The ideal pharmacokinetic properties of an antiepileptic drug: how close does levetiracetam come?

Emilio Perucca[1], Svein I. Johannessen[2]

[1]Clinical Pharmacology Unit, University of Pavia, Pavia, Italy
[2]The National Center for Epilepsy, Sandvika, Norway

ABSTRACT – The pharmacokinetic properties of a drug are the primary determinant of the extent and duration of drug action, and influence susceptibility to clinically important drug interactions. Most of the older-generation antiepileptic drugs (AEDs) are far from ideal in terms of pharmacokinetics and interaction potential. For example, phenytoin, carbamazepine, and valproic acid exhibit non-linear kinetics; carbamazepine and valproic acid have relatively short half-lives; and most of these drugs cause either enzyme induction (phenytoin, phenobarbital, primidone, carbamazepine) or enzyme inhibition (valproic acid). Compared with older agents, certain new-generation AEDs offer a number of pharmacokinetic advantages, particularly in terms of reduced inter-patient variability in drug clearance and a lower interaction potential. One of the most recently developed of these drugs, levetiracetam, comes especially close to fulfilling the desirable pharmacokinetic characteristics for an AED: (1) it has a high oral bioavailability, which is unaffected by food; (2) it is not significantly bound to plasma proteins; (3) it is eliminated partly in unchanged form by the kidneys and partly by hydrolysis to an inactive metabolite, without involvement of oxidative and conjugative enzymes; (4) it has linear kinetics; and (5) it is not vulnerable to important drug interactions, nor does it cause clinically significant alterations in the kinetics of concomitantly administered drugs. Although its half-life is relatively short (6 to 8 hours), its duration of action is longer than anticipated from its pharmacokinetics in plasma, and a twice-daily dosing regimen is adequate to produce the desired response.

KEY WORDS: antiepileptic drugs, levetiracetam, pharmacokinetics, drug interactions, review

Introduction

Pharmacokinetic properties have great practical importance: they are the primary determinant of the extent and duration of drug action and other parameters that determine a drug's ease of use. In particular, pharmacokinetic parameters play a significant role in determining the optimal frequency of administration during chronic dosing, the time to reach stable conditions (steady-state) following initiation of therapy (or dosage adjustments), the nature of the dose-response relationship, the degree of inter- and intra-patient variability in clinical effects, and the susceptibility to drug interactions [1]. In the pharmacological management of epilepsy, pharmacokinetic considerations are even more important than in other therapeutic areas. This is because antiepileptic drugs (AEDs) have

Correspondence:
Emilio Perucca
Clinical Pharmacology Unit
University of Pavia
Piazza Botta 10, 27100 Pavia Italy
Phone: + (39) 0382-506360
Fax + (39) 0382-22741
E-mail: perucca@unipv.it

a low therapeutic ratio (i.e., the effective dose is close to the dose that produces adverse effects), are administered for prolonged periods, often for a lifetime, and are commonly involved in pharmacokinetic interactions [2]. The importance of controlling pharmacokinetic variability in the treatment of epilepsy was recognised as early as four decades ago, when pilot studies were conducted to determine the value of monitoring serum concentrations of phenytoin and other AEDs as an aid to individualization of dosage [3-5].

While older-generation AEDs remain highly valuable in the modern treatment of epilepsy, these drugs have appreciable limitations in that they control seizures in only 50% to 70% of patients, they have considerable side effects and, not least, they exhibit undesirable pharmacokinetic features [6]. With regard to the latter, the metabolic and interaction profiles of the older AEDs are much less favourable than we would wish. Shortcomings include enzyme induction (phenytoin, phenobarbital, primidone, carbamazepine), enzyme inhibition (valproic acid), extensive plasma protein binding (phenytoin, valproic acid), short half-life for those AEDs whose action is closely related to their plasma levels (carbamazepine and, possibly, valproic acid), nonlinear kinetics (phenytoin, carbamazepine, valproic acid), and active metabolites (primidone, carbamazepine) [2]. Thus, there is a great need for new AEDs with improved pharmacodynamic and pharmacokinetic properties.

In recent years, several new-generation AEDs have become available in a number of countries. These agents differ greatly not only in efficacy spectrum and side-effect profile but also in kinetic parameters and susceptibility to interactions [6, 7]. While some of these newer drugs offer few or no pharmacokinetic advantages compared to older-generation anticonvulsants, others exhibit improved features that contribute to their ease of use in everyday clinical practice [8].

This review will discuss desirable pharmacokinetic requirements for an AED *(table 1)* and assess to what extent the novel agent levetiracetam approaches those requirements. Finally, levetiracetam's pharmacokinetic and interaction potential will be briefly compared with those of other new-generation AEDs.

Desirable pharmacokinetic features of an AED

High oral bioavailability

Since AEDs are usually administered orally, reliable gastrointestinal absorption and good oral bioavailability are essential to ensure effective plasma drug concentrations. All available AEDs fulfill this property, with the exception of gabapentin. This drug is absorbed through an active intestinal carrier whose progressive saturation leads to a

Table 1. Desirable pharmacokinetic properties of an antiepileptic drug

High oral bioavailability
Low plasma protein binding
Ready penetration across the blood-brain barrier
Long half-life
Significant renal elimination
Elimination by routes not involving oxidation or conjugation
Linear kinetics
No active metabolites
Low vulnerability to drug interactions
Low propensity to cause drug interactions

decrease in bioavailability with increasing dosages [9]. Ideally, bioavailability should be independent of food intake, so that a drug can be taken without regard to mealtime. However, it is recommended that the new AED tiagabine be administered with meals, since the resulting prolongation of absorption attenuates the large fluctuations in plasma levels associated with the drug's short half-life [10, 11].

