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Modern Methods for Analysis of Antiepileptic Drugs in the Biological Fluids for Pharmacokinetics, Bioequivalence and Therapeutic Drug Monitoring

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Epilepsy is a chronic disease occurring in approximately 1.0% of the world's population. About 30% of the epileptic patients treated with availably antiepileptic drugs (AEDs) continue to have seizures and are considered therapy-resistant or refractory patients. The ultimate goal for the use of AEDs is complete cessation of seizures without side effects. Because of a narrow therapeutic index of AEDs, a complete understanding of its clinical pharmacokinetics is essential for understanding of the pharmacodynamics of these drugs. These drug concentrations in biological fluids serve as surrogate markers and can be used to guide or target drug dosing. Because early studies demonstrated clinical and/or electroencephalographic correlations with serum concentrations of several AEDs, It has been almost 50 years since clinicians started using plasma concentrations of AEDs to optimize pharmacotherapy in patients with epilepsy. Therefore, validated analytical method for concentrations of AEDs in biological fluids is a necessity in order to explore pharmacokinetics, bioequivalence and TDM in various clinical situations. There are hundreds of published articles on the analysis of specific AEDs by a wide variety of analytical methods in biological samples have appears over the past decade. This review intends to provide an updated, concise overview on the modern method development for monitoring AEDs for pharmacokinetic studies, bioequivalence and therapeutic drug monitoring.

Key Words: Antiepileptic drugs (AEDs), Analytical method, Biological fluids, Pharmacokinetics, Therapeutic drug monitoring (TDM)

INTRODUCTION

It has been almost 50 years since clinicians started monitoring plasma concentrations of antiepileptic drugs (AEDs) to optimize drug therapy in patients with epilepsy. Nowadays, therapeutic drug monitoring (TDM) is widely accepted as method to improve the effectiveness and safety of the first generation of AEDs and to identify an individual's optimum concentration and to individualize drug therapy [1]. The rationale for the determination of AEDs and their metabolites in body fluids and tissues arises from different fields of investigations and clinical situations. Either drug or metabolites levels are required for regular monitoring of therapeutic drug levels, for adverse drug reactions, for drug-drug interaction studies, for issues of toxicity concern, for pharmacokinetic, pharmacokinetic/pharmacodynamic and bioequivalence studies. AEDs are often used in polypharmacy including up to three different AEDs, each of them having several own metabolites [2]. TDM is more important for drugs with a narrow therapeutic range, where a correlation has been established between drug concentration and its therapeutic and toxic effects (Fig. 1). Although reasonably well-defined target ranges in serum concentrations have been determined for most of the established AEDs [3,4], it should be remembered that these ranges only became established after the development and general availability of sensitive and reliable analytical methods. Thus, even though phenobarbital and phenytoin became use for clinical application in the early 1900s, after the development of analytical methods in the 1960s, it was only since the early 1970s that target ranges were identified [5,6]. Since then, monitoring AEDs such as carbamazepine, vaproate and ethosuximide has also become widely accepted in clinical practice [7].

Although the target ranges have been defined for some of the AEDs, the true therapeutic range is defined for a given patient as the concentration that prevents occurrence of epileptic episodes without causing side effects. Since 1989, several AEDs have been have been approved for clin-

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ABBREVIATIONS: AEDs, antiepileptic drugs; TDM, therapeutic drug monitoring; CBZ, carbamazepine; CBM, clobazam; CZP, clonazepam; ETX, ethosuximide; PHE, phenobarbital; PMD, primidone; VPA, valporic aci; FBM, felbamate; GBP, gabapentin; LMT, lamotrigine; LVT, levetiracetam; OXB, oxacarbazepine; TGB, tiagabine; TPM, topiramate; VGT, vigabatrin; ZSD, zonisamide.

ical use, and because their regulatory trials were not serum concentration controlled or designed to investigate the relationship drug concentration and effect, the value of monitoring these drugs is presently controversial. However, some of the newer AEDs have pharmacological properties suggesting that their optimal use may be facilitated by use of TDM, and this has been the subject of recent valuable debate [8,9]. The AEDs have been measured by a wide variety of analytical methods in serum, blood, saliva, urine and tissue. For the classic AEDs (carbamazepine, ethosuximide, phenobarbital, vaproate) and some of the new AEDs (felbamate, topiramate, zonisamide etc), automated enzyme-multiplied immunoassay technique (EMIT) and fluorescence polarization immunoassays (FPIA) are available and allow rapid and accurate determination of concentrations in biological fluids, usually serum or plasma. For other AEDs laboratories rely on chromatographic methods; gas-chromatography (GC) and high-performance liquid chromatography (HPLC) with a various detection methods, which are more labor-intensive and relatively more expensive. A number of simultaneous chromatographic assays for AEDs have been developed in the past (Table 1). The early initial simultaneous AED assays, from 1970s and 1980s, concentrated on separating the older AEDs such as ethosuximide, primidone, carbamazepine, carbamazepine-10,11-epoxide, phenytoin, and phenobarbital [10-14]. Many subsequent assays separated the same compounds with the inclusion or removal of one or more additional drugs or metabolites such as ethylpenacemide [12], 5-parahydroxyphenyl-5-phenylhydatoin, N-desmethylmethsuximide [13] and lamotrigine and phenyl-2-theyl-malonamide [15]. Another inclusive assay separated ethosuximide, primidone, carbamazepine, phenytoin, Phenobarbital, carbamazepine metatabolites, phenobabital metabolite and felbamate [16]. All of these assays employ ultraviolet (UV) detection, thereby increasing the risk of metabolite or metrix interferences. Assay developed over past 15 years have focused more separating newer AEDs. There are also new technological advance in the use of capillary electrophoresis (CE) for TDM. Like other chromatographic methods, CE allows simultaneous measurement of several AEDs and can provide automation of procedures, low cost, and rapid speed with high specificity [17,18]. The number of articles with the analytical assay of AEDs in various biological matrices is increasing in accordance with growing interest in the situations with pharmacokinetic, TDM and bioequivalence studies of clinical and research fields. The present review was to focus to current technologies applied to the analysis of AEDs in biological media for monitoring individual AEDs or simultaneous monitoring of AEDs in recent years.

