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Therapeutic drug monitoring of newer antiepileptic drugs

Therapeutic drug monitoring bei neueren Antiepileptika

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Abstract

Therapeutic drug monitoring (TDM) of antiepileptic drugs (AEDs) has been in clinical use for more than three decades. Its value has, however, been questioned recently for several reasons, e.g., the occurrence of newer AEDs, for which the use of TDM has to be evaluated, but also because of financial strains on health systems. The current review aims at assessing the use of TDM in newer AEDs, i.e., those that entered the market since the beginning of the 1990s. As some have been licensed only recently and others are only in very limited use, either because of orphan drug status or because of limited efficacy or potentially severe adverse events, only limited data exist for some of the newer AEDs. General considerations are made in the review, and each new AED is discussed, and, in some cases preliminary, assessment of the use of TDM is given.

Keywords: antiepileptic drugs; interactions; pregnancy; serum concentrations; therapeutic drug monitoring (TDM).

Zusammenfassung

Therapeutic drug monitoring (TDM) bei Antiepileptika (AED) ist seit mehr als drei Jahrzehnten Bestandteil der klinischen Praxis. Die Berechtigung wird jedoch immer wieder in Frage gestellt, einerseits wegen der Zulassung zahlreicher neuer AED, für die der Nutzen von TDM noch evaluiert werden muss, andererseits aber auch wegen finanzieller Einschnitte im Gesundheitswesen. Die vorliegende Übersicht soll den Nutzen von TDM bei neueren AED – also denjenigen AED, die seit dem Anfang der neunziger Jahre des 20. Jahrhunderts zugelassen wurden – darstellen. Für manche dieser Medikamente liegen nur wenige Daten vor, weil sie erst kürzlich zugelassen wurden oder weil sie *Orphan drug*-Status haben oder weil sie aufgrund potentiell schwerer Nebenwirkungen nur sehr selten eingesetzt werden. Zunächst werden Relevanz und Indikationen des TDM im Allgemeinen und nachfolgend für jedes neuere AED diskutiert, wobei die Einschätzung des Nutzens von TDM bei einzelnen Medikamenten gegenwärtig vorläufigen Charakter hat.

Schlüsselwörter: Antiepileptika; Interaktionen; Schwangerschaft; Serumkonzentrationen; Therapeutic drug monitoring; (TDM).

Introduction

Therapeutic drug monitoring (TDM) of antiepileptic drugs (AED) has been in clinical use for more than 30 years. Its usefulness has been clearly established for older AEDs, however, there is a debate concerning the value of TDM in newer AEDs. Several facets of this issue have to be taken into account: on the one hand, any unnecessary examinations have to be avoided, and cost-cutting in health systems is only one reason for this, on the other hand, clinicians must have access to methods which improve clinical care for the patients. The present paper besides making some general remarks concerning TDM of AEDs, aims at elucidating the available data on specific newer AEDs. As proper interpretation of gained data is essential, this will also be discussed. Many of the readers of this review will be non-neurologists or non-epileptologists. Therefore, each chapter concerning the newer AEDs will give a short summary of the clinical use of the drug.

Background: TDM of AEDs in general

TDM of AEDs may be especially helpful in the following situations [1–4]:

1. Initial treatment of epilepsy (aim at a value in the lower or middle therapeutic range).
2. Determination of postictal serum concentrations and serum concentrations at the time of side effects (determination of the individual "therapeutic range“ of a patient).
3. Diagnosis and differential diagnosis of chronic or acute intoxication.
4. Assessment of adherence to the therapeutic regimen.

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5. Dose adjustments in the growth period in children or after significant changes in body weight.
6. Monitoring of serum AED levels during pregnancy.
7. Interactions in combination therapies of different AEDs or with concomitant medication [5].
8. Suspected false dispense or intake of medication.
9. Diseases that alter the metabolism of the AED, for example, renal or hepatic insufficiency, or at the extremes of age.
10. Dose changes in AEDs with non-linear kinetics, such as phenytoin.
11. Monitoring of a drug withdrawal (especially phenobarbital or bromide).

TDM of AEDs is normally carried out in serum or plasma. Use of other body fluids is possible (e.g., saliva, breast-milk, or cerebrospinal fluid), but this is mostly done for scientific purposes rather than in clinical practice.