Low plasma protein binding and ready penetration across the blood-brain barrier

Although interactions involving displacement from plasma proteins are generally clinically unimportant [1], high plasma protein binding is usually regarded as unfavourable, generally because it complicates the assessment of the relationship between drug concentration in plasma and clinical effects. Most AEDs exhibit little or no protein binding, but phenytoin, valproic acid, benzodiazepines, and tiagabine are notable exceptions [2, 6].

All AEDs cross the blood brain-barrier to an extent sufficient to produce anticonvulsant effects, although there are differences in the rate at which penetration occurs [1].

Long half-life

The ideal half-life for an AED is generally in the range of 12 to 36 hours. This should allow twice-daily dosing (and, for half-lives in the upper range, even once-daily dosing) without excessive fluctuations in plasma drug levels. Very long half-lives may be undesirable because they lead to undue prolongation of the time to reach steady state, as well as slow recovery should toxicity occur. Some AEDs have half-lives that are shorter than desirable. This is the case with tiagabine, whose half-life may be as short as 2 to 4 hours in patients comedicated with enzyme inducers. As discussed below, levetiracetam and vigabatrin also have short half-lives (about 6 to 8 hours), but they are effectively given twice daily, as their duration of action exceeds their chemical half-life in plasma [8].

Significant renal elimination

It is generally considered beneficial for a drug to be eliminated entirely unchanged in urine, because inter-patient variability in drug clearance tends to be less than for drugs eliminated primarily by metabolism. Moreover, metabolic drug interactions seldom occur with renally eliminated drugs. Even when a drug is metabolized to a great extent, simultaneous renal elimination in unchanged form is considered beneficial, as these drugs are less vulnerable to large pharmacokinetic changes in conditions that affect renal or hepatic function. In other words, metabolic clearance compensates partly for impaired kidney excretion in renally impaired patients, whereas renal clearance compensates partly for metabolic clearance when liver function is impaired.

Elimination by routes not involving oxidation or conjugation

The activity of oxidative and conjugative enzymes is known to be subject to high interindividual variability under the influence of genetic, environmental, developmental, and disease-related factors, as well as drug interactions [12]. Drugs whose elimination is primarily mediated by oxidation and conjugation tend to exhibit high pharmacokinetic variability, which may complicate optimisation of dosage in the individual patient. Of available AEDs, only gabapentin, levetiracetam, and vigabatrin are exempt from significant oxidation or conjugation [8, 11].

Linear kinetics

A drug exhibits linear kinetics when its plasma levels are linearly related to dose; i.e., doubling the dose results in doubling of the plasma concentration at steady state [1]. Deviation from linearity makes the effect of dosage changes unpredictable, and this complicates clinical management. Phenytoin is the most notable example of an AED showing non-linear kinetics, due to saturation of the enzyme systems responsible for its metabolism [12]. Other deviations from linearity occur with carbamazepine (dose-dependent autoinduction), valproic acid (concentration-dependent plasma protein binding), and gabapentin (dose-dependent absorption) [2, 8].

No active metabolites

Active metabolites may complicate the relationship between plasma drug concentration and clinical response. Variability in plasma metabolite levels may itself become a factor complicating optimisation of therapy.

Low vulnerability to drug interactions

The kinetics of most AEDs, especially those that are metabolised by oxidation and conjugation, can be modified markedly as a result of enzyme induction or inhibition produced by concomitantly administered medications [12, 13]. Examples include the induction of valproic acid, carbamazepine, tiagabine, and lamotrigine metabolism by barbiturates or phenytoin, or the inhibition of phenobarbital and lamotrigine metabolism by valproic acid [2, 8]. Gabapentin, levetiracetam, oxcarbazepine, and vigabatrin are least vulnerable to drug interactions [8, 11].

Low propensity to cause drug interactions

Carbamazepine, phenytoin, and barbiturates are potent enzyme inducers, whereas felbamate and valproic acid may act as enzyme inhibitors [2, 8]. A large number of clinically important interactions can be ascribed to these mechanisms [13].

Pharmacokinetic and interaction profile of levetiracetam

Absorption

After administration at doses ranging from 250 to 5000 mg in healthy subjects and in patients with epilepsy, levetiracetam is rapidly absorbed, and bioavailability is close to 100% [14]. Time to peak plasma concentration is in the range of 0.6 to 1.3 hours. The extent of absorption is not affected by food, but the rate of absorption is somewhat slower when the drug is taken with food. Absorption is equally efficient whether levetiracetam is taken as a single dose or in multiple doses, and plasma drug concentrations are linearly related to dosage [14, 15].

Distribution and protein binding

The volume of distribution of levetiracetam ranges from 0.5 to 0.7 L/kg, and the plasma protein binding is less than 10% [14]. Animal studies have shown that levetiracetam crosses the blood-brain barrier readily and shows comparable distribution in the extracellular fluid of the hippocampus and the frontal cortex [16].

