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SPECIAL REPORT

Antiepileptic drugs—best practice guidelines for therapeutic drug monitoring: A position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies

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SUMMARY

Although no randomized studies have demonstrated a positive impact of therapeutic drug monitoring (TDM) on clinical outcome in epilepsy, evidence from nonrandomized studies and everyday clinical experience does indicate that measuring serum concentrations of old and new generation antiepileptic drugs (AEDs) can have a valuable role in guiding patient management provided that concentrations are measured with a clear indication and are interpreted critically, taking into account the whole clinical context. Situations in which AED measurements are most likely to be of benefit include (1) when a person has attained the desired clinical outcome, to establish an individual therapeutic concentration which can be used at subsequent times to assess potential causes for a change in drug response; (2) as an aid in the diagnosis of clinical toxicity; (3) to assess compliance, particularly in patients with uncontrolled seizures or breakthrough seizures; (4) to guide dosage adjustment in situations associated with increased pharmacokinetic variability (e.g., children, the elderly, patients with associated diseases, drug formulation changes); (5) when a potentially important pharmacokinetic change is anticipated (e.g., in pregnancy, or when an interacting drug is added or removed); (6) to guide dose adjustments for AEDs with dose-dependent pharmacokinetics, particularly phenytoin.

KEY WORDS: Children, Elderly, Pregnancy, Drug compliance, Saliva, Pharmacokinetics.

Background and historical introduction

Since drug action depends on the availability of the active principle at receptor sites, knowledge of the pharmacokinetic properties of the medication used is important for optimal treatment. The treatment of epilepsy was one of the first areas to benefit from pharmacokinetic studies.

Both physicians and pharmacologists have long been interested in ascertaining why the same drug dosage is effective in some patients but not in others. In the past, the most effective dosage for an individual was established by trial and error. The development of technology for quantifying drug concentrations in biological fluids has, however, made it possible to study the relationship between drug dosage,

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drug concentration in body fluids and pharmacologic effects, and thereby provide new insights into drug therapy. It was soon recognized that the desired therapeutic effect of many antiepileptic drugs (AEDs) was usually achieved within a specific range of serum concentrations (henceforth called "reference range") with lower concentrations being more likely to produce an insufficient effect, and higher concentrations being more often associated with adverse effects. Therapeutic drug concentration monitoring (TDM) was initiated for a number of AEDs and used to establish optimal therapy regimens for individual patients. This approach has provided physicians with a valuable tool to further understand why patients do not respond satisfactorily to a particular dose. Furthermore, TDM has made it possible to assess noncompliance and to study the variation in pharmacokinetics that occurs between individuals and the factors responsible for such variation.

The initial studies in this area were conducted in the fifties and early sixties by Buchthal and his group, who related serum concentrations of phenytoin and phenobarbital to seizure control and central nervous system (CNS) toxicity (Buchthal & Svensmark, 1960). Subsequently, a vast number of pharmacokinetic studies on AEDs were published. Results from this research have been presented at several specialized symposia and workshops. One of the first was held in Scottsdale, Arizona, USA, 1971, to create an authoritative reference book about AEDs, the first edition of a now much appreciated series, Antiepileptic Drugs (Woodbury et al., 1972). It was anticipated that new information concerning the relationship of serum concentrations to seizure control and toxicity would improve utilization of AEDs, and a multidisciplinary cooperation of pharmacologists, pharmacists, toxicologists, neurologists, and pediatricians was initiated at this meeting.

Between 1972 and 1979, a series of workshops known as WODADIBOFs (Workshop on the Determination of Antiepileptic Drugs in Body Fluids) were held. The first took place in Noodwijkerhout, The Netherlands, and dealt with methods for the quantitative determination of AEDs (Meijer et al., 1973). The second (Bielefeld, Germany, 1974) dealt with the clinical pharmacology of AEDs, including bioavailability, protein binding, distribution, metabolism, elimination, drug interactions, application of new assay methods and quality of the methods (Schneider et al., 1975). The third (Exeter, England, 1976) focused on TDM, including assay methods, clinical pharmacology and clinical applications (Gardner-Thorpe et al., 1977). At the fourth workshop (Oslo, Norway, 1979) the advantages and disadvantages of monitoring AED treatment were the main topics with emphasis on the influence of age and the problems of synergism, potentiation, and drug interactions. The quantification of epileptic manifestations, the influence of AEDs upon the natural history of epilepsy and methodological aspects of drug analyses were also discussed (Johannessen et al., 1980).

The need for quality control programs in drug measurements was recognized rapidly, since early surveys showed great variation of analytical results (Pippenger et al., 1978). Reliable measurements are mandatory for TDM to be of value and in 1972 the first quality control scheme for AED measurements was started in London, England by Alan Richens, and rapidly gained international participation. International cooperation on quality control improved over time and secured the analytical performance of many laboratories engaged in TDM (Wilson et al., 1989, 1992; Richens, 1995; Williams et al., 2003). The availability of simple, accurate, reproducible, and inexpensive analytical assays is pivotal for the successful use of TDM in patient management.

Objectives of this document

This position paper has been prepared by an international panel of authors who in their careers have been instrumental in developing and implementing practice parameters in the field of TDM and have used TDM of AEDs in their everyday clinical practice. In 1993, the International League Against Epilepsy (ILAE) issued guidelines for the TDM of AEDs in order to promote a more appropriate application of the technique (Commission on Antiepileptic Drugs, 1993). However, since 1993 knowledge has advanced considerably and many new AEDs have been introduced, some of which are attractive candidates for TDM.

This document is divided into three sections. The first section addresses the rationale for monitoring serum concentrations of AEDs, the clarification of the concept of "reference ranges" and "therapeutic ranges" and the impact of TDM on clinical outcome. The second section comprises a description of currently licensed AEDs (in alphabetical order) with regard to their pharmacokinetic characteristics, interaction profiles, relationship between drug concentrations, and clinical effect and assay methodologies. The third section describes specific situations in which TDM is likely to be particularly useful in patient management.

This document is not intended to provide a systematic review on the topic. Although an extensive literature search was made using electronic databases and searches through the authors' files, only references considered to be particularly significant to illustrate specific concepts or findings are quoted.

Monitoring Serum Concentrations of AEDs: Rationale, Interpretation and Impact on Clinical Outcome

Rationale

Although individualization of dose is essential in epilepsy therapy, identification of the optimal dose on

purely clinical grounds can be difficult. There are many reasons for this: (1) since AED treatment is prophylactic and seizures occur at irregular intervals, it is often difficult to determine rapidly whether the prescribed dosage will be sufficient to produce long-term seizure control; (2) clinical symptoms and signs of toxicity may be subtle, or difficult to differentiate from the manifestations of underlying disorders; (3) there are no direct laboratory markers for clinical efficacy or for the most common manifestations of AED toxicity, such as adverse CNS effects.

TDM seeks to optimize patient outcome by managing their medication regimen with the assistance of information on the concentration of AEDs in serum or plasma (serum and plasma usually can be used interchangeably for TDM, although it is preferable for each laboratory to use consistently one or the other). To this end, TDM seeks to optimize the seizure suppressing effects of AEDs whilst minimizing their adverse effects. The concept rests on the assumption that clinical effects correlate better with drug concentrations than with dose. There are some requirements that need to be fulfilled in part or in full to obtain a meaningful stable relationship between the serum concentration of a drug and its effect. The drug should have a rapidly reversible action and development of tolerance should not occur at its site of action. It should act per se and not through metabolites (but, if so, metabolites should be measured), and the concentration of the drug at the site of sampling (usually blood) should ideally be highly correlated with the concentration of the drug at receptor sites.

Although the epilepsy-related rationale and indeed the indications for TDM are similar for all AEDs, the usefulness of these measurements will vary between AEDs depending on their pharmacological properties. TDM is likely to be of particular value for drugs that exhibit pronounced intra- or interindividual variability in pharmacokinetics. Irrespective of the properties of the monitored drug, TDM is also expected to be helpful in ascertaining drug compliance, in attributing toxicity to drug treatment, and in managing overdoses and drug interactions.

Terminology and definitions

Terms such as "reference ranges," "therapeutic ranges," "optimal ranges," "desirable ranges," "effective ranges," "target ranges," and "target concentrations" have been variably used in the TDM literature, either interchangeably or with different meanings. Since this has resulted in much confusion, providing clear definitions is essential.

In the present paper, the recommendation is made that two separate terms be used to define drug concentration ranges in relation to their clinical effects. The "reference range" can be defined as a range of drug concentrations, which is quoted by a laboratory and specifies a lower limit below which a therapeutic response is relatively unlikely to occur, and an upper limit above which toxicity is relatively likely to occur. The aim of much TDM research has been to provide a reference range which laboratories can quote and which clinicians can use as a guide. As discussed in more detail in the sections below, clinicians using reference ranges should be aware that, because of individual variation, many patients can achieve therapeutic benefit at serum drug concentrations outside these ranges. In other words, the reference range is not a "therapeutic range": the latter can be defined, for the purposes of the present paper, as the range of drug concentrations which is associated with the best achievable response in a given person, and therefore it can only be determined for the individual since the range will differ in different individuals. However, if the reference range is a result of extensive and reliable research, for many individual patients their therapeutic range will lie within, or at least close, to the reference range quoted by the laboratory. Some individuals, however, will derive optimal benefit at concentrations outside the reference range and some will have toxic effects within this range. Concentrations lying within the reference range are not "normal" because the "normal" concentration of a drug in a living organism is zero. Concentrations lying within the reference range may not necessarily be "therapeutic," "effective," or "optimal" and therefore it is recommended that these adjectives not be used when reporting the results. The correct reporting terminology should be "The result lies within/above/below the reference range."

Historical perspective on reference ranges of AEDs

The reference range has been a controversial concept in TDM, partly because it was initially defined on the basis of limited data for individual AEDs. This can be illustrated with phenytoin as an example, although phenytoin without doubt is the AED with the best-documented relationship between serum concentration and clinical effect. The generally quoted range for phenytoin (10–20 mg/L, 40–79 μmol/L*) originates from the pioneering work of Buchthal and collaborators (Buchthal et al., 1960). Eighty patients with at least one "grand mal" seizure per week, despite use of phenobarbital in combination with phenytoin, were followed up. Only 6 out of 24 (25%) improved at serum phenytoin concentrations below 10 mg/L, while 21 out of 27 patients (77%) improved at concentrations exceeding 10 mg/L. The majority of patients with concentrations above 30 mg/L experienced adverse effects. The upper limit of the range was partly based on the results of another study by Kutt et al. (1964), who reported nystagmus among all patients with serum phenytoin concentrations above 20 mg/L. Ataxia was observed at phenytoin concentrations above 30 mg/L and in all patients at concentrations exceeding 40 mg/L.

*Molar digits have not been rounded up to ensure precise mathematical correspondence to the mg/L digits. However, laboratories quoting preferentially molar units may decide to round them up or down. Conversion factors from mg/L to μmol/L (and vice versa) for each of the major AEDs are reported in Table 1.

A prospective study of 32 outpatients with "grand mal" seizures gave further support to the quoted reference range (Lund, 1974). These patients, half of whom received phenytoin in combination with other AEDs, had at least one grand mal seizure per 2 months at inclusion, despite treatment with phenytoin for more than a year. They were followed up for 3 years, during which the mean phenytoin serum concentration was gradually increased from 6 mg/L in the first year to 12 mg/L in the second and 15 mg/L in the third. The annual mean number of "grand mal" seizures per patient decreased in parallel from 5.8 to 4.1, and 1.6, respectively. Cerebellar adverse effects were rare and noted only in relation to phenytoin concentrations above 20 mg/L. The results thus corroborated previous findings and supported a reference range of 10–20 mg/L. However, these early studies were all conducted in patients with severe epilepsy and frequent generalized tonic–clonic seizures despite a long history of epilepsy and several treatment attempts often with phenytoin. Patients with easy-to-treat epilepsy had thus been excluded. Subsequent studies demonstrated that the seizure type as well as the severity of the epilepsy has an influence on which serum concentration is needed to obtain seizure control (Schmidt & Haenel, 1984; Schmidt et al., 1986). In a prospective study, one-third of previously untreated patients with newly diagnosed epilepsy were controlled with phenytoin concentrations below the reference range (Shorvon et al., 1980). As a consequence, the value of the lower limit of the reference range has been seriously questioned and it has gradually become widely accepted that there is a considerable individual variation in what is the therapeutic serum concentration of phenytoin as well as other AEDs.

The limitations of reference ranges

The evidence discussed above indicates that, for all AEDs, reference ranges have purely a statistical meaning, being an estimate of the concentration interval at which the majority of patients showed an optimal response in a variable number of studies. Because of inherent methodological problems with such studies, however, these ranges may not necessarily be applicable to all patients. Most notably, due to the fact that many studies providing supportive evidence for reference ranges were undertaken in populations with difficult-to-treat epilepsy, some of these ranges may not describe adequately the concentration-response relationship in patients with newly diagnosed epilepsies, who not uncommonly respond well to serum AED concentrations below the commonly reported lower limit of the range (Feldman & Pippenger, 1976; Shorvon et al., 1978, 1980; Schmidt & Haenel, 1984). Based on this (and the fact that some difficult-to-treat patients may also respond at low serum AED concentrations), the suggestion has been made that "reference ranges" of AEDs be redefined by omitting a lower limit, and by simply advising physicians that the probability of seizure control decreases with decreasing drug concentration (Perucca & Richens, 1981). Although for every drug there must be a "threshold concentration" at which no patient will show a therapeutic effect, such a concentration is difficult to define based on available data.

Even when reference ranges are redefined by omitting a lower limit, their interpretation requires a good deal of flexibility. In probabilistic terms, the likelihood of seizure control would be expected to increase with increasing serum concentration, at least up to the upper limit of the range, even though it is recognized that concentrations above a certain threshold may paradoxically result in deterioration rather than improvement in seizure control (Perucca et al., 1998). Even the upper limit of the range may vary from one patient to another, and there are individuals who experience toxic symptoms at low drug concentrations while others may tolerate and indeed require concentrations into the nominally "toxic" range (Gannaway & Mawer, 1981). This has led to the recommendation that dose adjustments should never be made on the basis of serum drug concentrations alone, but should be primarily justified by careful assessment of the patient's clinical state. Specifically, dosage should not be modified in patients who achieved sustained seizure freedom at serum drug concentrations below the lower limit of the commonly quoted "reference range" (Woo et al., 1988), nor in patients who are doing clinically well at concentrations above this range (Gannaway & Mawer, 1981).

From reference ranges to "individual therapeutic concentrations"

Given the considerable interpatient variability in the concentration of an AED that produces optimal therapeutic responses, the argument can be made that ultimately AED therapy can be best guided by identification of the "individual therapeutic concentration" (Perucca, 2000). The latter can be defined as the concentration (or range of concentrations) which has been empirically found to produce the optimal response in the individual patient (i.e., complete seizure control without undesired effects or, if that is not achievable, the best compromise between seizure suppression and concentration-related adverse effects).

In practice, the individual therapeutic concentration can be established by determining, preferably on at least two separate occasions at steady state, the serum AED concentration once a patient has been stabilized on his/her optimal regimen. In a patient who had infrequent seizures before starting treatment, this can only be done after a long period of observation, in order to be able to confirm that remission has been really achieved. Of course, if a patient became free from seizures and from adverse effects on the initially prescribed dosage, it cannot be excluded that an even lower dosage might have been equally efficacious, and the individual therapeutic concentration measured in that patient might therefore be an overestimate. On the other hand, if a patient needed up-titration due to his/her

seizures continuing at the initially prescribed dosage, repeated TDM measurements in that patient can identify the individual range of subtherapeutic concentrations, as well as the individual threshold concentration at which seizures were brought under control.

Identification of the individual therapeutic concentration can be extremely useful in clinical management. In fact, knowledge of the serum concentration at which an individual patient has shown a good response provides a useful reference in making management decisions should a modification in clinical status occur over time. For example, if seizures subsequently recur in the same patient and the serum AED concentration at the time of the recurrence is found to be below the individual therapeutic concentration, management will be facilitated by bringing back the concentration to the level previously identified as effective, e.g., by restoring adequate compliance or by adjusting dosage to compensate for the effects of a drug interaction (Specht et al., 2003). An advantage of the "individual therapeutic concentration" approach is that it does not rely on fixed reference ranges, and can be applied to any AED, including second generation AEDs for some of which reference ranges have not yet been clearly defined (Perucca, 2000; Johannessen & Tomson, 2006).