Pitfalls in TDM

Use and misuse of the term "therapeutic range"

Sensibly used, the concept of a "therapeutic range" is warranted. It denotes the range of serum levels, defined by a lower and an upper limit, within which a majority of patients responding to a specific drug have therapeutic success without experiencing adverse events (AEs) or at least without experiencing intolerable AEs. See Table 1 for therapeutic ranges of newer AEDs. There is, however, a danger, which has been experienced in the past that the term is misunderstood in one of two ways. The doses of AEDs have been increased in patients in spite of a therapeutic success already with low serum concentrations, in order to reach the "therapeutic range", or a therapeutic regimen has been classified as failed as a patient did not have success or only partial success under a drug when the upper limit was crossed. In the latter case, therapeutic success can sometimes be gained by further dose increments, as long as the drug is still tolerated ("dose escalation to the maximal tolerated level"). As a consequence, proper use of the term "therapeutic range" in the sense of an individual therapeutic range has to be applied [6].

Measurement before reaching steady state

This may lead to falsely assuming lower serum concentrations and thus escalating AED doses unnecessarily and in a potentially harmful way. Also, when tapering AEDs, time to steady state is essential.

Disregard of non-linear kinetics

This may lead to larger dose increments, exposing the patient to the risk of intolerable dose-dependent AEs.

Trough concentrations vs. concentrations during the day

Drugs with short elimination half-life usually show marked fluctuations during the day. Use of serum concentrations during the day may lead to the incorrect assumption that the patient might be near or above the upper limit of the "therapeutic range" and thus lead to inappropriate decisions. It may also raise the incorrect suspicion that the drug had cumulated due to a concomitant (renal or hepatic) disease or due to interaction with other drugs. Furthermore, comparison of serial serum concentrations in a patient, e.g., in order to check adherence to the therapeutic regimen, is only possible if these are trough concentrations. Exceptions are serum concentrations assessed at the time of the occurrence of AEs or postictally.

Special considerations

TDM of newer AEDs during pregnancy, puerperium and lactation

Explicit recommendations for TDM during pregnancy are made below for lamotrigine, oxcarbazepine, topiramate and

Table 1 Therapeutic ranges of serum concentrations of newer AEDs.

Antiepileptic drug	Therapeutic range	Comments
Felbamate	20–100 µg/mL	
Gabapentin	2–10 µg/mL	
Lacosamide	1–10 µg/mL	Preliminary values
Lamotrigine	2–10 µg/mL	
Levetiracetam	10–40 µg/mL	
Oxcarbazepine/Eslicarbazapine acetate	10–35 µg/mL	Metabolite 10-hydroxy-carbazepine (Sum of R- and S-enantiomers)
Pregabalin	2–5 µg/mL	Preliminary values
Rufinamide	5–30 µg/mL	Preliminary values
Stiripentol	1–6 (–10) µg/mL	Preliminary values
Tiagabine	20–200 ng/mL	Preliminary values
Topiramate	2–10 µg/mL	
Vigabatrin	2–10 µg/mL	
Zonisamide	5–35 µg/mL	Preliminary values

levetiracetam. Data concerning other newer AEDs are sparse. Generally, the effect of pregnancies on the pharmacokinetics of AEDs is difficult to predict [7]. This should be considered when performing TDM during pregnancy and post-partum and also in those AEDs for which no sufficient information is available.

Assessment of adherence to the therapeutic regimen

Lack of adherence to the therapeutic regimen is a major problem in epilepsy treatment. It is regarded as a major cause of breakthrough seizures, and failure to detect non-adherence may lead to incorrectly classifying a patient's epilepsy as drug-resistant. In an explorative study, 61 postictal serum concentrations were assessed in 52 young adults with epilepsy, and a drop in serum levels >50% compared to baseline was noted in 44.3% of the seizures [8]. The majority of these patients were under treatment with carbamazepine, valproic acid and lamotrigine. Therefore, the results may only partially be applied to the current review, but in general the assessment of serum concentrations of AEDs is regarded as an important tool to detect non-adherence.

Change from a specific AED to a generic compound

Change from an AED to a generic form has to be done with caution. It should, for instance, be avoided in patients who are seizure-free and who do not suffer from AEs. If a change is necessary, serum concentrations have to be monitored in order to avoid a decrease leading to break-through seizures or an increase leading to AEs [9].