Metabolism and renal excretion

Levetiracetam is minimally metabolised. The major route of excretion is through urine, mostly in the form of unchanged drug (66% of the administered dose after 24 hours). A pharmacologically inactive, acidic metabolite resulting from enzymatic hydrolysis of the acetamide group accounts for about 24% of the dose recovered in urine within 24 hours [15]. The formation of this main metabolite occurs in a wide variety of tissues, including blood cells. Two minor inactive metabolites also have been identified and result from hydroxylation of the 2-oxo-pyrrolidine ring (2% of the dose) and from opening of the 2-oxo-pyrrolidine ring in position 5 (1% of the dose). Enantiomeric conversion does not occur [15, 17]. The major metabolic pathway of levetiracetam is not dependent on the hepatic cytochrome P (CYP) 450 system;

therefore, levetiracetam is unlikely to be involved in clinically important interactions by induction or inhibition of CYP reactions.

The total body clearance of levetiracetam in adults is close to 1 mL/min/kg. The elimination half-life in plasma is 6 to 8 hours, both in healthy volunteers and in patients with epilepsy receiving comedication with other AEDs [14, 15, 18]. Since absorption and elimination processes are dose-independent, levetiracetam exhibits linear pharmacokinetics, with plasma drug concentrations related linearly to the administered dosage. In view of the relatively short half-life, steady-state plasma concentrations are already achieved by the second day of treatment. Moreover, due to the high bioavailability, predominantly renal excretion, and lack of pharmacokinetic interactions (see below), inter-patient variability in plasma levetiracetam concentrations is much less than that observed with most other AEDs.

In children aged 6 to 12 years, the total body clearance of levetiracetam is about 30% to 40% higher than in adults [15, 19, 20]. Therefore, children require mg/kg doses that are on average one-third higher than in adults to achieve comparable plasma levels. The mean half-life of levetiracetam in children is about 6 hours, which is slightly shorter than in adults.

Because levetiracetam is eliminated predominantly by renal excretion in unchanged form, a reduction in clearance is expected in patients with physiological or pathological reduction in renal function. In agreement with this, elderly patients have been found to exhibit a modest prolongation in levetiracetam half-life (to a mean value of approximately 10 hours), with a reduction of about 40% in total body clearance [15, 20], suggesting that dosage requirements may be reduced in these patients in proportion with the age-related decrease in renal function. Further studies in patients with kidney disease have confirmed that levetiracetam clearance decreases with increasing impairment in renal function. Compared with normal subjects, mean levetiracetam clearance is reduced by 40% at creatinine clearance (CLcr) values of 50 to 80 mL/min, by 50% at CLcr of 30 to 50 mL/min, and by 60% at CLcr below 30 mL/min [15]. A study in five patients with end-stage renal disease undergoing dialysis demonstrated a levetiracetam half-life of about 25 hours [20]. After dialysis, plasma levetiracetam levels were reduced by approximately one-half. Based on these findings, dosage requirements have been estimated at about 500 to 1000 mg bid in patients with CLcr of 50 to 80 mL/min, 250 to 750 mg bid in those with CLcr of 30 to 50 mL/min, 250 to 500 mg bid in those with CLcr below 30 mL/min, and 500 to 1000 mg once daily in those with end-stage renal disease [20]. After dialysis, a supplemental dose of 250 to 500 mg is recommended.

Patients with mild to moderate hepatic dysfunction (Child-Pugh class A or B) show no significant alterations in levetiracetam clearance, while in those with severe impairment (Child-Pugh class C), levetiracetam clearance has been found to be reduced by about 50%. The patients with severe hepatic impairment, however, showed a concomitant decrease in renal function that accounted for the decreased excretion of the drug [20]. Therefore, no alterations in dosage requirements are required in liver disease, unless renal function is simultaneously impaired.

Drug interactions

Based on studies conducted to date, levetiracetam stands out among available AEDs for its virtual absence of clinically significant drug interactions [8, 14, 15]. Specifically, interactions affecting levetiracetam gastrointestinal absorption have not been described, and bioavailability was not altered when the drug was taken with antacids containing calcium carbonate and aluminium hydroxide [14]. Since the plasma protein binding of levetiracetam is negligible, levetiracetam does not influence the binding of other drugs.

Levetiracetam is not substantially metabolised by CYP450 or conjugating enzymes; therefore, the potential for metabolic drug interactions is minimal. In agreement with this, *in vitro* studies demonstrated that levetiracetam does not inhibit a wide variety of drug metabolising enzymes, including CYP3A4, CYP1A2, CYP2C19, CYP2E1, CYP2C9, CYP2D6, epoxide hydrolase, and various isoforms of uridine-5′-diphospho-glucuronyl-transferases (UGT) [14, 15, 21]. Additionally, levetiracetam did not increase CYP activity in primary cultures of rat hepatocytes, a model predictive of enzyme induction [14].

In vivo studies confirmed that levetiracetam pharmacokinetics are not affected to a significant extent by the concomitant administration of other frequently prescribed AEDs [14, 15, 22]. Likewise, levetiracetam has been found not to affect the plasma levels of concomitant anticonvulsants such as phenytoin, carbamazepine, valproic acid, phenobarbital, primidone, lamotrigine, or gabapentin [14, 15, 22, 23]. Studies with other comedications also failed to identify significant interactions. In particular, levetiracetam did not affect the pharmacokinetics of steroid oral contraceptives (ethinylestradiol and levonorgestrel) [24], digoxin [25], and R- and S-warfarin [26]. Likewise, levetiracetam pharmacokinetics were unaffected by probenecid [14].