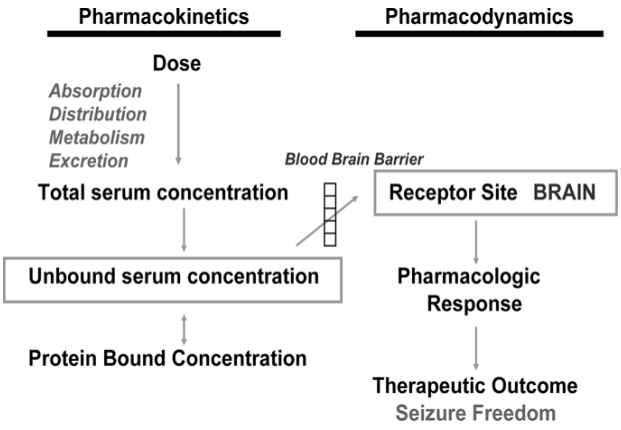

Fig. 1. Relationship between pharmacokinetics and pharmacodynamics [1].

METHODOLOY FOR DETERMINATION OF INDIVICUAL ANTIEPILEPTIC DRUGS

Carbamazepine (CBZ)

After 50 years since its discovery, CBZ is associated with relatively low and psychologic toxicity, infrequent serious adverse effects, and is still the first-line AED for simple or complex partial and generalized tonic-clonic seizures [19,20]. The unpredictable relationship between dose and blood concentration, its narrow therapeutic index, and the presence of numerous clinically significant drug inter-

Table 1. A common analytical method applied for major classic and new antiepileptic drugs

Classic AEDS		New AEDs	
Drugs	Methods	Drugs	Methods
Carbamazepine	FPIA; EMIT; GC; HPLC	Felbamate	HPLC-UV, –MS; GLC
Clobazam	GC-EC, NP, MS; HPLC-UV	Gabapentin	HPLC; GC; LC-MS, -MS/MS
Clonazepam	GC-EC, NP; MS; HPLC-UV	Lamotrigine	HPLC-UV; QMS immunoassay
Ethosuximide	FPIA; EMIT; GC; HPLC	Levetiracetam	HPLC-UV; GC
Phenobarbital	FPIA; EMIT; RIA; GC; HPLC	Oxacarbazepine	HPLC; GC
Phenytoin	FPIAEMIT; GC; HPLC	Tiagabine	HPLC-EC, -UV; GC-MS; LC-MS
Primidone	FPIAEMIT; GC; HPLC	Topiramate	FPIA; GC-FID, -NP, –MS; LC-MS
Sodium valproate	FPIA EMIT; GC; HPLC	Vigabatrin	HPLC-FD; GC
		Zonisamide	HPLC-UV; MEKC-DAD

HPLC, high-performance liquid chromatography; GC, gas chromatography; UV, ultraviolet; MS, mass spectrometry; GLC, gas liquid chromatography; EC, electron capture; NP, nitrogen-phosphorus; EMIT, enzyme-multiplied immunoassay technique; FPIA, fluorescence polarization immunoassays; CE, capillary electrophoresis; MS/MS, tandem mass spectrometry; FID, flame ionization detector; QMS, quantitative microsphere system; FD, fluorescence detector; MEKC-DAD, micellar electrokinetic chromatography-diode array detection.

actions support the need to individualize and maintain therapy using TDM. Because CBZ has a relatively short halt life, sampling time in relation to dose ingestion is important for the interpretation of the drug concentration. Ideally samples for TDM of CBZ should be drawn before the morning dose [21]. The primary methods for the analysis of serum CBZ are commercial reagent-based techniques like as FPIA and EMIT [22,23]. However, there are also many GC and HPLC techniques with UV or mass spectrometry (MS) detection available and these have the advantage of simultaneously measuring other AEDs and the active metabolite CBZ-10,11-epoxide [15,16,24-28]. But most of these assays employ UV detection, thereby increasing the risk of metabolite or matrix interferences. Otherwise, the use of liquid chromatography (LC)-MS and LC-tandem MS (MS/MS) allowed for improved selectivity during separation and detection [29-31].