TDM of the newer AEDs in detail

In the following paragraphs, individual AEDs are discussed according to the sequence of licensing, starting with a brief introduction to the labelling (using Germany as an example; the status for other countries may differ), mode of action, and important AEs. The latter information, if not otherwise stated, is cited from [10]. The lists of AEs are not complete, but those AEs mentioned either occur frequently or are of special relevance/severity. Relevant pharmacokinetic data and interactions [5] according to the literature are reported, followed by an assessment of the value of TDM for the drug. See Table 2 for indications of TDM in the specific AEDs.

Vigabatrin

Vigabatrin (VGB) is licensed for the add-on treatment of pharmacoresistant focal epilepsies with the restriction that all other adequate drug combinations have failed. It is also licensed as a monotherapy in infantile spasms. It is, at least in adult patients, rarely in use due to the occurrence of concentric visual field defects in 44% of patients [11]. Other AEs are sedation, encephalopathy, psychotic symptoms and depression.

Absorption of VGB is rapid and complete; the unchanged drug is eliminated renally with a plasma half-life (t½) of 5–8 h. VGB is not bound to plasma proteins.

Interactions: No clinically relevant effect of other AEDs on VGB levels.

VGB acts as an irreversible enzyme inhibitor [12] and thus is not expected to be a candidate for TDM because of dissociation between serum concentration and duration of effects. Indeed, the evaluation of an add-on study failed to show a well-defined therapeutic range [13]. A major limitation of that study, however, is the fact that not all serum concentrations were assessed as trough concentrations.

To our knowledge, no sufficient information about the pharmacokinetics of VGB in pregnancy is available.

As the drug is eliminated renally, intoxication might occur in patients with impaired renal function. However, there is, to our knowledge, no data concerning the routine use of TDM of VGB in this patient group.

Lamotrigine

Lamotrigine (LTG) is licensed as mono- or add-on therapy in focal and generalised epilepsies [including Lennox-Gastaut-Syndrome (LGS)] in patients aged 13 years and older, in younger patients (2–12 years) as add-on therapy in

Table 2 Indications for the use of TDM (see text for explanations of the indications and the abbreviations).

	ESL	FBM	GBP	LCM	LTG	LEV	OXC	PGB	RUF	STP	TGB	TPM	VGB	ZNS
1. Treatment initiation	+				+		+	–	+	+	+			
2. Postictal/side effects	+	+	+	+	+	+	+	+	+	+	+	+		+
3. Suspected intoxication	+	+	+	+	+	+	+	+	+	+	+	+	+	+
4. Adherence/false intake	+	+	+	+	+	+	+	+	+	+	+	+	+	+
5. Growth/gain or loss of body weight	+	+	+	+	+	+	+	+	+	+	+	+		+
6. Pregnancy	+	?	?	?	+	+	+	+	+	?	?	+	?	+
7. Interactions	+	+			+	+	+	+	+	+	+	+		+
8. Renal insufficiency	+	+	+	+	+	+	+	+	–	?		+	+	+
9. Hepatic insufficiency	?	c		+	+	+	?		?	?	+	+		+
10. Non-linear kinetics			+						+	+				?

"+", TDM is indicated. "?", no sufficient data but TDM should be performed for safety reasons according to our opinion. "c", Drug is contraindicated in this condition. Blank space: TDM is not indicated.

focal and generalised epilepsies, and as monotherapy for the treatment of typical absences. In adults, it is also licensed for the prevention of depressive episodes in patients with bipolar-I disorder and predominantly depressive episodes. LTG has a broad mechanism of action, including blockage of sodium channels.

A well-known AE of LTG is the development of skin reactions. As the occurrence of severe skin reactions is dependent on comedication and titration rate, a strict up-titration scheme has to be obeyed. Further adverse events are haematological AEs, sleep disturbances, double vision and impaired liver function. Cognitive side-effects are quite rare, as are psychiatric AEs [14].

LTG is rapidly and completely absorbed, and 55% of the drug is bound to plasma proteins. Metabolism is mainly hepatic by UDP-glucuronyl-transferases. t½ is 24–37 h in monotherapy, 9–14 h in comedication with enzyme-inducing drugs (EIDs) and 45–75 h when combined with valproic acid (VPA). Co-administration of methsuximide lowers the LTG concentration by 70% and oxcarbazepine concentration by 29% [15].