Comparison with other new AEDs

Felbamate

Felbamate is readily absorbed from the gastrointestinal tract; peak plasma levels are attained within 1 to 4 hours [8, 11, 27]. The binding to plasma proteins is 24% to 35%. Its major metabolic pathway involves hydroxylation and conjugation, and the elimination half-life is about

20 hours when the drug is given alone, decreasing to about 14 hours in patients who are also taking phenytoin or carbamazepine. Felbamate plasma levels decrease with chronic administration, suggesting some induction of metabolism [28]. The plasma levels of felbamate at steady state appear to be linearly related to dose, although a non-linear pharmacokinetic behaviour has been suggested for doses above 1600 mg/day [29].

From a pharmacokinetic viewpoint, the most striking difference between felbamate and levetiracetam lies in the fact that the former is involved in a large number of clinically important drug interactions. Felbamate significantly increases the plasma concentrations of phenytoin, phenobarbital, valproic acid, and N-desmethylclobazam (the active metabolite of clobazam), leading to potential toxicity when it is used in combinations with these agents [8, 27, 30]. Carbamazepine plasma levels decrease by about 20% when felbamate is added, but the levels of the active metabolite carbamazepine-10,11-epoxide increase by about 50%. Felbamate may also decrease the plasma levels of steroid oral contraceptives [8]. As previously discussed, plasma felbamate levels may be lowered by the concomitant use of enzyme-inducing AEDs [11].

Gabapentin

Gabapentin is rapidly but incompletely absorbed from the gastrointestinal tract. Its absorption is mediated by an active transport system which becomes easily saturated, and therefore oral bioavailability decreases with increasing dosages, resulting in a non-linear relationship between plasma concentration and dosage [9]. In clinical dosing regimens, between 30% and 60% of an administered dose is absorbed. Bioavailability may be decreased further after coadministration of certain antacids. Gabapentin is not bound to plasma proteins, is not metabolised, and is eliminated unchanged by the kidneys. The elimination half-life is about 5 to 7 hours. The clearance of the drug is reduced in the presence of renal impairment [9, 11]. Gabapentin shows no interactions with other AEDs, is not an enzyme inducer, and does not affect the pharmacokinetics of steroid oral contraceptives [6, 8].

Gabapentin and levetiracetam have in common favourable pharmacokinetic features such as a predominantly renal route of elimination and a virtual lack of drug interactions. However, gabapentin has major pharmacokinetic shortcomings in its inefficient absorption which, coupled with its short half-life, require multiple daily dosing and result in a poorly predictable, non-linear relationship between plasma concentration and dosage.

Lamotrigine

Lamotrigine is absorbed rapidly and completely from the gastrointestinal tract; it is about 55% bound to plasma proteins and is eliminated by conjugation with glucuronic acid [31, 32]. Its plasma levels are linearly related to dose.

As with other AEDs, lamotrigine clearance is higher in children than in adults [32, 33]. A significant increase of lamotrigine clearance during pregnancy, with a rapid return to baseline values after delivery, has been reported [34]. On the other hand, drug clearance is moderately reduced in the elderly [11], and it is decreased to an even greater extent in the presence of severe hepatic dysfunction [35].

The main pharmacokinetic difference between lamotrigine and levetiracetam is the high susceptibility of lamotrigine's metabolism to interactions caused by concomitant medication. While lamotrigine does not affect the plasma levels of concomitantly administered AEDs, and it does not modify the pharmacokinetics of steroid oral contraceptives and the anticoagulant response to warfarin [8, 31, 32], its metabolism is highly vulnerable to enzyme induction and inhibition. In the absence of comedication, the elimination half-life of lamotrigine is about 25 hours on average, but it is reduced to approximately 15 hours in patients taking enzyme-inducing AEDs such as phenytoin, carbamazepine, or barbiturates, resulting in increased lamotrigine dose requirements in patients comedicated with these drugs [8, 31, 32, 36]. Oxcarbazepine [8] and steroid oral contraceptives [37] may also stimulate lamotrigine metabolism. Conversely, valproic acid inhibits to a marked extent the metabolism of lamotrigine, whose half-life is prolonged to an average of 60 hours (range, 30 to 90 hours) in patients comedicated with valproate [8, 31, 32]. Because of this, lamotrigine dose requirements are reduced markedly when the drug is prescribed together with valproate [38].

Oxcarbazepine

Following oral administration, oxcarbazepine is rapidly and extensively converted to the active monohydroxy-derivative (MHD), 10-monohydroxycarbazepine, which is considered to be responsible for the pharmacological activity [39, 40]. The half-life of MHD is on the order of 8 to 10 hours, and its protein binding is about 40%. Oxcarbazepine and its major active metabolite are cleared mainly by non-oxidative processes, including ketone reduction and O-glucuronidation. The clearance of both compounds is reduced in patients with impaired renal function [41], and a reduction in MHD clearance has also been reported in the elderly [11]. Compared with carbamazepine, oxcarbazepine has a lower potential for clinically relevant drug interactions. Drugs such as propoxyphene, verapamil, cimetidine, viloxazine, and erythromycin, which are known to inhibit the metabolism of carbamazepine, do not alter the pharmacokinetics of oxcarbazepine or its MHD metabolite to a great extent [39, 40]. Oxcarbazepine does not modify the anticoagulant effect of warfarin, at oxcarbazepine dosages up to 900 mg/day for 1 week [40], whereas some reduction in felodipine concentration [40] and a clinically significant

reduction of the plasma levels and efficacy of steroid oral contraceptives [42] have been observed.

