentol has been reported to elevate brain γ-aminobutyric acid (GABA) levels and to interfere with uptake and metabolism [17]. It is bound strongly to plasma proteins (≈ 99 %) with extensive hepatic metabolism and low bioavailability. Major metabolites are excreted renally. The half-life of stiripentol increases with dose because of its dose-dependent pharmacokinetics. Stiripentol exhibits a significant reduction in clearance with dose escalation [18]. The reference serum concentration for stiripentol is not distinct, but a range of 4–22 mg/l may be associated with control of absence seizures in children, and a range of 8–12 mg/l may be associated with control of Dravet syndrome [19]. The pharmacokinetics of stiripentol are complex as a result of non-linearity, strong protein binding, and considerable metabolism [12]. Stiripentol inhibits many CYPs (CYP3A4, 1A2, 2C19) and interacts with many drugs, including AEDs. Stiripentol significantly decreases phenobarbital and phenytoin concentrations, whereas clobazam moderately increased stiripentol serum concentrations [20]. No data are available regarding the pharmacokinetics of stiripentol in pregnancy, or in patients with hepatic and renal impairment. TDM seems to be beneficial when using stiripentol because of the broad fluctuation in its concentration–dose ratio, age-dependent pharmacokinetics, non-linear relationship, extensive clearance, and drug–drug interactions [21]. Quantification of plasma/serum stiripentol via HPLC has been reported [22].

3 Newest Antiepileptic Drugs

3.1 Perampanel

Perampanel is prescribed for refractory partial onset seizures, tonic–clonic seizures in patients aged >12 years, and PGTCS [23]. Perampanel received regulatory approval from the FDA and the EMA in 2012. The minimum effective dose is 4 mg once daily, and larger doses provide a greater therapeutic effect with a comparable increase in adverse events [24]. Perampanel is not an enzyme inducer and acts as a selective non-competitive antagonist of ionotropic glutamate receptors [25]. Oral absorption of the drug is delayed up to 2 h with food. The high protein binding (96 %) and volume of distribution (77 l/kg) may lead to displacement interactions with other AEDs. The drug has a long half-life of 70–110 h, and steady state may be achieved after 14 days. Its primary route of hepatic metabolism is via enzyme CYP3A4. The bulk of the dose is excreted in the feces and the rest in the urine, with <2 % excreted unchanged in the urine. Although the drug is well tolerated, the prevalence of adverse events rises with increasing dosages. Serious psychiatric and behavioral reactions such as dizziness, fatigue, irritability, obesity, vertigo, ataxia, gait disturbance, anxiety, blurred vision, dysarthria, asthenia, and hypersomnia have been reported [26]. A recent investigation demonstrated a linear dose–concentration relationship with serum perampanel concentrations, independent of age and sex [27]. Carbamazepine and oxcarbazepine can significantly and dose-dependently reduce perampanel concentrations, presumably through CYP3A4-induced metabolism.

Perampanel dosage should be monitored carefully during pregnancy and after childbirth, with adjustments made on a clinical basis. Anticonvulsant effects are possibly antagonized by antipsychotics and antimalarials such as mefloquine. Antifungals such as ketoconazole can elevate plasma concentrations, and anxiolytics and hypnotics such as midazolam can reduce them. Concomitant administration with orlistat, an obesity drug, may lead to an increased risk of convulsions [28]. No adequate well-controlled studies have investigated the pharmacokinetics of perampanel in pregnancy, possible drug interactions, or TDM, and a reference range has not yet been established. HPLC with fluorescence detection and HPLC–MS has been used to assay serum perampanel [29].

3.2 Retigabine

Retigabine (also known as ezogabine) is used as an adjunctive treatment for partial epilepsies in adults and was approved by both the EMA and the FDA in 2011 [12, 30]. The mechanism of action of retigabine is due to the activation of voltage-gated potassium channels in the brain [31]. A placebo-controlled clinical trial has suggested that seizure frequency may be significantly reduced at higher doses [32]. The most frequently used dose in an open-label add-on study was 600 mg per day [33]. Ezogabine/retigabine was demonstrated to be effective as adjunctive therapy to specified monotherapies such as carbamazepine/oxcarbazepine, lamotrigine, levetiracetam, and VPA using a flexible dosing regimen in adults with partial-onset seizures. Retigabine increases lamotrigine (LTG) metabolism, whereas carbamazepine and phenytoin enhance the clearance of retigabine [12]. The drug and