LTG serum concentrations decline during pregnancy. In a study by Öhman et al., the mean dose/concentration ratio was approximately 250% higher in late pregnancy than at baseline (which was defined as a trough concentration assessed at least 1 month after delivery) [16]. Clearance (Cl) of LTG has been shown to increase by 94% from baseline before pregnancy to the third trimester [17]. This finding is of importance as an increase of LTG Cl may be associated with an increase in seizure frequency, and dose adjustment on the base of TDM may be helpful in preventing this increase [18, 19]. We recommend assessing LTG trough levels once a month during pregnancy, and in the case of a marked decline, even more frequently, combined with dose adjustments.

Oral contraceptives may increase LTG metabolism and thus decrease LTG serum concentration [20]. Changes in LTG concentration after introduction or withdrawal of oral contraceptives may occur within 7 days of change of the regimen and may be clinically relevant.

A significant decrease in LTG serum concentrations may also occur after epilepsy surgery [21]. This may be associated with early postoperative seizures and thus also warrants repeated assessments of LTG concentrations postoperatively. The reasons for the decrease are not yet clear; the authors discuss a postoperative alteration of gastrointestinal motility.

No significant differences have been found for serum concentrations between seizure-free patients without AEs and patients still experiencing seizures. For the first group, concentrations between 1.4 and 18.7 µg/mL (median: 3.8 µg/mL) have been found and for the latter between 0.4 and 18.5 µg/mL (median: 4 µg/mL) [22]. There is some criticism against this type of study as, for example, it is very difficult to determine whether patients without therapeutic success had had their medication properly up-titrated or not. TDM of LTG has been found to be useful in determining individual therapeutic ranges [23, 24]. A correlation between LTG serum level and tolerability, independent of the use of other AEDs, has been found [25].

Two single dose studies have been carried out in patients with different degrees of renal impairment [26, 27]. While Wootton et al. did not find significant differences between patients with renal impairment and healthy volunteers concerning relevant pharmacokinetic parameters, Fillastre et al. found a marked interindividual variability, and thus recommend careful monitoring of the patients. Dose adjustments may be necessary in patients with haemodialysis [28] or severe liver impairment (liver cirrhosis Child-Pugh grade B and C) [29]. Therefore, TDM may be of use in these situations.

Gabapentin

Gabapentin (GBP) is licensed for the add-on treatment of focal epilepsies in patients aged 6 years and older resp. in monotherapy in patients aged 12 years, and older. It is furthermore licensed for the treatment of peripheral neuropathic pain in adults. The main AEs are sedation, dizziness, headache, nausea, and increase in body weight. There is a large variability in the plasma concentrations associated with therapeutic response [30].

GBP is a GABAergic drug with a rapid, non-linear absorption (70%) from the gastrointestinal tract (GIT), renal elimination (therefore, dose reduction may be necessary in patients with renal impairment) and a t½ of 5–7 h. The drug is not bound to plasma proteins.

No sufficient data are available concerning GBP pharmacokinetics during pregnancy.

To date, no clinically relevant effects of other AEDs on GBP levels have been reported.

Felbamate

Felbamate (FBM) is licensed for the add-on therapy of LGS in patients aged 4 years and more. As severe AEs (hepatotoxicity and aplastic anaemia, both with fatalities) have been described, restrictions apply concerning the use of this drug. Besides the above-mentioned AEs, nausea, loss of appetite, dizziness, vomiting and sedation may occur.

Approximately 90% of the drug is absorbed from the GIT after oral administration, protein binding is 22%–25%, and t½ 2–6 h. The drug is excreted renally.

It has been reported that seizure control seems to be related to FBM concentrations, the drug has a narrow "therapeutic window" and serum concentrations show a large interindividual variability and may be affected by the patient's age. EIDs lower the FBM concentration [6]. Serum concentrations of FBM are higher in patients with renal impairment; the drug is contraindicated in patients with impaired liver function [6]. There is no sufficient information concerning the pharmacokinetics of FBM during pregnancy.

Oxcarbazepine

This drug is licensed for the treatment of focal epilepsies in mono- or combination therapy in patients aged 6 years or more. Important AEs are hyponatraemia, sedation, dizziness,

nausea, double-vision, headache and decreased white blood count.

Oxcarbazepine (OXC) and its metabolites act by sodium channel blockage. OXC is completely absorbed from the GIT and is rapidly and nearly completely metabolised to its active metabolite 10-monohydroxy-carbazepine (10-OH-CBZ). More than 95% of the drug is excreted renally, mainly as different metabolites. EIDs lower the 10-OH-CBZ concentration.

