Taking A Closer Look At AED Drug Interactions

Confused by the small print in drug ads? Those esoteric discussions can make a big difference in outcomes. Here, a pharmacology expert explains what you need to know.

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Epilepsy—already one of the most challenging neurological conditions to treat effectively—is further complicated by the multitude of drug interactions that can undermine therapy. These challenges are increased with the addition of a second or even third agent, as is typical later in the course of management if seizure control cannot be achieved via monotherapy. A more detailed understanding of the pharmacokinetics and pharmacodynamics of antiepileptic drugs (AEDs) can help clinicians make better-informed treatment decisions and raise awareness about the importance of routine drug monitoring during the course of pharmacologic management of seizure disorders.

A full medication history along with information on the metabolism of an AED can be important in the prediction of possible drug interactions that may be seen when co-medications are added or withdrawn from an AED dosing regimen. It is equally important to assess the potential for a "reverse" drug interaction when a potentially interfering substance is removed from a regimen. For example, phenytoin is known to be a general inducer of cytochrome P450 (CYP450) enzymes. If a patient is in the process of discontinuing phenytoin, one must assess the possibility of an increase in drug concentrations of the other medications used during and after the titration and discontinuation of phenytoin from the drug regimen.

The mechanism of metabolism for currently approved AEDs is presented in Table 1. There are two main metabolic enzyme systems involved: the CYP450 enzymes and glucuronyl transferases (UGT). The older AEDs are mostly metabolized by the CYP450 enzyme system, whereas a greater involvement of the glucuronidation system is seen with the newer AEDs. Few drug interactions are seen with medications that are mostly renally cleared. Some of the newer, but none of the older, AEDs are more than 50 percent renally cleared.

AEDs can also induce or inhibit the CYP450 enzyme system and thereby affect other medications. Administration of enzyme-inducing AEDs can markedly increase the hepatic clearance of drugs that are substrates for certain CYP450 enzymes, resulting in a decrease in drug concentrations of co-medications. Conversely, AEDs can also inhibit the metabolism of other drugs so that concentrations of the co-medication will be higher than if the co-medication had been given without the inhibiting AED (see Figure 1).

This article will present an overview of AED drug interactions of both the older and newer generation AEDs with an aim toward understanding the clinical relevance of each and the role they play in drug selection and monitoring.

Principle of Drug Interactions

Drug interactions occur when the effects of one drug are changed by the presence of another drug, food, drink or some environmental chemical agent.[1] Potential drug interactions should be assessed whenever a patient is taking more than one drug simultaneously. There are two types of mechanisms:

1. *Pharmacokinetic drug interactions* are interactions that occur during the processes of absorption, distribution, metabolism and excretion. Pharmacokinetic interactions can alter the drug concentration.

2. *Pharmacodynamic drug interactions* are interactions that usually happen when two or more drugs have similar or opposing mechanisms of action. Pharmacodynamic interactions occur at the site of action and usually do not result in a change of plasma concentration of either drug.

Figure 1. AED Interaction Effect on Drug Concentration

AEDs can also inhibit the metabolism of other drugs, so that concentrations of the co-medication will be higher than if the co-medication had been given without the inhibiting AED.