Compared with levetiracetam, oxcarbazepine has a considerably greater interaction potential. The plasma levels of MHD are reduced by 15% to 25% after coadministration of enzyme-inducing AEDs [40]. Oxcarbazepine also retains some enzyme-inducing activity, and it decreases the plasma levels of lamotrigine, carbamazepine, steroid oral contraceptives, and felodipine by this mechanism [8, 11, 39, 40, 42]. Conversely, due to inhibition of CYP2C19, the plasma concentration of phenytoin is elevated by up to 40% after addition of oxcarbazepine at dosages > 1200 mg/day. Phenobarbital concentrations may also be increased by oxcarbazepine, but to a lesser extent compared with phenytoin.

Tiagabine

The absorption of tiagabine is very rapid, with peak plasma levels attained at 1 hour. Although food has no effect on the extent of tiagabine absorption, the rate of absorption is considerably slower in the presence of food, and coadministration with a meal is recommended to minimise potentially excessive peak plasma drug concentrations and to reduce inter-dose fluctuations in plasma drug levels [10]. The protein binding of tiagabine is high at about 96%, and the drug is displaced from its binding sites by valproic acid, salicylates, and naproxen. Tiagabine is extensively metabolised by oxidation, and its elimination half-life is quite variable, ranging from 4 to 13 hours, with an average of about 7 hours. Its pharmacokinetics are linear. Children show higher tiagabine clearance values compared with adults [43]. Conversely, moderate to severe hepatic insufficiency reduces tiagabine clearance such that dosage should be reduced or dosing intervals increased [44].

Tiagabine does not affect the plasma levels of other AEDs; it may be administered safely with cimetidine, digoxin, theophylline, and warfarin, and it does not interact with steroid oral contraceptives [10, 45, 46]. However, tiagabine metabolism is highly sensitive to enzyme induction by barbiturates, phenytoin, and carbamazepine. In patients taking these drugs, the half-life of tiagabine is shortened to 2 to 3 hours, and dosage requirements are increased. The vulnerability of tiagabine to enzyme induction, and a very short half-life requiring multiple daily dosing, are the main pharmacokinetic features which differentiate tiagabine from levetiracetam.

Topiramate

After oral administration, peak plasma levels of topiramate are attained within 1 to 4 hours. When the drug is taken with food, absorption is slowed but not lessened [45]. The binding to plasma proteins is about 15%. Topiramate is mainly excreted unchanged in urine, but in patients taking enzyme-inducing agents, such as phenytoin, carbam-

azepine, and barbiturates, metabolism contributes significantly to the clearance of the drug [45, 47, 48]. The elimination half-life is 19 to 23 hours, but shorter values are observed in patients comedicated with enzyme inducing AEDs. Topiramate clearance is higher in children and, therefore, plasma topiramate concentrations for the same mg/kg dose are approximately 30% lower in children than in adults [45, 48].

Topiramate can be differentiated pharmacokinetically from levetiracetam by its longer half-life and its greater propensity to be involved in drug interactions. As mentioned above, the plasma levels of topiramate are reduced considerably by comedication with enzyme-inducing AEDs. The extent to which topiramate affects the plasma levels of carbamazepine and valproic acid is not clinically important; however, some patients on phenytoin attain higher plasma phenytoin concentrations when topiramate is added [45, 47, 48]. Topiramate may decrease the plasma levels of steroid oral contraceptives (an interaction only observed at topiramate doses around 200 mg/day or above) and, to a minor extent, the plasma concentration of digoxin.

Vigabatrin

Vigabatrin comprises two enantiomers, of which only the (S)-form is pharmacologically active [49]. Differences in pharmacokinetic features between the two enantiomers, however, are relatively modest. After oral administration, peak plasma vigabatrin levels are attained within about 2 hours. Vigabatrin is not bound to plasma proteins, and no metabolites have been identified in man [50]. The drug is excreted unchanged in the urine, and therefore patients with impaired renal function due to aging or kidney disease show a reduced drug clearance and require a corresponding reduction in dosage. Vigabatrin shows linear pharmacokinetics and an elimination half-life of about 6 to 8 hours. Children show a higher clearance of the active S-enantiomer compared to adults, and therefore they require larger mg/kg doses to achieve comparable plasma levels [11].

Because of its irreversible mode of action as a suicide inhibitor of gamma-aminobutyric acid transaminase, the duration of effect of vigabatrin outlasts considerably its half-life in plasma, and twice- or even once-daily dosing are appropriate with this drug [6, 8, 49]. From a pharmacokinetic point of view, vigabatrin shows some similarities to levetiracetam in that its elimination is predominantly in unchanged form, its duration of action is longer than the plasma half-life, and drug interactions are not generally a concern. However, vigabatrin has been reported to lower serum phenytoin levels in some patients, an interaction whose mechanism remains obscure [51].