A caveat in the use of the "individual therapeutic concentration" approach is that its applicability rests on the assumption that the relationship between serum AED concentration and response remains stable over time in the same patient. There are examples where this assumption may be incorrect, for example when there is change in drug binding to serum proteins, when there is progression (or regression) in the severity of the disease, or when another drug is added or withdrawn interacts pharmacodynamically with the monitored AED.

Impact of TDM on clinical outcome

While TDM has been established as an aid to individualize the dosage of AEDs since the sixties, the impact of TDM on outcome has rarely been assessed in a systematic manner. Open uncontrolled studies have demonstrated that the introduction of a TDM service may result in a larger proportion of patients being treated with serum AED concentrations within the reference ranges (Houtman et al., 1990; Larkin et al., 1991; McKee et al., 1993). However, studies on the effect of TDM on outcome in terms of complete seizure control and/or best compromise between improved seizure control and adverse effects are scarce (Patsalos et al., 1987; Tomson et al., 2007a). In fact, there are only two published randomized studies comparing treatment outcome with or without the use of TDM (Fröscher et al., 1981; Jannuzzi et al., 2000).

In the first randomized trial, 127 patients with chronic-uncontrolled epilepsy receiving mono- or polytherapy with AEDs were randomly assigned to treatment with or without the support of TDM (Fröscher et al., 1981). Blood samples for determination of drug concentrations were drawn from all patients but for one of the two groups, the treating physician was not informed about the results. Of the randomized patients, 105 completed the 1-year follow-up and therapeutic results in the two groups were not significantly different. However, a substantial proportion of the patients, similar in both groups, had AED concentrations that fell below or above the reference range. This observation suggests that the physicians responsible for the treatment did not utilize the information provided by the TDM service, which may have affected the negative outcome of the study. Such interpretation is in line with the observations made in a retrospective analysis of 164 patients with epilepsy (Beardsley et al., 1983). Seizure control 1 year before the introduction of TDM was compared to 1year after the service was made available. Seizure control was improved only when the physicians, according to the investigators, appropriately utilized information from TDM.

The second and most recent randomized controlled trial on the impact of TDM included 180 newly diagnosed patients with epilepsy who were about to start treatment with carbamazepine, valproic acid, phenytoin, phenobarbital, or primidone (Jannuzzi et al., 2000). Patients were randomized to either treatment with dosage adjusted on clinical grounds alone, or treatment with dosage adjusted to achieve serum concentrations within predefined target ranges. After a follow-up of up to 24 months, there were no significant differences between the two groups with respect to patients achieving 12-month remission (60% in the TDM group vs. 61% in the control group), patients remaining seizure-free since initiation of treatment, time to first seizure or to 12-month remission, or frequency of adverse effects. Hence, this study could not demonstrate an effect of routine use of TDM on the clinical outcome of early treatment of patients with epilepsy. It should be noted, however, that very few patients in this study were treated with phenytoin, the drug for which the value of TDM is probably highest and that the study was powered to detect a 25% absolute improvement in seizure freedom rate in the TDM group, which might have been an unrealistic expectation.

In conclusion, there is a need for studies assessing the impact of TDM on the outcome of treatment of epilepsy. The only two available randomized studies do not provide evidence for the usefulness of routine monitoring of AEDs in general, which, however, does not argue against the value of TDM in special situations.

Sample matrix and sampling time

Serum or plasma represents the matrix of choice for TDM, and although they can be used interchangeably it is preferable to use one or the other. Saliva is a matrix of increasing utility, but only for some AEDs.

In most clinical settings the measurement of total serum concentrations will suffice and indeed most routine

methods for measuring AEDs in sera do not discriminate between the component of drug that is free (unbound) and that that is bound to serum proteins. However, because only the free drug is available to move across the endothelium and to equilibrate with the concentration in the interstitial space in the brain where the pharmacological effect is to occur, in certain clinical settings when protein binding is altered, patient management would be best guided by monitoring free serum concentrations. Settings in which protein binding impairment occurs include hypoalbuminemia (e.g., during pregnancy, old age, liver disease, renal disease, and many other pathological conditions) conditions associated with accumulation of endogenous displacing agents (e.g., uremia), and administration of drugs which compete for serum protein binding sites. If the free fraction increases, the measurement of the total serum concentration will underestimate the amount of free, pharmacologically active, drug and under these circumstances therapeutic and toxic effects will be observed at total drug concentrations which are lower than usual (Perucca et al., 1981; Barre et al., 1988). Because phenytoin and valproic acid are highly protein bound and consequently susceptible to variable binding, free concentrations are most commonly monitored for these drugs (Perucca, 1984).

There are various techniques available for the measurement of free drug concentrations. The most commonly used involve ultrafiltration of the serum sample to separate a protein-free fluid containing the free drug. These methods are more expensive than those used to measure total concentrations and are also more cumbersome. Furthermore, an important consideration is that free concentration values are temperature dependent (i.e., they correlate directly with the temperature at which separation of free drug is undertaken) and therefore a standard temperature (typically 25°C) should be used (Ratnaraj et al., 1990). Despite these limitations, if a major change in unbound fraction is expected (or suspected), measuring unbound drug concentrations can be justified.

Saliva has been advocated as an alternative matrix to serum since the 1980s and the increasing interest in free drug concentration monitoring has provided a renewed impetus in saliva monitoring of AEDs (Liu & Delgado, 1999). There are many advantages to saliva as a matrix: (1) collection is simple and non-invasive; does not require expertise in drawing blood and therefore sampling can be undertaken by patients themselves or by their carers; (2) it can be especially useful in patients with disabilities and is preferred by children and their parents; (3) for most AEDs, measured concentrations reflect the free (pharmacologically relevant) concentration in blood. Disadvantages of saliva include: (1) the difficulty in measuring concentrations that may be lower than total serum concentrations; (2) the unacceptability of this matrix for some patients; (3) possibility of unreliable results due to the presence of drug residues in the mouth or leakage of drug-rich exudate, particularly in patients with gingivitis. To minimize contamination from drug residues, saliva sampling is best done before the next dose or after a few hours have elapsed since drug ingestion. AEDs for which there are substantial data suggesting useful correlations between saliva concentrations and free serum concentrations include carbamazepine, ethosuximide, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, primidone, topiramate, and vigabatrin (Grim et al., 2003; Ryan et al., 2003a, 2003b; Miles et al., 2003, 2004; Malone et al., 2006; Mecarelli et al., 2007). For drugs with pK values close to physiological pH (e.g., valproic acid and phenobarbital), however, salivary concentrations can be highly variable or erratic (Liu & Delgado, 1999), and monitoring based on saliva samples should not be attempted for these drugs.

Knowledge of sampling time and a meticulous dosage history is imperative if TDM is to be used to maximum utility. Sampling should be done at steady state, which occurs at 4–5 half-lives after starting treatment or a dose change. A summary of half-life values and other pharmacokinetic parameters of the major AEDs are reported in Table 1. For AEDs with long half-lives such as phenobarbital, zonisamide, and ethosuximide, the fluctuation in serum drug concentration during a dosing interval is negligible, and samples can be collected at any time. For most AEDs, however, particularly those with short or relatively short half-lives (e.g., carbamazepine, valproic acid, gabapentin, levetiracetam, pregabalin, tiagabine, vigabatrin, lamotrigine, and topiramate), it is important to standardize sampling time in relation to dose. Patient noncompliance within a period of 3–4 half-lives before the blood sample is drawn can significantly affect the serum concentration and cause misinterpretation of the result. If blood sampling is undertaken before reaching steady state following a dose increment, the steady-state serum concentration at that dose will be underestimated. Consequently, if a further dose increase is undertaken, this may eventually result in toxicity for the patient. In the case of carbamazepine, sampling before autoinduction is complete will result in overestimation of the steady-state concentration. This can result in a dose that is subtherapeutic and patients may continue to have unnecessary seizures.

The ideal blood sampling time for all AEDs is immediately before the next oral dose (trough), but if this is not possible, particularly when attending an outpatient clinic, patients should not be told to delay their morning dose for longer than 2 or 3 h in the case of AEDs with short (<8 h) half-lives, and it is then desirable to note the sampling time and the time medication was last ingested. In some cases, two blood samples, for example one taken at the time of trough and a second taken at the expected time of peak (or in conjunction with the appearance of symptoms suggestive of transient concentration-related toxicity) could be valuable to optimize the dosing schedule. During overdose, sampling should be undertaken as

Table 1. Pharmacokinetic parameters and serum reference ranges of the major antiepileptic drugs in adults

Drug	Oral bioavailability (%)	Serum protein binding (%)	Time to peak concentration (h)	Time to steady-state[l] (days)	Half-life in the absence of interacting comedication (h)	Half-life in patients comedicated with enzyme inducers (h)	Comment	Reference range (mg/L)	Conversion factor (F) (μmol/L = F × mg/L)
Carbamazepine	≤85	75	2–9[a]	2–4[b]	8–20[b]	5–12[b]	Active 10,11 epoxide metabolite contributes to clinical effects	4–12	4.23
Clobazam	≥95	85	1–3	7–10[c]	10–30	?	Active N-desmethyl-metabolite contributes to clinical effects	0.03–0.3 (clobazam) 0.3–3 (desmethyl metabolite)	3.33 (clobazam) 3.49 (desmethyl metabolite)
Clonazepam	≥95	85	1–4	3–10	17–56	11–35	7-amino metabolite retains some pharmacological activity	0.02–0.07	3.17
Ethosuximide	≥90	0	1–4	7–10	40–60	20–40		40–100	7.08
Felbamate	>90	25	2–6	3–4	16–22	10–18		30–60	4.20
Gabapentin	<60[d]	0	2–3	1–2	5–9	5–9		2–20	5.84
Lamotrigine	≥95	55	1–3[a]	3–6 (5–15 with valproic acid comedication)	15–35 (30–90 with valproic acid comedication)	8–20 (15–35 with valproic acid comedication)		2.5–15	3.90
Levetiracetam	≥95	0	1	1–2	6–8	5–7		12–46	5.87
Oxcarbazepine	90[e]	40[e]	3–6[e]	2–3[e]	8–15[e]	7–12[e]		3–35[e]	3.96[e]
Phenobarbital	≥95	55	0.5–4	12–24	70–140	70–140		10–40	4.31
Phenytoin	≥80[f]	90	1–12[f]	5–17	30–100[g]	30–100[g]		10–20	3.96
Pregabalin	≥90	0	1–2	1–2	5–7	5–7		NE[h]	6.28
Primidone	≥90	10	2–5	2–4	7–22	3–12	Metabolically derived phenobarbital contributes largely to clinical effects	5–10[i]	4.58
Tiagabine	≥90	96	0.5–2	1–2	5–9	2–4		0.02–0.2	2.66
Topiramate	≥80	15	2–4	4–5	20–30	10–15		5–20	2.95
Valproic acid	≥90	90[j]	3–6[k]	2–4	11–20	6–12		50–100	6.93
Vigabatrin	≥60	0	1–2	1–2	5–8	5–8		0.8–36	7.74
Zonisamide	≥65	50	2–5	9–12	50–70	25–35		10–40	4.71

[a]Immediate-release tablets; [b]at the initiation of treatment, time to reach state state may be up to 5 weeks due to autoinduction. Reported half-lives refer to patients on chronic therapy (half-lives are considerably longer after a single dose); [c]includes time to steady state for active metabolite N-desmethyl-clobazam; [d]bioavailability decreases with increasing dosages; [e]pharmacokinetic parameters, reference range and conversion factor refer to the active mono-hydroxy-derivative (MHD) metabolite; [f]bioavailability and rate of absoption depends on formulation; [g]elimination is not first order, and half-life increases with increasing serum concentration; [h]not established; [i]phenobarbital concentrations should also be monitored; [j]fraction bound to serum proteins decreases with increasing drug concentration; [k]enteric-coated tablets ingested in a fasting state; [l]these values are based on half-life values in the absence of interacting comedication.

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soon as the patient presents at casualty but repeated sampling might be necessary, depending on the timing of the overdose.

Relevance of TDM for Individual AEDs

Carbamazepine

Pharmacokinetics

The rate of carbamazepine absorption is relatively slow, variable, and formulation dependent. The time required to reach peak serum concentrations (T_{max}) following single oral doses of immediate-release tablets, chewable tablets, and suspension is in the range of 2–9 h, 1–7 and 0.5–4 h, respectively (Chan et al., 1985; Graves et al., 1985; Maas et al., 1987; Patsalos, 1990a). The bioavailability of carbamazepine is 75–85%, although the lack of an injectable formulation precludes precise determination of the exact value. Sustained-release formulations are associated with a slower absorption, and may have a lower bioavailability than immediate-release dose forms. Carbamazepine is 70–80% bound to serum proteins, primarily albumin and, to a lesser extent, alpha$_1$-acid glycoprotein and its apparent volume of distribution (Vd) is 0.9–1.4 L/kg. Carbamazepine undergoes extensive metabolism with less that 2% of an oral dose excreted unchanged in the urine. The major metabolic pathway involves oxidation, primarily by cytochrome P450 (CYP) 3A4, to carbamazepine-10–11-epoxide. Carbamazepine-10–11-epoxide, in turn, undergoes hydrolysis via microsomal epoxide hydrolase to an inactive trans carbamazepine diol. Carbamazepine undergoes autoinduction so that clearance can increase threefold within several weeks of starting therapy (Bertilsson et al., 1980; Kudriakova et al., 1992). Its elimination half-life varies as a function of time, extent of induction, and age. Following a single dose, carbamazepine half-life values in adults and children are in the range of 18–55 h and 3–32 h, respectively. During maintenance carbamazepine monotherapy, adults have half-lives of 8–20 h whereas in children 10–13 years of age half-lives are 10–14 h. In elderly patients on maintenance therapy, carbamazepine half-life is 30–50 h and oral clearance is 25–40% less than in younger adults (Cloyd et al., 1994; Graves et al., 1998; Battino et al., 2003).

Effect of other drugs on carbamazepine concentrations

A wide range of medications interacts with carbamazepine (Patsalos, 2005). Among AEDs, phenytoin, phenobarbital, and primidone increase carbamazepine clearance by as much as two-fold, via induction of CYP3A4, and reduce its half-life, in adults, to an average of 8 h. The clearance of carbamazepine-10–11-epoxide also appears to be affected by enzyme inducers, e.g., it is increased about two-fold by phenobarbital (Spina et al., 1991). Coadministration of valproic acid increases carbamazepine-10–11-epoxide concentrations by 50%, due to inhibition of epoxide hydrolase (Pisani et al., 1990). Felbamate, oxcarbazepine and possibly zonisamide can lower serum carbamazepine concentrations by 13–30%. Moderate to potent CYP3A4 inhibitors such as stiripentol, erythromycin and some other macrolide antibiotics, diltiazem, verapamil, isoniazid, fluoxetine, danazol, cimetidine, metronidazole, and propoxyphene can cause clinically important increases in serum carbamazepine concentrations (Cazali et al., 2003; Patsalos & Perucca, 2003a,b).

Drug concentrations and clinical effects

As with all AEDs, there are no prospective controlled trials that define the reference range for carbamazepine. Retrospective and observational studies suggest that optimal seizure control in patients on monotherapy is most likely to occur between 4 and 12 mg/L (17–51 μmol/L). In patients taking other AEDs, lower serum carbamazepine concentrations may be required, particularly with respect to the need to minimize toxicity. Lamotrigine, in particular, has been reported to interact pharmacodynamically with carbamazepine, implying that lower serum carbamazepine concentrations may be required in patients comedicated with lamotrigine or in whom lamotrigine is added (Besag et al., 1998). In any case, there is substantial overlap between carbamazepine concentrations associated with seizure control and those associated with toxicity. For example, Rowan et al. (2005) in a controlled trial found that the carbamazepine concentrations in patients remaining in the study were similar to those measured in patients who dropped out due to adverse effects (6.48 $\pm$ 3.72 vs. 4.95 $\pm$ 3.44 mg/L, respectively). Other prospective trials that permitted titration to optimal effect also report carbamazepine concentrations in the 4–12 mg/L range (Brodie et al., 1995, 1999). In most studies carbamazepine-10–11-epoxide concentrations have not been measured. The upper boundary of the reference range of the metabolite in patients on combination therapy may be around 8 mg/L (34 μmol/L), with some patients reporting transient CNS side effects such as dizziness at concentrations above this limit (Hoppener et al., 1980; Patsalos et al., 1985).

