

The clinical relevance of pharmacokinetics and drug interactions with anti epileptic drugs

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No single antiepileptic drug (AED) is appropriate in all clinical situations and therapeutic decisions on the selection of the appropriate AED should be made on a variety of specific factors. Pharmacokinetics has an important role to play in the clinical practice of antiepileptic drug therapy, as it is important in estimating individualised drug dosage regimens necessary to achieve drug plasma concentrations without causing unacceptable toxicity.

In this paper an overview will be given of how knowledge of pharmacokinetic mechanisms determines which pharmacokinetic characteristics an AED should have. Various clinical factors such as age, underlying physiological conditions and drug interactions will also affect the pharmacokinetics and efficacy of AED medication. It will be shown how by anticipating changes in pharmacokinetics due to possible drug interactions, or alterations in one of the pharmacokinetic parameters, adverse effects and breakthrough seizures may be averted and aid in the choice of optimal AED therapy for each patient.

Introduction

Data from the World Health Organization indicate that as many as 1 in 20 people may have an epileptic seizure during their lives and that at least 1 in 200 people will have epilepsy.¹ No single antiepileptic drug (AED) is appropriate in all clinical situations and epileptologists agree that proper seizure diagnosis and classification is important in individualizing pharmacotherapy.² Therapeutic decisions should be made on a variety of specific factors such as seizure type(s), onset of drug effect, the presence of renal or hepatic disease, possibility of drug or disease state interactions, the possibility of pregnancy, the age of the patient,

adherence to therapy issues, substance abuse history, and prior history of AED use. Many of the new drugs are approved only for adjunctive use; thus, polypharmacy and drug interactions should also be considered.³

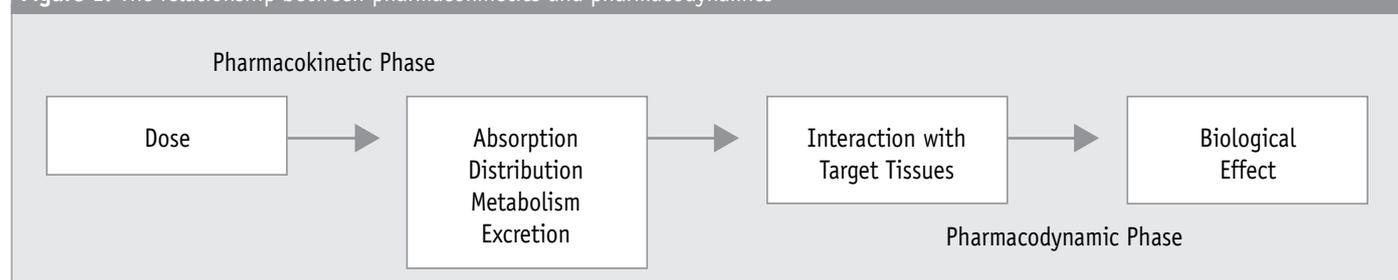
Pharmacokinetics has an important role to play in the clinical use of AED therapy.⁴ The term pharmacokinetics includes the quantitative assessment of changes of drug concentrations over time as a function of the absorption, distribution, metabolism and elimination processes. These processes determine drug plasma concentrations and in turn the drug plasma therapeutic ranges.⁵ Pharmacokinetics is thus important in estimating the drug dosage regimens necessary to achieve drug plasma concentrations and predicting the time to steady-state concentration that will control seizures without causing unacceptable toxicity.⁶ In this paper an overview will be given of how a knowledge of pharmacokinetic mechanisms will determine the ideal pharmacokinetic characteristics of an AED, and an appreciation of the relevance of parameters such as bioavailability, steady-state concentrations, protein-binding, metabolism and clearance in AED therapy.^{4,7}

Various clinical factors such as age, underlying physiological conditions and drug interactions will also affect efficacy of AED medication.² Interaction among AEDs, and between AEDs and other classes of drugs, can result in undesirable drug levels and thus difficulty in achieving seizure control.⁵ By anticipating possible drug interactions or alterations in metabolism, adverse effects and breakthrough seizures may be averted. An awareness of AED clinical pharmacokinetics will thus aid the choice of an appropriate drug and permits the design of an optimal dosage schedule for each patient.⁸

What is Pharmacokinetics?