Zonisamide

Zonisamide is well absorbed from the gastrointestinal tract; peak plasma levels are obtained within 4 hours [45,

Table 2. A comparative assessment of the extent to which older and newer antiepileptic drugs fulfill desirable pharmacokinetic properties. A « yes » rating is always indicative of a favourable feature. For oxcarbazepine, properties refer to the active monohydroxy derivative (MHD)

Drug	High oral bioavailability	Low plasma protein binding	Long half-life	Significant renal excretion in unchanged form	Absence of oxidation or conjugation	Absence of active metabolites	Linear kinetics	Uncommon target of drug interactions	Uncommon cause of drug interactions
Carbamazepine	Yes	Yes	No*	No	No	No	No	No	No (inducer)
Clobazam	Yes	No	Yes	No	No	No	Yes	No	Yes
Ethosuximide	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes
Phenytoin	Yes	No	Yes	No	No	Yes	No	No	No (inducer)
Primidone	Yes	Yes	No	Yes	No	No	Yes	No	No (inducer)
Phenobarbital	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No (inducer)
Valproic acid	Yes	No	No*	No	No	Yes	No	No	No (inhibitor)
Felbamate	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No (inhibitor)[+]
Gabapentin	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Lamotrigine	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes
Levetiracetam	Yes	Yes	No[‡]	Yes	Yes	Yes	Yes	Yes	Yes
Oxcarbazepine	Yes	Yes	No	No	No	Yes	Yes	Yes[§]	No[+]
Tiagabine	Yes	No	No	No	No	Yes	Yes	No	Yes
Topiramate	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes[+]
Vigabatrin	Yes	Yes	No[‡]	Yes	Yes	Yes	Yes	Yes	Yes
Zonisamide	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes

* Sustained-release formulations suitable for twice-daily dosing are available.
[+] Oxcarbazepine, topiramate (≥ 200 mg/day), and felbamate (in addition to phenytoin, carbamazepine, phenobarbital, and primidone) stimulate the metabolism of the contraceptive pill.
[‡] Prolonged effect despite short half-life allows twice-daily dosing.
[§] The plasma levels of MHD are moderately reduced by enzyme-inducing comedication.

52]. The drug is about 60% bound to plasma proteins and is eliminated partly by renal excretion and partly metabolically by glucuronidation, acetylation, and oxidation. On average, the elimination half-life of zonisamide has been estimated to be approximately 60 hours, but shorter values in the order of 25 to 35 hours are observed in patients comedicated with carbamazepine or phenytoin. This indicates that the metabolism of zonisamide is accelerated by enzyme-inducing AEDs. Within the therapeutic dose range, zonisamide pharmacokinetics do not appear to deviate substantially from linearity. As observed for other AEDs, children require higher mg/kg dosages to achieve plasma zonisamide levels comparable with those found in adults [11].

Zonisamide usually has no major effects on plasma levels of concomitant AEDs. However, as discussed above, enzyme-inducing AEDs stimulate zonisamide metabolism and decrease its concentration in plasma [45, 52]. In contrast, plasma zonisamide levels decrease only slightly when valproate is added.

Conclusions

A comparative evaluation of older- and newer-generation AEDs with respect to desired pharmacokinetic features is summarized in *table 2*. This table clearly indicates that, among available AEDs, levetiracetam fulfills most desirable pharmacokinetic characteristics: (1) it has a high oral bioavailability, which is unaffected by food; (2) it is not significantly bound to plasma proteins; (3) it is eliminated partly in unchanged form by the kidneys and partly by hydrolysis to an inactive metabolite, without involvement of oxidative and conjugative enzymes; (4) it has linear kinetics; and (5) it is not vulnerable to important drug interactions, nor does it cause clinically significant alterations in the kinetics of concomitantly administered drugs. The half-life of levetiracetam is shorter than usually considered desirable for an AED. However, when the suppression of paroxysmal EEG discharges elicited by photic stimulation in patients with photosensitive epilepsy was used as a model to investigate the time course of pharmacodynamic response, it was found that the duration of effect of levetiracetam could be longer than anticipated from the half-life in plasma [53]. This observation could have various theoretical explanations, such as a longer persistence of the drug at the site(s) of action in the brain, a complex mechanism of action not requiring stable drug concentrations, or a wide therapeutic index which ensures a therapeutic response over a wide range of concentrations. Whatever the mechanism involved, the feasibility of achieving high therapeutic efficacy with twice daily dosing has been demonstrated conclusively in controlled clinical trials [18].

Monitoring serum drug concentrations represents a valuable tool in individualising dosage with older-generation AEDs. With the newer anticonvulsants, serum drug level monitoring is not routinely practiced, even though for some of these agents, the wisdom of neglecting an adequate exploration of concentration-response relationships has been challenged [54, 55]. In the case of levetiracetam, however, measuring plasma drug concentrations is unlikely to be of value in the large majority of patients, due to the drug's wide therapeutic index and its limited pharmacokinetic variability.

Based on the above considerations, it can be easily understood how levetiracetam's pharmacokinetic profile represents a significant determinant of the ease of use of this drug in routine clinical practice.

References

1. Perucca E. Pharmacokinetics. In: Engel J Jr, Pedley TA. *Epilepsy—A Comprehensive Textbook.* New York: Raven Press, 1997: 1131-53.