The unpredictable relationship between dose and carbamazepine concentration, its narrow therapeutic index, and the presence of numerous clinically significant drug interactions support the need to individualize and maintain therapy using TDM. Because carbamazepine 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 carbamazepine measurements should be drawn before the morning dose.

Analytical methods

Commercial reagent-based techniques represent the primary methodology for the analysis of carbamazepine in serum (e.g., fluorescence polarization immunoassay [FPIA] and enzyme multiplied immunoassay technique

[EMIT]). However, there are also many gas chromatographic (GC) and high performance liquid chromatographic (HPLC) techniques available and these have the advantage of simultaneously measuring other AEDs and the active metabolite carbamazepine-10,11-epoxide (Romanyshyn et al., 1994; Bhatti et al., 1998; Queiroz et al., 2002; Lancas et al., 2003).

Clobazam

Pharmacokinetics

Clobazam is rapidly and completely absorbed from the gastrointestinal tract (T_{max}, 1–3 h) (Rupp et al., 1979; Divoll et al., 1982) and steady-state serum clobazam and N-desmethylclobazam concentrations are linearly related to dose. Clobazam is 85% bound to serum proteins and its Vd is 1 L/kg. Elimination involves hydroxylation at the 4 position of the unsubstituted aromatic ring, resulting in the formation of 4-hydroxyclobazam and 4-hydroxydesmethylclobazam, both of which are subsequently conjugated and excreted in urine (Hanks, 1979; Volz et al., 1979). The half-life of clobazam is 10–30 h, whilst the half-life of N-desmethylclobazam is 36–46 h. The desmethyl metabolite makes an important contribution to the pharmacological action (Aucamp, 1982) by accumulating to higher concentrations in serum than the parent drug. The elderly eliminate the drug more slowly than younger subjects (Greenblatt et al., 1981), and hepatic disease can reduce both clobazam elimination and protein binding (Monjanel-Mouterde et al., 1994).

Effect of other drugs on clobazam concentrations

Clobazam is more rapidly metabolized in patients comedicated with enzyme-inducing AEDs (Sennoune et al., 1992; Theis et al., 1997) and this results in lower clobazam and higher N-desmethylclobazam serum concentrations and an increased N-desmethylclobazam/clobazam ratio. CYP2C19 is predominantly responsible for the oxidation of N-desmethylclobazam (Contin et al., 2002) and patients with genetically determined low activity of CYP2C19 or taking drugs known to inhibit this isoenzyme show elevated N-desmethylclobazam concentrations. Felbamate comedication is associated with an increase in serum N-desmethylclobazam concentrations (Contin et al., 1999). Stiripentol is an inhibitor of clobazam and, more potently, of N-desmethylclobazam metabolism and it increases serum N-desmethylclobazam concentrations several-fold (Chiron et al., 2000; Giraud et al., 2006).

Drug concentrations and clinical effects

Because tolerance tends to develop to the adverse and, sometimes, therapeutic effects of clobazam, there is no clear relationship between efficacy and serum concentrations of either clobazam or N-desmethylclobazam. However, there are reports of CNS toxicity occurring at elevated serum concentrations of these compounds (Contin et al., 2002; Aylett et al., 2005).

In patients treated with therapeutic doses of clobazam, serum concentrations have been reported to be in the order of 30–300 ng/mL (0.1–1.0 μmol/L) for the parent drug and 300–3000 ng/mL (1–10 μmol/L) for the desmethylclobazam metabolite (Rupp et al., 1979).

Analytical methods

Many GC methods using electron capture (EC), nitrogen-phosphorus (NP) and mass spectrometry (MS) detection have been described for the quantitation of clobazam and N-desmethylclobazam in serum (Greenblatt 1980; Drouet-Coassolo et al., 1989; Lillisunde & Seppala, 1990; LeGatt & McIntosh, 1993). HPLC methods with ultraviolet (UV) detection are also available (Streete et al., 1991; LaCroix et al., 1993; Akerman, 1996; Knapp et al., 1999; Kunicki, 2001).

Clonazepam

Pharmacokinetics

Clonazepam is rapidly (T_{max} 1–4 h) and completely absorbed after oral ingestion (Berlin & Dahlstrom, 1975). Steady-state serum clonazepam concentrations increase linearly with dose in both children (Dreifuss et al., 1975) and adults (Labbate et al., 1994). Clonazepam is 85% bound to serum proteins (Pacifici et al., 1987) and its Vd is 1.5–4.4 L/kg in both adults and neonates (Berlin & Dahlstrom, 1975; Andre et al., 1986). The drug is extensively metabolized by reduction of the 7-nitro group to 7-amino-clonazepam, and hydroxylation to 3-hydroxyclonazepam. 7-amino-clonazepam is further metabolized by acetylation to form 7-acetamido-clonazepam. The 7-amino-clonazepam has some pharmacological activity and is present in serum at concentrations similar to those of clonazepam. The hydroxylated metabolites are further conjugated with glucuronic acid or sulphate. The half-life of clonazepam is 17–56 h in adults (Berlin & Dahlstrom, 1975), 23–33 h in children (Dreifuss et al., 1975; Walson & Edge, 1996) and 22–81 h in neonates (Andre et al., 1986).

Effect of other drugs on clonazepam concentrations

Clonazepam clearance is significantly increased by coadministration of enzyme-inducing AEDs such as carbamazepine, phenytoin, phenobarbital and primidone (Khoo et al., 1980). Nitroreduction is catalyzed by CYP3A4 and therefore inhibitors of this isoenzyme (e.g., ritonavir) can be expected to increase serum clonazepam concentrations.

Drug concentrations and clinical effects

Because tolerance to clonazepam develops in many patients, it has been difficult to identify a clear correlation between serum clonazepam concentrations and either efficacy or toxicity. In patients treated with therapeutic doses of clonazepam, serum concentrations in the order of 20–70 ng/mL (63–222 nmol/L) have been reported (Dreifuss et al., 1975). In children with absence seizures, efficacy

was reported at concentrations in the range of 13–72 ng/mL (Dreifuss et al., 1975). A second study produced similar results in 23 children with partial seizures who were controlled with serum concentrations of 14–68 ng/mL (Hosoda et al., 1991). In neonates receiving intravenous clonazepam for convulsions, anticonvulsant responses were achieved at serum concentrations ranging from 28 to 117 ng/mL (Andre et al., 1986).

Analytical methods

Many chromatographic methods have been described for the quantitation of clonazepam in serum. These include GC procedures using EC (de Boer et al., 1978; Lillisunde & Seppala, 1990; de Carvalho & Lanchote, 1991), NP (Dhar & Kutt, 1981; Lillisunde & Seppala, 1990) and MS (Song et al., 1996) detection, and various HPLC methods with UV detection (Petters et al., 1984; Sallustio et al., 1994; Tanaka et al., 1996).

Ethosuximide

Pharmacokinetics

Ethosuximide is rapidly absorbed with a bioavailability of 90–95% in both children and adults (Buchanan et al., 1969; Eadie et al., 1977). T_{max} values are 1–4 h in adults and 3–7 h in children (Eadie et al., 1977). Syrup has a faster absorption rate than capsules but the two formulations are bioequivalent (Buchanan et al., 1969). The Vd of ethosuximide is 0.62–0.65 L/kg in adults and 0.69 L/kg in children (Buchanan et al., 1969, 1973; Eadie et al., 1977). Ethosuximide is not bound to serum proteins, shows linear pharmacokinetics and undergoes extensive metabolism (80–90%), primarily by CYP3A isoenzymes but also by CYP2E and CYP2B/C, to form three inactive metabolites. The half-life of ethosuximide in adults, children and neonates is 40–60, 29–39, and 32–41 h, respectively (Buchanan et al., 1969; Eadie et al., 1977; Bauer et al., 1982).

Effect of other drugs on ethosuximide concentrations

Enzyme-inducing AEDs and rifampicin enhance the metabolism of ethosuximide, resulting in lower serum concentrations (Giaccone et al., 1996; Riva et al., 1996; Tanaka, 1999). In contrast, serum ethosuximide concentrations are increased by isoniazid (van Wieringen & Vrijlandt, 1983). Valproic acid exerts a variable effect, with ethosuximide clearance being reported to be increased, decreased, or unchanged following addition of valproic acid (Mattson & Cramer, 1980; Bauer et al., 1982; Pisani et al., 1984; Bourgeois, 1988; Tanaka, 1999).

Drug concentrations and clinical effects

The reference range for ethosuximide is predominantly based on data obtained from two studies (Sherwin et al., 1973; Browne et al., 1975). In the study by Browne et al. (1975), 18 of 37 patients with typical absence seizures had ≥90% reduction in seizures, while 35 of 37 exhibited a ≥50% reduction in seizures at serum ethosuximide concentrations ranging from 16.6 to 104 mg/L. The investigators concluded that the reference range was 40 to 100 mg/L (283–708 μmol/L). The other study was a prospective open label study that used TDM to maximize ethosuximide response in 70 patients with absence seizures (ages ranging from 4 to 28 years, median 12 years; Sherwin et al., 1973). Patients received ethosuximide at a dose of 9.4–73.5 mg/kg/day. In 33 patients, absence seizures were already completely controlled at enrolment: none of these patients had serum ethosuximide concentrations below 30 mg/L, and only three (9%) had concentrations below 40 mg/L. Conversely, 14 (35%) of the 37 patients with uncontrolled seizures had concentrations below 40 mg/L. During the subsequent 2.5 years, attempts were made to increase serum ethosuximide concentrations in uncontrolled patients, either by dose increments or by improving compliance: 13 of the 19 patients in whom ethosuximide concentrations increased improved clinically, and 10 achieved complete seizure control.

TDM can be useful for individualizing therapy with ethosuximide, although in most cases therapy can be optimized simply on the basis of clinical response and EEG checks. In most patients, therapeutic effects are observed at serum concentrations in the range of 40–100 mg/L, although some patients with refractory seizures or absence status may need concentrations up to 150 mg/L to achieve seizure freedom.

Analytical methods

Commercial reagent-based techniques represent the primary methodology for the analysis of ethosuximide in serum (e.g., FPIA and EMIT; Miles et al., 1989). However, there are also GC and HPLC techniques available which have the advantage of simultaneously measuring numerous other AEDs (Matar et al., 1999; Speed et al., 2000; Sghendo et al., 2002; Casas et al., 2004).

Felbamate

Pharmacokinetics

Felbamate is rapidly absorbed (T_{max} 2–6 h) with a bioavailability of >90% (Ward & Shumaker, 1990). Its Vd is 0.76 L/kg in adults and 0.91 L/kg in children. Protein binding is approximately 25%. The half-life in adults taking no other medications is 16–22 h and is shorter (10–18 h) in patients comedicated with enzyme-inducing AEDs (Sachdeo et al., 1993; Kelley et al., 1997). Felbamate clearance is 20–65% higher in children than in adults (Perucca, 2006). About 50% of an administered dose is metabolized to various inactive metabolites (Shumaker et al., 1990; Thompson et al., 1999). However, the atropaldehyde metabolite may be responsible for the development of serious organ toxicity (Shumaker et al., 1990).

Effect of other drugs on felbamate concentrations

The metabolism of felbamate is inducible and its clearance can be doubled by phenytoin and increased by 40% by

carbamazepine and phenobarbital so that serum felbamate concentrations are decreased (Wagner et al., 1991; Howard et al., 1992). Felbamate clearance is reduced by valproic acid (20%) (Ward et al., 1991) and possibly by gabapentin (37%) resulting in increased serum felbamate concentrations (Hussein et al., 1996).

Drug concentrations and clinical effects

In patients treated with therapeutic doses, serum felbamate concentrations in the order of 30–60 mg/L (126–252 μmol/L) have been reported. With respect to results of individual studies, serum concentrations of 65–80 mg/L were reported in adults on monotherapy taking 3600 mg/day (Sachdeo et al., 1992; Faught et al., 1993). In children, serum felbamate concentrations in mg/L were found to be approximately the same as the dose in mg/kg/day (The Felbamate Study Group in Lennox-Gastaut Syndrome, 1993). Also, there was a relationship between steady-state felbamate concentrations and the control of drop attacks: there was an average of 15 such seizures per day at a mean felbamate concentration of 17 mg/L, 13.5 seizures per day at 32 mg/L, and 11.5 seizures per day at 44 mg/L. Serum felbamate concentrations in 41 adults were analyzed by Harden et al. (1996), and divided into "low range" (9–36 mg/L), "mid range" (37–54 mg/L), and "high range" (54–134 mg/L). In the high-range group, anorexia and complaints of severe side effects occurred significantly more often, but significantly more patients in this group also reported decreased seizure frequency. Currently, the use of felbamate is highly restricted due to the risk of aplastic anemia and hepatotoxicity (Pellock, 1999).

Analytical methods

Felbamate concentrations can be determined by various HPLC methods with UV and MS detection (Romanyshyn et al., 1994; Gur et al., 1995; Behnke & Reddy, 1997; Contin et al., 2005). Also, a liquid chromatography/mass spectrometry (LC/MS) method has been described which can also measure felbamate metabolites (Thompson et al., 1999).

Gabapentin

Pharmacokinetics

Gabapentin is rapidly absorbed from the gastrointestinal tract by the L-amino acid transport system (T_{max}, 2–3 h). Bioavailability decreases with increasing dosage, probably because of saturation of the transporter's capacity (Vollmer et al., 1988). As a result, serum gabapentin concentrations increase linearly with doses up to about 1800 mg/day but increase less than expected at higher doses (Stewart et al., 1993), although there are studies suggesting a reasonably linear absorption in individual patients with doses up to 4800 mg/day (Berry et al., 2003). The drug is not bound to serum proteins (Vd, 0.9 L/kg), it is not metabolized and it is eliminated unchanged renally (Vollmer et al., 1988). The half-life is 5–9 h, and increases in the presence of impaired renal function (McLean, 1995). The concentration-to-dose ratio increases with age (Arminjo et al., 2004), and serum concentrations at any given dose vary markedly between individuals (Gidal et al., 2000).

Effect of other drugs on gabapentin concentrations

Cimetidine can cause a reduction in the renal clearance of gabapentin, while antacids containing aluminium or magnesium can reduce gabapentin absorption by up to 20% (Richens, 1993; McLean, 1995).

Drug concentrations and clinical effects

A wide range of serum gabapentin concentrations has been associated with seizure control. Therapeutic effects were evident in refractory patients with partial seizures only at serum concentrations above 2 mg/L (12 μmol/L) in a study by Sivenius et al. (1991). In another study using high-dose gabapentin in patients with refractory partial seizures, serum concentrations among responders ranged 6–21 mg/L, but one patient responded well to, and tolerated, 68 mg/L (Wilson et al., 1998). Other studies have reported mean gabapentin concentrations of 4.5 $\pm$ 2.1 mg/L (Lindberger et al., 2003) and 4.1 $\pm$ 1.9 mg/L (Gatti et al., 2003) among responders. These concentrations, however, did not differ from those of nonresponders in the same studies. Serum concentrations associated with a favorable response ranged from 2 to 10 mg/L in a small study of patients with partial seizures (Mirza et al., 1999).

The pronounced interindividual variation in pharmacokinetics and the dose-dependent bioavailability suggest that the monitoring of gabapentin concentrations may be useful in selected cases. Because gabapentin 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 gabapentin measurements should be drawn before the morning dose. Overall, in patients treated with therapeutic doses, serum gabapentin concentrations are in the order of 2–20 mg/L.

Analytical methods

Numerous HPLC methods have been described for the measurement of gabapentin in serum (Hengy & Kolle, 1985; Ratnaraj & Patsalos, 1998; Wad & Krämer, 1998; Chollet et al., 2000). GC and LC/MS methods have also been described (Hooper et al., 1990; Kushnir et al., 1999; Ifa et al., 2001).

Lamotrigine

Pharmacokinetics

Lamotrigine is rapidly and completely absorbed from the gastrointestinal tract (T_{max}, 1–3 h). Steady-state serum lamotrigine concentrations increase linearly with dose (Bartoli et al., 1997; Morris et al., 1998). The drug is 55% bound to serum proteins, and its Vd is 1.2 L/kg.