Pharmacokinetics is the quantitative description of what happens to a drug when it enters the body, and includes the processes of drug absorption, distribution, metabolism and elimination / excretion - ADME and how these processes affect the drug plasma concentrations obtained.⁹

Figure 1. The relationship between pharmacokinetics and pharmacodynamics⁶



Pharmacokinetics (PK) briefly is what the body is doing to the drug; while pharmacodynamics (PD) is what the drug is doing to the body.⁹

Pharmacodynamic effects include both wanted and unwanted drug pharmacological effects. The underlying assumption is that monitoring drug plasma concentrations is useful since they reflect drug concentration at the receptor site, and thus being able to predict drug plasma concentrations is important since it will have a bearing on the dose required to obtain therapeutic drug concentrations. The individualisation of the drug doses needed for specific patients as a result of varying pharmacokinetics is called clinical pharmacokinetics. Pharmacokinetics is useful because the basic principles are the same for all drugs.⁷ Figure 1.

Plasma concentration time curves are a snap shot of what happens to the drug in the body. If we had to mathematically represent what is happening a plasma concentration time curve is obtained.⁵

Figure 2 represents what happens to a single dose of drug when given by any non-iv route.⁶ The graph may be divided into 3 phases:

- A: an initial absorption phase
- B: a distribution phase
- C: an elimination phase, which is linear if the plasma concentration axis is logged.

This mathematical manipulation helps us to estimate various pharmacokinetic parameters such as:

- K_a rate of absorption
- K_{el} elimination rate constant
- V_d volume of distribution
- $T_{1/2}$ half life of the drug
- Cl drug clearance – generally renal or hepatic
- F bioavailability of the drug

These parameters can then be inputted into mathematical formulae that allow the estimation of the best dose of a drug in a specific patient depending on the pharmacokinetic parameters in that patient.⁷

If multiple doses have to be administered the graph would change as represented in Figure 3. The plasma concentrations increase until, at the certain point, the minimum and maximum plasma concentrations remain constant i.e. steady state is achieved.⁶ This usually takes about five half-lives and depends on the volume of distribution and clearance of the drug. Ideally plasma concentrations at steady state should be within the therapeutic index for the drug i.e. the concentration that achieves therapeutic effect, without going subtherapeutic or toxic levels, in order to ensure that the drug is exerting its effect maximally.⁷ Figure 3.

The pharmacokinetics of a drug are estimated in the first phases of drug discovery. Ideally the drug should:

- Be soluble in 250ml water
- Have a dose size < 500 mg
- Have complete passive absorption with no transporters such as p-glycoprotein involved in absorption/effusion
- Have bioavailability >80%
- Have Linear PK
- Have a half-life of 8-12 h i.e. permits a twice daily dosing
- Have balanced hepatic/renal clearance
- Have low cytochrome (CYP450) interactions with no cytochrome-2D6 metabolism
- Have no active metabolites and no genetic polymorphism in metabolic pathways.^{9,10}

Absorption

Absorption is the entry of drug molecules into the systemic circulation via the mucous membranes of the gut or lungs, via the

skin, or from the site of an injection. Most AEDs are administered orally since epilepsy is a chronic condition, and thus this will enhance patient compliance.⁷ AEDs also exist as formulations that are available for intravenous, intramuscular or rectal administration.⁹ Thus rectal administration e.g. with rectal diazepam is useful as it has been shown to terminate repetitive seizures in children with epilepsy and other disabilities, and can be administered by family members at home.² Intravenous administration e.g. phenytoin, phenobarbital, diazepam, lorazepam, levetiracetam and valproic acid are generally used for emergencies such as status epilepticus since the lengthy absorption phase is avoided.¹¹