metabolites are excreted almost completely by the kidneys [12]. Determination of retigabine and its acetyl metabolite via solid-phase extraction LC–MS has been reported [34]. A recent post-authorization safety study recognized the importance of TDM for adverse episodes of retinal pigmentation and alteration of vision in addition to established risks of urinary retention, central nervous system effects, and QTc prolongation [35]. An observational study suggested that retigabine is useful in patients with treatment-refractory seizures as a drug of reserve [36]. Data are limited regarding the pharmacokinetics of retigabine in pregnancy, possible drug interactions, and TDM. Identification and quantification of retigabine via HPLC has been described [37].

3.3 Eslicarbazepine Acetate

Eslicarbazepine acetate (ESL) is a prodrug that is structurally related to oxcarbazepine; it was approved by the FDA as a monotherapy and adjunct treatment for partial onset seizures in 2009 [38]. It was recently proposed that oxcarbazepine be switched to ESL with a dose ratio of 1–1.5:1 and that carbamazepine be switched to ESL with a dose ratio of 1–1.3:1 [39, 40]. ESL is extensively metabolized to S-licarbazepine (95 %), which, similar to oxcarbazepine, inhibits voltage-gated sodium channels [41]. A linear relationship exists between dose and serum concentration. It also induces CYPs and increases clearance (12–16 %) of carbamazepine, lamotrigine, and topiramate. A stable dose–response relationship was recognized between ESL serum concentrations and reductions in seizure frequency that were not altered by other AEDs. ESL has been reported as having minimum drug–drug interactions [42]. The pharmacokinetics of ESL are not influenced by enzyme-inducing AEDs or VPA, and ESL does not change the metabolism of lamotrigine [43]. ESL metabolites are primarily eliminated renally, and dose adjustment is particularly necessary in patients with a clearance rate of < 60 ml/min. Hemodialysis efficiently removes ESL and its metabolites from serum [44]. Moderate hepatic impairment has limited clinical effects [10]. This was endorsed in a single-dose study of ESL 800 mg once daily over a period of 1 week, which demonstrated no change in pharmacokinetic parameters [45]. Concomitant administration of drugs that prolong the PR interval should be avoided. ESL adversely interacts with oral contraceptives. There is a possible risk of developing Stevens–Johnson syndrome in the presence of human leukocyte antigen (HLA)-B 1502 allele [46]. No clinically relevant data are available with respect to pregnancy, and no data support the usefulness of TDM in ESL although it is expected to be similar to oxcarbazepine. An enantioselective HPLC–UV

detector [47] and LC [48] have been used to analyze ESL and its metabolites.

3.4 Vigabatrin

Vigabatrin has been indicated as adjunct therapy for adults and children aged >10 years with refractory complex partial seizures and to control infantile spasms. Vigabatrin was granted initial approval from the FDA in 2009 and received orphan drug status from the EMA in 2000. Vigabatrin is currently available in more than 50 countries. Its mechanism of action is based on the irreversible inhibition of GABA-transaminase (GABA-T), thus elevating the concentration of GABA in the brain [49]. Vigabatrin S (+) isomer is pharmacologically active and associated with irreversible visual field defects in 44 % of patients with epilepsy, which has resulted in prescription limitations [49, 50]. Clearance in children is greater than in adults, and therefore higher doses are required to attain comparable serum concentrations [51]. As the drug is eliminated renally, toxicity might occur in patients with renal impairment; therefore dosage adjustment is required [49]. Pharmacokinetic interactions are minimal since vigabatrin is neither metabolized nor protein bound. Due to irreversible inhibition of GABA-T, there is no rationale for TDM of vigabatrin, although it may be helpful in assessing compliance [52]. Serum GABA and GABA-T concentrations are not an indicator/marker for clinical response because the blood–brain barrier is relatively impermeable to GABA, and serum concentrations do not necessarily reflect cerebral spinal fluid concentrations [53]. Information about the pharmacokinetics of vigabatrin in pregnancy is inadequate. The use of nuclear magnetic resonance (NMR) spectroscopy to analyze brain GABA concentrations with vigabatrin treatment has been described [54]. Compliance can be verified by checking the anticipated trough serum vigabatrin target range (6–278 mol/l) at a dose level of 1000–3000 mg/day [55]. Serum vigabatrin has been quantified with HPLC, LC–MS [56], and gas chromatography (GC)-MS [51, 57]. Simultaneous HPLC analysis of vigabatrin, gabapentin, pregabalin, and topiramate has been reported as useful for monitoring polytherapy regimens including these drugs [58, 59].