Clobazam (CBM)

CBM probably exerts its antiseizure activity by potentiating the inhibitory actions of GABA that is rapidly and completely absorbed from the gastrointestinal tract and steady-state serum CBM and N-desmethyl-CBM concentrations, which are pharmacological active (20% compared to the parent drug), are linearly related dose. The desmethylmetabolite makes an important contribution to the pharmacological action [32] by accumulating to higher concentrations in serum than the parent drug. Because tolerance tends to develop to the adverse and therapeutic effects of CBM, there is no clear relationship between efficacy and serum concentrations of either CBM or N-desmethyl-CBM [21]. However, there are reports of CNS toxicity occurring at elevated serum concentrations of these compounds [33,34] and TDM is seldom required since the drug is rarely used to for long periods. For analytical methods for CBM in biological fluids, GC and HPLC are the methodology currently used [35]. Most of GC methods using electron capture (EC), nitrogen-phosphorus (NP) to achieve limits of detection of 3～5 ng/ml [36,37] and MS detection [34,38] have been described for the quantitation of CBM and N-desmethyl-CBM in serum. HPLC method with UV [29,39-41] and MS [4,42] detection are also available.

Clonazepam (CZP)

CZP is a facilitator of the GABA system and it also increases the central synthesis of serotonin and rarely used as a primary antiepileptic drug but is usually used as an adjunct or after other antiepileptic drugs have proven ineffective. The therapeutic window of CZP is not well established [43]. The target concentration range of CZP is described as 20～70 ng/ml [44,45]. Individual dose and concentration correlations are poor, and wide variations in measured concentrations have been observed in the same patient taking the same dose [46,47]. Because tolerance to CZP develops in many patients, it has been difficult to identify a clear correlation between its serum concentrations and either efficacy or toxicity. Steady-state serum CZP concentrations increase linearly with dose in both children [44] and adults [48,49]. Many chromatographic methods for determination of CZP in biological fluids have been described. These include GC method with ECD [50], NP [51] and MS [52,53] detection. A number of analytical HPLC methods for the simultaneous determination of benzodiazepines in biological matrices have been published [54]. Among these, most common UV detection [50,55] with the detection of limit of 2 ng/ml, while one method reaches 1 ng/ml in analyzing post-mortem blood [56] and applied other detection method such as spectorphotometric and fluorimetric method [57] and recently, LC-MS method have been also described [58-61].

Ethosuximide (ETX)

ETX is mainly used for its selective effect on absence seizures that acts by reducing low-threshold, transient, voltage-dependent calcium currents in thalamic neurons (T-currents) [62]. Because side effects are often not correlated with high plasma concentrations [63], TDM of ETX is not common due to its low protein binding and to the infrequent incidence of absence seizures [64]. But TDM can be useful for individualizing therapy with ETX, although in most cases therapy can be optimized simply on the basis of clinical response and EEG data. Commercial reagent-based immunoassay techniques are primary method for the analysis of ETX in serum. However, reversed-phase HPLC-UV detection is commonly used [10,11,65,66]. GC methods with ECD or FID have been developed. More recently sensitive GC-MS method has also been used and has the advantage of simultaneously measuring numerous other AEDs [67,68]. To date one UPLC-MS/MS procedure [69] has been reported for simple, rapid, sensitive and specific method for quantification of ETX in human plasma.

Phenobarbital (PHE)

PHE, the eldest modern AED discovered in 1912, was the first effective organic anti-epileptic agent that is still of widespread use. Clinically, PHE is useful, as it is effective against various forms of partial and generalized seizures, but not against absence seizures. Generally, PHE is rapidly and completely absorbed from the gastrointestinal tract, with a bioavailability of 95～100% in adults, but in newborns, it oral PHE exhibit delayed and incomplete absorption. Due to the variability in PHE pharmacokinetics, measuring its concentration can be useful for individualizing pharmacotherapy. Since over time patients develop tolerance to the sedative effects of PHE, previously intolerable serum concentrations may become tolerable. Therefore, the upper limit of the reference range varies considerably both inter- and intra-subjects. The relationship between the plasma concentration of PHE and its adverse effects varies with the development of tolerance. For TDM to be clinically useful, it is essential that drug concentrations be measured reliably. The TDM of unchanged PHE is performed mainly now by means of high throughput automated analyzers those require low sample volumes [70]. The primary methodology for the analysis of PHE in serum are commercial reagent-based techniques such as FPIA, EMIT, and radioimmunoassay (RIA) [71,72]. Because of its widespread use, there are also many GC [25,73-76] and HPLC techniques with various sample preparation procedures or detection methods such as UV or MS [30,77-80] available, which can measure simultaneously other AEDs in biological fluids. MLC procedures involving direct injection of biological fluids have been reported for the determination of PHE levels [81]. The simultaneous determination of methyl-PHE enantiomers and PHE in human plasma by on-line coupling of an achiral pre-column to a chiral HPLC column has been

described [82].

