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The Importance of Drug Interactions in Epilepsy Therapy

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Summary: Long-term antiepileptic drug (AED) therapy is the reality for the majority of patients diagnosed with epilepsy. One AED will usually be sufficient to control seizures effectively, but a significant proportion of patients will need to receive a multiple AED regimen. Furthermore, polytherapy may be necessary for the treatment of concomitant disease. The fact that over-the-counter drugs and nutritional supplements are increasingly being self-administered by patients also must be considered. Therefore the probability of patients with epilepsy experiencing drug interactions is high, particularly with the traditional AEDs, which are highly prone to drug interactions. Physicians prescribing AEDs to patients with epilepsy must, therefore, be aware of the potential for drug interactions and the effects (pharmacokinetic and pharmacodynamic) that can occur both during combination therapy and on drug discontinuation. Although pharmacokinetic interactions are numerous and well described, pharmacodynamic interactions are few and usually concluded by default. Perhaps the most clinically significant pharmacodynamic interaction is that of lamotrigine (LTG) and valproic acid (VPA); these drugs exhibit synergistic efficacy when coadministered in patients with refractory partial and generalised seizures. Hepatic metabolism is often the target for pharmacokinetic drug interactions, and enzyme-inducing drugs such as phenytoin (PHT), phenobarbitone (PB), and carbamazepine (CBZ) will readily enhance the metabolism of other AEDs [e.g., LTG, topiramate (TPM), and tiagabine (TGB)]. The enzyme-inducing AEDs also enhance the metabolism of many other drugs (e.g., oral contraceptives, antidepressants, and warfarin) so that therapeutic efficacy of coadministered drugs is lost unless the dosage is increased. VPA inhibits the metabolism of PB and LTG, resulting in an elevation in the plasma concentrations of the inhibited drugs and consequently an increased risk of toxicity. The inhibition of the metabolism of CBZ by VPA results in an elevation of the metabolite CBZ-epoxide, which also increases the risk of toxicity. Other examples include the inhibition of PHT and CBZ metabolism by cimetidine and CBZ metabolism by erythromycin. In recent years, a more rational approach has been taken with regard to metabolic drug interactions because of our enhanced understanding of the cytochrome P450 system that is responsible for the metabolism of many drugs, including AEDs. The review briefly discusses the mechanisms of drug interactions and then proceeds to highlight some of the more clinically relevant drug interactions between AEDs and between AEDs and non-AEDs. Understanding the fundamental principles that contribute to a drug interaction may help the physician to better anticipate a drug interaction and allow a graded and planned therapeutic response and, therefore, help to enhance the management of patients with epilepsy who may require treatment with polytherapy regimens. **Key Words:** Antiepileptic drugs—Drug interactions—Epilepsy—Polytherapy—Cytochrome P450.

Epilepsy is a chronic disease that may require antiepileptic drug (AED) therapy for many years. The efficacy of AED monotherapy in the treatment of epilepsy is well established (1). Approximately 60–70% of newly diagnosed patients will have their seizures controlled effectively by one AED, and switching to an alternative AED will offer effective seizure control in up to half of the remaining 30–40% of patients. AED polytherapy may be helpful for a small population of patients who do not respond to monotherapy, but careful consideration should be given to the consequences of any drug interactions between the various AEDs that are coadministered. Indeed, it has been estimated that in 6% of patients experiencing AED intoxication, a drug interaction was the cause (2). All new AEDs are given a first prescription as add-on therapy in patients with chronic refractory partial epilepsy (3), so polytherapy will initially be the only option for new AEDs. Even when using AED monotherapy, patients may not be free of the consequences of potential drug interactions, as in many patients, concomitant diseases or other debilitating conditions will develop, which will require the coadministration of non-AED drugs. The widespread use of the oral contra-

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ceptive pill by young women with epilepsy may result in unwanted drug interactions if it is administered with AEDs. Furthermore, patients with epilepsy, like many people, may use over-the-counter medications either intermittently or even throughout their lives, and these too may be associated with drug interactions. The therapeutic relevance of drug interactions is important not only when additional drugs are coadministered, but also when one or more drugs are removed from a multiple drug regimen. Interaction processes go into reverse when an interacting drug is discontinued from a patient's drug regimen; therefore physicians must be aware that drug discontinuation may have a serious impact on the efficacy or toxicity of the remaining drug(s).

The purpose of this review is (a) to present an overview of the important principles and fundamental characteristics that contribute to and are associated with drug interactions; (b) to highlight some clinically relevant drug interactions between coadministered AEDs and between AEDs and non-AEDs, which may present problems for patients with epilepsy and frequently require therapeutic adjustment; and (c) to provide guidelines with regard to the various considerations that should be made by the prescribing physician.

THE NATURE OF DRUG INTERACTIONS

What is a drug interaction?

Drug interactions can occur whenever a patient is administered two or more drugs simultaneously. A drug interaction occurs when one drug modifies the activity of another, either enhancing or reducing its pharmacologic effect. The outcome either may be beneficial, if the therapeutic potency of the drug is enhanced, or harmful if the interaction causes an increase in the adverse effects of the drug or if a reduction in efficacy occurs. Beneficial effects resulting from the coadministration of drugs that are synergistic at their site of action also can result in an adverse drug interaction if the doses of the drugs are not reduced to limit the risk of concurrent side effects. Conversely, if the drug interaction results in a reduction in the activity of one or more of the coadministered drugs, then it may be necessary to increase the dose of the affected drug(s). If patients are taking multiple medications, there is always the potential to discontinue one or more of the medications. When an interacting drug is discontinued from a polytherapy regimen, the interaction goes into reverse and, depending on the underlying mechanism of the drug interaction, may result in either reduced drug efficacy or enhanced toxicity.

In some circumstances drug interactions are complicated and problematic. For example, interactions involving the active metabolite(s) of the coadministered drugs may not always be obvious if concurrent plasma-concentration changes in the parent drug do not occur. It is not common practice to monitor plasma metabolite concentrations; therefore if one is unaware of the interaction, blood-concentration monitoring of the parent drug could be misleading. Such problematic interactions are associated with carbamazepine (CBZ)-epoxide, the pharmacologically active metabolite of CBZ. For example, during valproate (VPA) and CBZ combination therapy, patients can experience adverse effects as a result of an elevation of epoxide concentration resulting from an inhibition of epoxide metabolism by VPA, without concurrent changes in CBZ concentrations. The combination of VPA and lamotrigine (LTG) offers a further example of how a drug interaction can be complex and somewhat problematic. These two AEDs interact both pharmacokinetically and pharmacodynamically. These AED combinations are discussed in more detail in subsequent sections.

Awareness of the mechanism of a drug interaction can be used to clinical advantage; for example, when one drug reduces the rate of elimination of another and increases the half-life of the affected drug, this can have an impact on the frequency of dosing, which in turn may improve compliance, or it may mean that a reduction of the dose of the affected drug is necessary. In patients with a subtherapeutic plasma concentration of drug, elevation of the concentration may result in better seizure control. In some circumstances, drug interactions may be considered desirable if they lead to economic benefits if the cost of the combined treatment is cheaper than that when treating with either drug alone. An example of this is the comedication with VPA and LTG: VPA increases the plasma concentration of LTG, allowing the dose of the latter to be reduced when these two AEDs are used together (4).

Clinically relevant drug interactions related to epilepsy treatment have been identified in the past by empiric observation, and physicians were often unaware of the potential for drug interactions, or the importance of them. A more rational approach has been adopted in recent years with the discovery and characterisation of the enzyme systems responsible for the metabolism of AEDs, as these enzyme systems are potentially major targets for interference by concomitantly administered drugs. The development of in vitro screening assays for studying the interactions of new AEDs with the cytochrome P450 enzyme system has allowed potential drug interactions to be anticipated before the drugs reach the clinical stage of development. Consequently, in vitro screening for drug interactions is usually undertaken early in the development of an AED, and pharmacokinetic investigations are usually undertaken in phase I and II studies, which means that specific drug interactions can be anticipated and looked for in early clinical trials. More observations of drug interactions are made subsequent to drugs being licensed.

There are two basic types of drug interaction:

- Pharmacokinetic interactions, in which one drug interferes with the disposition of another, alter the concentration of the drug at the site of action. These interactions are associated with a change in plasma concentration of either the drug or its metabolite(s) or both.
- Pharmacodynamic interactions between drugs that have similar or opposing pharmacologic mechanisms of action. These interactions take place at the cellular level where the drugs act and are not associated with any change in the plasma concentration of either drug.

Pharmacokinetic interactions

Pharmacokinetic interactions can occur during any stage of drug disposition (i.e., during absorption, distribution, metabolism, or elimination), and they are associated with drug-concentration changes in the peripheral plasma compartment. They also may take place, in the case of centrally acting agents such as AEDs, in the central brain compartment (e.g., cerebrospinal fluid or the extracellular fluid site of drug action). Pharmacokinetic interactions that take place in the brain central compartment are currently very difficult to measure in humans and may be confused with pharmacodynamic interactions. Animal models do exist to look at this type of pharmacokinetic interaction (5), and with the continuous enhancement of nuclear magnetic resonance (NMR) spectroscopy and magnetic resonance imaging (MRI) scanning technologies, such studies will be possible in humans in the foreseeable future.

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. Drug interactions with AEDs are rare during absorption, although antacids have been shown to reduce the absorption of some AEDs [e.g., phenytoin (PHT), PB, CBZ, and gabapentin (GBP)] by decreasing the acidity of the stomach and also by formation of insoluble complexes.