3.5 Lacosamide

Lacosamide has been approved as an adjunctive treatment for partial-onset seizures and focal epilepsies in adult patients [60]. It was approved by both the FDA and the EMA in 2008. It enhances the inactivation of voltage-gated sodium channels, leading to the stabilization of hyper-excitable neuronal membranes [61]. Lacosamide has been proposed for the treatment of neuropathic pain of various

etiologies in patients who do not respond to standard treatments [62]. Lacosamide has a high level of oral bioavailability (≈ 100 %) and a short time to C_{max} (t_{max}), is unaffected by food, and has linear pharmacokinetics, which are all advantages in the clinical use of lacosamide [61]. The presence of high free drug concentrations of lacosamide led to the hypothesis that the drug should be effectively eliminated by hemodialysis, although published data to support this are limited [63]. It is primarily metabolized via the hepatic route by demethylation to an inactive O-desmethyl metabolite by CYP2C19 (30 %) [64]. Approximately 40 % of lacosamide is eliminated unchanged via renal excretion mechanisms. Population pharmacokinetic data from phase II clinical studies of lacosamide have shown that lamotrigine, levetiracetam, topiramate, oxcarbazepine, and VPA have no significant effects on the pharmacokinetics of lacosamide [65]. Enzyme inducers such as carbamazepine and phenytoin can significantly reduce plasma lacosamide concentrations and thereby enhance clearance [66, 67]. Although data are limited, overall, lacosamide does not affect the pharmacokinetics of many AEDs [60]. Frequent adverse effects include diplopia, nausea, vomiting, dizziness, abnormal coordination, and blurred vision [42]. Daytime fluctuations can be lowered by increasing the frequency of administration from twice daily to three times daily [68]. Lacosamide serum levels are elevated in patients with hepatic or renal impairment. Dose-dependent escalation of serum lacosamide concentrations have been reported to be independent of age and higher in women than in men [69]. No clinically relevant information is available regarding serum lacosamide concentrations in pregnancy. A rapid sensitive HPLC and GC–MS method for the measurement of lacosamide and desmethyl lacosamide has been reported [70, 71].

4 Newer Antiepileptic Drugs

4.1 Pregabalin

Pregabalin is a short-acting (elimination half-life [$t_{1/2}$] 5–7 h) analogue of gabapentin used as an adjunct treatment for focal epilepsies, neuropathic pain, fibromyalgia, and anxiety disorder in adult patients [72, 73]. Initial approval was granted by the FDA and EMA in 2004. Although pregabalin is patent protected in the USA until 2018, a generic version is currently available in the UK and Canada. Pregabalin has been investigated for use in cancer-induced bone pain [74] and as a premedication to provide postoperative analgesia [75, 76]. Pregabalin can be an effective treatment for peripheral neuropathic pain provided adverse reactions are carefully monitored and dosages are correctly determined [77]. It demonstrates good

bioavailability (≈ 98 %), minimal drug interactions, and low protein binding [78]. The poor binding of pregabalin means it can be effectively cleared by hemodialysis techniques [79]. A major portion of the drug is excreted unchanged in the urine, with a clearance equal to the glomerular filtration rate. Thus, the dosage regimen should be adjusted in geriatric patients as well as those with renal impairment [80]. TDM of pregabalin is restricted to dosage adjustment and to assess compliance. Although no specific reference concentration range has been established, a comparative value of 3–8 mg/l has been suggested [81]. Pregabalin trough concentrations are subject to high inter-subject variability [82]. Significant adverse drug reactions are sedation, obesity, cerebellar symptoms, and peripheral edema. Enzyme-inducing AEDs can moderately lower pregabalin concentrations [80]. An increased risk of major birth defects after first-trimester exposure to pregabalin has been recently documented [83]. An initial clinical study has demonstrated the use of pregabalin as an adjuvant to labor pain relief associated with late termination of pregnancy [84]. Plasma drug concentrations can be determined via HPLC [85], LC–MS/MS [85, 86], GC–MS [87], or a fluorometric method [88].