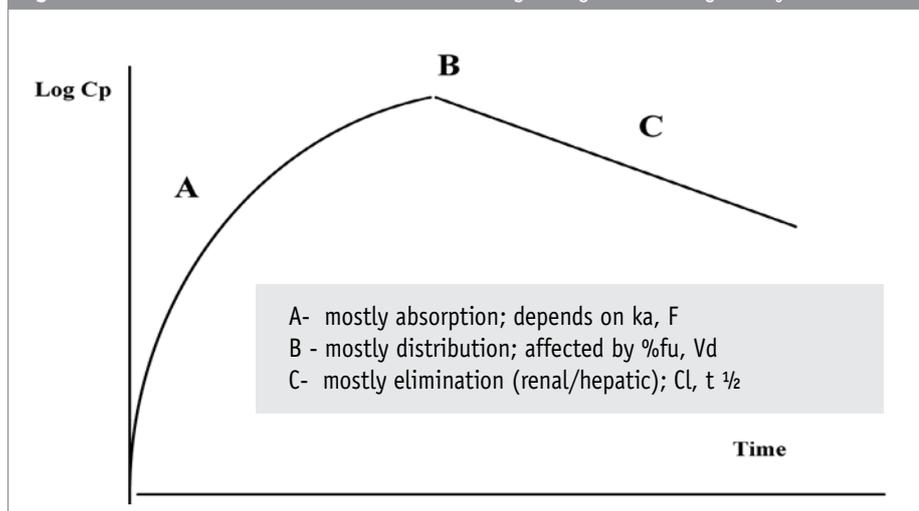
With oral formulations, the rate of absorption and bioavailability varies widely by drug, formulation, patient characteristics, concomitant drugs, and food. Absorption can also be altered by drug interactions.¹² Absorption depends also on the excipients that make up the formulation, and in fact differences between AEDs from different manufacturers may result in differences in bioavailability of the active drug. Thus changes in drug supply may result in breakthrough seizures.² Calcium containing antacids may interfere with phenytoin, phenobarbital, carbamazepine, and gabapentin absorption by decreasing the acidity of the stomach and also by the formation of insoluble complexes that cannot be absorbed.¹¹ Gabapentin (but not its chemical relative, pregabalin) is absorbed by a saturable amino acid transport system and thus larger doses will cause saturation.¹³

Of particular concern is the issue of concomitant administration of an AED with an enteral nutrition supplement. Concomitant administration of phenytoin with these nutritional formulations can result in marked reductions in oral bioavailability of this drug and it is commonly suggested that the administration of phenytoin and enteral feedings be separated by at least 2 hours.¹¹ Unfortunately, this may not be practical, particularly for patients requiring continuous feedings. Alternatively, clinicians can overcome this interaction by simply increasing the phenytoin dosage, and using serum drug concentrations as a guide.⁹ Co-administration of the newer AEDs such as valproate, levetiracetam, lamotrigine or gabapentin with enteral feeding supplements does not appear to result in significant declines in AED serum concentrations.¹³

Distribution

Following absorption into the general circulation, the drug is distributed throughout the body. The volume of

Figure 2. Plasma concentration time curve following a single dose not given by the IV route⁶



distribution is a virtual volume that gives an indication of the extent of distribution of the drug to the various tissues. It may vary if the patient has liver or cardiac problems or if the patient is pregnant.⁷

Drugs are generally protein bound, to a variable extent in the plasma, however this process is reversible. It is the unbound drug that crosses membranes and is thus responsible for the drug's action (both therapeutic and toxic), so changes in unbound, or free serum concentrations have the potential to cause unanticipated effects.⁶ Drug-protein binding displacement interactions can occur when two highly protein bound agents (>90%) are administered together and compete for a limited number of binding sites.¹¹ In most cases, protein binding displacement interactions are transient clinical events, however if only total drug serum concentrations are being monitored, this may lead to misinterpretation of plasma drug levels.²

Among the AEDs, the potential for protein-binding interactions is greatest for phenytoin and valproic acid. Both phenytoin, and valproic acid are extensively bound to plasma proteins (>90%). Valproic acid is also an inhibitor of cytochrome P₄₅₀2C19, one of the enzymes responsible for phenytoin metabolism.¹¹ When these two agents are co-administered, unbound phenytoin concentrations are higher than expected and total concentrations are lower.⁹ In this setting, the clinician should consider monitoring both unbound and total phenytoin concentrations.² The most important implication of this interaction is that in the presence of valproic acid the "therapeutic" range of total plasma phenytoin concentrations is shifted towards lower values.¹² With the exception of tiagabine (96% protein bound) an advantage of the newer generation AEDs is that they are not extensively protein bound, and therefore in this group these types of pharmacokinetic interactions are not likely.³