Phenytoin (PHT)

PHT pharmacokinetics is complex due to variable absorption, high-protein binding, saturable metabolism that follows nonlinear Michalelis-Menten pharmacokinetics, i.e., the rate of metabolism decreases with increasing dosages, and drug interactions. PHT is a drug whose plasma concentration is frequently, yet its concentration is unquestionably the most difficult to interpret pharmacokinetically [83]. Interpretation of many studies that described PHT concentration-response relationships since the introduction of PHT is complicated by the use of different analytical methods ranging from spectrophotometeric method to immunoassays and, in the early years, by the absence of quality assurance programs. These circumstances are likely to contribute to the widely varying reports of PHT concentrations associated with seizure control and toxicity. The unpredictable relationship between dose and PHT concentration, its narrow therapeutic index, and the presence of numerous clinically significant drug interactions support the need to individualize and maintain therapy using TDM [21,84]. For the analytical method for PHT, various immunoassays are employed since PHT is an often-used drug that has critical pharmacokinetics. FPIA, nephelometric or turbidimetric inhibition, linked enzyme-catalyzed reactions and other techniques offer quick, sensitive and reproducible results [22,85]. The immunological methods are generally specific; however, cross-reactivity with compounds similar to PHT can occur, e.g., fos-PHT [86-88]. For example, in patients with uremia there have been reports of PHT level being substantially higher when measured by the EMIT procedure than GLC or HPLC procedures [12]. Presumably this is because of the accumulation of PHT metabolites; however, much of the cross-reactivity has been minimized or eliminated in more recent assay development [86]. However, there are also many GC with various detection [25,89] and HPLC methods have been reported [10,11,80,90]. Treatments for refractory epilepsy with a second drug or a combination of drugs indicate the need for simultaneous HPLC analysis for other AEDs [15,16,24,76,91,92].

Primidone (PMD)

Like PHE, PMD is an old AED that was withdrawn for market in Jan. 2004 in most western European countries. The antiepileptic activity of PMD is achieved by three molecules, PMD and its two metabolites, PHE and phenylethylmalonamide (PEMA). PMD is well absorbed from gastrointestinal tract and is a hepatic enzyme inducing agents. The relationship between PMD dose and the concentration of the drug and its metabolites is subject to great individual variability. The ratio of PHE to PMD increases in combination therapies with other anticonvulsants drug or in children patients [93]. Since PHE is the major metabolite, the latter immunoassay can be used. Since PMD is metabolized to PHE, it is difficult to separate the effects of PMD from those of PHE, and often serum PHE concentrations are used as a guide to therapy [94]. Because PHE is the major active metabolite during chronic therapy, the usefulness of PMD measurements alone is limited. However measuring both PMD and PHE to obtain a ratio may be helpful in detecting recent noncompliance, as in this situation the ratio of PHE to PMD may be reversed, with the concentrations of PMD being higher than those of PHE [21]. Nowadays, the TDM of unchanged PMD is performed mainly by means of high throughput automated analyzers [86]. These systems, which need small volumes, are mainly based on commercial reagent-based immunoassay (FPIA or EMIT) techniques that represent the primary methodology for analysis PMD in serum [95,96]. Chromatographic methods involving GC and HPLC are nevertheless of importance when both the unchanged drug and its metabolites have to be quantified in plasma [97,98] or when the simultaneous determination of several AEDs is required [2,80] as well as in the toxicological or forensic analysis [99,100]. Because the targeted drugs are well known, methods based on HPLC and MS coupling should be available soon for the fast simultaneous determination of a greater numbers of AEDs. However, the cost of such instruments seems to be an obstacle for extensive investigations in this field [101,102].

Valproic acid (VPA)

VPA and its sodium salt are widely used to treat a various types of seizure as major AEDs [103]. VPA is well absorped orally and metabolized in the body by a combination of mitochondrial, microsomal and cytosolic enzymes to produce at least 20 known metabolites [104]. Due to large interindividual differences in metabolic rate, there is a poor correlation between dose and serum concentration of VPA, especially in patients who are comedicated with enzyme-inducing AEDs [105,106]. Children require higher mg/kg doses to achieve serum VPA concentrations compared with those observed in adults [107]. For any given dose, elderly patients have total serum VPA concentrations, but unbound drug concentrations are increased in the elderly [108]. Therefore, the unpredictable relationship between dose and VPA concentration support the need to individualize and maintain therapy using TDM. Because VPA has a relatively short half-life, sampling time relation to dose injection is important for interpretation of the drug concentration. Ideally samples for VPA measurements should be drawn before the morning dose [21,109]. For quantificative methodology for VPA, GC is considered as analytical method of choice for the simultaneous determination of VPA and its 5～20 metabolites [110,111] and for metabolism studies or VPA hepatoxicity studies [104]. GC methods with either MS or FID were obviously widely used for the determination of unchanged VPA only or VPA and some unsaturated metabolites or VPA in the presence of other AEDs [112]. Various immunoassays and FPIA methods for detection and quantification of VPA are available [113,114] and since VPA lacks UV absorption, it cannot be assayed with common HPLC simultaneous anticonvulsant procedures. Despite the wide use of immunoassays and FPIA and GC methods, HPLC assays have been reported. Methods with UV detection at low wavelengths of underivatized VPA or derivatized VPA by fluorescence detection are reported to be suitable for the determination of therapeutic concentrations of VPA with range of 1.25～150 μg/ml [115-119]. Some procedures require sample volumes as low as 10 μl to 50 μl [119]. Automated fluoroimmunoassay of VPA was reported by using a flow-injection analysis with use of HPLC [120] and GC system [121]. Monitoring of free VPA concentration may be helpful in patient care because VPA has an unusual nonlinear protein binding charadteristics and a wide interindividual variation [122]. Both GC and