4.2 Zonisamide

Zonisamide is used as an adjunct treatment for partial seizure epilepsy and off label for bipolar disorder [89], chronic pain, migraine [90], and myoclonic dystonia [91]. It was initially approved by the FDA in 2000, and the EMA granted a marketing authorization valid throughout the EU in 2005. It exhibits low capacity strong binding to red cell components and carbonic anhydrase enzymes. The dual mechanism of action is due to weak inhibition of enzymes and modulation of GABAergic and glutamatergic neurotransmission via alteration of voltage sensitive sodium and calcium channels [92]. Zonisamide exhibits linear pharmacokinetics with metabolism via phase I and phase II biotransformation pathways to produce inactive metabolites [93]. The $t_{1/2}$ decreased from 60 h to 30 h in patients concomitantly receiving enzyme inducers. However, enzyme inhibitors such as cimetidine, erythromycin, ketoconazole, and VPA can extend the half-life of zonisamide [93]. Inter-individual variability in patients who are also receiving CYP enzyme inducers or inhibitors should be monitored. Zonisamide is cleared efficiently from serum via hemodialysis [94]. In general, children need larger doses than adults, calculated on the basis of weight [95]. A serum/plasma target range of 10–40 mg/l has been suggested for seizure management [96]. Many analytical methods to assay zonisamide in biological fluids have been reported, including HPLC [97], LC–MS [98], and solid-phase extraction techniques [99].

4.3 Levetiracetam

Levetiracetam is an enantioselective (S) isomer used for focal epilepsies in adult patients as monotherapy and as adjunctive treatment in children. It is also used for the management of juvenile myoclonic and generalized tonic–clonic seizures in patients aged ≥12 years [100]. Levetiracetam obtained initial approval from the FDA in 1999. It may be effective for prophylaxis of early traumatic brain injury [101]. Its $t_{1/2}$ is increased in patients with renal impairment; therefore dosage adjustments will be necessary. The clearance value of the drug is greater in children than in adults [102]. Correlation between efficacy and serum levels of levetiracetam has been demonstrated in children with refractory epilepsy [103]. Levetiracetam has all the optimal characteristics of an AED and follows linear pharmacokinetics [104]. It undergoes minimal metabolism, meaning drug interactions with enzyme inducers or inhibitors are unlikely. SDC monitoring is not yet established for levetiracetam by virtue of its wide therapeutic index and minimal side effects. For a daily dosage of 1–3 g, a target reference range of 12–46 mg/l is suggested for monitoring for compliance, drug overdose, and dose adjustment. A reduction in SDC of $\cong$60 % has been reported in pregnancy [105]. A 12-year comparative study of AED use in pregnancy indicated that levetiracetam was more effective and better tolerated than older AEDs and lamotrigine [106]. Levetiracetam can be measured in biological fluids using either HPLC [107], GC [108], or GC/MS [71].

4.4 Tiagabine

Tiagabine is used as add-on treatment for focal epilepsies not responding to other AEDs [109] and was approved by the FDA in 1997. Tiagabine follows linear pharmacokinetics with extensive oxidative hepatic metabolism [110]. The half-life of tiagabine decreases from 7 h to 3 h in patients receiving concomitant enzyme inducers [111]. Higher clearance was observed in children than in adults [109]. Metabolism is gradual in patients with hepatic impairment; consequently, the half-life in these patients is ≈14 h [112]. Therefore, dose individualization may be necessary in hepatic dysfunction but not in renal dysfunction [112]. A placebo-controlled clinical trial demonstrated that the frequency of complex partial seizures was concentration dependent [113]. Accordingly, a broad reference range of 20–200 ng/ml (53–532 nmol/l) has been proposed [114]. It has been demonstrated that tiagabine may induce generalized non-convulsive status epilepticus (NCSE) in patients with focal lesional epilepsy in addition to those with generalized syndromes [115]. Data regarding the pharmacokinetics of tiagabine during pregnancy are limited. TDM may be helpful in cases of noncompliance and toxicity, provided assay techniques are sensitive and robust [116]. Strong protein binding and high inter-subject variability due to hepatic metabolism makes TDM necessary. Ideally, the serum sample for TDM should be taken before the morning dose because the half-life of the drug is short. Tiagabine in serum can be quantified with HPLC [117], LC/MS [118], and GC/MS [118, 119].