Metabolism

Enzymatic biotransformation and metabolism is the principal determinant of the pharmacokinetic properties of most AEDs, although some drugs are excreted by the kidneys predominantly as unchanged drug.² Most AEDs exhibit linear enzyme kinetics, in which clearance remains constant so changes in daily dose lead to proportional changes in serum concentration. It is to be noted that some metabolites are themselves active (carbamazepine, oxcarbazepine, primidone).⁷

The metabolic pathways of AEDs can vary, however, most metabolism is achieved via oxidative metabolism and/or glucuronidation.⁹ Oxidative metabolism occurs via the cytochrome P450 (CYP) isoenzyme system. This system consists of three main families of enzymes: CYP1, CYP2, and CYP3. There are seven primary isoenzymes that are involved in the metabolism of most drugs: CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. Of these, those commonly involved with metabolism of AEDs include CYP2C9, CYP2C19, and CYP3A4.¹⁴ Another important metabolic pathway for several AEDs including valproic acid, lorazepam and lamotrigine is conjugation via the enzyme uridine diphosphate glucuronosyltransferase (UGT).¹³

By far the most important pharmacokinetic interactions with AEDs are those related to induction or inhibition of drug metabolism.⁶

Enzyme induction is due to increased synthesis of drug-metabolising isoenzymes in the liver and in other tissues and may be caused by carbamazepine, phenytoin, and barbiturates. If the affected drug has an active metabolite, enzyme induction can result in increased metabolite concentration and possible toxicity due to the metabolite.²

Enzyme inhibition is the phenomenon by which a drug or its metabolite blocks the activity of one or more drug-metabolising enzymes, which results in a decrease in the rate of metabolism of the affected drug. This, in turn, will lead to high plasma concentrations of the drug and, possibly, clinical toxicity.¹⁴

In some cases, AED-AED interactions are bi-directional. In other words, both drugs impact the pharmacokinetics of the other. In general, enzyme inducers decrease the serum concentrations of other drugs metabolized by the same isoenzyme and enzyme inhibitors have the opposite effect.⁸ The bi-directional interaction between carbamazepine and valproate is one common example. In this setting, valproate can inhibit the enzyme epoxide hydrolase, which is responsible for the metabolism of the active metabolite of carbamazepine, carbamazepine-epoxide. Elevated carbamazepine-epoxide concentrations have been associated

Figure 3. Plasma concentration time curve following multiple doses given by the non IV route⁶

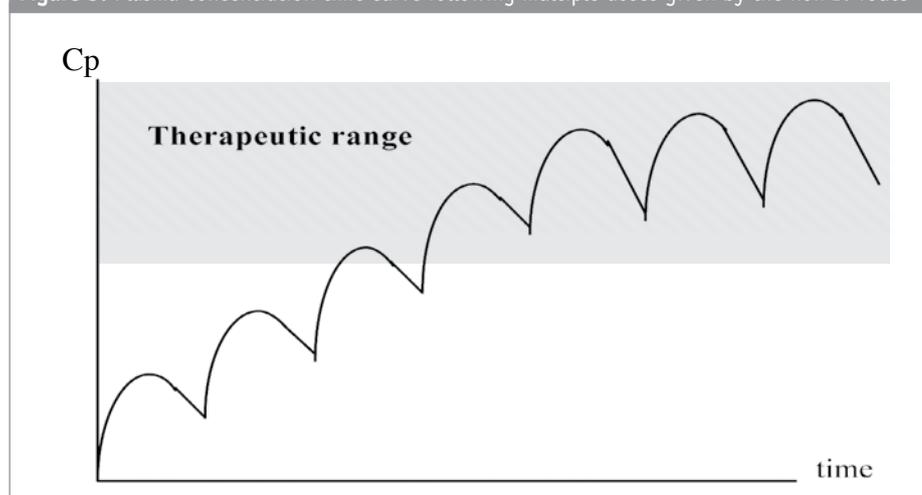
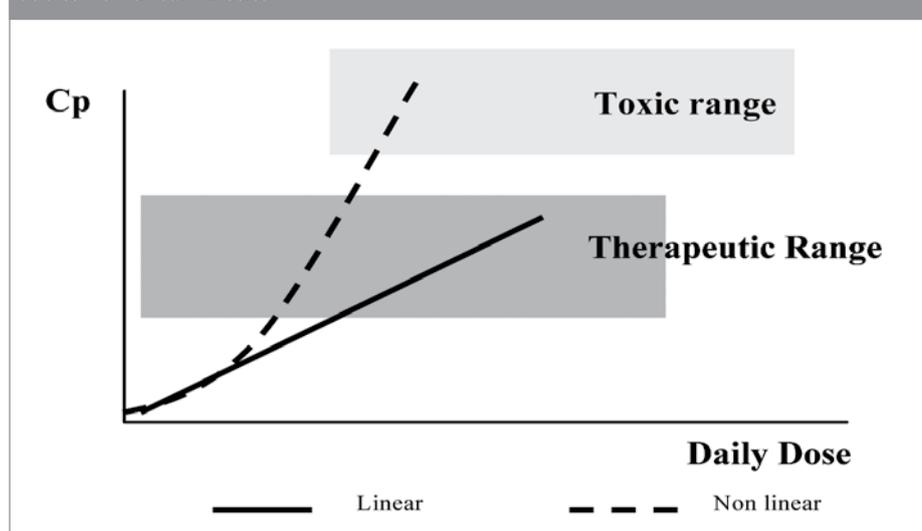