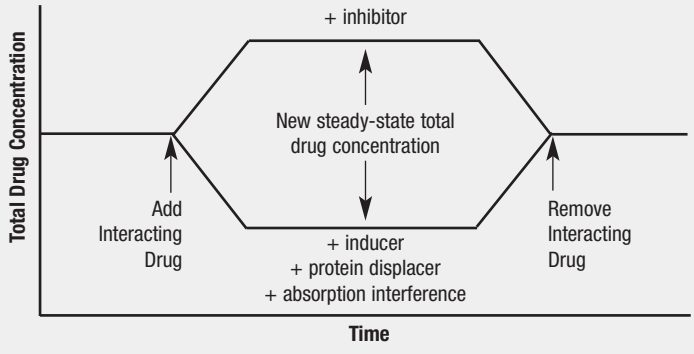

Table 1. AED Metabolism Characteristics

AED	Majority of Elimination Pathway	Half Life (hrs)	Enzyme System	Effect on Enzyme System
Carbamazepine	Hepatic	6-15	CYP450 (CYP3A4)	Inducer
Felbamate	50% renal partially hepatic metabolism	14-23	UGT and CYP450 (CYP3A4 and CYP2E1)	Inducer of CYP3A4 Inhibitor of CYP and non-CYP isoenzymes
Gabapentin	mostly renal	5-7	none	No effect
Lamotrigine	Hepatic	18-30	UGT	No effect
Levetiracetam	66% renal	4-8	Not CYP450 dependent	No effect
Oxcarbazepine	Hepatic	5-11	reduced by a cytosolic arylketone reductase	Inhibitor of CYP2C19 Inducer of CYP3A4
Phenobarbital	Hepatic	72-124	CYP450 (CYP2C9 and CYP2C19)	Inducer
Phenytoin	Hepatic	12-60 (depends on concentration)	CYP450 (CYP2C9 and CYP2C19)	Inducer
Pregabalin	Renal	5.8	none	No effect
Tiagabine	Hepatic	5-13	CYP450 (CYP3A4)	No effect
Topiramate	55-66% renal	20-30	not well defined	Inducer of CYP enzyme
Valproic acid	Hepatic	6-18	UGT	Inhibitor
Zonisamide	Hepatic	63-69	CYP450 (CYP3A4)	No effect

Pharmacokinetic Drug Interactions

• ***Absorption:*** The absorption of most drugs after oral administration occurs in the gastrointestinal tract, in particular the small intestine. Most absorption issues result in an overall decrease in the amount of drug that reaches the systemic circulation. AED interactions affecting gastrointestinal absorption are rare. Antacids such as calcium carbonate that are taken at the same time as the AED can pose a problem by decreasing the acidity of the stomach and by forming insoluble complexes.[2] Antacids have been shown to reduce the absorption of phenytoin, phenobarbital, carbamazepine, and gabapentin.[2] Fluctuations in drug concentration can be particularly problematic with AEDs since deviations in drug concentrations may lead to an increase in seizure frequency or adverse effects. Since it is important to maintain constant drug concentrations, advise patients to always take their AED medication in the same way when they are also taking antacids. It may be best to instruct patients to not take antacids within two hours of drug administration.

• ***Distribution.*** Once a drug reaches the systemic circulation, it is then transported to tissues throughout the body or eliminated from the body. Drugs exist in two forms: unbound drug and total drug. The unbound drug concentration refers to that drug which does not bind to tissues or other proteins in the blood such as albumin and is thought to be indicative of the amount of drug at the site of action. The total drug concentration is usually the value reported from laboratories and is the unbound drug concentration plus the drug that is bound to plasma proteins, mostly albumin. The unbound drug concentration becomes more important if the drug of interest is considered to be highly protein bound (over 85 percent).

Distribution interactions are usually from competition of plasma protein binding. Highly protein-bound drugs given concomitantly can result in displacement of drugs from plasma protein, resulting in an increase in the free fraction (unbound drug concentration/total drug concentration). When two or more drugs that are highly bound to plasma albumin are co-administered, protein displacement can result. Displacement of AEDs from plasma proteins can produce a transient change in free concentration of drug, but a decrease in the total drug concentration. This can be misleading clinically since it is the total drug concentration that is frequently measured during routine care. There is usually no need to change doses based on protein binding interactions alone.[3]

• ***Metabolism.*** The most clinically significant and possibly better anticipated AED drug interactions are related to induction or inhibition of metabolic enzymes. These enzymes are located in the liver as well as other areas of the body such as the gut wall. The most commonly used AEDs are metabolized by several CYP450 isoenzymes and UGTs (see Table 1).