Distribution. Distribution is the movement of drug molecules between the various water, lipid, and protein compartments in the body, including the movement of drugs to their sites of action, metabolism, and elimination. Interactions involving the distribution of drugs are difficult to ascertain. After ~1 month of coadministration of vigabatrin (VGB) with phenytoin (PHT), the plasma concentration of PHT is reduced by ~30%. To date the mechanism of this interaction remains unknown, although it is thought to involve an effect on PHT distribution (6).

As drugs enter the systemic circulation they can become bound to plasma proteins, for example, PHT, diazepam (DZP), VPA, and tiagabine (TGB) are >90% protein bound: drugs that are protein bound compete for protein binding, and this can result in displacement of AEDs from their plasma protein–drug complex, resulting in increases in the free fraction (unbound concentration/total concentration) of the previously protein-bound AED. The unbound drug is available to interact not only with pharmacologic receptors but also with hepatic drug-metabolising enzymes. As the free fraction of the drug increases, total systemic clearance also increases, leading to a decline in total drug concentration. Unbound (pharmacologically active) drug concentrations are dependent on drug dose and hepatic intrinsic clearance. Therefore although at steady-state, a displacement interaction may transiently increase the unbound drug concentration, the concentration should return to its preinteraction value, assuming there has not been any alteration in hepatic intrinsic clearance. In practice, these interactions are of potential clinical significance in that they confound therapeutic drug monitoring. It is important, in this setting, to guide dosing strategies by monitoring free drug concentrations. When PHT and VPA are coadministered, a complex interaction can occur that includes both a displacement of PHT from its plasma protein–binding sites and an inhibition of PHT metabolism, and this increase in plasma PHT concentration can lead to toxicity in some patients (7,8). Felbamate (FBM), GBP, LTG, levetiracetam (LEV), topiramate (TPM), and VGB are not significantly bound to plasma proteins and are not subject to this type of drug interaction.

Elimination. Elimination is the removal of drug molecules from the body by excretion, usually by the kidneys, or by biotransformation/metabolism (primarily by the cytochrome P450 system), mainly in the liver. Excretion is important for water-soluble drugs and the water-soluble metabolites of lipid-soluble drugs. Conjugation, another metabolic process involving hepatic uridine diphosphate glucuronosyltransferase (UGT) enzymes, usually results in the production of pharmacologically inactive and less lipid-soluble metabolites, which are often excreted in the urine or in the bile. Although drug interactions affecting renal excretion are rare with AEDs, other drugs have been reported to interact at this site. For example, probenecid increases the plasma concentration of penicillin by competing for the same active transport system in the kidneys and consequently reduces the renal excretion of penicillin (9). People with epilepsy are not routinely treated with probenecid; therefore this potential interaction is currently of minor significance. It should be borne in mind that although VGB, GBP, LEV, TPM, and FBM are renally excreted, it has not been established whether this occurs by active transport systems. Nevertheless other drugs that are similarly excreted could potentially interact with these AEDs. However, probenecid does not affect LEV, although it does decrease the renal excretion of the in-

active metabolite L057 (10). A potentially useful interaction is that with ammonium chloride and other urine-alkalinising drugs (11). These drugs increase urinary elimination by reducing reabsorption of acidic drugs from the renal tubules, and this characteristic is exploited clinically to manage patients who have overdosed with barbiturates.

Metabolism. Metabolism is the most important mechanism of elimination and accounts for the majority of clinically relevant drug interactions with AEDs. Metabolic pathways such as conjugation involving UGTs (for example, LTG and VPA) and β-oxidation (for example, VPA) are relevant, but the cytochrome P450 system is by far the most important system for AED metabolism [for example, PHT, PB, CBZ, TPM, TGB, zonisamide (ZNS), and FBM].

Cytochrome P450 enzymes and AED interactions. Cytochrome P450 (CYP) enzymes are a major component of the mixed-function oxidase system that is located in the smooth endoplasmic reticulum of the cells of almost all tissues. The highest concentrations of CYP enzymes are found in the liver, and these enzymes are responsible for the metabolism of not only exogenous chemicals (xenobiotics), but also endogenous substances (e.g., corticosteroids). Three families of CYP enzymes are primarily responsible for xenobiotic metabolism: CYP1, CYP2, and CYP3. These three families of isoenzymes account for ~70% of total CYPs in the human liver, with ~50% being composed of members of the CYP3A and CYP2C subfamilies (30 and 20%, respectively) (12). With regard to drug metabolism, four CYP isoenzymes are responsible for the metabolism of 95% of all drugs (CYP3A4, 50%; CYP2D6, 25%; CYP2C9, 15%; CYP1A2, 5%) (13). A number of AEDs and non-AEDs are able to induce or inhibit the CYP isoenzymes, a process that is dose dependent and may involve different CYP isoenzymes. Of the ~25 different isoenzymes of CYP that have been identified, eight are known to be involved in the metabolism of AEDs (Table 1), and three are considered to be of particular importance in AED interactions: CYP2C9, CYP2C19, and CYP3A4 (5,14, 15). CYP3A4, in particular, is susceptible to induction and inhibition by many compounds, and CBZ is capable of inducing its own metabolism (autoinduction) via this

TABLE 1. *AED drug interactions involving the cytochrome P450 system*

AED	Metabolism	Cytochrome P450 isoenzyme associated with AED metabolism							
		CYP1A2	CYP2A6	CYP2B	CYP2C8	CYP2C9	CYP2C19	CYP2E1	CYP3A4
First-generation AEDs									
Carbamazepine	Cytochrome P450	Substrate Inducer	NA	NA	Substrate	Inducer	Inducer? Inhibitor?	NA	Substrate Inducer
Clobazam	Cytochrome P450	—	—	—	—	—	—	—	—
Clonazepam	Cytochrome P450	—	—	—	—	—	—	—	Substrate
Diazepam	Cytochrome P450	—	—	Substrate?	—	—	Substrate	—	Substrate
Ethosuximide	Cytochrome P450	—	—	Substrate	—	Substrate?	—	Substrate	Substrate
Phenobarbitone	Cytochrome P450	Inducer	—	Inducer	Inducer	Substrate? Inducer	Substrate? Inducer	Substrate	Inducer
Phenytoin	Cytochrome P450	Inducer	NA	Inducer	Substrate	Substrate Inducer	Substrate Inducer	NA	Inducer
Primidone	Cytochrome P450	Inducer	—	Inducer	Inducer	Substrate? Inducer	Substrate? Inducer	Substrate	Inducer
Valproate	Cytochrome P450, glucuronidation (UGT), β-oxidation	NA	Substrate	—	—	Substrate Inhibitor	Substrate	NA	Substrate? Inhibitor?
Second-generation AEDs									
Felbamate	Cytochrome P450	—	NA	—	—	—	Inhibitor	Substrate	Substrate Inducer
Gabapentin	Not metabolised	—	—	—	—	—	—	—	—
Lamotrigine	Glucuronidation (UGT)	—	—	—	—	—	—	—	—
Levetiracetam	Nonhepatic hydrolysis	NA	NA	—	—	NA	NA	NA	NA
Oxcarbazepine	Glucuronidation of MHD (UGT) and limited cytochrome P450 metabolism of MHD	—	—	—	—	—	Inhibitor	—	Inducer
Tiagabine	Cytochrome P450	—	—	—	—	—	—	—	Substrate
Topiramate	Cytochrome P450, glucuronidation (UGT)	NA	NA	NA	NA	NA	Inhibitor	NA	NA
Vigabatrin	Not metabolised	NA	NA	NA	NA	NA	NA	NA	NA
Zonisamide	Primarily cytochrome P450	NA	NA	—	—	NA	NA	NA	Substrate

NA, not affected; —, no data available; MHD, 10,11-dihydro-10-hydroxy-5H-dinenzo[*b*,*f*]azepine-5-carboxamide (the primary pharmacologically active metabolite of oxcarbazepine); AED, antiepileptic drug; UGD, uridine diphosphate glucuronosyl transferase.

isoenzyme. If two drugs are metabolised by, or act on, the same isoform of CYP, then drug interactions are more likely. PB, primidone (PRM), PHT, and CBZ are inducers of CYP isoenzymes, whereas VPA is an inhibitor (Table 1) (5,15). Although in vitro screening allows predictions to be made about potential drug interactions, it is not possible to anticipate the exact magnitude of a particular interaction, and this still has to be determined by clinical investigation.

A number of problems experienced with AEDs are due to drug interactions with PHT. PHT is associated with more drug interactions than any other AED: PHT binds loosely to CYP isoenzymes and is easily displaced by other drugs; therefore its metabolism is readily inhibited. Furthermore, the fact that the metabolism of PHT is saturable makes PHT particularly susceptible to problematic interactions. The isoenzyme CYP2C9 is responsible for ~80% of the metabolism of PHT, the remaining 20% being metabolised by CYP2C19. If a concomitantly administered drug interacts with CYP2C9 (for example, amiodarone), it will have a greater effect on the plasma concentration of PHT compared with a drug that interacts with CYP2C19 (for example, cimetidine).