Figure 4. Changes in phenytoin plasma concentration after increase in dose due to non linear kinetics⁶



with increased neurotoxicity. In addition carbamazepine can also significantly increase the metabolism of valproate, necessitating larger doses of this medication.²

Other interactions may be of benefit in certain cases e.g. the synergistic effect of valproic acid and lamotrigine which are metabolized by (UDP)-glucuronyltransferase.¹⁴

Renal elimination

Elimination is the removal of drug molecules from the body, usually by excretion of the parent drug or metabolites through the kidneys. Drug elimination rate is usually expressed as the biological half-life and is defined as the time required for the serum concentration to decrease by 50% following absorption and distribution. The half-life also determines the dosing frequency required for a drug to be maintained at a steady state in the serum.⁶

Drugs that undergo extensive renal elimination in unchanged form may be susceptible to interactions affecting the excretion process, particularly when it involves active transport mechanisms or when the ionised state of the drug is highly sensitive to changes in urine pH, e.g. agents that cause alkalinisation of urine increase the elimination of phenobarbital by reducing the reabsorption of this acidic drug from renal tubuli.⁷

Particular mention should be made of phenytoin since it has unusual pharmacokinetics which are saturable or non-linear.⁶ In other words, unlike drugs that display linear elimination kinetics (where changes in serum concentration are proportional to dose), phenytoin concentrations will show disproportionate changes in concentration following dose adjustment. In clinical terms, this suggests that dose adjustments with this medication be small since increasing the dose by 50% could increase the plasma concentration four fold.²

Some AEDs eg gabapentin and pregabalin are only eliminated renally and do not undergo any metabolism.⁷

Drug interactions: impact of AED treatment on commonly used medical therapies

As has been explained, the occurrence of pharmacokinetic interactions has the potential to substantially complicate the management of the patient with epilepsy. This may be particularly true when dealing with the elderly patient.⁸ In treating the older patient with epilepsy, it is important for the clinician to recognize that treatment with AEDs, particularly the older enzyme inducing AEDs such as phenobarbital, phenytoin and carbamazepine¹⁵, may

complicate the management of other co-morbid disorders such as cardiovascular disease and affective disorders which more commonly occur in the group of patients.¹² The following sections provide an overview of potentially clinically meaningful interactions that are likely to be encountered in practice. Tables 1-2.

Interactions of AEDs with drugs used in the treatment of hypertension

The pharmacologic management of hypertension may require multiple antihypertensive drugs of differing classes. Several commonly used antihypertensive medications may be susceptible to interactions with enzyme-inducing antiepileptic drugs.¹⁶ For example, lipophilic beta antagonists such as propranolol and metoprolol are extensively metabolized by several isozymes of the CYP system. Therefore, larger doses of these medications might be required in patients receiving AEDs, which would be expected to increase their rate of clearance.² Conversely, fewer potential interactions would be expected with the hydrophilic beta antagonists, such as atenolol and labetalol, which are primarily renally excreted.¹⁵

Another commonly used class of antihypertensive medication are the calcium channel antagonists. Drugs such as felodipine, nifedipine, nicardipine, amlodipine, and nimodipine are members of the dihydropyridine class of agents, and these agents are extensively metabolized by CYP3A4. Concomitant treatment with enzyme inducers such as carbamazepine and phenytoin can result in substantial reductions in the oral bioavailability of these medications.¹³ Other commonly used antihypertensive drugs such as diuretics and ACE inhibitors are not extensively metabolized, and thus would not be expected to interact with AEDs.