Lamotrigine undergoes extensive metabolism to an inactive glucuronide metabolite. An autoinduction

phenomenon completes within 2 weeks, with a 17% reduction in lamotrigine serum concentrations (Hussein & Posner, 1997). The half-life of lamotrigine is 15–35 h when given as monotherapy, and it is substantially shorter (8–20 h) in patients taking enzyme-inducing AEDs and prolonged (about 60 h on average) in patients taking valproic acid (Rambeck & Wolf, 1993; Biton, 2006). Patients taking a combination of an enzyme-inducing AED with valproic acid exhibit half-life values similar to those found in patients on monotherapy. A sustained release-formulation, which minimizes intraday fluctuations in serum lamotrigine concentrations and is suitable for once daily dosing even in patients comedicated with enzyme inducers, is being introduced (Tompson et al., 2007). Lamotrigine clearance is higher in children than in adults (Bartoli et al., 1997; Perucca, 2006) and moderately reduced in the elderly (Perucca, 2006). Clearance may be increased by up to 300% during pregnancy (Ohman et al., 2000; Tran et al., 2002; Pennell et al., 2004, 2007), but such increase is attenuated in women comedicated with valproic acid (Tomson et al., 2006).

Effect of other drugs on lamotrigine concentrations

Lamotrigine metabolism is accelerated by enzyme-inducing AEDs and inhibited by valproic acid (May et al., 1996a; Battino et al., 2001). The inhibitory interaction with valproic acid is particularly important and underlines the need to use smaller doses of lamotrigine as well as a slower titration rate to minimize the risk of skin rashes (Fitton & Goa, 1995). Oxcarbazepine and methsuximide may enhance the metabolism of lamotrigine, resulting in lower serum lamotrigine concentrations (May et al., 1999; Besag et al., 2000; Wellington & Goa, 2001). A lowering effect of oxcarbazepine on serum lamotrigine levels, however, has not been confirmed in all studies (Theis et al., 2005).

Sertraline increases serum lamotrigine concentrations, possibly by inhibiting its glucuronidation (Kaufmann & Gerner, 1998). Rifampicin, ritonavir and paracetamol can accelerate the metabolism of lamotrigine (Depot et al., 1990; Ebert et al., 2000). Estradiol containing contraceptives can lower the serum concentration of lamotrigine by 50% (Sabers et al., 2003; Christensen et al., 2007), and in women on oral contraceptives this interaction results in fluctuating steady-state lamotrigine concentrations during the days of pill intake compared with the pill-free interval (Sidhu et al., 2006). Interestingly, the lowering effect of estrogen-containing contraceptive steroids on serum lamotrigine concentrations does not appear to occur in women comedicated with valproic acid (Tomson et al., 2006).

Drug concentrations and clinical effects

It has been reported that between patients no clear-cut relationship exists between clinical response and serum lamotrigine concentrations (Bartoli et al., 1997; Besag et al., 1998). However, the incidence of toxicity increases significantly with concentrations >15 mg/L (>58 μmol/L; Besag et al., 1998; Morris et al., 1998). Morris et al. (1998) suggested that an appropriate reference range of serum concentrations for lamotrigine would be 3–14 mg/L in patients with refractory epilepsy. In their study, the median lamotrigine concentration was 8 mg/L (range, 2–15 mg/L) in responders (patients with >50% seizure reduction), compared with 16 mg/L (range, 8–19 mg/L) in patients with adverse effects. Fröscher et al. (2002) reported a median concentration of 3.6 mg/L (range, 1.3–7.1 mg/L) among responders and a mean concentration of 14 mg/L in patients with side effects. In the serum concentration range of 5–13 mg/L, the frequency of lamotrigine concentrations which were accompanied by adverse effects increased only slowly, while there was a steep increase in adverse effects above 13–14 mg/L, suggesting a reference range of 1–13 mg/L. Hirsch et al. (2004) reported a correlation between concentrations and tolerability, independent of the use of other AEDs. Adverse effects requiring a dose change were uncommon with lamotrigine concentrations below 10 mg/L, suggesting an initial reference range of 1.5–10 mg/L, though concentrations up to 20 mg/L were often tolerated with additional efficacy in refractory patients. In most studies, however, there is a considerable overlap in serum concentrations between responders and nonresponders or between patients with or without adverse effects (Kilpatrick et al., 1996; Bartoli et al., 1997; Perucca, 2000; Tomson & Johannessen, 2000).

Several characteristics of lamotrigine suggest that its effective use may be facilitated by application of TDM. These include a large interindividual variation in dose versus serum concentration relationship, the possibility of marked changes in serum concentrations due to conditions such as pregnancy and drug interactions, and a major role of pharmacokinetic variability on lamotrigine dosage requirements (May et al., 1996a). Overall, in patients treated with therapeutic doses, serum lamotrigine concentrations mostly in the order of 2.5–15 mg/L have been reported.

Analytical methods

Many methods have been described for the assay of lamotrigine, which are based primarily on HPLC with UV detection (Fraser et al., 1995; George et al., 1995; Forssblad et al., 1996; Lensmeyer et al., 1997; Croci et al., 2001). A homogeneous turbidimetric immunoassay especially developed for TDM has recently been described (Wall et al., 2006).

Levetiracetam

Pharmacokinetics

Levetiracetam is rapidly (T_{max}, 1 h) and almost completely absorbed from the gastrointestinal tract (Patsalos, 2000). Although food has no effect on the extent of absorption, the rate of absorption is slowed in the presence of food. Administration of a crushed levetiracetam tablet together with 120 mL of an enteral nutrition formula

(Sustacal) has been associated with a mean 27% decrease in peak levetiracetam concentration, but the effect was not statistically significant (Fay et al., 2005). It is not bound to serum proteins and its Vd is 0.5–0.7 L/kg. Levetiracetam shows linear pharmacokinetics. Its major route of elimination is renal, with approximately 66% of a dose eliminated unchanged and 27% as inactive metabolites (Patsalos, 2004a). The major metabolic route is hydrolysis in blood and various tissues to LO57 (approximately 24% of the dose) and other minor inactive metabolites (Patsalos et al., 2006).

Renal function determines the rate of elimination of levetiracetam. The half-life is 6–8 h in healthy adults, 16–18 h in neonates at birth, 5–7 h in children aged 6–12 years and 10–11 h in the elderly (Patsalos, 2004b; Johannessen et al., 2005; Allegaert et al., 2006; Glauser et al., 2007). However, the apparent clearance is 30–40% higher in children than in adults (Pellock et al., 2001). In persons over 65 years of age, apparent clearance is 0.93 L/kg/day compared to 1.19 L/kg/day for those aged 18–64 years (Leppik et al., 2003). A recent report suggests a significant 60% decrease in serum levetiracetam concentrations in pregnancy (Tomson et al., 2007b).

Effect of other drugs on levetiracetam concentrations

Because levetiracetam does not undergo oxidative metabolism in the liver and is not protein bound, it is not associated with any major pharmacokinetic interactions (Patsalos, 2005). Enzyme-inducing AEDs, however, can moderately decrease serum levetiracetam concentrations (Perucca et al., 2003; Contin et al., 2004; Hirsch et al., 2007).

Drug concentrations and clinical effects

Serum concentrations of levetiracetam associated with the highest doses used were evaluated in 470 patients treated in an epilepsy specialty clinic. For persons $\leq$18 years of age, the mean highest dose was 1993 mg/day (32.8 mg/kg/day) with a mean concentration of 26.2 $\pm$ 15 mg/L. For the 19–64 age group, the mean highest dose was 2611 mg/day (35.3 mg/kg/day) with a mean concentration of 29.6 $\pm$ 17 mg/L. For the $\geq$65 years age group, the mean highest dose was 1765 mg/day (23.0 mg/kg/day) with a mean concentration of 24.7 $\pm$ 16.9 mg/L. Thus, the reference range in these patients appeared to be in the order of 12 to 46 mg/L (70–270 μmol/L; Leppik et al., 2002).

The role of TDM for levetiracetam has not yet been established. Nevertheless, its use in ascertaining compliance and managing patients that are overdosed would be helpful. Because levetiracetam 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 levetiracetam measurements should be drawn before the morning dose. Because levetiracetam can undergo in vitro hydrolysis in whole blood, it is important to separate whole blood from serum as soon as possible so as to avoid levetiracetam hydrolysis that would result in spuriously lower concentrations being measured (Patsalos et al., 2006).

Analytical methods

Numerous chromatographic methods for the quantitation of levetiracetam in serum have been described. These include HPLC with UV detection and GC with various detection systems (Vermeij & Edelbroeck, 1994; Ratnaraj et al., 1996; Isoherranen et al., 2003; Ivanova et al., 2003; Shihabi et al., 2003; Pucci et al., 2004).

Oxcarbazepine

Pharmacokinetics

Following oral administration, oxcarbazepine is rapidly and almost completely absorbed (May et al., 2003). Metabolism is via presystemic 10-keto reduction to the two enantiomers of a monohydroxy derivative (MHD), which are equipotent in terms of anticonvulsant activity and are found in serum at concentrations much higher than those of the parent drug (Schultz et al., 1986; Lloyd et al., 1994). MHD is 40% protein bound with a Vd of 0.75 L/kg. T_{max} for MHD serum concentrations is 3–6 h. Oxcarbazepine shows linear pharmacokinetics. Because the conversion of oxcarbazepine to MHD is stereoselective, the concentrations of the S-enantiomer are much higher than those of the R-enantiomer (Volosov et al., 1999; Wellington & Goa, 2001). The half-life of both enantiomers is 7–12 h, and their elimination occurs primarily by glucuronidation. In children aged 2–6 years, a higher dose/kg body weight of oxcarbazepine is required compared with older children and adults to obtain comparable serum MHD concentrations (Battino et al., 1995b). The clearance of oxcarbazepine and MHD is reduced in patients with impaired renal function (Rouan et al., 1994), and MHD clearance is reduced by 25–35% in elderly patients compared with nonelderly adults (Perucca, 2006). Preliminary data suggest a pronounced increase in oxcarbazepine and MHD clearance in pregnancy (Christensen et al., 2006; Mazzucchelli et al., 2006).

Effect of other drugs on oxcarbazepine concentrations

Enzyme-inducing AEDs enhance the metabolism of MHD and lower its serum concentrations (McKee et al., 1994; May et al., 2003). Valproic acid displaces MHD from its serum protein binding sites by 11% (May et al., 1996b). Verapamil can decrease serum MHD concentrations by 20% (Krämer et al., 1991) whilst viloxazine increases MHD concentrations by 11% (Pisani et al., 1994).

Drug concentrations and clinical effects

A retrospective analysis of data from 947 patients treated with oxcarbazepine revealed a mean serum MHD concentration of 5 mg/L (20 μmol/L), with a range of 3–40 mg/L (Friis et al., 1993), but the relation to efficacy and toxicity was not determined. A study of 19

seizure-free adults treated with oxcarbazepine in combination with other AEDs reported mean serum MHD concentrations of 16 mg/L (range, 3–32 mg/L). However, this concentration range was similar to that achieved in patients who did not respond to oxcarbazepine (van Parys & Meinardi, 1994; Borusiak et al., 1998). Adverse effects were more frequent at serum concentrations of 35–40 mg/L (Borusiak et al., 1998). Striano et al. (2006) found that adverse effects were particularly likely to occur at serum MHD concentrations above 30 mg/L. In many patients adverse effects occurred intermittently in relation to fluctuations in serum MHD. Monitoring MHD concentrations could therefore help in the management of patients on high-dose oxcarbazepine therapy. Overall, in most patients treated with therapeutic doses of oxcarbazepine, serum concentrations of MHD are in the order of 3–35 mg/L.

Analytical methods

There are numerous HPLC (Elyas et al., 1990; Rouan et al., 1995; Levert et al., 2002) and GC (Von Unruh & Paar, 1985) methods for the measurement of MHD in serum. More recently, enantioselective HPLC techniques have become available, but their use is primarily for research purposes (Flesch et al., 1992: Volosov et al., 2000; Mazzucchelli et al., 2007).

Phenobarbital

Pharmacokinetics

In adults, phenobarbital is rapidly (mean T_{max}, 1.4 h, range 0.5–4 h) and completely absorbed from the gastrointestinal tract, with a bioavailability of 95–100% (Viswanathan et al., 1978; Nelson et al., 1982; Wilenski et al., 1982). In contrast, newborns receiving oral phenobarbital exhibit delayed and incomplete absorption (T_{max} 1.5–6 h) (Jalling, 1974). In adults, the Vd is 0.54–0.73 L/kg and protein binding is 50–60% (Nelson et al., 1982; Wilenski et al., 1982). Older infants and children have similar Vd values (0.57–0.70 L/kg) (Jalling, 1974; Heimann & Gladtke, 1977). However, neonates and young infants have a higher Vd (0.71–1.17 L/kg) and lower protein binding (neonates 36–43%; Jalling, 1975; Painter et al., 1977, 1981; Fischer et al., 1981). Serum phenobarbital concentrations increase linearly with dose.

Approximately 25% of a phenobarbital dose is excreted unchanged, with considerable variability between subjects (Whyte & Dekaban, 1977; Bernus et al., 1994a); the remainder is metabolized partly by oxidation via CYP2C9 and to a lesser extent via CYP2C19 and CYP2E1 (Glauser, 2002), and partly by N-glucosidation (Tang et al., 1984). There is a significant age-dependent variation in phenobarbital half-life (Battino et al., 1995a; Perucca, 2006). Rapid changes in half-life are noted between the first 10 postnatal days (114.2 ± 40.3 h) through days 11–30 (73.2 ± 24.2 h) and continuing from days 31 to 70 (41.2 ± 13.9 h) (Alonso Gonzalez et al., 1993). Little change is noted through childhood (37 h) but the half-life increases as patients reach adulthood (73–139 h; Garrettson & Dayton, 1970; Wilenski et al., 1982). Phenobarbital clearance is higher in children (5.3–14.1 mL/kg/hr) compared to adults (2.1–4.9 mL/kg/h; Nelson et al., 1982; Wilensky et al., 1982; Browne et al., 1985; Pullar et al., 1991).

Effect of other drugs on phenobarbital concentrations

The metabolism of phenobarbital is inhibited by felbamate, oxcarbazepine, phenytoin, stiripentol, and valproic acid (Levy et al., 1984; Patsalos & Perucca, 2003a) so that serum phenobarbital concentrations are increased by these medications. Other drugs that inhibit phenobarbital metabolism and increase serum phenobarbital concentrations include dextropropoxyphene, chloramphenicol, and dicoumarol (Patsalos, 2005).

Drug concentrations and clinical effects

There are no rigorous trial data that delineate the relationship between serum phenobarbital concentration and either seizure reduction or toxicity (Feldman & Pippenger, 1976). The usually quoted reference range of 10–40 mg/L (43 and 172 μmol/L) is predominantly based on data obtained from adults. One study reported that serum phenobarbital concentrations required to prevent simple and complex partial seizures (with or without secondary generalization) were higher than those necessary to prevent generalized tonic–clonic seizures only (38 ± 6 mg/L vs. 18 ± 10 mg/L, respectively; Schmidt et al., 1986). Adverse effects, such as drowsiness become more frequent as serum phenobarbital concentrations increase from 30 to 50 mg/L (Livingstone et al., 1975).

Due to the variability in phenobarbital pharmacokinetics, measuring its concentration can be useful for individualizing therapy. Since over time patients develop tolerance to the sedative effects of phenobarbital, previously intolerable serum concentrations may become tolerable (Perucca & Richens, 1981). Therefore, the upper limit of the reference range varies considerably, both between and within patients. Because of the long half-life of the drug, little variability is noted in serum phenobarbital concentrations during a dosing interval at steady state, blood samples can be obtained at any time of the day.

Analytical methods

Commercial reagent-based techniques (e.g., FPIA, EMIT, and radioimmunoassay [RIA]) (Oeltgen et al., 1984) represent the primary methodology for the analysis of phenobarbital in serum. However, there are also many GC and HPLC techniques available, which can measure simultaneously other AEDs (Romanyshyn et al., 1994; Queiroz et al., 2002).