Interactions involving the induction of CYP isoenzymes become apparent more slowly than those resulting from inhibition; induction requires the synthesis of new protein, and it may take several days or weeks before a clinical effect is observed. When enzyme inhibition is involved, the time scale of the interaction depends on the elimination half-life of the affected drug, with potentiation of drug activity occurring more quickly if the drug has a short half-life. For example, LTG and PB have half-life values of 1.5 and 4 days, respectively, and therefore their maximal potentiation occurs 7.5 and 20 days later, respectively. If drug interactions result in an increased plasma concentration of a drug or its active metabolite, then the patient may experience toxicity and side effects, in which case, it may be necessary to reduce the dose of the affected drug. However, in some patients, an increase in plasma drug concentration may actually enhance the therapeutic response, particularly if the concentration was previously subtherapeutic. An extended half-life also may mean that the frequency of dosing can be reduced, which may help to improve compliance. In contrast, if drug interactions involving the metabolism of coadministered drugs result in a reduction in the plasma concentration of the affected drug or its active metabolite, there may be a reduction in efficacy and a dosage increase may be required.

Because most clinically important interactions involving AEDs are the consequence of alterations in drug metabolism, an AED that does not undergo metabolism or alter the activity of hepatic enzymes is less likely to be involved in metabolic interactions. AEDs that are not metabolised or undergo minimal metabolism include GBP, LEV, and VGB.

The pharmacokinetic profiles of new AEDs versus established AEDs. The ideal pharmacokinetics for an AED are: good oral bioavailability; a half-life of 12–24 h that allows once- or twice-daily dosing; linear kinetics so as to minimise inter- and intrapatient variability; minimal plasma protein binding so as to minimise the potential for plasma protein–displacement interactions and to make the interpretation of plasma-concentration monitoring less complicated; no metabolism so as to minimise the potential for drug interactions and the production of pharmacologically active metabolites; and no drug interactions (16). The appreciation of these pharmacokinetic goals has resulted in more rational drug design. AEDs with simple pharmacokinetic characteristics allow more rational prescribing of multiple drug therapy, which should result in increased efficacy and reduced toxicity. The pharmacokinetic profiles of the currently available AEDs are shown in Tables 2 and 3.

Of the nine established AEDs, CBZ, VPA, and PHT are associated with nonlinear pharmacokinetics. In contrast, most of the new AEDs such as LTG, LEV, oxcarbazepine (OXC), TGB, and TPM exhibit linear pharmacokinetics (Table 2). Some of the second-generation AEDs are not metabolised and undergo renal elimination, which results in less pharmacokinetic variability and a lower potential for drug interactions (for example, VGB, LEV, and GBP). Furthermore, many of the second-generation AEDs (for example, LTG, LEV, GBP, and VGB) do not induce or inhibit enzymes involved in drug metabolism (10,17). It should be borne in mind that although the interaction profiles between the second-generation AEDs and other drugs are selectively investigated during clinical development, more drug interactions may become apparent after an AED is licensed and as clinical experience of coadministration with other drugs increases over time.

Pharmacodynamic interactions

Pharmacodynamic interactions result in a modification of the pharmacologic action of a drug without an alteration in its plasma or central nervous system (CNS) concentration. Pharmacodynamic interactions can take place directly at the site of action of the drug (e.g., synergistic or antagonistic effects at the target receptor) or indirectly by interfering with other physiologic mechanisms. A pharmacodynamic interaction can be useful when efficacy is additive and toxicity is infraadditive. However, pharmacodynamic interactions are more difficult to identify and measure than pharmacokinetic interactions and are often only concluded by default when a pharmacokinetic interaction has been ruled out. Animal studies have provided useful evidence of pharmacodynamic interactions involving AEDs (18–22), and results from in

TABLE 2. *Pharmacokinetic profiles of AEDs*

AED	Linear kinetics	Nonlinear kinetics	Plasma protein binding (%)	Elimination half-life (h)		
				Coadministered with a non-interacting drug	Coadministered with an AED cytochrome P450 inducer	Coadministered with an AED cytochrome P450 inhibitor
First-generation AEDs						
Carbamazepine		Yes[a]	75	16–24	9–10	A
Clobazam	Yes		85	10–58	<10–58	A
Clonazepam	Yes		85	19–40	<19–40	A
Diazepam	Yes		98	24–48	16–32	A
Ethosuximide	Yes		0	40–60	34–56	A
Phenobarbitone	Yes		50	80–100	80–100	>80–100
Phenytoin		Yes[b]	90	7–42[f]	<7–42	>7–42
Primidone	Yes		25	8–12	3–11	A
Valproate		Yes[c]	90	8–18	2–12	A
Second-generation AEDs						
Felbamate	Yes		25	13–23	14	A
Gabapentin		Yes[d]	0	5–9	—	—
Lamotrigine	Yes		56	22–38	14–15[g]	70[h]
Levetiracetam	Yes		0	6–8	—	—
Oxcarbazepine[e]	Yes		40	5–30	6–19	5–28
Tiagabine	Yes		98	5–8	2–5	A
Topiramate	Yes		15	19–25	9–12	A
Vigabatrin	Yes		0	5–7	4–6	A
Zonisamide		Yes[b]	60	57–68	27–37	—

A, Half-life values have not been formally investigated, but plasma levels would be expected to be increased during combination therapy; —, no data available, but an effect is not expected; AED, antiepileptic drug.

[a] Due to autoinduction.
[b] Due to saturation of metabolism.
[c] Due to saturation of plasma protein binding.
[d] Due to saturation of gastrointestinal absorption.
[e] Refers to MHD metabolite (see Table 1).
[f] Dose or plasma concentration dependent.
[g] Glucuronidation induced.
[h] Glucuronidation inhibited.

vitro studies are promising (23), although there is still little evidence of the applicability of such interactions in humans (24). However, anecdotal evidence and clinical experience has shown that some combinations of AEDs are more effective in controlling seizures than either drug used alone, and such combinations will be used despite a lack of scientific evidence to explain the favourable drug interaction; examples of these AED combinations include VPA and ethosuximide (ESM) (25), clonazepam (CZP) plus VPA (26), and CBZ plus VPA (27,28). Similar enhancement in clinical efficacy has been reported for combinations that include the newer AEDs [for example, TGB plus VGB (29), VGB plus LTG (30), LTG plus TPM (31), and VPA plus LTG (32–34)]. Low doses of LTG coadministered with VPA appear to produce a therapeutically desirable pharmacodynamic interaction in patients with typical absence seizures (35). However, the possibility that some of these therapeutic enhancements result from pharmacokinetic interactions taking place in the central brain compartment, rather than as a result of pharmacodynamic interactions, cannot be ruled out at this time.

VULNERABLE PATIENT GROUPS

Various factors must be considered when treating particularly vulnerable patient groups, and it is important to try to identify individuals who may be susceptible to drug interactions before treatment is initiated.

Genetic polymorphism

It is difficult to predict the full extent of drug interactions because of the large interindividual variation between patients. One of the reasons for this variation may be the genetic polymorphism of the isoenzymes involved in drug metabolism, which exists in human populations, in particular among the cytochrome P450 family of hepatic enzymes. CYP2D6 is responsible for the metabolism of ~25% of all licensed drugs, but is inactive in 6% of the white population (36). Patients with inactive CYP2D6 are at risk of toxicity from agents that are usually metabolised by this isoenzyme. Polymorphism of CYP2C9 and CYP2C19 accounts for the variable metabolism of some AEDs, including PHT (37–39). The frequency of mutations of the CYP2C9 gene is much higher in whites than in Japanese or other Asians, whereas the frequency of mutations of the CYP2C19 gene is much higher in Japanese than in whites (37,40). Pharmacogenetic screening, which will become a reality in the future, is likely to make it possible for physicians to select the most appropriate AED(s) and dose for each patient.

TABLE 3. *Pharmacokinetic characteristics of new AEDs versus old AEDs*

AED	Undergo renal elimination	Undergo metabolic transformation	Affects drug-metabolising enzymes	Does not affect drug-metabolising enzymes	Associated with AED interactions	Not associated with AED interactions
First-generation AEDs						
Carbamazepine		Yes	Yes		Yes	
Clobazam		Yes		Yes	Yes	
Clonazepam		Yes		Yes	Yes	
Diazepam		Yes		Yes	Yes	
Ethosuximide		Yes		Yes	Yes	
Phenobarbitone	Yes	Yes	Yes		Yes	
Phenytoin		Yes	Yes		Yes	
Primidone	Yes	Yes	Yes		Yes	
Valproate		Yes	Yes		Yes	
Second-generation AEDs						
Felbamate	Yes	Yes	Yes		Yes	
Gabapentin	Yes			Yes		Yes
Lamotrigine		Yes[a]		Yes	Yes	
Levetiracetam		Yes[b]		Yes		Yes
Oxcarbazepine	Yes	Yes	Yes		Yes	
Tiagabine		Yes		Yes	Yes	
Topiramate	Yes	Yes	Yes		Yes	
Vigabatrin	Yes			Yes	Yes	
Zonisamide	Yes	Yes	Yes		Yes	

[a] Refers to the glucuronide metabolite of lamotrigine.
[b] Indicates that metabolism is nonhepatic.
AED, antiepileptic drug.