Interactions of AEDs with drugs used in the treatment of lipid disorders

HMG-CoA reductase inhibitors ("statins") are among the most commonly prescribed lipid-lowering medications. Lovastatin, simvastatin, and atorvastatin are metabolized extensively via CYP3A4. Simvastatin and atorvastatin are also metabolized via glucuronidation (UGT 1A3) in both the gut and the liver. Fluvastatin is metabolized by CYP2C9. All of these agents would therefore be expected to be susceptible to interaction with enzyme inducing AEDs.¹⁵ Indeed, one pharmacokinetic study suggested that systemic exposure to simvastatin may be reduced by nearly 80% in patients receiving carbamazepine. Alternatively, other related

drugs such as pravastatin and rosuvastatin are not extensively metabolized, so significant pharmacokinetic interactions with AEDs would not be anticipated.¹⁶ Among the newer AEDs, only topiramate and oxcarbazepine appear to display modest CYP3A4 inducing potential and thus the potential for interactions between these lipid-lowering drugs and AEDs is expected to be minimal. Unfortunately, at present no studies have been performed to document this.¹¹

Interactions of AEDs with anticoagulants

Warfarin is administered as a racemic mixture of R- and S- enantiomers. S-warfarin is exclusively metabolized via CYP2C9, while R-warfarin is metabolized by several CYP isozymes including CYP1A2 and CYP3A4.² Since the S- enantiomer of warfarin is considerably more active than the R- enantiomer, interactions involving CYP2C9 are far more likely to have important clinical consequences. Carbamazepine and phenobarbital can in fact reduce the anticoagulant effect by increasing warfarin metabolism.¹⁶

The interaction between warfarin and phenytoin is far more complex. Initially, the coadministration of phenytoin may result in an increase in anticoagulant effect, possibly due to the combined effect of protein-binding displacement and competitive inhibition of CYP2C9², causing a seemingly "paradoxical" anticoagulant effect (i.e. increased prothrombin time, INR). In the long term however, enzyme induction will probably lead to increased warfarin metabolism, necessitating increased warfarin doses.¹¹

Clearly, in patients receiving warfarin and AED treatment, careful monitoring of international normalized ratios is crucial. Whenever possible, this drug combination should be avoided. Newer AEDs such as gabapentin, pregabalin, lamotrigine, levetiracetam and zonisamide do not appear to interact with warfarin, and may be safer (from a drug interaction viewpoint) alternatives.^{15,16}

Interactions of AEDs with drugs used in the treatment of depression

Most psychotropic drugs are metabolized by one or more of the CYP isozymes.¹⁴ Therefore, co-medication with an inducing drug would be expected to increase the metabolism, and therefore systemic clearance of these medications. Serum concentrations of tricyclic antidepressants such as amitriptyline, nortriptyline, imipramine, and desipramine, as well as nontricyclics such as sertraline, paroxetine, mianserin, citalopram, and nefazodone, would be expected to be

reduced in patients receiving enzyme inducers.¹⁶

Conversely, treatment with some SSRI compounds has the potential to impact AED pharmacokinetics. For example, fluoxetine has been shown to inhibit several CYP isozymes, and concomitant treatment with phenytoin or carbamazepine may result in elevated serum concentrations of those agents.² In contrast to the inducers, valproate can inhibit certain CYP and UGT enzymes and may cause significant increases (50%-60%) in serum concentrations of antidepressants such as amitriptyline and nortriptyline.¹⁴ In some patients, this increase may be sufficient to result in the emergence of adverse effects. Given that many of the newer AEDs are, in general,

less likely to interact with the CYP isozyme system the likelihood of meaningful pharmacokinetic interactions is also reduced.¹¹

Patient influences on drug pharmacokinetics

Various physiological and pathological conditions can influence pharmacokinetic and pharmacodynamic parameters.⁹