Phenytoin

Pharmacokinetics

Phenytoin pharmacokinetics are complex due to variable absorption (partly formulation-dependent), high-protein binding, saturable metabolism, and drug interactions (Richens, 1979). The rate of absorption from capsules varies depending on whether the product is labeled as immediate release (T_{max} = 1–6 h) or extended release (T_{max} = 4–12 h) (Sawchuk et al., 1982). T_{max} may be further extended when larger doses are taken, or under steady-state conditions (Jung et al., 1980). Phenytoin is 90% bound to serum albumin, and the degree of binding decreases in the presence of hypoalbuminemia and in disease states, such as renal and hepatic insufficiency, which are associated with accumulation of endogenous compounds displacing phenytoin from plasma protein-binding sites (Perucca, 1980).

The Vd of phenytoin is 0.7 ± 0.1 L/kg. Less than 5% of a phenytoin dose is excreted unchanged. The drug is extensively para-hydroxylated, primarily by CYP2C9 and CYP2C19, to an inactive metabolite (Glazko et al., 1969; Bajpai et al., 1996). Elimination follows nonlinear Michaelis-Menten pharmacokinetics, i.e., the rate of metabolism decreases with increasing dosages. Therefore, increments in dosage can results in disproportionately large increments in serum concentration (Richens, 1979). The population estimates of V_{max} and K_m are 5–9 mg/kg/day and 5–6 mg/L, respectively (Bauer & Blouin, 1982; Wilder et al., 2001). V_{max} values are higher in young children, whereas older patients (≥60 years) have mean V_{max} values that are 20% smaller than younger adults (Chiba et al., 1980; Bauer & Blouin, 1982). The half-life of phenytoin is dependent on its serum concentration. In adults and elderly individuals with phenytoin concentrations >10 mg/L, the half-life is 30–100 h, while in young children or in patients with head trauma the half-life is often <10 h (Cloyd et al., 2001).

Effect of other drugs on phenytoin concentrations

A number of interactions involving phenytoin are clinically significant, as many drugs affect serum phenytoin concentrations (Patsalos & Perucca, 2003a, 2003b). Concurrent administration of aluminium-magnesium or calcium containing antacids (≥15 mls) and selected nasogastric or enteral tube feedings reduce the absorption of phenytoin (Carter et al., 1981; Bauer, 1982). Valproic acid, tolbutamide, aspirin, and some other nonsteroidal antiinflammatory drugs displace phenytoin from albumin binding sites (Wesseling & Mols-Thurkow, 1975; Patsalos & Lascelles, 1977; Fraser et al., 1980; Monks & Richens, 1980; Dasgupta & Timmerman, 1996) resulting in a decrease in total drug concentrations, while the unbound concentration remains unchanged or may even increase when the displacing drug also inhibits phenytoin metabolism. Valproic acid, for example, is among the drugs that can inhibit the biotransformation of phenytoin resulting in an increase in serum unbound phenytoin concentration (Lai & Huang, 1993). The net effect of valproic acid on total and unbound phenytoin concentrations depends on the extent of displacement and inhibition of metabolism. These serum protein-binding interactions are important for TDM, because they alter the relationship between total serum phenytoin concentration and clinical response.

Enzyme-inducing AEDs such as carbamazepine and phenobarbital produce variable and unpredictable effects on phenytoin concentration (Patsalos & Perucca, 2003a, 2003b). On the other hand, felbamate, oxcarbazepine (>1200 mg/day), topiramate, stiripentol, and valproic acid can increase serum phenytoin concentrations (Levy et al., 1984; Patsalos & Perucca, 2003a), the effect being more prominent at phenytoin concentrations >15 μg/mL. Vigabatrin has been reported to cause a 20–30% reduction in serum phenytoin concentrations via an unknown mechanism (Gatti et al., 1993).

Many non-AEDs such as propoxyphene, fluoxetine, fluvoxamine, trazodone, viloxazine, fluconazole, isoniazid, tamoxifen, cimetidine (high doses), omeprazole, and amiodarone increase serum phenytoin concentrations due to inhibition of CYP2C9 or CYP2C19 (Ragueneau-Majlessi et al., 2002; Patsalos, 2005). Rifampin and chronic ethanol intake, conversely, may lower serum phenytoin concentrations through enzyme induction (Sandor et al., 1981; Kay et al., 1985).

Drug concentrations and clinical effects

Interpretation of many studies that described phenytoin concentration-response relationships since the introduction of phenytoin is complicated by the use of different analytical methods ranging from spectrophotometric techniques 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 phenytoin concentrations associated with seizure control and toxicity. The evidence supporting a reference range of 10–20 mg/L (40–79 μmol/L) oversimplifies the actual situation, and more information about this is provided in the section above on the historical perspective on reference ranges of AEDs. Some patients only require low phenytoin concentrations to attain complete seizure control, while others obtain benefit from concentrations greater than 20 mg/L without adverse effects. This variability may be due to the seizure type, the severity of the underlying disorder, or to genetic abnormalities (Kutt & McDowell, 1968; Mattson et al., 1985; Siddiqui et al., 2003). Lambie et al. (1976) studied the effect of increasing phenytoin concentrations in 20 patients with chronic epilepsy. They observed a reduction in major seizures in 10 of 16 patients when phenytoin concentrations were increased to ≥10 mg/L, while none of the 20 patients had a reduction in minor seizures, including 5 individuals with

phenytoin concentrations between 20 and 30 mg/L. Moreover, there appears to be a concentration-response gradient whereby seizure control improves with higher concentrations, but at the cost of increasing risk of concentration-dependent adverse effects such as ataxia, diplopia, and reduced cognition. Studies have shown that seizure control is usually attained with phenytoin total concentrations ranging from 5 to 30 mg/L (Schmidt & Haenel, 1984; Schmidt et al., 1986). These authors noted that patients requiring serum phenytoin concentrations greater than 15 mg/L more often had simple or complex partial seizures and a greater number of seizures in the year prior to therapy. For most patients, however, seizure control is achieved at concentrations in the range of 10–20 mg/L. In the elderly, the range appears to be shifted downward, which may be due to increased sensitivity to phenytoin, altered protein binding, or both (Ramsay et al., 1994).

The unpredictable relationship between dose and phenytoin concentration, its narrow therapeutic index, and the presence of numerous clinically significant drug interactions support the need to individualize and maintain therapy using TDM. Because of the relatively long half-life of the drug, little variability is noted in serum phenytoin concentrations during a dosing interval at steady state, blood samples can be obtained at any time of the day, particularly in patients receiving extended-release formulations. However, standardization of sampling time is recommended in patients expected to have comparatively shorter half-lives, such as children and patients with serum phenytoin concentrations in the low range.

Analytical methods

Commercial reagent-based techniques represent the primary methodology for the analysis of phenytoin in serum (e.g., FPIA and EMIT). However, there are also many GC and HPLC techniques available, which can simultaneously measure other AEDs (Romanyshyn et al., 1994; Bhatti et al., 1998; Queiroz et al., 2002; Lancas et al., 2003).

Pregabalin

Pharmacokinetics

After oral ingestion, pregabalin is rapidly (T_{max}, 1.3 h) absorbed, with a bioavailability of >90%, which is independent of dose (Busch et al., 1998). Pregabalin is not protein bound and its Vd is 0.4 L/kg (Dworkin et al., 2003). Within the clinically used dose range, serum pregabalin concentrations are linearly related to dosage (Bockbrader et al., 2000). Pregabalin is not metabolized and is primarily (98%) excreted unchanged in urine with a clearance similar to the glomerular filtration rate (Corrigan et al., 2001). The elimination half-life of pregabalin in serum is 4.6–6.8 h (Bockbrader et al., 2000). Patients with impaired renal function show a reduced drug clearance and require a reduction in dosage (Randinitis et al., 2003).

Effect of other drugs on pregabalin concentrations

Because pregabalin is neither bound to serum proteins nor metabolized, pharmacokinetic interactions with concurrently administered drugs are not expected. Indeed although none have been reported to date (Ben-Menachem, 2004) a recent study has suggested that enzyme-inducing AEDs (e.g., carbamazepine) can moderately decrease pregabalin serum concentrations by ~20–30% (May et al., 2007).

Drug concentrations and clinical effects

There is sparse information on the relationship between serum pregabalin concentrations and efficacy or toxicity. Arroyo et al. (2004) reported on steady-state pregabalin concentration measurements in 300 samples, collected at random times with respect to time elapsed from last dose, from patients administered 150 mg/day and 600 mg/day and found a range of 0.29–2.84 mg/L (1.8–17.8 μmol/L) and 0.87–14.2 mg/L (5.4–89.2 μmol/L) respectively. Berry and Millington (2005) investigated a group of patients receiving 600 mg/day pregabalin, in whom blood sampling was set at 8 ± 0.5 h after the last dose, and found a concentration range of 2.8 to 8.3 mg/L.

The role of TDM for pregabalin has not yet been established and a reference range for the drug has yet to be identified. Nevertheless, its use in ascertaining compliance and managing patients that are overdosed would be helpful.

Analytical methods

There are only two published methods for the determination of pregabalin in serum, one involves HPLC analysis with fluorescence detection (Vermeij & Edelbroek, 2004) and the other HPLC analysis by UV detection (Berry & Milligton, 2005).

Primidone

Pharmacokinetics

Primidone is rapidly (T_{max}, 2.7–4.2 h) absorbed after oral ingestion (Booker et al., 1970; Gallagher et al., 1972). Differences in formulation, however, may affect the rate and extent of absorption (Wylie et al., 1987). Although absolute bioavailability determinations have not been undertaken, a study of ^{14}C-labeled primidone in patients indicated that almost 100% is absorbed (Zavadil & Gallagher, 1976). Serum protein binding is negligible (~10%). Primidone shows linear pharmacokinetics and is eliminated partly in unchanged form in urine (15–65% of the dose) and partly converted to phenylethylmalonamide (16–65%) and phenobarbital (1–8%; Zavadil & Gallager, 1976; Kauffman et al., 1977). The half-life of primidone is highly variable because of the ability of its major metabolite, phenobarbital, to induce hepatic enzymes, and may range from 3 to 22 h (Cloyd et al., 1981). Furthermore, because of the long half-life of phenobarbital, concentrations of the latter are usually much higher than those

of primidone and phenylethylmalonamide during chronic therapy (Cloyd et al., 1981).

Effect of other drugs on primidone concentrations

Carbamazepine and phenytoin enhance the metabolism of primidone and lower serum primidone concentrations while simultaneously increasing serum phenobarbital and phenylethylmalonamide concentrations. In patients receiving primidone monotherapy, the phenobarbital:primidone ratio has been found to average 1.45 ± 0.10 but in patients comedicated with phenytoin the ratio was 3.82 ± 2.4 (Battino et al., 1983). In children receiving primidone, clobazam may decrease the clearance of primidone and increase serum primidone concentrations (Theis et al., 1997). Isoniazid (Sutton & Kupferberg, 1975) and nicotimamide (Bourgeois et al., 1982) inhibit the metabolism of primidone and increase serum primidone concentrations. Drugs that inhibit phenobarbital metabolism (see Phenobarbital section above), such as valproic acid, will increase the serum concentration of phenobarbital derived metabolically from primidone.

Drug concentrations and clinical effects

Since primidone is metabolized to phenobarbital, it is difficult to separate the effects of primidone from those of phenobarbital, and often serum phenobarbital concentrations are used as a guide to therapy. The reference range for the serum concentrations of primidone per se was reported to be 5–10 mg/L (23–46 μmol/L), based on a study of over 100 patients with epilepsy in one clinic (Booker et al., 1970). Because phenobarbital is the major active substance during chronic therapy, the usefulness of primidone measurements alone is limited. However, measuring both primidone and phenobarbital to obtain a ratio may be helpful in detecting recent noncompliance, as in this situation the phenobarbital:primidone ratio may be reversed, with the concentrations of primidone being higher than those of phenobarbital.

Analytical methods

Commercial reagent-based immunoassay techniques (e.g., FPIA and EMIT) represent the primary methodology for the analysis of primidone in serum. However, there are also many GC and HPLC techniques that allow the simultaneous measurement of other AEDs, including the metabolite phenobarbital (Queiroz et al., 2002; Lancas et al., 2003).

Tiagabine

Pharmacokinetics

After oral ingestion, tiagabine is rapidly absorbed (T_{max}, 0.5–2 h) with a bioavailability of 90–95% (Gustavson & Mengel, 1995). Although food has no effect on the extent of absorption, the rate of absorption is considerably slower in the presence of food. Tiagabine is highly protein bound (96%) and has a Vd of about 1.4 L/kg. Tiagabine shows linear pharmacokinetics and undergoes extensive oxidative metabolism with <1% of a tiagabine dose excreted unchanged in urine (Gustavson & Mengel, 1995; Uthman et al., 1998). The half-life of tiagabine is 5–9 h in patients not receiving enzyme inducers (So et al., 1995; Wang & Patsalos, 2002), and 2–4 h in patients comedicated with enzyme-inducing AEDs (So et al., 1995). Children have higher clearance values of tiagabine compared with adults (Gustavson et al., 1997). The metabolism of tiagabine is slower in patients with hepatic dysfunction, the half-life in these patients being 12–16 h (Lau et al., 1997).

Effect of other drugs on tiagabine concentrations

Carbamazepine, phenobarbital, phenytoin, and primidone enhance the metabolism of tiagabine so that its half-life is reduced to 2–4 h, and serum tiagabine concentrations are markedly lowered (So et al., 1997). In vitro data suggest that valproic acid can displace tiagabine from its serum protein binding sites and increases unbound tiagabine concentrations (Patsalos et al., 2002).

Drug concentrations and clinical effects

The relationship between serum tiagabine concentrations and efficacy or toxicity has been little investigated, partly due to the difficulties in measuring the low serum tiagabine concentrations that are typically encountered clinically. In one double-blind, placebo-controlled trial where clinical observations were made at three mean tiagabine trough concentrations (10, 22 and 33 ng/mL), corresponding to daily dosages of 16, 32 and 56 mg/day, respectively, the reduction in the frequency of complex partial seizures was concentration-dependent (Uthman et al., 1998). Furthermore at 1 h postdosing, mean tiagabine concentrations were 38, 65 and 140 ng/mL, respectively. Overall, in patients treated with therapeutic doses of tiagabine, serum tiagabine concentrations are in the order of 20–200 ng/mL (53–532 nmol/L) and this represents the reference range of the drug (Uthman et al., 1998).

The role of TDM for tiagabine has not yet been established. Nevertheless, its use in ascertaining compliance and managing patients that are overdosed would be helpful, provided that utmost care is placed in ensuring the reliability of the analytical assay (Wilson et al., 2003). If monitoring were to be undertaken, sampling time in relation to dose is critical because large interdose fluctuations in concentrations occur consequent to the short half-life of the drug. Ideally, samples for tiagabine measurements should be drawn before the morning dose.

Analytical methods

Because serum tiagabine concentrations are in the nanomolar range, analytical techniques are not straightforward and interlaboratory differences in analytical reliability is of great concern (Wilson et al., 2003). Three chromatographic methods have been described, one requiring EC detection (Gustavson & Chu, 1992), the second UV

detection (Cleton et al., 1999) and the third LC/MS (Chollet et al., 1999).

Topiramate

Pharmacokinetics

Following oral ingestion, the absorption of topiramate is rapid (T_{max}, 2–4 h), with a bioavailability of 81–95% (Easterling et al., 1988). While food coingestion delays topiramate absorption by about 2 h, the maximum serum concentrations attained are unaffected (Doose et al., 1996). The Vd of topiramate is 0.6–1 L/kg. Topiramate is only 15% bound to serum proteins, but it does have a high affinity/low capacity binding site on erythrocytes (Doose & Streeter, 2002). There is a linear relationship between topiramate dose and serum concentration. Approximately 50% of the dose is metabolized, with a serum half-life of 20–30 h, but in patients coprescribed enzyme-inducing AEDs, the hepatic metabolism of topiramate becomes more important causing a shortening of the half-life to about 12 h, an increase in clearance, and a corresponding decrease in serum topiramate concentrations by approximately 50% (Sachdeo et al., 1996; Britzi et al., 2005). Topiramate is eliminated at a faster rate in children, the magnitude of the increase in clearance compared with adults ranges in different studies from 25% to 170% (Rosenfeld et al., 1999; Perucca, 2006).