A significant decline of 10-OH-CBZ serum concentrations during pregnancy has been reported [31]. The authors found a trend toward a correlation between seizure deterioration and decrease in 10-OH-CBZ plasma concentration.

The effect of OXC appears to be related to dose and serum concentrations of 10-OH-CBZ with high interindividual variability [32, 33]. t½ increases in severe renal impairment [34]; there are no sufficient data concerning severely impaired liver function.

Tiagabine

Tigabine (TGB), a GABAergic drug, is licensed for the add-on treatment of focal epilepsies not sufficiently treatable with other AEDs. Its use is limited to patients aged 12 years and older. Important AEs are dizziness, sedation, visual field defects (rare), diarrhoea and ecchymoses. A very important AE is the provocation of a non-convulsive status epilepticus.

Absorption of the drug from the GIT is rapid and nearly complete. Pharmacokinetics is linear; t½ is approximately 7–9 h and in combination with EIDs, 2–3 h. 96% of TGB is bound to plasma proteins and the drug is metabolised by isoenzymes of cytochrome P450.

EIDs significantly induce TGB metabolism when compared to monotherapy or a combination with non-inducing drugs [35]. An in-vitro study indicated that VPA may displace TGB from protein binding [36]. This is most probably not clinically significant, but may be of importance for the interpretation of (decreased) total TGB serum concentrations.

To our knowledge, there is no sufficient information concerning the pharmacokinetics of TGB during pregnancy.

Dose adjustment may be necessary in hepatic, but not in renal impairment [37, 38].

Topiramate

Topiramate (TPM) is licensed for the treatment of focal epilepsies and generalised tonic-clonic seizures in patients aged 6 years and older in monotherapy and in patients aged 2 years and more as add-on treatment and in LGS also from the age of 2 years. Furthermore, it is licensed for migraine prophylaxis. It has a broad mechanism of action, including blockade of sodium channels, GABAergic and anti-glutamatergic properties and carboanhydrase inhibition. Important AEs are sedation, cerebellar symptoms, paraesthesias, cognitive disturbances (especially impaired word finding), psychoses, renal calculi, metabolic acidosis, narrow-angle glaucoma, and oligohidrosis (especially in children).

TPM is rapidly absorbed from the GIT and has a t½ of approximately 21 h. Of the drug 13%–17% is bound to plasma proteins, and the drug is eliminated renally mainly unchanged. Pharmacokinetics has been shown to be linear, irrespective of the patient's age. Children aged <10 years, however, show an increased clearance of the drug [39]. EIDs lower the TPM concentration [40].

Mean TPM concentrations show neither significant differences when comparing responders (patients having a reduction of the seizure frequency of at least 50%) to non-responders, nor when patients with AEs are compared to those without [39]. The latter finding is, however, controversial, as another study has found significant differences in TPM serum concentrations between patients suffering from several AEs (abnormal thinking, impaired concentration, weight loss, dizziness, speech problems, somnolence, ataxia, increased seizure frequency and paraesthesia) and those without any AE [41]. To avoid AEs, the authors recommend aiming at a serum concentration below 4 µg/mL. However, the serum concentration does not give additional information compared to TPM dosage, as with up to a maintenance dose of 100 mg TPM (or 1.5 mg/kg, respectively) also only a minority of patients complained about AEs. Limitations of the study are small sample size and a combined evaluation of TPM concentrations before and after intake. So, from the available data, no proposal for routine use of TDM of TPM can be made. A case report has shown TDM to be helpful in differentiating non-convulsive status from severe TPM intoxication [42].

Mean concentration/dose ratios of TPM have been shown to decline during pregnancy [43, 44] and TPM concentration should be monitored in patients with renal or hepatic insufficiency.

Levetiracetam

Levetiracetam (LEV) is licensed for the treatment of newly diagnosed focal epilepsies in patients aged 16 years or more in monotherapy. Furthermore, it is used for the add-on treatment of focal epilepsies in patients aged 1 month or older, myoclonic seizures in the context of juvenile myoclonic epilepsy in patients from 12 years or more, and primarily generalised tonic-clonic seizures in patients aged 12 years or more with idiopathic generalised epilepsies. A formulation for i.v. use is available. LEV has a novel mechanism of action (binding to the synaptic vesicle protein SV2A). Important AEs are sedation, ataxia, and psychiatric symptoms (e.g., depressed mood, aggressiveness).