Elderly patients

Administration of drugs to elderly patients tends to result in complex pharmacokinetics because of age-related changes in their physiology and other concurrent disease-related changes. Elderly patients usually have a reduced capacity to metabolise drugs, reduced plasma protein–drug binding because of reduced albumin concentrations, and reduced capacity to eliminate drugs via the kidneys. A small clinical study of 66 patients aged 4–83 years showed that age-related reductions in hepatic metabolism and in the levels of nonglycated albumin, the major ligand for CBZ, resulted in increased free CBZ concentrations, and increased sensitivity to this AED (41). Concomitant medical conditions such as hepatic and renal diseases may alter drug distribution, metabolism, or excretion. These disease-related changes in physiology, and the fact that the elderly are pharmacodynamically more sensitive to many CNS drugs (42), make them more susceptible to toxicity, and consideration must be given to these factors when prescribing AEDs. Furthermore, elderly patients often take other medications such as antacids, antipsychotic agents, antidepressants, calcium channel blockers, aspirin, and benzodiazepines (BZDs), all of which increase the risk of drug interactions (43). A survey of elderly residents in nursing homes found that 49% of the residents receiving AEDs were prescribed six or more medications (44).

Children

Children tend to metabolise drugs more rapidly than adults, and dosing of children is usually guided by age and body weight; when LTG is coadministered with other AEDs, care must be taken, as plasma LTG concentrations can exhibit wide interindividual variability, depending on the age of the child and the coadministered AED (45).

Pregnancy

Special consideration must be taken when managing epilepsy in women of childbearing age with respect to fertility, contraception, and pregnancy. Numerous AEDs (for example, CBZ, PHT, PB, FBM, OXC, and TPM) increase the metabolism and clearance of oral contraceptives, reducing their contraceptive efficacy, with the potential for unwanted pregnancy.

In pregnant women, the potential teratogenic effects of AEDs given alone or in combination must be considered. Teratogenic effects resulting from AED treatment occur in 5–6% of infants born to women with epilepsy, which is almost double the rate of the general population (46). Certain AED combinations are associated with enhanced risk (e.g., VPA), and an enzyme-inducing AED (e.g., PB, PHT, and CBZ) enhances the risk of malformations and hepatotoxicity and therefore alternative AEDs should perhaps be considered (47–49). Furthermore, there is evidence to suggest, from a study of a relatively small number of patients receiving polytherapy, that the incidence of malformations increases with increasing number of AEDs; exposure to two, three, or four AEDs is associated with an incidence rate of malformations of 5.5, 11, and 23%, respectively (50). A recent prospective study reported that whereas the odds ratio of malformations for an infant exposed to a single AED was 2.8, the odds ratio for two or more AEDs was 4.2 (51). However,

a study that involved a small number of patients receiving polytherapy failed to show a significant association between a particularly high rate of malformations and maternal polytherapy (52). The teratogenic potential of the second-generation AEDs is unknown; it also is not known whether they enhance the teratogenic potential of the older AEDs when prescribed as combination therapy.

CLINICALLY RELEVANT DRUG INTERACTIONS

A number of factors must be considered when patients are administered multiple AEDs (Fig. 1). In the following section, the most clinically important AED–AED interactions that may affect the clinical management of patients with epilepsy are discussed (Table 4). This is not intended to be an exhaustive list of all potential drug interactions. It is acknowledged that many other drug interactions occur in selected patients under certain circumstances or are observed infrequently, but are nevertheless important to individual patients. Clinical guidance on how to manage the use of multiple AEDs and non-AEDs in patients with epilepsy is provided in Fig. 2.

AED–AED interactions

VPA, LTG, TPM, TGB, and OXC coadministered with enzyme-inducing AEDs

PB, PHT, and CBZ are potent enzyme inducers (53–55), capable of increasing the level of activity of various cytochrome P450 and UGT isoenzymes (Table 1) (5,15). This usually results in an increase in the rate of metabolism of the affected coadministered drug, followed by a decrease in the plasma concentration of the coadministered drug, and possibly a loss of clinical efficacy. The amount of enzyme induction is dependent on the dose of the inducing drug, and consequently the coadministration of multiple enzyme inducers can have a significant effect, particularly if they induce common P450 isoenzymes.

When PB, PHT, or CBZ are coadministered with either VPA, LTG, TPM, or TGB, they induce an increase in the metabolism of these drugs and a subsequent reduction in their half-lives. For example, the plasma concentration of VPA was reduced to 76% when coadministered with PB, to 49% with PHT, and to 66% with CBZ (56). It may be necessary to increase the dose of the affected AED to maintain clinical efficacy with the combination therapy.

Generally the discontinuation of enzyme-inducing AEDs also should be considered when treating patients with epilepsy. For example, in the case of TPM, the discontinuation of CBZ or PHT from a regimen leads to an increase in the plasma concentration of TPM (57,58). If CBZ is discontinued from coadministration with LTG, the plasma concentration of LTG can be expected to increase (59,60). A similar effect is seen with TGB and OCBZ after the discontinuation of coadministered CBZ (61).

Lamotrigine coadministered with valproate

VPA is an enzyme inhibitor, capable of reducing the rate of metabolism of the coadministered drug, usually via CYP2C9. Enzyme inhibition usually occurs because

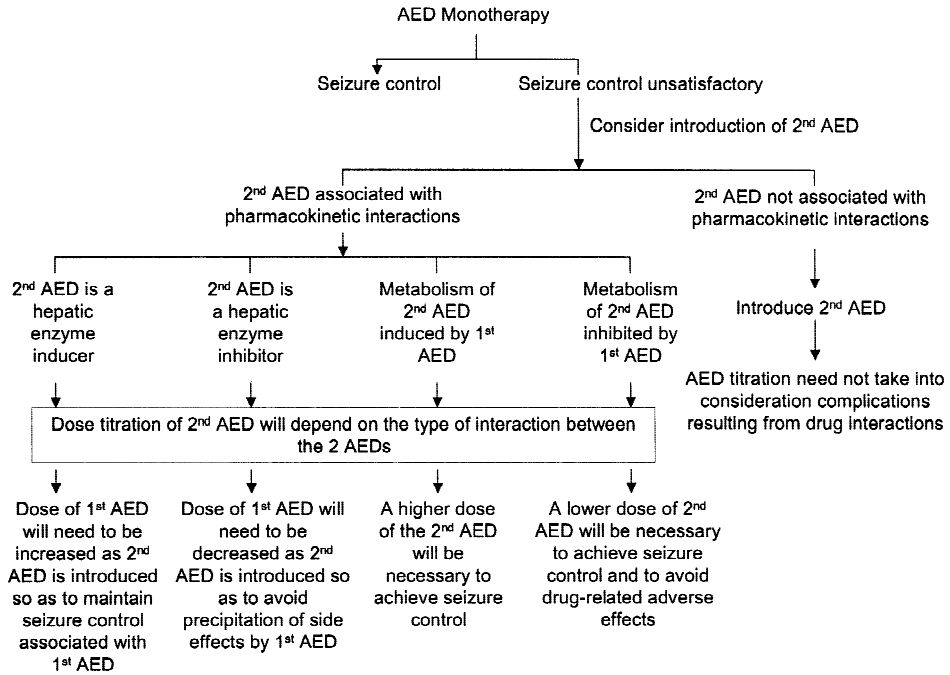

FIG. 1. Drug-interaction considerations in antiepileptic drug (AED) polytherapy.

TABLE 4. *Clinical outcome of AED–AED interactions*

Primary AED	Secondary AED	Pharmacologic outcome of drug interaction	Response needed in clinical practice
Enzyme-inducing AEDs (e.g., carbamazepine, phenytoin, and phenobarbitone)	AEDs metabolised by liver enzymes (e.g., lamotrigine, topiramate, tiagabine, valproate, and oxcarbazepine)	Increased liver metabolism and reduced half-life of the secondary AED. Lower plasma concentrations of the secondary AED achieved. Optimal seizure control may not be achieved with the standard dose	A higher dose of the secondary AED will be needed to compensate for the interaction. AED dose must be reduced if the enzyme-inducing AED is removed at a later date, to avoid toxicity
Lamotrigine	Valproate	Valproate inhibits the metabolism of lamotrigine, prolongs the half-life, and increases the plasma concentration of lamotrigine	A lower lamotrigine starting dose is recommended to compensate for this pharmacokinetic interaction and to avoid lamotrigine-induced skin rash
		Pharmacodynamic interaction resulting in enhanced efficacy of the combination	May need to reduce the doses of the two agents to reduce the risk of toxicity
Valproate	Phenobarbitone	Valproate inhibits the metabolism of phenobarbitone, prolongs the half-life, and increases the plasma concentration of phenobarbitone	May lead to phenobarbitone-induced toxicity, including sedation and drowsiness. Reduce the dose of phenobarbitone
Phenytoin	Valproate	A complex interaction can occur between valproate and phenytoin, in that valproate both displaces phenytoin from plasma proteins and inhibits the metabolism of phenytoin. In most patients, total phenytoin plasma concentration tends to decline, but the free (pharmacologically active) phenytoin concentration is unchanged	Patient management may best be guided by monitoring unbound (pharmacologically active) phenytoin concentrations
Carbamazepine	Valproate	Valproate inhibits the metabolism of carbamazepine-epoxide. Toxic plasma concentrations of carbamazepine-epoxide may result.	Toxic concentrations of carbamazepine-epoxide can result in vomiting and tiredness, particularly in children. If this occurs, reduce carbamazepine dose
Carbamazepine	Phenobarbitone	Phenobarbitone increases the metabolism of carbamazepine, reducing the plasma concentration of carbamazepine	A higher dose of carbamazepine will be needed to compensate for the interaction
Carbamazepine	Lamotrigine	A pharmacodynamic interaction may result in neurotoxic symptoms	If toxicity occurs, it may be necessary to reduce the dose of carbamazepine
Phenytoin	Topiramate	Topiramate reduces the clearance of phenytoin, which can lead to increases in plasma concentrations of phenytoin	If the patient experiences toxicity, then reduce the dose of phenytoin
Phenytoin	Oxcarbazepine (OCBZ)	Oxcarbazepine reduces the clearance of phenytoin, which can lead to increases in plasma concentrations of phenytoin	If the patient experiences toxicity, reduce the dose of phenytoin
Ethosuximide	Valproate	Possible pharmacodynamic interaction leading to improved seizure control in children with refractory absence seizures	May allow the doses of the two agents to be reduced
Phenobarbitone	Phenytoin	Bidirectional inhibition of each other's metabolism may lead to unpredictable changes in plasma drug concentrations	Monitor plasma drug concentrations of both drugs and adjust dosage accordingly
Valproate	Felbamate	Felbamate inhibits the β-oxidation of valproate, resulting in increased plasma concentrations of valproate	The frequency and clinical significance of this interaction is unknown, but this is the first interaction that demonstrates that the metabolism of valproate can be inhibited

AED, antiepileptic drug.