HPLC methods with various detection systems are developed for the determination of free VPA [116,117,123,124] and its metabolites using VPA-d_{15} as the internal standard [125].

Felbamate [FBM]

FBM has been used as add-on therapy and as monotherapy for partial seizures with and without generalization in adults. The mechanism of action of FBM is not completely known, but reduces the repetitive firing of action potentials through inhibition of sodium channels [126]. FBM is well absorbed from the gastrointestinal tract and its half-life of 15～23 h in healthy volunteers [7,127]. Although there is an overall lack of data from prospective studies, there was a relationship between steady-state FBM concentrations and control of drop attacks. Currently, the use of FBM is highly restricted due to the risk of aplastic anemia and hepatotoxicity [128]. Monitoring FBM concentrations may be particularly useful since levels are not easily predicted from administered dosages, and FBM appears to have narrow therapeutic windows [7]. Many analytical methods were developed for the determination of FBM levels and its metabolites in serum, plasma, urine and tissues from animals [129] and humans. Because of the restricted use of FBM, no convenient immunoassays are available. GC methods using capillary columns and NPD or FID detectors are available [129-131]. FBM concentrations also can be determined by various HPLC methods with UV or MS detection [80,129,132-135] or simple and direct injected CE based on micellar electrokinetic capillary chromatography [136]. Also recently LC procedures with MS or tandem MS method has been described which can also measure its metabolite and other AEDs [137,138].

Gabapentin (GBP)

Gabapentin (GBP) is currently approved for adjunctive management of partial seizures with or without secondary generalization in patients older than 12 years and for children aged between 6 and 12 years and more recently, for the management of neuropathic pain in adults [7]. Even if GBP is structurally related to the neurotransmitter GABA, it is not metabolized to GABA or an agonist of GABA receptors. GBP is orally absorbed and bioavailability is reported to be dose and frequency dependent, probably because of saturation of the transporter's capacity [139,140]. As a result, serum GBP concentrations increase linearly with doses up to about 1,800 mg/day but increases less than expected at higher doses [141], although there are studies suggesting a reasonably linear absorption in individual patients with doses up to 4,800 mg/day [142]. Hence, TDM is used to clarify whether a poor response is caused by impaired oral absorption [143]. The concentration-to-dose ratio increases with age [144], and serum concentrations at any given dose vary markedly between individuals [145]. The pronounced interindividual variation in pharmacokinetics and the dose-dependent bioavailability suggest that the monitoring of GP concentrations may be useful in selected case. Because GBP has a relatively short half-life of 5～9 h and sampling time in relation to dose ingestion is important for the interpretation of the drug concentration, samples for GBP measurements should be drawn before the morning doses [21]. For the validated analytical procedures for GBP concentration in biological fluids, various chromatographic methods have been reported. The method most commonly used for GBP quantification in blood or serum is reversed-phase HPLC with derivatization and fluorometric detection [146-148]. GC methods have also been reported [149], and more recently, more sensitive and validated LC procedures with MS or MS/MS methods for both clinical and experimental monitoring of GBP in human and animal have been also been described [149-153].

Lamotrigine (LMT)