LEV is rapidly and completely absorbed, bound to plasma proteins <10%, eliminated renally to an extent of 95%, and t½ is approximately 7 h. LEV trough concentrations show a high interindividual variability [45].

The pharmacokinetics of LEV is influenced by EIDs, i.e., concentration-to-dose ratio is moderately, but significantly lower in combinations of LEV with phenytoin, carbamazepine or oxcarbazepine, when compared to LEV monotherapy [45].

LEV concentrations have been shown to decrease markedly during pregnancy with a rapid increase after delivery [46–48].

Accumulation of LEV has been reported in severe renal [49] and in severe hepatic insufficiency (liver cirrhosis Child-Pugh grade C) [50].

The issue of the usefulness of routine TDM of LEV is still open. A retrospective study on 66 patients failed to show a significant difference of mean plasma concentrations of LEV between 50% responders and non-responders [51].

Pregabalin

Pregabalin (PGB) is licensed for the add-on treatment of focal epilepsies in adult patients, and also for central and peripheral neuropathic pain and for generalised anxiety disorder. It acts as a ligand for the α-2-δ subunit of voltage-gated calcium channels in the central nervous system. Important AEs are sedation, weight gain, cerebellar symptoms, and peripheral oedemas.

PGB is rapidly and extensively absorbed from the GIT, does not bind to plasma proteins, and is excreted virtually unchanged by the kidneys. t½ is approximately 6 h. PGB trough concentrations are subject to high interindividual variability [52]. Although not expected by initial observations, the EIDs phenytoin, carbamazepine and oxcarbazepine moderately lower PGB concentration [52].

No information is available on the pharmacokinetics of PGB during pregnancy. Dose reduction is necessary in patients with renal impairment [53].

Zonisamide

Zonisamide (ZNS) is licensed for the add-on treatment of focal epilepsies in adults. It has a broad mechanism of action, including sodium and T-type calcium channel modification, GABAergic action and carboanhydrase inhibition. Important AEs are sedation, dizziness, loss of appetite, weight loss, renal calculi, psychotic symptoms, metabolic acidosis, oligohidrosis and hyperthermia (predominantly reported in children).

The absorption of ZNS from the GIT is nearly complete; binding to plasma proteins is 40%–50%. The drug is metabolised by CYP3A4, N-acetylisation, and glucuronidation. The unchanged drug and its metabolites are mainly excreted renally. t½ is approximately 60 h (in the absence of EIDs), and it takes about 2 weeks to reach steady-state.

The serum concentration to dose relationship has mostly been reported to be linear [54], although there is one contradictory study reporting non-linear pharmacokinetics in patients with a multi-drug regimen [55]. EIDs markedly reduce the t½ of ZNS to 27–36 h.

No direct relationship between serum concentration and clinical response has been reported and there is only a weak relationship between concentration and the occurrence of AEs [54].

There is only very limited data concerning the pharmacokinetics during ZNS in pregnancy. Reports of a few cases suggest an increase in ZNS clearance at the end of the second trimester [56].

There is only limited data on the pharmacokinetics of ZNS in patients with impaired hepatic or renal function. Dose adjustments may be necessary. ZNS concentration has been shown to decrease after haemodialysis [57].

Rufinamide

Rufinamide (RUF), a sodium-channel modulator, has orphan drug status in the EU as add-on therapy in LGS in patients aged 4 years and older. Common AEs are dizziness, fatigue, nausea, vomiting, diplopia and somnolence [58].

Absorption from the GIT is at least 85% (with food), and approximately 34% of the drug is bound to plasma proteins. RUF is mainly metabolised by hydrolysis, and approximately 85% of RUF and its metabolites are eliminated by the kidneys with a t½ of 6–10 h. The results of a recent study using routine TDM data showed a moderate, but statistically significant non-linear RUF level-dose relationship. Children aged <12 years had significantly lower RUF levels (approx. 19.0%, $p<0.001$) than adults on comparable RUF doses per body weight [59]. Serum levels were higher, when VPA was co-administered. In combination with EIDs, RUF levels were approximately 21.8% lower ($p=0.002$) compared to combinations without EIDs. RUF concentrations show a marked interindividual variability.