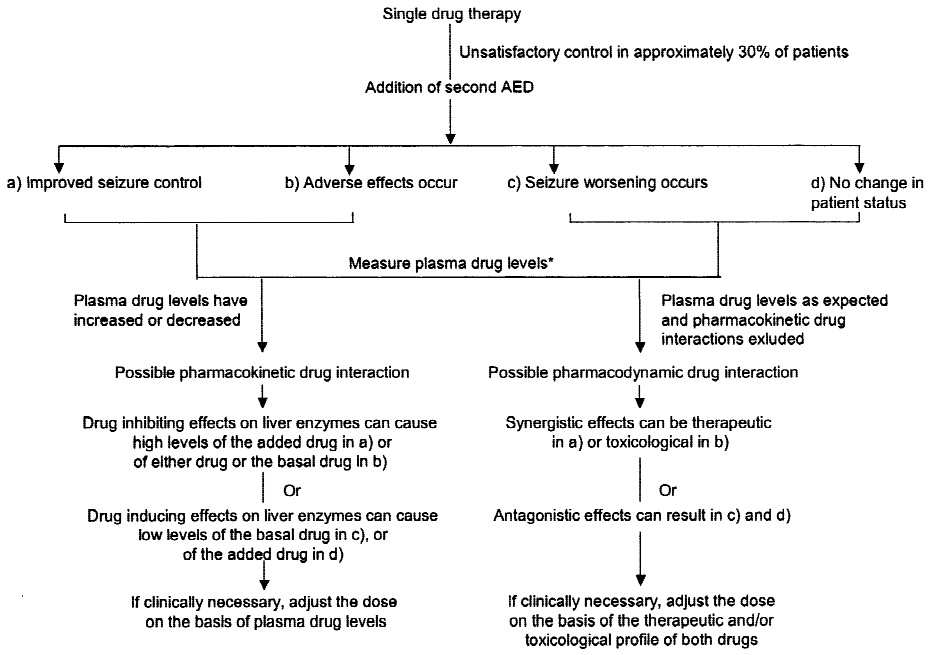

FIG. 2. Impact of antiepileptic drug (AED) interactions on therapeutic outcome. Plasma drug concentration determinations should be undertaken at the time of the clinical event (e.g., patient complaining of side effects) and the drug dosage adjusted accordingly. In the situation in which the clinical status of the patient is unaffected, plasma drug concentration levels should be determined under steady-state conditions, ideally just before the next dose ingestion (trough).

one drug competes with another for the same enzyme site. When VPA and LTG are coadministered, VPA competes with LTG for glucuronidation (a conjugation reaction) (62); this interaction inhibits the metabolism of LTG, increases the half-life of LTG from 30 to 59 h (63), and increases the plasma concentration of LTG. The dose of LTG should be reduced to avoid problems with toxicity, particularly cutaneous skin rash. In clinical practice, the introduction of LTG to a patient already taking VPA should be undertaken with caution, and typically a lower LTG dose and a slower dose titration is undertaken compared with those in patients coprescribed enzyme-inducing AEDs (e.g., PHT, PB, and CBZ). However, there is no risk of rash if VPA is introduced to a patient already stabilised with LTG.

A recent study of eight patients with epilepsy demonstrated that low to moderate doses of VPA could be used to achieve significant and beneficial increases in the plasma concentration of LTG (4). In this study, a dose of VPA as low as 200 mg/day significantly increased the area under the curve (AUC) of LTG (mean increase of 84%). Prolonging the half-life of LTG gave a flatter dose-interval profile and offered more reliable protection from seizures than may result from low plasma concentrations of LTG. However, the benefits of this combination must always be weighed against the potential increased risk of adverse events associated with the addition of VPA.

Treating patients with refractory complex partial seizures with a combination of LTG and VPA has been shown to be more effective at controlling seizures than when either drug was administered alone (33,34), although lower doses of LTG were used during combination therapy. Furthermore, the peak plasma AED concentrations achieved were lower in combination than when each drug was used as monotherapy. These findings suggest a favourable pharmacodynamic interaction between LTG and VPA. However, it may be necessary to reduce the dose of both agents to reduce the risk of toxicity, particularly severe hand tremor (64). Further clinical evidence in support of a pharmacodynamic interaction between LTG and VPA has been found in patients with intractable myoclonic epilepsy (65) and in patients with typical absence seizures (35).

Phenobarbitone coadministered with valproate

When VPA is coadministered with PB, the metabolism of PB is reduced (by inhibiting CYP2C9), resulting in an increase in plasma PB concentration. This pharmacokinetic interaction is important clinically because it occurs in most patients receiving the combination therapy and may lead to sedation and drowsiness (66–68). Consequently, the dose of PB may need to be reduced in $\leq$80% of patients when it is coadministered with VPA to reduce the risk of increased toxicity (68). It should be noted that this interaction can have highly variable outcomes in different patients, and this is partly dependent upon the concentration of PB. Furthermore, in some patients, stupor or coma (VPA-induced encephalopathy) may occur with this combination and can occur

without a significant elevation of the plasma concentrations of PB; the mechanism of this interaction is currently unclear (69–71).

Phenytoin coadministered with valproate

Drug interactions with PHT are frequently observed because it possesses some unique characteristics. PHT is substantially, but loosely, bound to plasma proteins. It is also extensively metabolised by, but loosely bound to, cytochrome P450 enzymes. These characteristics make it prone to competitive displacement and inhibitory metabolic processes (7,8,72). In addition, the metabolism of PHT is saturable at plasma concentrations associated with seizure control (73); therefore a slight inhibition of metabolism can lead to disproportionate increases in drug concentration and a risk of toxicity. VPA can both displace PHT from its plasma protein–binding sites (albumin) and weakly inhibit PHT metabolism. Generally, this complex interaction, which results in a reduction in total plasma PHT concentrations, does not require any PHT dose adjustment because the unbound (pharmacologically active) concentration is unaffected. In the event of a need to adjust the dose of PHT, adjustment should be guided by measurement of free PHT concentrations in plasma. It should be noted, however, that in some patients, adding VPA to a PHT regimen may lead to elevation of both total and free PHT concentrations and cause intoxication. If the patient experiences toxicity, than the dosage of PHT should be reduced. Other drugs that interact with PHT in the same manner as that of VPA include phenylbutazone, tolbutamide, and amiodarone (74). With regard to amiodarone, its inhibition of PHT is more pronounced. Consequently, elevation of both total and free PHT concentrations occurs more consistently during amiodarone and PHT coadministration.

Carbamazepine coadministered with valproate

CBZ is almost completely metabolised to CBZ-10,11-epoxide and then to CBZ-10,11-diol by cytochrome P450 enzymes. The formation of the epoxide is mediated primarily via CYP3A4, although CYP2C8 also contributes, whereas the metabolism of the epoxide is via the enzyme epoxide hydrolase (75). CBZ is an enzyme inducer, and its own metabolism is susceptible to autoinduction after repeated administration. VPA increases the plasma concentration of the epoxide metabolite by inhibiting epoxide hydrolase, without any marked changes in the concentration of CBZ (76–78). The clinical significance of this interaction is particularly important in children, in whom concentrations of epoxide of $\leq$13 μg/ml have been observed, along with severe side effects such as vomiting and tiredness (79). There also is some clinical evidence that there is a synergistic pharmacodynamic interaction between CBZ and VPA against complex partial seizures (27,28).

Valpromide, an amide derivative of VPA that is considered to be a VPA prodrug, is an even more potent inhibitor of epoxide hydrolase than VPA. Comedication with CBZ results in up to eightfold increases in epoxide concentrations and frequently results in clinical toxicity (80,81). Although valpromide has been used interchangeably with VPA, caution must be exercised if patients also are being treated with CBZ.

Carbamazepine coadministered with phenobarbitone

Concomitant administration of the enzyme-inducing AED PB increases the metabolism of CBZ and reduces CBZ plasma concentrations (82,83). The consequence of this interaction is reduced CBZ efficacy. Interestingly, when PRM (which is metabolised to PB) is coadmistered with CBZ, there is a concurrent decrease in CBZ and an increase in CBZ-epoxide (the pharmacologically active metabolite of CBZ) plasma concentrations (78). This may result in both reduced efficacy and toxicity, and CBZ dose adjustment guided by the monitoring of plasma epoxide concentrations may be useful if toxicity occurs.