Children

Drug metabolism and disposition in children can differ significantly from that in adults.¹⁷ Beyond the neonatal period, when protein binding and drug metabolic rates are low, children usually have faster drug elimination rates and reduced serum

half-lives relative to adults.² Some children require almost twice the adult mg/kg dosage, particularly if combination therapy with enzyme-inducers is employed.¹⁷

Despite frequent drug administration, large swings in peak-to-peak concentrations are possible, especially in young children, because of their fast elimination rates.¹⁸ Solid oral dosage forms overcome this problem by providing a longer absorption phase that reduces peak and increases trough concentrations. Crushed tablets are preferable to liquids in younger children for similar reasons. Rapid gastrointestinal transit times in children may, however, impede absorption.¹⁷ In children, drug metabolism and disposition can differ significantly from that in adults. Beyond the neonatal period, when protein binding and drug metabolic rates are low, children usually have faster drug elimination rates and reduced serum half-lives relative to adults.⁸ Some children require almost twice the adult mg/kg dosage, particularly if combination therapy with enzyme-inducers is employed. Furthermore, because of shorter paediatric half-lives, most AEDs require at least three times daily administration in children 1-10 years of age.¹³

Elderly

In the elderly, AEDs should usually be started at a lower dose and increased at a slower rate than in younger patients.¹⁸ Elimination of many drugs is slower in the elderly, mainly because of reduced hepatic and renal blood flow, which lengthens drug half-life above published values based on young adults. In addition, albumin levels fall with age; this increases the free fraction of drugs that are highly protein bound, thus increasing risk of toxicity, especially for highly protein-bound drugs.¹⁷ Regarding the elderly, elimination of many drugs is slower, mainly because of reduced hepatic and renal blood flow, which lengthens drug half-life above published values based on young adults.² In addition, albumin levels fall with age and this increases the free fraction of drugs that are highly protein bound, thus increasing risk of toxicity, especially for highly protein-bound drugs. Further, older people are often more sensitive to drug effects at a given free level. In the elderly, AEDs should usually be started at a lower dose and increased at a slower rate than in younger patients.⁸

Pregnancy

Pregnancy increases the volume of distribution and the rate of drug metabolism, and decreases protein binding. For most AEDs, the optimal dose increases as pregnancy progresses.² It is also noteworthy that in cases of pregnancy, the volume of distribution and the rate of drug metabolism

Table 1. Effect of older AEDs on newer AEDs^{3,8,16}

	<i>gabapentin/ pregabalin</i>	<i>lamo- trigine</i>	<i>topiramate</i>	<i>tiagabine</i>	<i>levetir- acetam</i>	<i>zonisa- mide</i>	<i>Ox-carbazepine</i>
phenytoin	none	↓	↓	↓	none	↓	mhd ¹ st
carbamazepine	none	↓	↓	↓	none	↓	mhd st
valproic acid	none	↓	none	none	none	none	none
phenobarbital	none	↓	↓	↓	none	↓	mhd st
primidone	none	↓	↓	↓	none	↓	mhd st

1: Monohydroxy-derivative

Table 2. Effect of newer AEDs on older AEDs^{3,8,16}

	<i>phenytoin</i>	<i>carbamazepine</i>	<i>valproic acid</i>	<i>phenobarbital</i>	<i>primidone</i>
Gabapentin	none	none	none	none	none
Pregabalin	none	none	none	none	none
lamotrigine	none	none	↓ 25%	none	none
topiramate	may ↑	none	none	none	none
tiagabine	none	none	none	none	none
zonisamide	none	none	none	none	none
levetiracetam	none	none	none	none	none
oxcarbazepine	none	none	none	none	none

Table 3. Summary of PK characteristics of AEDs^{3,4,8,16}

<i>Drug</i>	<i>Absorption</i>	<i>Elimination</i>	<i>Half life (Hours)</i>	<i>Protein binding</i>	<i>Causes interactions</i>
Carbamazepine	80%	100% hepatic	6 -12	75-80%	yes
Valproic Acid	100%	90% hepatic	12-20	85-95%;	yes
Phenobarbitone	100%	75% hepatic	17-124	50%	yes
Phenytoin	95%,	100% hepatic	12-60	70-95%	yes
Clobazepam	90%;	100%	10-50	83%	yes
Gabapentin	< 60%	100% renal	5-8	0%	no
Flebamate	well absorbed	40-49% renal	13-30	20-25%	yes
Lamotrigine	98%	100% hepatic	18-30	55%	yes
Levetiracetam	100%	66% renal	4-8	<10%	no
Oxcarbazepine (MHD)	100%	100% hepatic	5-11	40%	yes
Pregabalin	90%	90% renal	no		
Tiagabine	96%.	97% hepatic	5-13	96%	no
Topiramate	>80%;	30-55% renal	18-30	15%	yes
Zonisamide	80-100%	50-70% hepatic	50-80	40-60%.	no