Effect of other drugs on topiramate concentrations

Enzyme-inducing AEDs reduce serum topiramate concentrations by approximately 50% (Britzi et al., 2005, Mimrod et al., 2005), while valproic acid lowers topiramate concentrations by 10–15% (Rosenfeld et al., 1997). Topiramate clearance can be decreased by propranolol, amitriptyline, lithium, and sumatriptan resulting in slightly increased serum topiramate concentrations (Patsalos, 2005).

Drug concentrations and clinical effects

In one of the earliest reports, Reife et al. (1995) measured serum concentrations in three double-blind placebo-controlled add-on trials, and the results suggested that seizure control was improved at serum topiramate concentrations in the narrow range of 3.5–5 mg/L (10–15 μmol/L). Another study comparing three serum concentration ranges (<1.7 mg/L; 1.7–10 mg/L; >10 mg/L), indicated that median seizure-free duration was significantly correlated with topiramate concentrations (Twyman et al., 1999). Penovich et al. (1997) showed a trend for higher serum topiramate concentrations (>10 mg/L) in patients with improvement compared with those without seizure reduction. Lhatoo et al. (2000), on the other hand, reported mean topiramate serum concentrations of 7 mg/L in responders and 9 mg/L in seizure-free patients, compared with 6 mg/L in patients in whom topiramate was stopped because of adverse effects, with a wide variation in the relationship between serum drug concentration and therapeutic or toxic effects.

In another study, a wide range of doses and serum concentrations produced a favorable response in 70% of 170 patients with drug refractory (mostly partial) epilepsy, with 23% becoming seizure-free (Stephen et al., 2000). Serum topiramate concentrations in this group ranged between 2.4 and 18 mg/L. More recently, the results of a triple-blind, concentration-controlled, parallel-group trial which randomized 65 patients to one of three prespecified serum concentrations (low = 2 mg/L, medium = 10 mg/L and high = 19 mg/L) were reported (Christensen et al., 2003). Patients assigned to the medium serum concentration had the best outcome with regard to seizure reduction, and those in the medium and high groups experienced more adverse events than patients in the low group. The authors concluded that an optimal response is most likely to be achieved at serum concentrations of 2–10 mg/L. May et al. (2002) reported topiramate concentrations in the range of 2.4–8 mg/L in patients receiving topiramate doses of 125–400 mg in addition to other AEDs. Some patients receiving considerably higher doses (up to 2000 mg/day) had topiramate concentrations as high as 27 mg/L but no mention was made as to whether or not these concentrations were well tolerated.

Overall, in most studies published to date, serum topiramate concentrations in the order of 5–20 mg/L have been reported in patients treated with therapeutic doses (Johannessen et al., 2003). Since in recent years there has been a trend toward using dosages lower than those tested in the initial studies, most patients will probably have concentrations in the low to mid portion of that range.

Analytical methods

A commercial reagent-based FPIA technique is available for the measurement of topiramate in plasma or serum (Berry & Patsalos, 2000). Also, various capillary GC methods have been described using flame ionization (FI) (Holland et al., 1988), NP (Riffitts et al., 1999; Tang et al., 2000) and MS (Chen & Carvey, 2001; Contin et al., 2001; Christensen et al., 2002) detection.

Valproic acid

Pharmacokinetics

The bioavailability of valproic acid is almost complete for all formulations. T_{max} values are 1–2 h for conventional tablets and solutions, 3–6 h for enteric-coated tablets and 10–12 h for sustained-release tablets (Perucca, 2002a). In the case of enteric-coated formulations, intake with a meal can delay the onset of absorption for up to several hours (Levy et al., 1980). An intravenous formulation is also available. Food coingestion can delay absorption but not the extent of absorption of valproic acid from some formulations (e.g., enteric-coated) but not others (e.g., gelatine or sustained release; Hamilton et al., 1981; Fischer et al., 1988; Retzow et al., 1997). The Vd of valproic acid is 0.15–0.20 L/kg. Its binding to serum proteins is 90%,

and this decreases with increasing serum concentrations within the clinically occurring concentration range. The unbound fraction of valproic acid increases in late pregnancy, in the elderly and in patients with renal disease, chronic liver disease, and other conditions associated with low albumin concentrations. Valproic acid kinetics deviate from linearity, due to a decrease in serum protein binding with increasing concentrations and, in some cases, a more than dose-proportional increase in unbound drug concentration (Bowdle et al., 1980). The half-life of the drug is about 11–20 h, but shorter values (6–12 h) are observed in patients receiving enzyme-inducing comedication (Johannessen, 1990; Perucca, 2005). Valproic acid is almost completely metabolized, mainly in the liver by β-oxidation (30%), glucuronidation (40%), and other pathways (Johannessen, 1990; Perucca, 2005). Due to large interindividual differences in rate of drug metabolism, there is a poor correlation between valproic acid dose and serum concentration, especially in patients who are comedicated with enzyme-inducing AEDs. Children require higher mg/kg doses to achieve serum valproic concentrations comparable with those observed in adults (Cloyd et al., 1993). For any given dose, elderly patients have total serum valproic acid concentrations comparable with those observed in nonelderly adults, but unbound drug concentrations are increased in the elderly (Perucca, 2006).

Effect of other drugs on valproic acid concentrations

Serum valproic acid concentrations are decreased in patients on enzyme-inducing comedication, due to enhancement of metabolism (Johannessen, 1990; Perucca, 2005). Felbamate (Glue et al., 1997), clobazam (Theis et al., 1997) and stiripentol (Levy et al., 1984) may increase valproic acid concentrations, while ethosuximide (Pisani et al., 1984), topiramate (Rosenfeld et al., 1997) and methsuximide (Besag et al., 2001) can lower valproic acid concentrations. Other drugs that can lower serum valproic acid concentrations include rifampicin, cisplatin, methotrexate, and carbapenem antibiotics (Patsalos & Perucca, 2003b). Preliminary data suggest that hormonal contraceptives may also increase the clearance of valproic acid and lower serum valproic acid concentrations by about 20% (Galimberti et al., 2006). By contrast, drugs that may increase serum valproic acid concentration include isoniazid and sertraline (Patsalos & Perucca, 2003b).

Drug concentrations and clinical effects

Overall, most patients are optimally treated with serum valproic acid concentrations of 50–100 mg/L (346–693 μmol/L; Gram et al., 1979; Henriksen & Johannessen, 1982; Sundqvist et al., 1997; Neels et al., 2004).

Three different serum concentrations of valproic acid were compared in a triple-blind, multiple crossover trial of 13 patients with mixed seizure types receiving valproic acid in combination with other AEDs (Gram et al., 1979). A lower limit of 42–50 mg/L was associated with a better seizure control among these patients. In a prospective open study of 54 previously untreated adults, concentrations above 70 mg/L were associated with a better control of partial seizures (Turnbull et al., 1985). Patients with generalized tonic–clonic seizures only became seizure-free at concentrations above 47 mg/L. In a double-blind, crossover, dose-effect monotherapy study in 16 patients with juvenile myoclonic epilepsy, the mean serum concentration for those rendered seizure-free was 80 mg/L and the lowest concentration in a seizure-free patient was 57 mg/L (Sundqvist et al., 1997). In a long-term observational study of 100 children treated with valproic acid for different seizure disorders, optimal clinical effects were usually seen at serum concentrations between 43 and 86 mgl/L (Henriksen & Johannessen, 1982).

The unpredictable relationship between dose and valproic acid concentration support the need to individualize and maintain therapy using TDM. Because valproic acid has a relatively short half-life, sampling time in relation to dose ingestion is important for interpretation of the drug concentration. Ideally, samples for valproic acid measurements should be drawn before the morning dose.

Analytical methods

Commercial reagent-based immunoassay techniques represent the primary methodology for the analysis of valproic acid in serum (e.g., FPIA and EMIT). There are also many GC and HPLC techniques available (Pokrajac et al., 1992; Lin et al., 2004; Amini et al., 2006).

Vigabatrin

Pharmacokinetics

Vigabatrin is commercially supplied as a racemic mixture of two enantiomers, the S(+)-enantiomer, which is pharmacologically active, and the R(−)-enantiomer, which is inactive and does not undergo in vivo chiral inversion (Haegele & Schechter, 1986; Schechter, 1989). Vigabatrin is rapidly absorbed from the gastrointestinal tract (T_{max}, 1–2 h), with a bioavailability of 60–80% (Durham et al., 1993; Patsalos & Duncan, 1995). Food coingestion does not affect either the rate or the amount of vigabatrin absorbed (Frisk-Holmberg et al., 1989). It is not protein bound and its Vd is 0.8 L/kg. Within the clinically used dose range, serum vigabatrin concentrations are linearly related to dosage. Vigabatrin is not metabolized and is primarily excreted unchanged in urine (Rey et al., 1990). Patients with impaired renal function show a reduced drug clearance and require a reduction in dosage. The half-life of vigabatrin is 5–8 h (Rey et al., 1992). Because children have a higher vigabatrin clearance compared with adults, they require higher mg/kg doses to attain comparable serum concentrations (Armijo et al., 1997).

Effect of other AEDs on vigabatrin concentrations

Because vigabatrin is neither bound to serum proteins nor metabolized, interactions affecting the

pharmacokinetics of vigabatrin are not expected. Indeed none have been reported to date.

Drug concentrations and clinical effects

Since vigabatrin acts by irreversibly inhibiting GABA-transaminase, the enzyme responsible for the metabolism of GABA, there is a clear dissociation between its concentration profile in serum and the duration of pharmacological effect, which is related to the regeneration time of the enzyme (Rey et al., 1992). Whether the measurement of serum vigabatrin 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 vigabatrin (Patsalos, 1990b), although measurement of serum vigabatrin concentrations may be useful as a check on recent compliance. At doses between 1000 and 3000 mg per day, the expected trough serum concentrations are in the range of 0.8–36 mg/L (6–279 μmol/L) (Gram et al., 1983; Patsalos, 1990b).

Analytical methods

There are numerous HPLC methods for the determination of vigabatrin in serum, all of which entail fluorescent detection (Grove et al., 1984; Wad et al., 1998 Ratnaraj & Patsalos, 1998; George et al., 2000; Chollet et al., 2000). Various enantioselective chromatographic techniques are also available, which are used primarily for research purposes (Schramm et al., 1993; Vermeij & Edelbroek, 1998; Zhao et al., 2006).

Zonisamide

Pharmacokinetics

Following oral ingestion, zonisamide is rapidly (T_{max}, 2–5 h) absorbed (Taylor et al., 1986). Food coingestion does not affect the absorption of zonisamide. Serum protein binding is 40–60% and its Vd is 1.5 L/kg. Zonisamide shows high affinity, but low-capacity binding to erythrocytes, which can be attributed to high-affinity binding to carbonic anhydrase and other red cell protein components (Matsumoto et al., 1989). Zonisamide pharmacokinetics do not deviate substantially from linearity at daily doses up to 10–15 mg/kg. The drug is extensively metabolized by oxidation, acetylation, and other pathways (Ito et al., 1982; Buchanan et al., 1996). The half-life of zonisamide is 50–70 h in patients on monotherapy, and 25–35 h in patients comedicated with enzyme-inducing AEDs (Perucca & Bialer, 1996). Compared with adults, children require higher mg/kg doses to attain comparable serum concentrations (Perucca, 2006).

Effect of other AEDs on zonisamide concentrations

Enzyme-inducing AEDs such as carbamazepine, phenytoin, phenobarbital, and primidone enhance the metabolism of zonisamide and reduce its concentration in serum (Perucca & Bialer, 1996; Patsalos, 2005).

Drug concentrations and clinical response

Evidence for a relationship between serum zonisamide concentrations and clinical effect was initially derived from work in animals. Masuda et al. (1979) demonstrated in five animal species that the effects of the drug correlate more closely with serum concentrations than with dose. Furthermore, a critical concentration was identified in each individual animal at which either anticonvulsant or neurotoxic effects occurred, and these concentrations were relatively constant between different species. The authors concluded that in the animals tested, zonisamide was effective at serum concentrations above 10 mg/L (47 μmol/L) and toxicity was likely to occur at concentrations above 70 mg/L (Masuda et al., 1979).

In patients with epilepsy a 50% reduction in seizures was observed at serum concentrations that ranged from 7 to 40 mg/L (Mimaki et al., 1992). However, for reasons discussed in other sections of this document, considerable overlap of serum zonisamide concentrations is expected between seizure-free patients and nonresponders, and between patients with and without adverse effects (Mimaki, 1998). Three reports indicate an increased incidence of adverse effects at serum concentrations in excess of 30 mg/L (Wilensky et al., 1985; Berent et al., 1987; Miura et al., 1993), and there is one report of a mixed drug overdose with coma in a patient with a zonisamide serum concentration of 100 mg/L (Naito et al., 1988). Based on this evidence a reference range of 10–40 mg/L has been suggested (Mimaki, 1998; Glauser & Pippenger, 2000).

Analytical methods

Several HPLC methods using UV detection have been described for the measurement of zonisamide in serum (Jurgens, 1987; Noguchi et al., 1988; Berry, 1990; Shimoyama et al., 1999). Additional methods include micellar electrokinetic capillary chromatography with diode array detection (Makino et al., 1997) and an enzyme immunoassay method (Kaibe et al., 1990).

When Should Drug Concentrations Be Monitored?

Dose optimization on the initially prescribed treatment

The general approach to optimization of therapy in newly diagnosed patients involves prescription of a single drug. While some AEDs such as phenytoin can be started at therapeutic doses and do not need gradual dose escalation, most require a gradual increase in dosage to minimize toxicity (Perucca et al, 2001). The initial target maintenance dosage is usually set at the lower end of the expected effective dose range, and further dose adjustments can be made if seizures persist or adverse effects occur. However, an argument can be made for targeting initially a desired serum AED concentration rather than a predefined dose. If this approach is used, the target concentration should be

selected depending on the individual characteristics of the patient and associated circumstances. For example, an individual who had a second seizure following a first seizure 1 year earlier may do well with a low concentration, while a patient with a history of a severe head injury and three or more seizures in close succession might need to have a target concentration in the higher range (Schmidt & Haenel, 1984). Measurement of serum concentrations of the initially prescribed AED can be of particular value in the following indications:

1. whenever, for medical or psychosocial reasons, it is imperative to minimize the risk of seizure recurrence. In this situation, an argument can be made for tailoring the initial maintenance dosage to achieve a concentration within the published reference range or close to the upper limit of such a range. The drawback of such a strategy, however, is that some patients may become stabilized at a concentration higher than needed, with the attendant risk of adverse effects (Eadie, 1997);
2. in patients receiving phenytoin therapy, because the dose-dependent pharmacokinetics of this drug make it particularly difficult to predict whether a high or low serum concentration has been achieved on the initially prescribed dose (Richens, 1979);
3. whenever there are uncertainties in the differential diagnosis of signs or symptoms suggestive of concentration-dependent AED toxicity (Eadie, 1997);
4. whenever, irrespective of the dosing strategy used, seizure freedom has been achieved and maintained for a sufficient period of time to be confident that dosage has been optimized. In this situation, measuring the serum AED concentration at a standardized sampling time will allow identification of the "individual therapeutic concentration," which will be valuable to interpret the clinical picture should a change in response occur during further follow-up (Eadie, 1997; Perucca, 2000; Johannessen & Tomson, 2006). When establishing the individual therapeutic concentration, two separate determinations obtained at intervals of months or years will be preferable to a single determination, because they provide an estimate of the variability of the measure;
5. in the presence of any of the additional indications detailed in the sections below.

Uncontrolled seizures or suspected toxicity

In patients who develop breakthrough seizures after a prolonged period of seizure control, management can be facilitated by knowledge of the individual therapeutic concentration. In particular, the finding of a concentration much lower than the individual therapeutic concentration in a sample collected within hours of a breakthrough seizure provides suggestive evidence for suboptimal compliance or for a clinically important change in the pharmacokinetics of the AED (Specht et al., 2003). This information is clearly useful in establishing the cause for the loss in seizure control, and taking the appropriate corrective action. Persistence of seizures on an apparently adequate dosage of an appropriate AED is a clear indication for serum AED concentration monitoring (Eadie, 1997). Measurement of serum drug concentrations in these patients is useful to identify potential causes of therapeutic failure, and to differentiate between poor compliance (typically characterized by highly variable serum concentrations, which increase following supervised drug intake) and low-serum drug concentrations due to poor absorption, fast metabolism, or drug interactions. Moreover, determining what concentrations at any dose have been associated with lack of efficacy (or with toxicity) can be used to characterize the concentration-response profile within each individual patient, which is the premise upon which the use of the "individual therapeutic concentration" concept is built.