An analysis of pharmacokinetic and pharmacodynamic data from a pooled population found a reduction of seizure frequency in a dose-dependent manner [58] and revealed interesting findings concerning RUF plasma concentrations. In children, adolescents, and adults, the mean plasma concentration which was needed to reduce the seizure frequency by 50% was predicted to be approximately 30 μg/mL. This is, however, above the concentration range normally reached in clinical practice. With regard to a reduction of seizure frequency by 25%, the concentration needed was predicted to be approximately 15 μg/mL. In the above-mentioned study by May et al., mean RUF concentration was 10.0±6.5 μg/mL in the age group <12 years, 10.6±7.0 in the age group 12–17.9 years, and 15.9±8.5 in the age group ≥18 years. RUF plasma concentrations were higher for patients complaining about nausea, vomiting, somnolence or dizziness than for patients not suffering from AEs [58].

There is no information concerning RUF pharmacokinetics during pregnancy. Dose adjustments in patients with renal impairment or undergoing haemodialysis should not be necessary. There is no data on RUF use in hepatic impairment [58].

Stiripentol

Stiripentol (STP) has been granted orphan drug status in the EU for the treatment of primarily generalised tonic-clonic seizures in patients with severe myoclonic epilepsy of infancy (Dravet syndrome) as add-on treatment to valproic acid and clobazam. The drug exhibits GABAergic actions [60]. Frequently reported AEs include drowsiness, slowing in mental function, ataxia, diplopia, loss of appetite, nausea and abdominal pain.

STP is rapidly absorbed and 99% bound to plasma proteins with extensive hepatic metabolism. Seventy percent of the drug is excreted renally in the form of metabolites. The

drug shows non-linear pharmacokinetics, with a decrease in Cl with increasing drug dosage. Cl is higher in patients on EIDs [60]. An effect of other AEDs with a high protein binding (e.g., VPA) on protein binding of STP was, at least to our knowledge, not investigated until now. However, even if such an effect exists, this effect would probably not be clinically significant, but may be of importance for the interpretation of (decreased) total STP serum concentrations.

No data concerning STP pharmacokinetics during pregnancy or in patients with renal or hepatic impairment could be found.

Lacosamide

Lacosamide (LCM) is licensed for the add-on treatment of focal epilepsies in patients aged 16 years and older. The drug acts by enhancing the slow inactivation of voltage-gated sodium channels. An i.v. formulation is available. Common AEs are dizziness, diplopia, nausea, vomiting, abnormal coordination and blurred vision [61].

LCM is rapidly and completely absorbed from the GIT. The t½ is approximately 13 h. There is limited hepatic transformation to its major, inactive *O*-desmethyl metabolite, and the drug is excreted almost entirely in urine. To date, no clinically relevant effects of other AED on LCM levels were reported.

Data concerning the use of TDM of LCM are currently only sparse. According to recent observations, LCM serum concentrations show high fluctuations during the day with a steep increase within the first 3 h after intake. After conversion from b.i.d. to t.i.d. dosing or dose reduction, LCM serum concentrations showed lower fluctuations during the day and a lower increase after drug intake [62]. Although these observations are of a very limited nature, especially because of the small sample size, use of TDM might be justified in assessing AEs and determining the individual AE threshold under LCM.

There is no information on LCM pharmacokinetics during pregnancy. LCM serum levels are increased in patients with renal or hepatic impairment.

Eslicarbazepine acetate

Eslicarbazepine acetate (ESL) is licensed for the add-on treatment of focal epilepsies in adult patients. The drug is structurally related to OXC. ESL is rapidly and extensively metabolised. Unlike OXC that is metabolised to S-licarbazepine to an extent of 80% and to R-licarbazepine to 20%, ESL is, according to the literature, metabolised to 95% to S-licarbazepine. The drug acts on voltage-gated sodium channels [61]. AEs seem to be similar to those under OXC.

Plasma protein binding is <40%, t½ is 20–24 h, and pharmacokinetics linear. The metabolites of ESL are eliminated primarily by renal excretion. Cl is dependent on renal function. Moderate liver impairment has no relevant effect [61].

Interactions should be comparable to OXC. There is no information concerning ESL pharmacokinetics in pregnancy. Effects similar to OXC should be expected.

The pharmacokinetics of ESL was not affected by moderate hepatic impairment in eight patients under 800 mg ESL once daily over 1 week [63]. ESL dosage adjustment may be necessary in patients with a creatinine clearance <60 mL/min [64].

Until now, no sufficient data are available concerning the usefulness of TDM under ESL therapy. It can be assumed that the use of TDM is similar to OXC.

Conclusions

Although some of the newer AEDs have only limited data concerning the use of TDM, usefulness can be assumed in several specific situations.

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