are increased whereas protein binding is decreased. For most AEDs, the optimal dose increases as pregnancy progresses.¹⁹

Others

Fever can increase the metabolic rate, resulting in more rapid drug elimination and lower serum concentrations. Febrile illnesses may also elevate serum proteins that bind AEDs, resulting in decreased free levels.²

Severe hepatic disease impairs metabolism, increasing serum levels and risk of toxicity of many drugs. However, complex interactions among hepatic blood flow, biliary excretion, and hepatocellular function make the net effect of hepatic disease on drug levels difficult to predict.¹⁸

Renal disease reduces elimination of some drugs such as gabapentin. In chronic renal disease where there is protein loss, one can commonly see a higher free fraction of highly protein bound AEDs which then are more susceptible to elimination lower serum concentration of the drug. More frequent doses may need to be given. Effects of dialysis differ among AEDs. Some, such as phenobarbital, are significantly removed.² Table 3.

PK parameters and drug interactions of AEDs: which way to go?

Determining the pharmacokinetics and the avoidance of drug-drug interactions are useful selection criteria for AED selection. Indeed, the characterization of the clinical pharmacokinetic profile of a new antiepileptic drug is an integral and early component of drug development.⁹

Consequently, pharmacokinetic considerations are especially relevant with

- Pharmacokinetics is the quantitative description of what happens to a drug when it enters the body, and is important in estimating the drug dosage regimens necessary to achieve drug plasma concentrations without causing unacceptable toxicity.
- Knowledge of pharmacokinetic mechanisms will determine the ideal pharmacokinetic characteristics of an AED, and an appreciation of the relevance of parameters such as bioavailability, steady-state concentrations, protein-binding, metabolism and clearance in AED therapy.
- Various clinical factors such as age, underlying physiological conditions and drug interactions will also affect efficacy of AED medication.
- Interaction among AEDs, and between AEDs and other classes of drugs, can result in undesirable drug levels and thus difficulty in achieving seizure control. By anticipating possible drug interactions or alterations in metabolism, adverse effects and breakthrough seizures may be averted.
- An awareness of AED clinical pharmacokinetics will thus aid the choice of an appropriate drug and permits the design of an optimal dosage schedule for each patient.

antiepileptic drugs for several reasons.⁹ Patients with epilepsy generally require chronic therapy, and, therefore, a dosing strategy that enhances compliance is essential. Also, many patients will be prescribed two or more antiepileptic drugs, often times at the highest possible doses.⁸

Additionally, all patients with chronic epilepsy can be expected to develop during their lifetime concomitant nonepilepsy-related diseases that require additional drug therapy, increasing the potential for drug interactions and toxicity. Thus, it is desirable that the drugs do not cause interactions that can precipitate toxicity.¹³

Finally, it is important to recognize that drug interactions are not a "one-way street". Interactions can be bi-directional, meaning that two drugs can influence each other.¹⁸ In addition, another important concept is

that drug interactions may occur not only when an inducer or inhibitor is added to a patient's medication regimen, but also when the inducing (e.g. carbamazepine) or inhibiting (e.g. valproate) agent is removed.

Removal of an enzyme-inducing drug will result in "deinduction," and if doses are not adjusted, serum concentrations of many metabolized concomitant drugs may increase.² Loss of enzyme induction can occur with days to several weeks following discontinuation of the inducing drug. Given that it will take about five half-lives for the previously induced medication to reach a new steady-state level, these de-induction interactions may have an insidious onset.¹⁰

Thus good knowledge of the pharmacokinetic mechanisms of the various AEDs will significantly aid the decision of which dosing strategy is the most efficient and enhance clinical therapy of AEDs.

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