LMT is a synthetic anticonvulsants phenyltriazine, unrelated to other agents. LMT is rapidly and completely absorbed from gastrointestinal tract (Tmax, 1～3 h) with bioavailability of approximately 98% and steady-state serum concentrations increases linearly with dose and is unaffected by food [7,154]. LMT metabolism is activated by enzyme-inducing AEDs and inhibited by VPA that its inhibitory interaction is particularly important and underlines the need to use smaller doses of LMT as well as a slower titration rate to minimize the risk of skin rashes [155]. LMT was shown a correlation between concentrations and tolerability, independent of the use of other AEDs [156,157]. Several characteristics of LMT suggest that its effective and safe use may be facilitated by application of TDM. These include a large interindividual variation in dose to serum concentration relationship, the possibility of marked changes in serum concentrations due to pregnancy and drug interactions, especially other AEDs and pharmacokinetic variability, which depends on other AEDs medication, complicates dosing [8,158]. Many analytical methods proposed for the determination of LMT in biological fluids that include HPLC, CE, GC methods and immunoassays. HPLC separations on reversed-phase columns in isocratic mode are widely applied but normal-phase columns have been also used [159-161]. Although the chemical structure of LMT allows the preparation of suitable hepten, the major difficulty in immunoassay development has been the high concentrations of LMT found in the clinical samples [162,163]. But currently, automated high-throughput Seradyn quantitative microsphere system immunoassay method for LMT has been developed and may be useful as a convenient alternative method that TDM guidance if a chromatographic assay was not available [164]. An automated HPLC system combining sequential trace enrichment and gradient HPLC has been developed. CE has been applied to the determination of LMT in serum and is faster than the HPLC method selected for comparison [165,166]. GC-NPD assay method requiring no derivatization and minimal sample preparation has been shown to be alternative to HPLC methods despite the fact that the required run times are longer [167]. GC-MS has been developed for TDM of LMT but the method requires a complicated derivatization step of extracts obtained by liquid-liquid extraction process and a relatively long run time [168,169]. Most common method for LMT analysis in biological fluids is HPLC procedures with UV detection and short run times within 2 min can be easily obtained on regular columns. Setting of UV detector to wavelength of about 310 nm allows a high specificity of detection because all other AEDs and their metabolites are UV-transparent at this wavelength with very few exceptions [76,170,171]. Assays developed over past 15 years have focus more on separating older and newer AEDs [64]. The use of LC-MS for LMT allowed for improved selectivity and sensitivity

during and detection [30,172-174].

Levetiracetam (LVT)

LVT is effective for use as adjunctive therapy in the management of partial onset seizures in adults with epilepsy and children with partial seizure. LVT is completely and rapidly (Tmax, 1 h) absorbed after oral ingestion with bioavailability of 100% [175,176]. Although drug-food interactions do not show on the extent of absorption, rate of absorption is slowed in the presence of food. Administration of a crushed LVT tablet together with 120 ml of an entral nutrition formula has been associated with a mean 27% decrease in peak LVT concentration, but the effect was not statistically significant [177]. LVT shows linear pharmacokinetic and renal elimination with approximately 66% of a dose eliminated unchanged and 27% as inactive metabolite [178]. The relationship between LVT serum concentrations and clinical effect has not been ascertained, and consequently the value of serum concentrations measurements is not established. Because of its favorable therapeutic index, low plasma protein binding and minimal side-effect profile, routine monitoring of LVT serum concentrations appears to be unnecessary for safe use of the drug, and dosing can be readily guided by the therapeutic response [7,143]. Nevertheless, its use in ascertaining compliance and managing patients that are overdoses would be helpful. Because LVT has a relatively short half-life, sampling time in relation to dose ingestion is important for the interpretation of the drug concentration. Ideally samples for LVT measurements should be drawn before the morning dose. Because LVT can undergo in vitro hydrolysis, it is important to separate whole blood from serum as soon as possible so as to avoid LVT hydrolysis that would result in spuriously lower concentrations being measured [179]. Although AED monitoring in saliva may some clinical applicability, it has not yet come into routine use, but, a significant positive correlation exists between LVT saliva and serum concentrations, LVT like other AEDs, can be measures in saliva as an alternative to blood-based assays for minotoring the LVT therapy [180,181]. Numerous chromatographic methods have been reported for the quantification of LVT in biological fluids. Different HPLC methods for the determination of LVT in human plasma have been reported coupled with UV [182,183] or diode array detection [23,184,185], mostly after sample pretreatment by expensive solid-phase extraction or time-consuming liquid-liquid extraction procedures [183,185]. The availability of simple, accurate and inexpensive analytical assays is crucial for the successful use of TDM in clinical practice. LVT spiked plasma sample preparation by different kinds of deproteinization before HPLC-diode array detection was first explored by Pucci et al. [184] and subsequently applied to patient samples analysis by HPLC-UV [176,182,186]. Otherwise, these involve GC-NPD [187] and GC-MS [188]. Most of the reported methods lack selectivity, sensitivity, and reliability. Moreover, they encounter problems particularly tedious and time-consuming sample preparation as well as high sample volume. Recently, LC-tandem MS is considered a gold standard to utilize in analysis of drugs in biological fluids. The high sample throughput, selectivity and sensitivity for analytes of interest increase the applicability of tandem MS in clinical chemistry as well as clinical studies [189-191].