4.5 Topiramate

Topiramate is licensed for the treatment of epilepsies in adults and children, for adjunct treatment in polytherapy, LGS, and migraine prophylaxis [120, 121]. The FDA initially approved topiramate in 1996 and endorsed it for migration prophylaxis in 2003. The mechanism of action includes sodium channel blockade, GABAergic, anti-glutamergic, and carbonic anhydrase inhibition. Increased clearance of the drug was found in children aged <10-years and in the presence of enzyme inducers [95, 122]. The half-life of topiramate is 25 h, which reduces to 12 h in patients receiving concomitant enzyme-inducing AEDs [123]. Topiramate clearance is decreased by lithium, propranolol, amitriptyline, and sumatriptan, thereby elevating serum topiramate concentrations [61]. Food can delay oral absorption of the drug ($\approx$2 h), but serum topiramate concentrations are unaffected [124]. Average drug concentrations did not differ significantly between responders, non-responders, and patients with adverse reactions [125], but did decrease during pregnancy [126]. A higher topiramate concentration of >10 mg/l [127] and according to another study an average serum concentration of 7 mg/l has been reported to result in marked improvements in seizure frequency [128]. A topiramate concentration of 2.4–8 mg/l was reported with dose ranges between 125 and 400 mg in combination with other AEDs [20]. Serum concentrations between 5 and 20 mg/l have also been reported with therapeutic doses [129]. The available literature indicates routine TDM is only necessary in patients with hepatic and renal impairment; it may also be used to differentiate between non-convulsive epilepsy and drug intoxication [130]. Salivary drug concentrations can be considered an alternative TDM method in patients receiving chronic therapy [131]. Fluorescence polarization immunoassay (FPIA) is commercially available to estimate serum concentrations [132]. Many analytical methods are available for estimating serum topiramate concentrations, including GC [133], HPLC [114], LC/MS [134], and immunoassay [135]. Simultaneous HPLC–MS/MS analysis of topiramate, zonisamide, lamotrigine, carbamazepine, and levetiracetam in serum has been discussed [136].

4.6 Lamotrigine

Lamotrigine is effective as monotherapy or adjunctive therapy in partial, generalized tonic–clonic, and absence seizures [137], and in LGS [138]. It has also been investigated for off-label use in treatment-resistant depressive disorders [139]. Lamotrigine received initial FDA approval in 1994 and approval for bipolar disorder in 2003. Estradiol-containing oral contraceptives and pregnancy can drastically decrease serum lamotrigine concentrations [140]; however, this effect was not observed in women also receiving VPA [141]. Transient declines in lamotrigine serum concentrations has also been observed after epilepsy surgery; thus, TDM will be helpful in the prevention of early postoperative seizures [142]. TDM appears beneficial both for the finalization of individual reference ranges and for the optimization of individual dosage regimens [143]. TDM and dose adjustments may be necessary in patients undergoing hemodialysis or in those with severe liver impairment [144, 145]. Lamotrigine should be introduced with slow dose titrations because of the possibility of severe dermatological reactions, including Stevens–Johnson syndrome and toxic epidermal necrolysis. Enzyme-inducing AEDs can halve the $t_{1/2}$ of lamotrigine (8–20 h), resulting in decreased lamotrigine concentrations. The half-life of lamotrigine increased to 60 h when combined with VPA [146]. In polytherapy regimens with VPA, its inhibitory effect counteracts the inducing effect of enzyme-inducing AEDs [147]. Co-medication with methsuximide lowers lamotrigine concentration by 70 % [148]. Lamotrigine serum concentrations have been shown to increase by 90 % from pre-pregnancy baseline to third-trimester [149]; however, this was not observed in patients receiving concomitant VPA [148]. Therefore, TDM is important in the prevention of seizure episodes during pregnancy, and dose adjustments are based on trough serum concentrations at least once a month [148]. Trans-placental transfer of lamotrigine in maternal blood, amniotic fluid, and cord blood has been measured and correlated [150]. Lamotrigine clearance has been reported to be higher in children and the elderly [95]. TDM is valuable for dosage adjustments in pregnancy, and to check inter-individual variability and drug interactions. In general, reference concentrations of 2.5–15 mg/l have been suggested in patients receiving therapeutic doses [2, 3]. The prevalence of toxicity increases significantly with concentrations >15 mg/l [143]. TDM of lamotrigine may be further complicated by pharmacodynamic interactions as demonstrated for co-medication with carbamazepine [95]. Assay of lamotrigine based on HPLC [151, 152], turbidimetric immunoassay [153], GC–MS [154], and GC and densitometric methods [155] have been reported.