In patients in whom toxic symptoms are suspected, serum AED concentrations can aid in confirming a diagnosis of AED toxicity, though clinicians should be aware that relatively low concentrations do not necessarily exclude such a diagnosis. Serum AED concentration monitoring can also be useful in differentiating whether poor seizure control is due to insufficient dosing or rather reflects a paradoxical worsening of seizures due to an excessive drug load (Perucca et al., 1998). The finding of serum AED concentrations below the upper limit of the reference range, however, does not allow the clinician to exclude the possibility of paradoxical intoxication, particularly in patients receiving complex polytherapies (Perucca, 2002b). The measurement of serum AED concentrations as an aid to the diagnosis of suspected toxicity may also be valuable in patients whose status is difficult to assess clinically, such as young children and subjects with mental disability.

In patients with difficult-to-treat epilepsy, determination of serum AED concentrations aids in determining the magnitude of the required dose increment, particularly with drugs showing dose-dependent pharmacokinetics such as phenytoin (Richens, 1979). These patients may also require multiple drug therapy, and monitoring serum AED concentrations is useful in identifying pharmacokinetic drug interactions and in making compensatory dosage adjustments. In polytherapy patients who exhibit signs of overdosage, measuring the concentration of the individual AEDs can aid in determining which drug is more likely to be responsible for the toxicity. Interpretation of AED concentrations in this situation, however, should be cautious because in the presence of polytherapy adverse effects are often encountered at unusually low serum AED concentrations (Shorvon & Reynolds, 1979).

Children

Children are a special population for application of the TDM concept. There are several features that differentiate children from adults with regard to monitoring AED concentrations:

1. the pharmacokinetics of AEDs is markedly influenced by age, especially during infancy and childhood (Hadjiloizou & Bourgeois, 2007). For most AEDs studied in infants and young children, pharmacokinetic characteristics include shorter elimination half-lives and, at times, larger Vd values compared with adults (Pitlick et al., 1978; Dodson & Bourgeois, 1994; Kelley et al., 1997; Perucca, 2006). Because of their higher clearance, infants may require a mg/kg dosage that may be 2–3 times higher than that required to achieve the same drug concentration in an adult. Clearance values decrease gradually throughout childhood, but the precise time course of this process is not well established and is characterized by pronounced interindividual variability (Perucca, 2006). Thus, for any child of any age, dosage requirements are less predictable than in adults and drug concentrations are more likely to be relevant for optimal management (Walson, 1994; Hadjiloizou & Bourgeois, 2007). This issue is particularly complex during the neonatal period. For drugs such as phenobarbital and phenytoin, it has been shown that their clearance is quite low during the first week of life and then rapidly accelerates to reach the high values found in older infants by the fourth or fifth week of life (Pitlick et al., 1978; Bourgeois & Dodson, 1983). In addition, there is a wide interindividual variability of pharmacokinetic parameters. Because of rapidly changing clearance values, it is very difficult to treat newborns with AEDs without monitoring drug concentrations. Steady-state drug concentrations do not practically exist in newborns, because their pharmacokinetics will have changed well before a steady-state is reached (Pitlick et al, 1978; Bourgeois & Dodson, 1983);
2. whatever evidence there is concerning reference ranges, it was derived almost exclusively from studies in adults and there is little evidence concerning reference ranges in the pediatric age. There seems to have been no attempt to determine whether the limits of the quoted reference ranges may differ in children. For instance, the observations by Kutt et al. (1964) on the serum concentrations at which phenytoin causes nystagmus or ataxia have strengthened the notion that TDM is valuable, yet there has been no study to assess whether the phenytoin concentrations at which these symptoms appear in children are lower, higher, or the same;
3. pharmacokinetic interactions among AEDs, or between AEDs and other medications, can cause substantial changes in drug concentrations. The fact that their precise extent cannot be predicted contributes to the value of serum concentration monitoring when there is a potential for interaction. The same interactions are likely to occur in children, and this has actually been documented in several instances, including valproic acid (Henriksen & Johannessen, 1982; Lundberg et al., 1982), lamotrigine (Vauzelle-Kervroedan et al., 1996; Battino et al., 2001), and topiramate (Glauser et al., 1999; Rosenfeld et al., 1999). However, the extent of these interactions may be different in children. This was recently suggested by an analysis of the population pharmacokinetics of rufinamide, in which the increase in rufinamide blood concentrations associated with coadministration of valproic acid was found to be much more prominent in children than in adolescents and in adults (70% vs. 26% and 16%, respectively), a difference possibly ascribed to the fact that serum valproic acid concentrations were higher in children than in older patients (Perucca et al., 2008). In a pediatric population, it has been suggested that therapeutic concentrations of valproic acid may not be achieved even at doses greater than 100 mg/kg/day in a high percentage of patients comedicated with enzyme-inducing AEDs (Henriksen & Johannessen, 1982);
4. Schmidt et al. (1986) have demonstrated that different seizure types may respond to different serum concentrations of phenytoin, phenobarbital, and carbamazepine. Children may have different types of epilepsies and seizures, which may require lower or higher drug concentrations for their control. This raises several questions. Should the same reference range of serum ethosuximide concentrations be applied to the treatment of typical and atypical absences? If treatment is indicated for benign rolandic epilepsy, are effective concentrations of a given drug lower than the reference range of the same drug in other focal epilepsies? Does the same reference range of serum valproic acid concentrations apply to the treatment of Lennox-Gastaut syndrome as well as juvenile myoclonic epilepsy? For instance, Lundberg et al. (1982) reported that the optimal dose range of valproic acid was 20–40 mg/kg/day for children with absences, and 30–60 mg/kg/day in children with the "myoclonic types of epilepsy";
5. Finally, AEDs may have long-term adverse effects on the immature brain that do not occur in the mature brain (Bittigau et al., 2003). If a concentration threshold for these effects could be established, this might help to determine a specific reference range for newborns and infants. Also, clinical toxicity may

be more difficult to assess in children, especially in young infants, and the upper limit of the reference range needs to be assessed carefully in this age group (Walson, 1994).

Overall, there is a greater need to monitor serum AED concentrations in infants and children, but also a greater uncertainty regarding reference ranges in these age groups.

Pregnancy

During pregnancy, maternal serum concentrations not only reflect concentrations that determine therapeutic and adverse effects in the woman, but also the extent of drug exposure to the embryo or fetus. Drug concentrations and alterations thereof are therefore of particular importance in this specific situation. The pharmacokinetics of many AEDs undergo important changes during pregnancy, due to a combination of factors such as modifications in body weight, altered serum composition, hemodynamic alterations, hormonal influences, and contribution of the fetoplacental unit to drug distribution and disposition (Perucca, 1987). Pregnancy may affect drug absorption, binding to serum proteins and distribution, metabolism, and renal elimination (Pennell, 2003). These alterations need to be taken into consideration in order to optimize AED treatment. The aim is to maintain seizure control with the lowest effective serum drug concentration, in order to avoid harm from seizures and from drugs to the mother and the foetus. The effect of pregnancy on drug disposition varies with different AEDs, and the extent of this effect will also vary between patients (Pennell, 2003). TDM during pregnancy aims at facilitating individualized dosing by identifying pregnancy-induced pharmacokinetic changes.

Pregnancy-associated pharmacokinetic changes have been reasonably well characterized for the old generation AEDs (Yerby et al., 1992; Pennell, 2003). At constant dosages, serum concentrations of most of these AEDs tend to decrease during pregnancy, and return to prepregnant concentrations within the first month or two after delivery. These alterations appear to be due mainly to decreased drug binding to serum proteins and increased metabolism and elimination. A decrease in protein binding per se will result in lower total (protein bound plus unbound) drug concentrations, but may leave unchanged the unbound, pharmacologically active, concentration of the drug.

By the end of pregnancy, total and unbound concentrations of phenobarbital decline by up to 50–55% (Yerby et al., 1992). Primidone concentrations are only slightly affected decreasing by 10–30%, whereas there is a pronounced decrease in the order of 70% or more in metabolically derived phenobarbital concentrations in late pregnancy (Battino et al., 1984). Total serum concentrations of carbamazepine decline to a lesser extent (0–40%) and the changes in unbound carbamazepine concentrations are insignificant (Yerby et al., 1992; Tomson et al., 1994). Marked decreases in total phenytoin concentrations to about 40% of prepregnancy concentrations have been reported (Yerby et al., 1992; Tomson et al., 1994), whereas free concentration decrease to a lesser extent (20–30%). For valproic acid, no significant changes are noted in unbound concentrations despite a fairly marked decrease (sometimes 50% or even more) in total concentrations (Koerner et al., 1989; Yerby et al., 1992). Hence, for highly protein bound drugs such as valproic acid and phenytoin, total serum concentrations may be misleading during pregnancy, underestimating the pharmacological effects of the drugs.

Several studies have demonstrated pronounced alterations in the pharmacokinetics of lamotrigine during pregnancy (Tomson et al., 1997; Öhman et al., 2000; Tran et al., 2002; de Haan et al., 2004; Pennell et al., 2004; Öhman et al., 2007; Pennell et al., 2007). The decrease in serum concentrations during pregnancy appears to be more pronounced for lamotrigine (with a fall sometimes down to 30% of prepregnancy concentrations) than for other AEDs, is probably the consequence of an increased metabolism of lamotrigine by glucuronidation and can result in increased seizures (de Haan et al., 2004; Pennell et al., 2007), prompting the need for more frequent dose adjustments. Recent observations indicate that clinically important declines (30–50%) in serum drug concentrations during pregnancy also occur with levetiracetam (Tomson et al., 2007b) and with the active MHD derivative of oxcarbazepine (Christensen et al., 2006; Mazzucchelli et al., 2006). Much less is known about the pharmacokinetics of other new generation AEDs during pregnancy and clearly more data are needed.

The pharmacokinetic changes quoted above represent average changes, but the effect of pregnancy varies between individuals. The decline in serum drug concentration may be insignificant in some patients and pronounced in others, requiring dosage adjustments to maintain seizure control. Monitoring drug concentrations is therefore recommended during pregnancy. For highly protein bound AEDs such as valproic acid and phenytoin, there may be advantages in monitoring the unbound drug concentrations. A single drug concentration is of limited value, since the optimal concentration is individual. When pregnancy is planned in advance, it is therefore advisable to obtain one or, preferably, two serum concentration values when seizure control is optimal, before pregnancy, for future comparison. The timing and frequency of drug concentration monitoring during pregnancy also needs to be individualized based on the type of AED used and the patient's characteristics. Once each trimester is often recommended and is probably sufficient in most women with stable seizure control. More frequent sampling is advisable in patients with complicated epilepsy, in those previously known to be sensitive to modest alterations in dose and serum concentrations, and in those under treatment

with lamotrigine and oxcarbazepine. In the latter patients, sampling once a month is sometimes justified. The need for monitoring in the postpartum period will depend on the clinical situation and on whether dose changes have been made during pregnancy. Lamotrigine pharmacokinetics, for example, appears to revert to prepregnancy conditions within a few days after delivery. In order to avoid toxicity, monitoring every second day for a week after delivery could be justified if the lamotrigine dose was increased during pregnancy.

Elderly

Suboptimal compliance such as underdosing, overdosing, missed doses, or make-up doses are common in older patients and alter serum AED concentrations and, potentially, clinical response (Cramer et al., 1989). TDM is useful in identifying noncompliance, but caution must be exercised because age-related alterations in absorption and protein binding mimic the effect of noncompliance on serum AED concentrations.

Advancing age alters both the way in which the body responds to medications and the way it absorbs, binds, and eliminates drugs (Perucca, 2006). Although there is a general pattern in these age-related changes, substantial inter- and intraindividual variability exists in all pharmacokinetic parameters. Changes in pharmacokinetics affect serum drug concentration, while changes in pharmacodynamics affect response to any given serum concentration, which may complicate the interpretation of TDM data.

Alterations in gastrointestinal function, body mass composition, serum proteins, and hepatic and renal function are all associated with advancing age (Hammerlein et al., 1998). Reduced intestinal motility, altered gastric and intestinal pH, and altered intestinal structure can affect both the rate and extent of absorption. Serum albumin declines gradually with age while the reactive protein alpha$_1$-acid glycoprotein modestly increases in healthy elderly and markedly increases with many diseases common with aging. For AEDs that are highly bound to serum proteins (carbamazepine, phenytoin, valproic acid, and tiagabine), decreased albumin binding due to hypoalbuminemia will result in lower total drug concentration, whilst an increased binding due, for carbamazepine, to increased alpha$_1$-acid glycoprotein will result in higher total drug concentrations. As an example of the latter circumstance, Rowan et al. (2005) found that the mean carbamazepine unbound fraction in elderly patients enrolled in their study was 12.5%, a much lower value than that reported for younger adults with epilepsy. Although unbound drug concentrations will not be affected by changes in serum proteins, changes in protein binding need to be taken into account when interpreting total serum drug concentrations in these patients. For example, due to the increase in unbound phenytoin fraction, the therapeutic and toxic effects of phenytoin will occur in the elderly at total drug concentrations lower than usual.

Renal function, as measured by creatinine clearance, and CYP–mediated oxidative metabolism decrease by approximately 1% a year after age 40, although there is considerable variability and limited data in individuals 80 or older for both routes of elimination (Vestal et al., 1975; Hammerlein et al., 1998). There is emerging evidence that glucuronidation reactions undergo a similar decline with age (Perucca et al., 1984a; van Heiningen et al., 1991). The effect of advancing age on induction of CYP-mediated metabolism is controversial. Some studies suggested that the degree of enzyme induction in the elderly is attenuated (Salem et al., 1978), while Battino et al. (2004) provided evidence that phenobarbital increases the apparent carbamazepine clearance to a similar extent in elderly and nonelderly adults.

Despite the widespread use of AEDs in the elderly, there is limited information on their pharmacokinetics in this age group, and the available data is largely based on studies in the young-old (65–74 years) (Bernus et al., 1997; Perucca, 2006). The AEDs most extensively studied in the elderly are phenytoin, valproic acid, and carbamazepine. A recent report by Birnbaum et al. (2003) described widely fluctuating serum phenytoin concentrations in a large percentage of elderly nursing home residents. The frequency and direction of change suggests that altered bioavailability is the most likely cause of this phenomenon. Several studies have found higher and more variable phenytoin free fractions in elderly patients, even in the presence of normal serum albumin (Bernus et al., 1997). Phenytoin half-lives are prolonged and metabolism is approximately 20% slower in the elderly (Bauer & Blouin, 1982; Perucca et al., 1984a). As a consequence of Michaelis-Menten kinetics, a modest age-related decline in phenytoin metabolism can be clinically significant, because very small changes in dose or absorption can result in disproportionately large changes in serum concentration. Perucca et al. (1984a) compared the pharmacokinetics of a single dose of valproic acid in six elderly and six younger individuals. Total serum valproic acid concentrations were similar between the two groups, but the free fraction of the drug in older subjects was twice that in the younger group (11% vs. 6%) and the unbound drug concentrations were approximately 60% greater. This study further exemplifies the pitfalls of monitoring highly protein bound AEDs in the elderly. Measurement of total valproic acid concentrations may not provide an accurate estimate of unbound concentrations, leading either to inappropriate increases in dose or to failure to decrease dose in the presence of concentration-dependent side effects such as tremor. Information about carbamazepine absorption is unavailable, but apparent protein binding may increase, presumably due to elevated alpha$_1$-acid glycoprotein concentrations, while clearance declines by 20–40% in old age, and half-life is likely to be prolonged (Cloyd et al.,

1994; Battino et al., 2004; Rowan et al., 2005). Although much less is known about the effect of advancing age on newer AEDs, available data suggest that the pharmacokinetic changes observed with these agents in the elderly are similar to those described for the older AEDs (Perucca et al., 2006a).