2. Perucca E. Established antiepileptic drugs. In: Brodie MJ, Treiman DM. *Modern Management of Epilepsy.* Baillère's Clinical Neurology, vol 5. London: Baillière-Tindall, 1996: 693-722.

3. Buchtal F, Svensmark O, Schiller PJ. Clinical and electroencephalographic correlations of serum levels of diphenylhydantoin. *Arch Neurol* 1960; 2: 624-30.

4. Lund L. Anticonvulsant effect of diphenylhydantoin relative to plasma levels. A prospective three-year study in ambulant patients with generalized epileptic seizures. *Arch Neurol* 1974; 31: 289-94.

5. Feldman RG, Pippenger CE. The relation of anticonvulsant drug levels to complete seizure control. *J Clin Pharmacol* 1976; 16: 51-59.

6. Perucca E. The new generation of antiepileptic drugs: advantages and disadvantages. *Br J Clin Pharmacol* 1996; 42: 531-43.

7. Gatti G, Bonomi I, Jannuzzi G, *et al.* The new antiepileptic drugs: pharmacological and clinical aspects. *Curr Pharm Des* 2000; 6: 839-60.

8. Perucca E. The clinical pharmacology and therapeutic use of the new antiepileptic drugs. *Fund Clin Pharmacol* 2001; 15: 405-17.

9. Goa KL, Sorkin EM. Gabapentin. A review of its pharmacological properties and clinical potential in epilepsy. *Drugs* 1993; 46: 409-27.

10. Adkins JC, Noble S. Tiagabine. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the management of epilepsy. *Drugs* 1998; 55: 437-60.

11. Perucca E. The clinical pharmacokinetics of the new antiepileptic drugs. *Epilepsia* 1999; 40(Suppl 9): S7-13.

12. Perucca E, Richens A. Biotransformation. In: Levy RH, Mattson RH, Meldrum B. *Antiepileptic Drugs.* New York: Raven Press, 1995: 31-50.

13. French JA, Gidal BE. Antiepileptic drug interactions. *Epilepsia* 2000; 41(Suppl 8): S30-6.

14. Patsalos PN. Pharmacokinetic profile of levetiracetam: toward ideal characteristics. *Pharmacol Ther* 2000; 85: 77-85.

15. Radtke RA. Pharmacokinetics of levetiracetam. *Epilepsia* 2001; 42(Suppl 4): 24-7.

16. Tong X, Patsalos PN. A microdialysis study of the novel antiepileptic drug levetiracetam: extracellular pharmacokinetics and effect on taurine in rat brain. *Br J Pharmacol* 2001; 133: 867-74.

17. Isoherranen N, Yagen B, Soback S, et al. Pharmacokinetics of levetiracetam and its enantiomer (R)-alpha-ethyl-2-oxo-pyrrolidine acetamide in dogs. *Epilepsia* 2001; 42: 825-30.

18. Dooley M, Plosker GL. Levetiracetam. A review of its adjunctive use in the management of partial onset seizures. *Drugs* 2000; 60: 871-93.

19. Pellock JM, Glauser TA, Bebin EM, *et al.* Pharmacokinetic study of levetiracetam in children. *Epilepsia* 2001; 42: 1574-9.

20. French J. Use of levetiracetam in special populations. *Epilepsia* 2001; 42 (Suppl 4): 40-3.

21. Nicolas JM, Collart P, Gerin B, *et al. In vitro* evaluation of potential drug interactions with levetiracetam, a new antiepileptic agent. *Drug Metab Dispos* 1999; 27: 250-4.

22. Perucca E, Gidal BE, Ledent E, *et al.* Levetiracetam does not interact with other antiepileptic drugs. *Epilepsia* 2000; 41(Suppl 7): 254-5.

23. Browne TR, Szabo GK, Leppik IE, *et al.* Absence of pharmacokinetic drug interaction of levetiracetam with phenytoin in patients with epilepsy determined by new technique. *J Clin Pharmacol* 2000; 40: 590-5.

24. Giuliano RA, Hiersemenzel R, Baltes E, *et al.* Influence of a new antiepileptic drug (levetiracetam. Ucb L059) on the pharmacokinetics and pharmacodynamics of oral contraceptives. *Epilepsia* 1996; 37 (Suppl 4): 90.

25. Levy RH, Ragueneau-Majlessi I, Baltes E. Repeated administration of the novel antiepileptic agent levetiracetam does not alter digoxin pharmacokinetics and pharmacodynamics in healthy volunteers. *Epilepsy Res* 2001; 46: 93-9.

26. Ragueneau-Majlessi I, Levy RH, Meyerhoff C. Lack of effect of repeated administration of levetiracetam on the pharmacodynamic and pharmacokinetic profiles of warfarin. *Epilepsy Res* 2001; 47: 55-63.

27. Palmer KJ, McTavish D. Felbamate: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in epilepsy. *Drugs* 1993; 45: 1041-65.

28. Perhach JL, Weliky I, Newton JJ, *et al.* Felbamate. In: Meldrum BS, Porter RJ. *New Anticonvulsant Drugs.* London: John Libbey, 1986: 117-25.