Carbamazepine coadministered with lamotrigine

The original suggestion that during combination therapy with CBZ, LTG increases CBZ-epoxide concentrations, resulting in neurotoxicity, has not been confirmed (32,84–87). However, combination therapy with CBZ and LTG can result in a pharmacodynamic interaction causing neurotoxic symptoms including headache, nausea, dizziness, and ataxia (32,88). If toxicity occurs, it may be necessary to reduce the dose of CBZ

Phenytoin coadministered with topiramate

TPM reduces the clearance of PHT in some patients (58) and may lead to increases in plasma concentration and increased PHT-induced toxicity. If patients experience toxicity, a reduction in the dose of PHT should be considered (89).

Phenytoin coadministered with oxcarbazepine

OXC inhibits the isoenzyme CYP2C19. Consequently, during comedication with PHT, PHT plasma concentrations can increase by $\leq$40%, leading to toxicity, particularly in patients prescribed a higher OXC dosage. PHT dosage adjustments will be necessary in these patients (90).

Ethosuximide coadministered with valproate

Interactions with ESM are rarely important; however, VPA may increase plasma concentrations of ESM in some patients (91,92). In turn, ESM may decrease the plasma concentration of VPA (79). There is limited clinical evidence to suggest that ESM and VPA work synergistically via a pharmacodynamic interaction: in one study patients with atypical absence seizures refractory to either drug alone were shown to become seizure free when given combination therapy (25).

TABLE 5. *Clinical outcome of AED–non-AED interactions*

Non-AED	AED	Pharmacologic outcome of drug interaction	Potentially clinically relevant outcome of the drug interaction
Oral contraceptive pill	Enzyme-inducing AEDs (e.g., carbamazepine, phenytoin, phenobarbitone, felbamate, oxcarbazepine, and topiramate)	Increased metabolism of the contraceptive pill and reduced hormone levels	Pregnancy
Theophylline	Enzyme-inducing AEDs (e.g., carbamazepine, phenytoin, and phenobarbitone)	Increased metabolism of theophylline	Reduced efficacy against asthma and chronic bronchitis
Dicoumarol/warfarin	Enzyme-inducing AEDs (e.g., carbamazepine, phenytoin, and phenobarbitone)	Increased metabolism of dicoumarol/warfarin and reduced anticoagulant activity	Decreased anticoagulant activity could be life threatening. If the AED is subsequently removed, there is the risk of dicoumarol/warfarin toxicity (e.g, haemorrhage)
Digoxin	Phenytoin, topiramate	Decreased plasma concentrations of digoxin	Reduced efficacy in cardiac failure
Corticosteroids	Enzyme-inducing AEDs (e.g., carbamazepine, phenytoin, and phenobarbitone)	Increased metabolism of the corticosteroid	Reduced therapeutic effects. May need to increase the dose of the corticosteroid
Antacids	Phenobarbitone, phenytoin, carbamazepine, and gabapentin	Reduced gut absorption of the AEDs	Reduced efficacy of the AEDs and seizure exacerbation
Omeprazole	Phenytoin	Inhibition of phenytoin metabolism	If the patient experiences phenytoin toxicity, phenytoin dose reduction will be necessary
Cimetidine	Phenytoin	Inhibition of phenytoin metabolism	If the patient experiences phenytoin toxicity, phenytoin dose reduction will be necessary
Tricyclic antidepressants (TCAs)	Enzyme-inducing AEDs (e.g., carbamazepine, phenytoin, and phenobarbitone)	Bidirectional interaction with TCA concentrations reducing and AED concentrations increasing	Reduced efficacy of the TCAs and possible toxicity of the AEDs
Fluoxetine	Carbamazepine and phenytoin	Inhibition of AED metabolism and increased plasma concentrations of carbamazepine and phenytoin	Initiate at or lower the dose of carbamazepine/phenytoin to the lower end of the therapeutic dose range. Look for signs of carbamazepine/phenytoin toxicity (e.g., dizziness)
Sertraline	Lamotrigine	Inhibition of AED metabolism and increased plasma concentrations of lamotrigine	Look for the signs of lamotrigine toxicity, and reduce the dose of lamotrigine if necessary
Benzodiazepines	Carbamazepine, phenytoin, and phenobarbitone	Increases metabolism and decreases plasma concentrations of benzodiazepines	Adjust doses if necessary
Haloperidol	Enzyme-inducing AEDs (e.g., carbamazepine, phenytoin, and phenobarbitone)	Increased metabolism of haloperidol with a subsequent decrease in plasma concentration	It may be useful to monitor the plasma concentrations of haloperidol and adjust the dose if necessary
Fluconazole	Phenytoin	Inhibition of phenytoin metabolism with a possible increase in phenytoin plasma concentrations	If the patient experiences phenytoin toxicity, phenytoin dose reduction may be necessary
Griseofulvin	Enzyme-inducing AEDs (e.g., carbamazepine, phenytoin, and phenobarbitone)	Increased metabolism of griseofulvin and reduced plasma concentrations	Reduced antifungal activity
Erythromycin	Carbamazepine	Inhibition of the metabolism of the AEDs and increased plasma concentrations	Observe the patient carefully for signs of AED toxicity and, if necessary, reduce the dose
Clarithromycin	Carbamazepine	Inhibition of AED metabolism and increased plasma concentrations of carbamazepine	If coadministered, the patient must be carefully monitored for signs of carbamazepine toxicity. Reduce the dose if necessary

TABLE 5. *Continued*

Non-AED	AED	Pharmacologic outcome of drug interaction	Potentially clinically relevant outcome of the drug interaction
Antiviral agents that are metabolised by CYP3A4	Enzyme-inducing AEDs (e.g., carbamazepine, phenytoin, and phenobarbitone)	AEDs can increase the metabolism and reduce the plasma concentrations of antiviral agents	Reduced efficacy, increased viral replication, and the development of resistance
Cyclosporine	Enzyme-inducing AEDs (e.g., carbamazepine, phenytoin, and phenobarbitone)	AEDs can increase the metabolism and reduce the plasma concentrations of cyclosporine	Reduced immunosuppressant activity. It will be necessary to increase the dose of cyclosporine
Anticancer agents	Enzyme-inducing AEDs (e.g., carbamazepine, phenytoin, and phenobarbitone)	AEDs can increase the metabolism of anticancer agents and reduce therapeutic efficacy	Reduced efficacy of the anticancer agent and the potential for a poorer outcome for the patient
St. John's wort	Carbamazepine and phenytoin	The metabolism of carbamazepine and phenytoin may be increased by St. John's wort	AED efficacy reduced with possible loss of seizure control

The interactions highlighted may not occur in all patients prescribed the drug combinations indicated.
AED, antiepileptic drug.

Phenobarbitone coadministered with phenytoin

PB and PHT are metabolised by the same phenylhydroxlyating enzyme system; therefore they may inhibit each other's metabolism. This bidirectional drug interaction is complex and can lead to unpredictable changes in drug concentrations. Low doses of PB induce the metabolism of PHT, thus reducing its concentration. However, higher doses of PB competitively inhibit PHT metabolism and increase PHT concentrations (79).

Felbamate coadministered with valproate, phenytoin, carbamazepine, and phenobarbitone

Administration of FBM to patients treated with VPA has been shown to significantly decrease the clearance of VPA and to increase VPA plasma concentrations by ~50% (93). The exact clinical significance of this interaction is not known. This is the first report of an interaction in which the metabolism of VPA is inhibited (the β-oxidation pathway is inhibited) (94), and this may represent a potential target for interactions with new AEDs that are presently undergoing development. FBM is associated with numerous clinically significant interactions with a variety of AEDs. For example, FBM inhibits the metabolism of PHT, clobazam (CLB), and PB, resulting in increased plasma concentrations of these drugs (95–97). Dosage reductions of these AEDs is essential if patient toxicity is to be avoided. Furthermore, FBM increases plasma CBZ-epoxide concentrations while at the same time reducing CBZ concentrations (98). These interactions complicate the use of FBM for the treatment of patients with multiple AEDs.

AED–non-AED interactions

In the following section the most clinically important AED–non-AED drug interactions that may affect the clinical management of patients with epilepsy are discussed (Table 5); as in the previous section, this is not intended to be an exhaustive list of all potential drug interactions but highlights those most commonly encountered in the clinic.

Oral contraceptives

The enzyme-inducing AEDs, PB, PHT, CBZ, and PRM (53–55), are capable of increasing the level of activity of various cytochrome P450 isoenzymes (Table 1) (5,15), which may accelerate the hepatic metabolism of oral contraceptives. The consequence of the drug interaction is a potential reduction in contraceptive efficacy, particularly with low-dose estrogen oral contraceptives, and the increased risk of unwanted pregnancy. It may be necessary to increase the dose of estrogen to >50 μg when oral contraceptives are used concomitant with enzyme-inducing AEDs (99). Women with epilepsy who choose to use oral contraceptives should be advised also to use a barrier method of contraception, such as a cap, condom, or diaphragm.