4.7 Felbamate

Felbamate is used as add-on therapy in LGS in patients aged >4 years [156]. It was approved by the FDA in 1993. The half-life decreases from ≈19 to ≈14 h in patients receiving concomitant enzyme inducers [157]. Felbamate serum concentrations vary widely between patients and are affected by age; they are higher in patients with renal impairment, and the longer half-life depends on the degree of renal function [158]. The clearance value is quite high in children (20–65 %) compared with adults [95]. Atropaldehyde, an intermediate metabolite, is responsible for serious progressive organ toxicity [156]. The drug is contraindicated in patients with liver impairment [3]. Data on the pharmacokinetics of felbamate during pregnancy are insufficient. Life-threatening adverse reactions such as liver toxicity and aplastic anemia strongly restrict the use of this drug. Serum concentrations of felbamate can be decreased by enzyme-inducing AEDs [159] and increased by enzyme inhibitors such as VPA [159]. Clinical investigators have divided felbamate concentrations into lower (9–36 mg/l), intermediate (37–54 mg/l), and higher (54–134 mg/l) ranges [160], and a therapeutic reference range of 210–462 μmol/l has been proposed [159] in patients with epilepsy. The drug is less well-tolerated in elderly populations. The serum concentration of felbamate can be determined via HPLC–MS [161, 162], HPLC–UV [163], LC–MS [164], and GC with flame ionization detection [162] methods.

4.8 Gabapentin

Gabapentin is approved as an adjunctive in the management of focal epilepsies in patients aged >6 years and as monotherapy in patients aged >12 years. It is also used for the management of peripheral neuropathy in adults [165]. Gabapentin was granted initial FDA approval in 1993. Gabapentin is rapidly absorbed (t_{max} 2–3 h) from the GI tract by capacity-limited L-amino acid transport systems [166]. It has an indirect effect on voltage-gated calcium channels and increases brain GABA concentrations [167]. This was demonstrated by linearity of concentration with doses up to 1800 mg/day and non-linearity at higher doses [168]. The half-life of gabapentin (5–9 h) increases with renal impairment [169]. Dose adjustment is mandatory in patient with creatinine clearance <60 ml/min and in the elderly because of reduced renal function. The concentration/dose ratio progresses with age, and inter-subject variability is common at any dose [170]. Capacity-limited GI transport means gabapentin can be administered safely and effectively either twice or three times daily as steady state fluctuations are minor. Data are limited regarding the

pharmacokinetics of gabapentin during pregnancy and in terms of drug–drug interactions. Antacids reduce gabapentin absorption from the GI tract, and H-2 receptor blockers decrease the renal clearance of gabapentin [171]. The main adverse reactions are sedation, dizziness, headache, nausea, and obesity. Therapeutic concentrations of gabapentin in treatment-refractory patients with partial seizures range from 2 to 20 mg/l [55]. HPLC [58], LC/MS-coupled GC [172], and GC-electron ionization-MS [173] methods have been used to quantify serum gabapentin.

5 Conclusion

TDM is a valuable tool in the optimization of individual dosage regimens to maximize clinical efficacy while minimizing adverse drug reactions. Although reference concentration ranges indicate the range in which most patients display therapeutic response, many patients may require target concentrations outside the reference range. When interpreting SDC, situations or factors that may modify the relationship between serum AED and clinical effect should be considered, such as type and severity of epilepsy, pathological and physiological states, drug interactions, and the variability of pharmacogenetics. It is worthwhile remembering that clinical decisions should not be made on the basis of drug concentrations alone. In short, dosage regimens must be individualized based on patient history, clinical signs and symptoms, pharmacogenetics, and interpretation of clinical laboratory data.

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