Oxacarbazepine (OXB)

OXB is an antiepileptic drug that is quickly replacing the CBZ in the recent therapeutic protocols. OXB is often used for patients who are intolerant to CBZ [192] which gives many unpredictable adverse reactions associated with high mortality rates. The OXB is essentially a pro-drug in humans in fact, after the administration, it is completely absorbed by the gastrointestinal tract and completely (96～98%) converted by an hepatic cytosolic arylketon reductase, a cytosolic enzyme of hepatic cells, into its main active metabolite monohydroxy derivative (MHD), 10,11-dihydro-10-hydroxy-5H-dibenz [*b,f*] azepine-5-carboxamide [193]. Both OXB and MHD do not show self-induction characteristics and, moreover, do not seem to influence, by inhibition or by induction, the P450 system, avoiding problems of interactions with other drugs in eventual multiple therapies [194,195]. Because the OXB has a minor tendency to interact with other drugs, it can be administered both as monotherapy and polytherapy in association with other AEDs [196]. The OXB is detectable in the blood at very low concentrations and just for some hours before its conversion in MHD. Monitoring MHD and OXB concentrations could therefore help in the management of patients with OXB therapy. Based on the available evidence, therapeutic drug monitoring of MHD is not routinely warranted but may be beneficial in optimizing seizure control at the extremes of age, during pregnancy, in renal insufficiency, or to determine the significance of potential drug interactions or rule out noncompliance [197]. There are many HPLC [198,199] and GC [200, 201] methods for the measurement of MHD and OXB in biological fluids. More recently, entantioselective HPLC-MS method for the individual or simultaneously detection with other AEDs has become available [202,203].

Tiagabine (TGB)

TGB is a recently approved AED that inhibits y-aminobutyric acid (GABA) reuptake into neurons and glia, a mechanism of action that is specific and unique among the AEDs [204]. Oral TGB is rapidly and completely absorbed with a bioavailability of 90～95% [205]. The relationship between serum TGB concentrations and efficacy or toxicity has been little investigated, partly due to the difficulties in measuring the low serum TGB concentrations that are typically encounters clinically. The role of the TDM for TGB has not yet established. Nevertheless, its use in ascertaining compliance and manging patients that are overdosed would be helpful, provided that utmost care is dependent on ensuring the reliability of the analytical assay [206,207]. If morning were to be undertaken, sampling time in relation to dose is critical because large interdose fluctuation in concentrations occur consequent to the short half-life of drug. Because serum TGB are in the nanomolar range, analytical methods are not simple and interlaboratory differences in analytical reliability is of great concern [207]. Several GC [208] and LC method with various detectors such as ECD [209] or MS [206] are available.

Topiramate (TPM)

TPM is used for the adjunctive treatment of partial seizures, wuth or without secondary generalization, in adults

and children aged 2 to 16 years and also Lennox-Gastaut syndrome [7,21,210]. TPM is orally well absorbed with a bioabailability of 81～95% [211] and there is a linear relationship between TPM dose and serum concentrations [212,213]. In three double-blind placebo-controlled add-on trials, seizure control was improved with serum TPM concentrations in the narrow range of 10 to 15 μmol/l and adverse events were also generally associated with higher TPM concentrations [214]. A preliminary study were report that no consistent relationship between TPM serum concentrations and adverse effects. TPM serum concentrations were similar in patients with or without TPM-related adverse effects, regardless of concomitant AEDs [215]. Some study was reported mean TPM serum concentrations around 21 μM/l in positive responders and 27 μM/l in seizure-free patients compared with 18 μM/l in patients in whom TPM was stopped because of side effects, with a wide variation in the relationship between the concentration and therapeutic or toxic response [216]. For the analytical methods for TPM in biological fluids, two capillary gas chromatographic methods have described the determination of TPM in serum using flame ionization detection [217] and NPD [218]. A commercial reagent-based FPIA method is available for the measurement of TPM in plasma or serum [219,220]. More recently, an improved GLC-NPD method was reported [221] and either GLC or HPLC with MS [222-224] and tandem MS detection have developed [221,225].

Vigabatrin (VGT)