Data available to date suggest that the second-generation AEDs are less likely to have unfavourable drug interactions with oral contraceptive agents. It is reported that GBP, LTG, LEV, TGB, and VGB can be administered with oral contraceptives without the risk of contraceptive failure (100,101). Women who are prescribed FBM, OXC, and TPM should be advised to use additional barrier methods of contraception and may benefit from higher doses of estrogen, as these AEDs have been shown to have some enzyme-inducing activity (101). For TPM, although the mechanism of the effect on ethinyl estradiol is not known, induction of CYP3A4 does not appear to be involved (102). There is now insufficient evidence regarding the interaction between ZNS and oral contraceptives, and care should be taken to

prevent unwanted pregnancies when using this combination (101).

Theophylline

Theophylline is indicated for the management of bronchospasms in reversible airway obstruction associated with stable asthma and chronic bronchitis. Theophylline is metabolised by hepatic enzymes (primarily CYP1A2, but CYP2E1 also is involved) and the enzyme-inducing AEDs, PB, PHT, CBZ, and PRM are capable of increasing the metabolism of this drug, in which case, an increase in the dose of theophylline may be necessary (103,104). In view of the seizure-inducing effects of theophylline, the use of this drug in patients with epilepsy is now limited. The second-generation AEDs, such as VGB, LTG, TGB, LEV, and GBP, which do not induce CYP isoenzymes, are unlikely to interact with theophylline.

Dicoumarol and warfarin

Dicoumarol is an anticoagulant indicated for the prevention of thrombosis associated with cardiovascular diseases and surgical procedures for vascular disease. Dicoumarol interferes with coagulation by competitively binding to vitamin K, which is essential for the formation of several coagulation factors. Warfarin is an anticoagulant that is therapeutically similar to dicoumarol. Its metabolism is primarily via CYP2C9, although CYP3A4 and CYP1A2 also are involved (105). Enzyme-inducing AEDs, such as PB, PHT, and CBZ can reduce the anticoagulant effects of both drugs by increasing their metabolism, possibly via an induction of CYP2C9 (106,107). During polytherapy, care must be taken to maintain appropriate plasma concentrations of dicoumarol/warfarin, as significant changes in plasma concentration could be life-threatening; this is achieved by checking the patient's coagulation function. The effects of discontinuing a concomitantly administered AED also should be considered. This is particularly important if the AED is removed or replaced by one that does not induce hepatic enzymes, because the loss of enzyme induction may lead to haemorrhaging due to elevated dicoumarol/warfarin plasma concentrations. As drug interactions with dicoumarol/warfarin are dependent on the CYP system, the second-generation AEDs that do not induce CYP isoenzymes (e.g., VGB, LTG, TGB, LEV, and GBP) are unlikely to interact with dicoumarol/warfarin. In addition, OXC does not appear to interact with warfarin to any clinically relevant extent (108).

Digoxin

Digoxin, the most frequently prescribed cardiac glycoside, is indicated in the management of chronic cardiac failure. Digoxin is excreted mainly by filtration in the kidneys without being metabolised. Consequently, interactions with digoxin relate mainly to effects on renal excretion, tissue and plasma protein binding, distribution within the body, alterations in gut absorption, and pharmacodynamic sensitivity to digoxin and other digitalis glycosides. Concomitant administration of digoxin with PHT may result in reduced plasma concentrations of digoxin and an unfavourable effect on the management of cardiac failure. As a result of the narrow therapeutic index of digoxin, physicians are advised to check the plasma digoxin concentration and to adjust drug doses accordingly. TGB, the most protein bound of the second-generation AEDs, does not have any clinically significant effect on the plasma concentrations of digoxin. Coadministration of TPM and digoxin may result in a small reduction in the plasma concentrations of digoxin, although the mechanism of this interaction is currently unknown (102,109). A pharmacokinetic study in healthy adults has shown no pharmacokinetic interaction between LEV and digoxin (110).

Corticosteroids

Corticosteroids are indicated for hormone replacement and in the management of inflammatory disorders such as rheumatoid arthritis, rheumatic fever, ulcerative colitis, Crohn disease, and chronic active hepatitis. The enzyme-inducing AEDs, PB, PHT, and CBZ may increase the metabolism of corticosteroids and reduce their therapeutic efficacy. If the physician observes a lack of therapeutic response in a patient receiving polytherapy, then the dosage of corticosteroid may need to be increased (111). AEDs that do not induce hepatic CYP isoenzymes, such as VGB, LTG, TGB, LEV, ZNS, and GBP, are unlikely to interact with corticosteroids.

Antiulcer drugs

If the dissolution process of an orally administered drug is dependent on the acidity of the gut, then absorption may be altered considerably by the coadministration of drugs that modify the pH of the stomach. Antacids (e.g., aluminium hydroxide and calcium carbonate) rapidly raise gastric pH. In general, the alteration in gastric pH does not result in clinically important drug interactions, as the absorption of most drugs is not affected by a less acidic pH in the gut (9). With respect to the AEDs, antacids have been shown to reduce the plasma concentrations of PB, PHT, CBZ, and GBP (112).

Omeprazole is a proton-pump inhibitor whose action blocks the release of gastric acid from gastric parietal cells. It provides effective treatment of gastric and duodenal ulcers and is the drug of choice for the treatment of oesophageal reflux disease. Omeprazole can increase PHT plasma concentrations (113) by inhibiting CYP2C19, resulting in toxicity. If omeprazole is subsequently removed from a PHT-based regimen without an

appropriate PHT dose adjustment, seizures may recur because of the reduction in plasma concentration of PHT.

Cimetidine, a histamine H_2-receptor antagonist that rapidly reduces the basal and stimulated secretion of gastric acid and pepsin, is indicated for the treatment of duodenal and gastric ulceration and other conditions in which the reduction of gastric acid production is beneficial. It is also an inhibitor of cytochrome P450 isoenzymes CYP2C19, CYP2D6 (9), and CYP3A4 (114), and is capable of prolonging the half-lives of those AEDs that would normally be metabolised by these isoenzymes (e.g., PHT and CBZ) (115–118). The inhibitory effect of cimetidine on CYP3A4 is not substantial, and the interaction with CBZ is of modest clinical significance (118,119). PB and PRM also are metabolised by CYP2C19 and may be affected by coadministration with cimetidine. The interaction of cimetidine and PHT is of clinical significance, and close monitoring of patients prescribed both agents is recommended, with the dose of PHT being reduced if necessary. None of the second-generation AEDs is a substrate for either CYP2C19 or CYP2D6, and they are therefore unlikely to interact with cimetidine.

Psychotropic drugs

In some patients with epilepsy and psychiatric disorders (e.g., depression), it may be necessary to coadminister psychotropic drugs and AEDs. The drug interactions between these two classes of agents focus on the cytochrome P450 enzymes. For example, the enzyme-inducing AEDs PB, PHT, and CBZ stimulate the metabolism of tricyclic antidepressants (TCAs), and the TCAs have an inhibitory effect on the metabolism of some AEDs (120), resulting in a reduction in the plasma concentration of TCAs, with a concomitant increase in the plasma concentration of the coadministered AED. Examples of TCAs that interact in this complex manner include nortryptiline, imipramine, nomifensine, and trazodone (121,122).

The newer antidepressants that inhibit serotonin reuptake, for example fluoxetine (Prozac), inhibit the isoenzymes CYP3A4, CYP2D6, and CYP2C19 and may result in an increase in the plasma concentrations of CBZ and PHT (123–126). When CBZ is coadministered with fluoxetine, it should be initiated at the lower end of the therapeutic dose range to allow for the increase in plasma concentration, while reducing the risk of toxicity. If fluoxetine is to be added to a patient's drug regimen, which already comprises CBZ, the CBZ dosage adjustment should be guided by CBZ plasma drug-concentration monitoring. This advice also applies to PHT. Sertraline, a 5HT-reuptake inhibitor that is indicated for the treatment of depression and anxiety, when coadministered with LTG can lead to LTG toxicity (127). It is thought that sertraline inhibits the glucuronidation of LTG by inhibition of UGT isoenzymes.

Many of the anxyolytic BZDs are metabolised by CYP3A4 (128), and consequently their metabolism may be altered by concomitant administration with AEDs, the result depending on whether the CYP isoenzyme is induced or inhibited. For example, CBZ and PHT, both potent inducers of CYP3A4, decrease the plasma concentration of midazolam (MDL), (129) whereas VPA increases the plasma concentration of lorazepam (LZP) by inhibiting UGT activity (130,131).

The antipsychotic agent, haloperidol, which is used for the treatment of schizophrenia and mania, is metabolised by CYP2D6 and in part by CYP3A. Hence the plasma concentration of haloperidol may be reduced if it is coadministered with a CYP3A isoenzyme–inducing AED (132). Monitoring of plasma concentrations of concomitantly administered AEDs and psychotropic drugs may be useful in preventing any adverse consequences of drug interactions.

Antifungal agents

Fluconazole is indicated for the treatment of fungal infections, for example, genital candidiasis, and it is a potent and selective inhibitor of fungal enzymes necessary for the synthesis of ergosterol. Fluconazole is an inhibitor of the cytochrome P450 isoenzymes CYP2C9 and CYP2C19, the principal metabolising enzymes for PHT (9,133). The coadministration of fluconazole and PHT can be expected to be associated with a clinically significant increase in PHT plasma concentrations, and these may require adjustment to maintain safe therapeutic concentrations (134). Most of the second-generation AEDs, such as VGB, LTG, TGB, LEV, OXC, ZNS, and GBP, are not substrates of either CYP2C9 or CYP2C19 and are therefore unlikely to interact with fluconazole.