Elderly individuals with epilepsy take more medications than other patients in the same age group, resulting in a greater risk of drug interactions (Linjakumpu et al., 2002). In a recent US study investigating the safety and efficacy of carbamazepine, gabapentin, and lamotrigine in elderly patients with seizure disorders, the mean number of prescription comedications per patient was 6.7 (Ramsay et al., 2004). In contrast, the average number of comedications in a similar study in elderly patients with newly diagnosed epilepsy in Europe was 3.0 (Saetre et al., 2007). The most commonly used medications in the elderly are cardiovascular, CNS, and analgesic agents, all of which have a high potential for interactions with AEDs (Perucca et al., 2006). The elderly also often take natural products such as St. John's wort which are known to interact with AEDs (Kaufman et al., 2002). The addition or discontinuation of enzyme-inducing and inhibiting drugs may have a particularly important impact on older patients, because these patients are at a high risk of adverse events (Gurwitz et al., 2003). For example, the addition of fluoxetine, an antidepressant frequently prescribed for older patients, can increase both carbamazepine and carbamazepine-10,11-epoxide concentrations by as much as 50% (Grimsley et al., 1991).

In conclusion, TDM may be particularly helpful in guiding AED therapy in elderly patients. Greater morbidity, poor medication compliance, variable age-related changes in pharmacodynamics and pharmacokinetics, and an increased likelihood of drug interactions affect the safety and efficacy of both AEDs and concomitant therapy in these patients. TDM can assist the clinician in attaining targeted concentrations and maintaining these concentrations over time, especially as comedications are added or discontinued. Measurement of unbound concentrations may be indicated for highly protein bound AEDs. Interpretation of drug concentrations in the elderly should also take into account the fact that these patients may show increased pharmacodynamic sensitivity to AEDs, and therefore therapeutic and toxic effects may develop at relatively low concentrations (Perucca, 2006).

Changes in AED formulation and generic substitution

When an AED formulation is changed, e.g., when switching to/from generic formulations, measuring the serum concentration of the AED before and after the change may help in identifying potential alterations in steady-state drug concentrations resulting from differences in bioavailability (Perucca et al., 2006b). As in other situations involving intrapatient comparison of drug concentrations obtained at different times, interpretation of data must take into account alternative explanations for a change in reported values, including day-to-day assay variability, differences in sampling times, and background day-to-day pharmacokinetic variation.

When patients are switched to a formulation with modified-release characteristics (for example, from an immediate-release to a sustained-release formulations), or when dosing schedule is changed (for example, from twice daily to once daily administration), interpretation of TDM data should also take into account the expected variation in diurnal drug concentration profile. In some instances, collection of two or more blood samples at different intervals after drug intake may be desirable to fully assess the concentration profile change.

Pathological states

The absorption, distribution, and elimination of AEDs can be markedly affected by the changes in homeostasis caused by various illnesses, including hepatic or renal failure, infections, burns, stroke, cardiac failure, and other conditions (Boggs, 2001). In addition to the alterations caused by the pathological state per se, drugs used to treat these conditions can cause interactions that also affect AED concentrations. The monitoring of serum AED concentrations is valuable in helping the clinician to identify these pharmacokinetic changes and enabling him or her to make dose adjustments whenever appropriate.

Measurement of unbound drug concentrations is essential for highly protein bound AEDs whenever the associated condition is known or suspected to alter the degree of protein binding (Perucca, 1984). This was first demonstrated for phenytoin in cases of renal failure, where binding is markedly diminished and total concentrations are misleading (Hooper et al., 1974). Serum protein binding changes shortly after dialysis or renal transplantation, but clearance may not change markedly (Kang & Leppik, 1984), and failure to monitor unbound concentrations can lead to errors in dosing. Although other highly bound AEDs such as valproic acid have not been as extensively studied, it would be prudent to measure free concentrations of all highly bound AEDs during renal failure or other states in which endogenous binding sites may be altered, such as hypoalbuminemia, or in patients receiving drugs competing for protein binding sites such as aspirin, naproxen, tolbutamide, phenylbutazone, and other highly protein-bound agents (Perucca et al., 1985).

Many AEDs are excreted in part or primarily by the kidneys (Asconape & Penry, 1982; Perucca, 1999). The concentrations of primidone, levetiracetam, pregabalin, gabapentin, and vigabatrin are particularly dependent on renal clearance, and although formulas exist for calculating dose based on creatinine clearance, these calculations are not always easy or accurate. A better approach is to measure concentrations of these drugs and adjust the doses

based on actual concentrations whenever there is a compromised renal function. TDM can also help in guiding the magnitude of replacement dosages for patients receiving AEDs, which are efficiently removed during dialysis. For highly bound drugs, the unbound fraction increases markedly in patients with renal disease, and therefore monitoring total serum concentrations can be misleading in this situation (Perucca et al., 1985).

Burns extensive enough to require admission to a burns unit may result in significantly impaired serum protein binding of phenytoin, phenobarbital, and diazepam (Bloedow et al., 1986; Pugh, 1987). Other AEDs have not been studied. However, it would be advisable to monitor AED concentrations in patients with severe burns, and to determine unbound concentrations when highly protein bound drugs such as phenytoin and valproic acid are monitored.

Phenytoin clearance can be accelerated by various illnesses. This was first observed in a case of mononucleosis and later shown to occur with febrile illnesses and even with vaccination (Leppik et al., 1986). Anyone treated with phenytoin having breakthrough seizures should if possible have the phenytoin concentration measured, and, if low, the dose should be increased for the duration of the illness. Studies for other AEDs during febrile illnesses have not been undertaken, but it may be prudent to monitor their serum concentrations during illnesses. Certainly diarrheal illnesses may be associated with decreased absorption, and even without monitoring concentrations, strategies to supplement drug intake should be considered.

Because many AEDs are metabolized by the liver, hepatic disease may alter their clearance (Asconape & Penry, 1982; Perucca, 1999). In addition, as the liver is the source of many proteins, serum protein binding may also be affected. Only a few studies evaluating serum AED concentrations during hepatic illness have been undertaken, and it is not possible to predict the degree of change in clearance (Asconape & Penry, 1982). Thus, in any person with hepatic failure, total concentrations (and unbound concentrations for highly bound drugs) should be monitored.

Some studies have shown that carbamazepine clearance is altered by surgery for epilepsy (Gidal et al., 1996). Other AEDs have not been well studied. Head trauma may also be associated with changes in unbound drug fraction and drug metabolism, as shown for example for phenytoin (Stowe et al., 2000). Therefore, it is useful to monitor AED concentrations after surgery or head trauma.

In summary, although only a few studies have been undertaken, it is apparent that renal failure, infectious diseases, hepatic failure, burns, surgery, and illness severe enough to warrant placement in an intensive care unit do alter physiology to the degree that AED concentrations can be affected. AED concentrations should be monitored in these situations. Specific guidelines for extent of monitoring are not available, but clinical judgment with an awareness of the potential changes in serum protein binding, absorption, and clearance should guide the clinician caring for ill patients.

Pharmacokinetic interactions

An important objective of AED treatment is to anticipate and minimize the risks of clinically relevant pharmacokinetic interactions (Patsalos & Perucca, 2003a, 2003b). An unexpected loss of seizure control or development of toxicity during AED therapy may accompany the addition or removal of a concurrently administered drug. Prevention of AED interactions is best achieved by avoiding unnecessary polytherapy, or by selecting alternative agents that have less potential to interact. The management of interactions begins with anticipating their occurrence and with being familiar with the mechanisms involved.

Pharmacokinetic interactions involve a change in the absorption, distribution, metabolism, or elimination of the affected drug. If an interaction is anticipated, it makes sense to obtain a drug concentration measurement before adding a new drug, in order to establish a baseline. Further measurements should be taken at appropriate times after the potentially interacting agent has been added, and the need for a dose adjustment can then be assessed (Patsalos & Perucca, 2003a).

Serum protein binding interactions usually do not modify clinical response, because as a general rule compensatory changes in drug clearance lead to a new situation whereby the total serum concentration of the displaced drug is reduced, but the concentration of unbound, pharmacologically active drug is unaffected (MacKichan, 1989). Nevertheless, these interactions need to be considered when interpreting TDM data in the clinical setting; in fact, in the presence of a displacing agent, therapeutic and toxic effects of the affected drug will be obtained at total serum concentrations lower than usual. Such a situation applies, for example, to the interpretation of total serum phenytoin concentrations in the presence of valproic acid, a displacing agent (Mattson et al., 1978). Patient management in this situation would benefit from monitoring unbound drug concentrations (Perucca et al., 1985).

The most important and prevalent pharmacokinetic AED interactions are those associated with induction or inhibition of drug metabolism. With the exception of gabapentin, pregabalin and vigabatrin, all AEDs undergo some degree of hepatic metabolism and consequently their clearance is susceptible to enzyme inhibition and/or induction. An elevation in enzyme activity, consequent to enzyme induction, results in an increase in the rate of metabolism (particularly oxidation and/or glucuronide conjugation) of the affected drug (Patsalos & Perucca, 2003a). This will lead to a decrease in its serum concentration and possibly a reduction in therapeutic response. If the affected drug has a pharmacologically active metabolite, induction can result in increased metabolite concentrations and possibly

Table 2. Some general indications for measuring serum concentrations of antiepileptic drugs (AEDs)[a]

1. After initiation of treatment or after dose adjustment, when the clinician decides to aim at a preselected target concentration for that patient.
2. Once the desired clinical response has been achieved, to establish the "individual therapeutic range."
3. To assist the clinician in determining the magnitude of a dose increase, particularly with AEDs showing dose-dependent pharmacokinetics (most notably, phenytoin).
4. When there are uncertainties in the differential diagnosis of signs or symptoms suggestive of concentration-related AED toxicity, or when toxicity is difficult to assess clinically (for example, in young children or in patients with mental disability).
5. When seizures persist despite an apparently adequate dosage.
6. When an alteration in pharmacokinetics (and, consequently, dose requirements) is suspected, due to age-related factors, pregnancy, associated disease, or drug-drug interactions.
7. To assess potential changes in steady state AED concentration when a change in drug formulation is made, including switches involving generic formulations.
8. Whenever there is an unexpected change in clinical response.
9. When poor compliance is suspected.

[a]For terminology and detailed discussion, see text.

an increase in efficacy and in drug toxicity, as it can occur with induction of the conversion of carbamazepine to carbamazepine-10,11-epoxide. The magnitude of interaction and the time it takes for the serum concentration of the affected drug to stabilize at a new steady-state concentration after adding an enzyme inducer depend on a number of factors, including the half-life of the affected drug and the dose, enzyme-inducing potency and half-life of the enzyme-inducing agent. For example, studies that assessed the time course of enzyme induction by carbamazepine by investigating the degree of autoinduction demonstrated that induction is dose-dependent (Kudriakova et al., 1992), is already present after 1 to 2 days after initiation of carbamazepine treatment, (McNamara et al., 1979; Bernus et al., 1994b) but may require from 1 week (Mikati et al., 1989) to 5 weeks (Bertilsson et al., 1986) to develop fully. Of the AEDs presently used in clinical practice, carbamazepine, phenobarbital, phenytoin, and primidone are associated with clinically important enzyme-inducing properties (Perucca et al., 1984b). Other inducing agents include felbamate, oxcarbazepine, and topiramate (at doses $\geq$200 mg/day), but these AEDs stimulate the activity of fewer isoenzymes and they induce the metabolism of only a restricted number of substrates such as, most notably, oral contraceptive steroids (Patsalos & Perucca, 2003a, 2003b). Lamotrigine, at a dose of 300 mg/day, can also stimulate the metabolism of contraceptive steroids (Sidhu et al., 2006). Felbamate and oxcarbazepine may also inhibit some CYP enzymes, underlining the fact that induction and inhibition are not mutually exclusive phenomena (Patsalos, 2005).

Enzyme inhibition results in a reduction of enzyme activity which leads to a decrease in the rate of metabolism of the affected drug and, consequently, an increase in its serum concentration and, potentially, clinical toxicity. Inhibition is usually competitive in nature and therefore dose-dependent, and begins as soon as sufficient concentrations of the inhibitor are achieved (Levy et al., 2003). This usually occurs within 24 h of the inhibitor's addition, and the maximal increase in serum concentrations of the affected drug is determined by the time required to attain steady-state conditions for both the inhibitor and the affected drug, which will now have a more prolonged half-life (Patsalos & Perucca, 2003a). After discontinuation of the inhibitor, the time course for the decrease in serum concentrations of the affected drug depends on the same factors. When enzyme inhibition is noncompetitive and irreversible in nature, the rate of synthesis of the enzyme may also play a role in determining the time required to reach a new steady state. The relative contribution of the inhibited pathway to the elimination of the affected drug is also important. If the inhibited pathway accounts for only a small fraction (e.g., <30%–40%) of the total clearance of a drug, the impact of the interaction on the drug serum concentration and clinical effect will be minimal. Among available AEDs, valproic acid, oxcarbazepine, and felbamate have been most frequently associated with causing inhibitory interactions (Hachad et al., 2002; Patsalos & Perucca, 2003a). Furthermore, whilst oxcarbazepine and felbamate are primarily selective inhibitors of CYP2C19, valproic acid is a broader spectrum inhibitor because it reduces the activity of CYP2C9, uridine glucuronyl transferases (UGTs), and microsomal epoxide hydrolases.

It should be stressed that many important AED interactions involve medications used in the management of concurrent nonepilepsy-related conditions (Patsalos, 2005). Many such drugs, including antimicrobials (e.g., erythromycin, ketoconazole, rifampicin, and ritonavir), cardiovascular drugs (e.g., amiodarone, verapamil, and diltiazem) and psychotropic drugs (e.g., fluoxetine and sertraline) can substantially affect the pharmacokinetics of AEDs, resulting in significant changes in serum AED concentrations (Patsalos & Perucca, 2003b). In these settings TDM can be an invaluable tool in guiding patient management.

Table 3. Ten golden rules concerning the use of therapeutic drug monitoring (TDM) in antiepileptic drug (AED) therapy

1. The application of TDM requires adequate knowledge of the specific pharmacokinetic and pharmacodynamic properties of the AED to be monitored.
2. Ensure that the laboratory has adequate measures for quality control.
3. Request the measurement of serum AED concentrations only when there is a clear clinical question.
4. Except for situations requiring immediate action (e.g., suspected toxicity, or drug overdose), serum AED concentrations should be determined at steady state.
5. Sampling time should be standardized, particularly with AEDs having short half-lives ($\leq$12 h). Under most circumstances, a sample taken immediately before the next dose will be adequate.
6. Interpretation of serum AED concentrations must take into account the interval since the last dose intake and the expected pharmacokinetic profile of the AED being monitored.
7. Be aware that reference ranges of AED concentrations have solely a probabilistic value, and that many patients may require concentrations below or above these ranges. Make sure that the patient is informed about the limitations of reference ranges.
8. When interpreting serum AED concentrations, consider situations which may alter the relationship between serum AED concentration and clinical response (e.g., old age, type, and severity of epilepsy, clinical conditions resulting in altered serum protein binding, presence of pharmacologically active metabolites, possibility of pharmacodynamic interactions with concurrently administered drugs).
9. Consider the possibility of applying the individual therapeutic concentration concept (see text).
10. Treat the patient and not the serum concentration! Never make clinical decisions on the basis of drug concentrations alone. Take into account information on patient history, clinical signs and symptoms, and any relevant additional laboratory information.

Conclusions

TDM has been used as a tool to optimize treatment of epilepsy for almost 50 years. Although solid evidence for its usefulness in improving clinical outcome is scarce, TDM continues to play a role in epilepsy management, partly due to the nature of the condition and partly because of the pharmacokinetic variability of AEDs. The primary indications for TDM have been defined (Table 2) and recommendations for their optimal use is summarized in Table 3. The relative value of TDM will depend on the characteristics of the AED, and many newer generation AEDs also have properties that suggest a role for TDM. It is clear from this review that the documentation of drug concentration-effect interrelationships is less than satisfactory. For most AEDs, reference ranges have been reported wihich define the serum concentrations at which most patients are expected to exhibit an optimal clinical response. Due to individual variation, however, many patients may require concentrations outside the reference ranges. In many situations, patient management is best guided by determination of the "individual therapeutic concentration," defined as the concentration at which an individual has been found to achieve seizure freedom with good tolerability, or the best compromise between improvement in seizure control and concentration-related adverse effects. With this concept, TDM may provide important information for decisions on dosage adjustments of most AEDs in patients with unexpected treatment outcomes or in situations associated with pharmacokinetic alterations e.g., during pregnancy, in different pathological states, in conjunction with drug interactions, and in specific age groups (children and the elderly) where the clinical assessment of treatment effects may be particularly difficult.

Conflicts of interest: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that that this report is consistent with those guidelines.

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