VGT is an antiepileptic drug introduced in clinical practice in the early 90s with its pharmacological activity by increasing brain GABA levels through selective and irreversible inhibition of GABA-transaminase, the enzyme responsible for the degradation of GABA in the central nervous system [226]. VGT was widely used as adjunctive treatment of refractory partial seizures until the discovery, in 1997, of severe irreversible visual field constriction associated with its chronic use [227]. Today, VGT is rarely used in the treatment of partial seizures, but it is regarded by many authorities as a drug of choice in infants with West syndrome (infantile spasms), particularly in cases associated with tuberous sclerosis [228-230]. Since VGT acts by irreversiblely inhibiting GABA-transaminase, the enzyme responsible for the metabolism of GABA, there is a clear dissociation between its concentration profile in serum and duration of pharmacological effect, which is related to the regeneration time of the enzyme [231]. Whether the measurement of serum VGT concentrations could be of value in evaluating patients with suspected toxicity has not been established. Overall, the rationale behind the application of TDM does not appear to apply to VGT [8], although measurement of serum VGT concentrations may be useful as a check on recent patient's compliance. Measurement of plasma VGT concentrations can also be valuable for research purposes to investigate its pharmacokinetics in special patients groups, and in the presence of potentially interacting drugs. Since the two enantiomers differ in pharmacodynamic and pharmacokinetic properties, these studies can only be meaningfully conducted by using an enantioselective assay [232,233] that offers significant advantages in terms of simplicity and ease of use, and it has sufficient sensitivity to allow quantification of the concentrations of each enantiomer which are observed after administration of single oral doses of the racemate in infants [234] and in adults [235]. VGT is freely soluble in water and therefore its quantification in biological fluids cannot be based on the typical extraction procedures [2]. There are many HPLC methods for the determination of VGT in serum have been reported in the literature. Some paper described a non-enantioselective method which made use of an amino acid analyser, microcolumns, and fluorimetric detection that involved a long analysis time, with column regeneration after each run [236]. An improved non-enantioselective HPLC assay with fluorimetric detection requires a complex derivatization procedure in which the cupric ion is used to bind the plasma α-amino acids before VGT and the internal standard are reacted with dansyl-chloride [237]. The earliest enantioselective methods reported were a GC-MS assay using a chiral capillary column [238] and a reversed-phase HPLC assay which involves a diastereomeric derivative formation with tert-butyloxy-L-leucine *N*-hydroxy-succinimide ester [239]. The latter, however, does not appear to have been applied to biological matrices. More recently, some results demonstrated that the enantioselective separation of mixtures of D,L-aminoacids can be accomplished by HPLC after converting each enantiomer to the corresponding diastereomeric isoindolyl derivative using o-phtaldialdehyde (OPA) and chiral *N*-acylated cysteines [240]. This procedure has been applied to the separation and quantification of the enantiomers of VGT in serum [241]. The OPA derivatization of samples previously deproteinized with either methanol or acetonitrile is advantageous because it allows full automation of the derivatization step and the simultaneous determination of VGT and GBP, another antiepileptic drug [242,243]. The enantiomers of VGT have been also analyzed as their *N*-trifluoroacetyl-o-propylester derivatives using a selected ion monitoring technique in the chemical ionization mode [234]. More recently, simple and simultaneous determination of VGT and other AEDs by GC-MS method are also available [233].

Zonisamide (ZSD)

ZSD is used as an anticonvulsant with the recommended therapeutic range of the serum concentration of this drug is usually attained with plasma concentrations of 17～50 μg/ml in patients with epileptic disorders [244,245]. Determination of the ZSD serum concentration is required in epileptic patients in order to establish a proper concentration of the drug for the inhibition of epileptic seizures and to avoid side-effects. HPLC assay, using a porous silica column, is commonly used for separation and quantification of many drugs, but it has been reported that 1.5～2.0-μm particle non-porous silica columns provide superior performance over the 3.5～10-μm particle porous silica columns in several parameters and the method on the non-porous silica column was faster, used less solvent, and provided greater analyte peak area [246-248]. Several HPLC methods using a conventional reversed-phase porous silica column for monitoring the serum concentration of ZSD have been reported [249,250]. However, these methods have common problems of long run time and high solvent consumption. It is very important to reduce both analysis time and solvent costs without compromising quality. Some methods describe HPLC detection of ZSD but this compound optimally absorbs UV light at a somewhat lower UV range [26,80,183,201,251]. Initial method development for ZSD analysis was done on a simple and single-pump HPLC

with a UV detector, but HPLC-UV method has some limitation for method sensitivity. To improve sensitivity of the assay and detects simultaneously other commonly prescribed AEDs that do not have UV absorbance such as TPM and VPA, this assay was subsequently transferred to an LC-MS or LC-tandem MS. The first LC-MS assay that can monitor concentrations of a wide range of AEDs with acceptable accuracy and precision included with newer AEDs such as ZSD and TPM developed. A simultaneous LC-MS assay would be faster and more reliable than multiple analytical assays when quantification of multiple AED is needed for patients with AED polytherapy [30]. Additional methods included micellar electrokinetic capillary chromatography with diode array detection [252] and an immunoassay method [253].

CONCLUSION

A large number of studies have been performed for the analysis of AEDs in various biological matrix and currently still in progress and achievement for method development for determination of individual or simulateneous AEDs. In this article, I reviewed recent progress in the analytical methods for quantification of AEDs in various clinical situations. The results from many applications cited in this review has demonstrated that innovative chromatography techniques are approving the way of simultaneous analysis for various AEDs and their metabolites in the biological samples. These methods have been reported to be accurate and reproducible commercial-based immunoassay, GC, HPLC with various detectors such as UV, ECD, FID, MS and tandem mass spectrometry. For the sake of validated and high throughput analytical method development for quantification of AEDs, we have recently observed the emergence of GC or LC coupled to MS or tandem MS as an alternative to traditional HPLC techniques for simultaneous determination of various AEDs and their metabolites in clinical samples. Recently, novel HPLC method with a monolithic column for quantification of 10 AEDs or metabolites in serum/plasma is reported. However, the increasing number of AEDs makes it difficult to offer such a monitoring service in routine clinical situations on a regular and pharmacoeconomic base. No procedure has been yet reported to be suitable for simultaneous determination of all commons AEDs currently in use despite the application of powerful techniques. Therefore, integration of as much as possible AEDs or their metabolites within our one analytical method, which can be also be automatized is a usable approach, especially in patients on polypharmacy with AEDs.

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