Griseofulvin, indicated for the treatment of fungal diseases of the skin, hair, and nails, is metabolised by the liver, and the enzyme-inducing AEDs may enhance the metabolism of griseofulvin and reduce its efficacy (135). However, in addition, AEDs may interact, at least in part, by decreasing griseofulvin gastrointestinal absorption (136).

Antibiotics

Erythromycin is indicated for the treatment of erythromycin-sensitive bacteria. It is used in a wide range of clinical infections including tonsillitis, secondary infections in influenza, eye infections, pre- and postoperative prophylaxis, and genitourinary infections. Erythromycin is an inhibitor of CYP3A4; therefore coadministration with CBZ may lead to an increase in plasma concentrations of CBZ (137,138). Patients should be closely monitored and the CBZ dosage adjusted if necessary. Two small studies of healthy volunteers demon-

strated that the second-generation AEDs, OXC and TGB, were not affected by coadministration with erythromycin (139,140).

Clarithromycin is indicated for the treatment of susceptible microorganisms causing infections of the respiratory tract, skin, and soft-tissue infections. In addition, clarithromycin is used for the treatment of *Helicobacter pylori* infections in patients with duodenal ulcers. Clarithromycin is both a substrate for, and an inhibitor of, CYP3A, so it has the potential to reduce the metabolism of drugs that are metabolised by CYP3A. For example, clarithromycin increases the plasma concentration of CBZ, and coadministration of these drugs should be monitored very carefully to avoid CBZ toxicity (141,142). The use of second-generation AEDs that are not substrates for CYP3A, such as GBP, LEV, LTG, OXC, and VGB, in combination with clarithromycin may be less problematic.

Antiviral agents

Seizures may occur in ≤11% of patients with human immunodeficiency virus (HIV), compared with 1–2% of the general population (143–146). Coadministration of antiviral agents and AEDs is therefore very likely in HIV-infected patients, and there is the potential for these agents to interact in a number of ways. The wide range of both antiviral agents and AEDs means that the number of potential drug interactions is considerable. Romanelli et al. (147) provided an overview of the potential drug interactions that should be considered by any physician treating HIV-infected patients that require AED therapy. Many of the antiviral agents, such as nevirapine, indinavir, ritonavir, and saquinavir, are metabolised by CYP3A4, which is readily induced by CBZ, PHT, and PB; concomitant administration of a combination of these agents is likely to lead to insufficient plasma concentrations of the antiviral agent, leading to increased viral replication and the development of resistance. The dose of the antiviral drug may need to be adjusted upward, although this therapeutic adjustment/intervention has not been tested in clinical studies (147). Consequently, it may be advantageous to use one of the second-generation AEDs that do not affect CYP3A4, such as GBP, LTG, LEV, TGB, or VGB, in combination with antiviral agents.

Cyclosporine

Cyclosporine, which is used as an immunosuppressant, is metabolised by CYP3A. Hence, enzyme-inducing AEDs, such as CBZ, PB, and PHT may reduce the plasma concentration of coadministered cyclosporine (148,149). Patients that require cyclosporine are best treated for their epilepsy with one or more of the second-generation AEDs that are known not to induce CYP3A (e.g., GBP, LTG, LEV, TGB, or VGB). As OXC, which induces CYP3A4 and CYP3A5 (150), may reduce plasma levels of cyclosporine (151), its use should be avoided in patients requiring immunosuppression with cyclosporine.

Anticancer agents

The potential for drug interactions between anticancer agents and other drugs is increasing with the enhanced availability of new drugs and the increase in life expectancy of patients treated for cancer. Drug interactions in oncology are of particular concern. Anticancer agents generally have a very narrow therapeutic index, they have the potential for lethal side effects, and they are often given at doses that are very close to toxic levels (152). Hence any increase in the therapeutic activity as a result of a drug interaction may lead rapidly to the patient experiencing toxicity and adverse side effects. Subtle reductions in activity may reduce efficacy of anticancer agents and lead to a poorer prognosis in terms of a cure for the patient. Cytochrome P450 isoenzymes such as CYP3A are important in the metabolism of anticancer agents (e.g., etoposide, cyclophosphamide, and paclitaxel), and drug interactions with these enzymes may play an important role in anticancer drug safety and efficacy (153). PB and PHT have been observed to enhance the clearance of these drugs by up to threefold (154). Oncologists should be aware of the potential for adverse drug interactions in patients that may already be receiving AEDs for their epilepsy or in patients who are prescribed AEDs to minimise cancer- and anticancer agent–induced seizures (155–157). There are no data reporting how the second-generation AEDs affect anticancer agents. In theory, those AEDs that do not undergo metabolism or interfere with cytochrome P450 isoenzymes should not interact with the anticancer agents currently in use, and should be the preferred treatment option in such patients.

St. John's wort

St. John's wort (*Hypericum perforatum*) is a complementary over-the-counter medication that is becoming more widely used. Various claims of its activity include mood elevation and stabilisation, stress relief, and antibiotic and antiviral effects. A recent survey of patients with epilepsy found that 7% of responders used St. John's wort for mood disturbance and fatigue (158). St. John's wort may induce CYP3A4 and CYP2C9 activities and therefore has the potential to increase the metabolism of concomitantly administered AEDs, reducing their plasma concentrations, which may lead to a reduction in seizure control (159). However, a recent study in healthy volunteers did not show an effect of St. John's wort on CBZ metabolism, and the authors suggested that autoinduction, CBZ dosage, and duration of treatment with St. John's wort may contribute to the manifestation of the interaction (160). Overall, CBZ and PHT, which are metabolised by CYP3A4 and CYP2C9, respectively, can be

potentially affected by coadministration with St. John's wort, and it may be appropriate to increase the dose of these AEDs to maintain seizure control.

FUTURE DIRECTIONS

As our knowledge of the pharmacokinetic and pharmacodynamic profiles of both AEDs and non-AEDs increases, it should become easier to anticipate which combinations of drugs will produce either beneficial or adverse drug interactions when administered in combination. Evidence is increasing to support the idea that pharmacokinetic interactions take place in the brain, in addition to in the peripheral compartment, and there is a need to develop ways to measure these interactions in humans. Not only would this lead to a better understanding of some of the drug interactions that are observed in the clinic, but it would also enable researchers to distinguish between pharmacokinetic and pharmacodynamic interactions that take place at the site of drug activity. A greater understanding of the pharmacodynamic interactions, in particular the synergistic effects that enhance the therapeutic index of drug combinations, should allow drug combinations to be used to the maximal benefit of the patient.

Continued research into the metabolic processes that lead to so many of the clinically relevant drug interactions, and the ability to screen for these in vitro, should lead to the development of AEDs that have less complex or ideally negligible drug interactions. Our understanding of the role of genetic polymorphism of the drug-metabolising enzymes in determining how individuals respond to certain drug combinations will improve with time, and the exciting field of pharmacogenetics is set to make huge progress in this area (161). In time, pharmacogenetics may lead to screening tests that would allow physicians to select the most appropriate treatment combinations for individual patients based on their genetic profiles. Armed with the ability to anticipate potential drug interactions, both with respect to the drugs and to the biochemical profile of the patients, physicians should be able to make more rational decisions about polytherapy, thus ensuring the maximal therapeutic benefit to the patient with minimal toxicity. It is clear from the evidence detailed in this review that our understanding of drug interactions is already extensive, and their importance is increasingly being realised.

CONCLUSIONS

Drug interactions are a major problem in combination drug therapy. Although many of the predisposing factors that determine whether an interaction will occur are known, in practice, it is still very difficult to predict exactly what will happen when an individual patient is administered two drugs that have the potential to interact. The solution to this practical problem is to choose noninteracting drugs. However, if such an alternative is not available, it is frequently possible to give interacting drugs together if appropriate precautions are taken. Many interactions are dose related; therefore, by monitoring the patient closely, the effects of the interaction can often be allowed for by adjusting the dosage. Some interactions can be avoided by using another member of the same group of drugs.

When comparing the second-generation AEDs with the older established AEDs, there is an obvious contrast in both their interaction potential and their mode of interaction. Most of the established AEDs (PB, PRM, PHT, and CBZ) are potent hepatic enzyme inducers, whereas none of the second-generation AEDs can be considered to be associated with significant induction (TPM and OXC exhibit weak enzyme induction). VPA is both a potent inhibitor of drug metabolism and a protein-binding displacer. Of the second-generation AEDs, enzyme inhibition is a prominent feature of only FBM. The metabolism of LTG is significantly induced or inhibited by other AEDs, but this occurs via an action on glucuronidation and is not CYP dependent. Overall, many of the second-generation AEDs have a limited propensity for drug interaction because they are eliminated primarily by the renal system and are not protein bound. However, the exact propensity of these AEDs to interact with many other "prescription" and "over-the-counter" drugs will be realised only after they have been licensed for clinical use and extensively prescribed to the general patient population.

This review has concentrated on the fundamental principles and underlying properties associated with AED interactions and has used specific but important examples to highlight these. It has not been our intention to review all known interactions associated with AED treatment. By understanding these mechanisms, it is possible to anticipate the therapeutic consequence of the interaction and allow a proactive therapeutic adjustment (Fig. 2). During AED polytherapy, plasma-concentration monitoring may help to identify problematic and unexpected pharmacokinetic interactions. Monitoring also may serve to guide the physician to make the appropriate dose adjustments to achieve optimal patient therapy.

It should be noted that the interactions highlighted may not occur in all patients prescribed the drug combinations indicated.

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