29. Sofia RD, Kramer L, Perhach JL, *et al.* Felbamate. *Epilepsy Res* 1991; 3(Suppl 3): 103-8.

30. Glue P, Banfield CR, Perhach JL, *et al.* Pharmacokinetic interactions with felbamate. *In vitro-in vivo* correlation. *Clin Pharmacokinet* 1997; 33: 214-24.

31. Goa KL, Ross SR, Chrisp P. Lamotrigine. A review of its pharmacological properties and clinical efficacy in epilepsy. *Drugs* 1993; 46: 152-76.

32. Fitton A, Goa KL. Lamotrigine. An update of its pharmacology and therapeutic use in epilepsy. *Drugs* 1995; 50: 691-713.

33. Bartoli A, Guerrini R, Belmonte A, *et al.* The influence of dosage, age and comedication on steady state plasma lamotrigine concentrations in epileptic children: a prospective study with preliminary assessment of correlations with clinical response. *Ther Drug Monit* 1997; 19: 252-60.

34. Ohman I, Vitols S, Tomson T. Lamotrigine in pregnancy: pharmacokinetics during delivery, in the neonate, and during lactation. *Epilepsia* 2000; 41: 709-13.

35. Marcellin P, de Bony F, Garret C, *et al.* Influence of cirrhosis on lamotrigine pharmacokinetics. *Br J Clin Pharmacol* 2001; 51: 410-4.

36. Jawad S, Yuen WC, Peck AW, *et al.* Lamotrigine: single-dose pharmacokinetics and initial 1 week experience in refractory epilepsy. *Epilepsy Res* 1987; 1: 194-210.

37. Sabers A, Buchholt JM, Uldall P, *et al.* Lamotrigine plasma levels reduced by oral contraceptives. *Epilepsy Res* 2001; 47: 151-4.

38. Pisani F, Oteri G, Russo MF, *et al.* The efficacy of valproate-lamotrigine comedication in refractory complex partial seizures: evidence for a pharmacodynamic interaction. *Epilepsia* 1999; 40: 1141-6.

39. Grants SM, Faulds D. Oxcarbazepine. A review of its pharmacology and therapeutic potential in epilepsy, trigeminal neuralgia and affective disorders. *Drugs* 1992; 43: 873-88.

40. Wellington K, Goa KL. Oxcarbazepine: an update of its efficacy in the management of epilepsy. *CNS Drugs* 2001; 15: 137-63.

41. Rouan MC, Lecaillon JB, Godbillon J, *et al.* The effect of renal impairment on the pharmacokinetics of oxcarbazepine and its metabolites. *Eur J Clin Pharmacol* 1994; 47: 161-7.

42. Fattore C, Cipolla G, Gatti G, *et al.* Induction of ethinylestradiol and levonorgestrel metabolism by oxcarbazepine in healthy women. *Epilepsia* 1999; 40: 783-7.

43. Gustavson LE, Boellner SW, Granneman GR, *et al.* A single-dose study to define tiagabine pharmacokinetics in pediatric patients with complex partial seizures. *Neurology* 1997; 48: 1032-7.

44. Lau AH, Gustavson LE, Sperelakis R, *et al.* Pharmacokinetics and safety of tiagabine in subjects with various degrees of hepatic function. *Epilepsia* 1997; 38: 445-51.

45. Perucca E, Bialer M. The pharmacokinetics of the newer antiepileptic drugs. Focus on topiramate, zonisamide and tiagabine. *Clin Pharmacokinet* 1996; 31: 29-46.

46. Schmidt D, Gram L, Brodie M, *et al.* Tiagabine in the treatment of epilepsy—a clinical review with a guide for the prescribing physician. *Epilepsy Res* 2000; 41: 245-51.

47. Perucca E. Pharmacokinetic profile of topiramate in comparison with other new antiepileptic drugs. *Epilepsia* 1996; 37 (Suppl 2): S8-13.

48. Langtry HD, Gillis JC, Davis R. Topiramate. A review of its pharmacodynamic and pharmacokinetic properties and clinical efficacy in the management of epilepsy. *Drugs* 1997; 54: 752-73.

49. Grant SM, Heel RC. Vigabatrin. A review of its pharmacokinetic properties, and therapeutic potential in epilepsy and disorders of motor control. *Drugs* 1991; 41: 889-926.

50. Rey E, Pons G, Olive G. Vigabatrin. Clinical pharmacokinetics. *Clin Pharmacokinet* 1992; 23: 267-78.

51. Gatti G, Bartoli A, Marchiselli R, *et al.* Vigabatrin-induced decrease in serum phenytoin concentration does not involve a change in phenytoin bioavailability. *Br J Clin Pharmacol* 1993; 36: 603-6.

52. Peters DH, Sorkin EM. Zonisamide. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in epilepsy. *Drugs* 1993; 45: 760-87.

53. Kasteleijn-Nolst Trenité DG, Marescaux C, Stodieck S, *et al.* Photosensitive epilepsy: a model to study the effects of antiepileptic drugs. Evaluation of the piracetam analogue, levetiracetam. *Epilepsy Res* 1996; 25: 225-30.

54. Perucca E. Is there a role for therapeutic drug monitoring of new anticonvulsants? *Clin Pharmacokinet* 2000; 38: 191-204.

55. Tomson T, Johannessen SI. Therapeutic monitoring of the new antiepileptic drugs. *Eur J Clin Pharmacol* 2000; 55: 697-705.