Enzyme induction usually is a result of an increase in synthesis of drug-metabolizing enzymes; the time to reach maximum

induction occurs over days to several weeks. In general, addition of inducers increases the clearance of some drug and can result in lower concentrations than are seen when the non-inducing drug is given alone. This can be particularly troublesome in some therapies where the effected co-medications are critical to life and/or expensive.

Co-administration of inducers can reduce efficacy as well as add to the overall costs of drug therapy since more of the effected drug will be required to maintain desired concentrations. If a substrate is metabolized to an active substance, induction can increase metabolism of the parent drug, resulting in increases in the concentration of the active metabolite. This increase in metabolite concentration can increase the possibility of drug toxicity. Equally important is de-induction, which is observed after removal of an inducer. The addition or discontinuation of inducing AEDs can be difficult to manage since multiple medications may be simultaneously effected.

Enzyme inhibition can be a result of one drug inactivating an isoenzyme or a drug competing for binding at the active site of the isoenzyme needed for metabolism of a second drug. By inhibiting drug AED metabolism, patients may have higher drug concentrations than when the drug is given alone, which can result in toxicity.

• ***Excretion.*** Drugs that undergo renal excretion and that are not metabolized by the liver are considered more pharmacokinetically desirable. Since most drug interactions happen due to effects on metabolizing enzymes, drugs that do not undergo extensive metabolism have a lower chance of drug-drug interactions. Urine pH can determine the amount of drug that is excreted from the body. In general, acidic urine (lower pH) facilitates the excretion of weakly basic drugs, inhibits their resorption, and promotes excretion. Alkalization (higher pH) causes ionization of weak acids and can result in more polar compounds and thereby enhance excretion of drug.

Drug-Drug Interactions of Older AEDs

Most of the clinically important drug interactions of antiepileptic drugs result from the co-administration of the older AEDs (carbamazepine, phenobarbital, phenytoin and valproic acid). These interactions mostly involve inhibition or induction of liver enzymes. Carbamazepine, phenobarbital and phenytoin are potent inducers of various CYP450 isoenzymes, whereas valproic acid is a weak inhibitor of epoxide hydrolase, CYP2C9 and UGT enzymes.[4] These interactions can cause common problems for clinicians. A summary of drug interac-

Table 2. Drug Interactions of the Older AEDs

AED	Common Drugs Affecting AED			Common Drugs Affected by AED
Carbamazepine	↓	*CBZ*	felbamate,* phenobarbital, phenytoin, primidone, rifampin	↓ cyclosporine, ethosunamide, felbamate, itraconazole, lamotrigine, oral contraceptives, topiramate valproic acid, warfarin
	↑	*CBZ*	cimetidine, erythromycin, ketoconazole, fluoxetine, fluvoxamine, valproic acid, vigabatrin	
Phenobarbital	↓	*PB*	activated charcoal	↓ carbamazepine, cimetidine, cyclosporin, dexamethasone, oral contraceptives verapamil, warfarin
	↑	*PB*	felbamate, phenytoin, valproic acid	
Phenytoin	↑↓	*PHT*	phenobarbital, primidone, valproic acid	↓ carbamazepine, itraconazole, lamotrigine, oral contraceptives, oxcarbazepine, primidone tiagabine, topiramate, zonisamide
	↓	*PHT*	carbamazepine, rifampin, vigabatrin	
	↑	*PHT*	cimetidine, felbamate, fluconazole, omeprazole, oxcarbazepine, topiramate	
Valproic acid	↓	*VPA*	carbamazepine, phenobarbital, phenytoin, primidone, rifampin	↑ lamotrigine, phenobarbital, phenytoin free fraction,** zidovudine
	↑	*VPA*	felbamate	

↓ = decrease ↑ = increase ↑↓ = increase or decrease

** carbamazepine concentrations decrease and carbamazepine-10,11-epoxide concentrations increase*
*** unbound phenytoin concentrations and total phenytoin concentrations can increase*

tions for the older AEDs is presented in Table 2. Phenytoin and carbamazepine follow nonlinear pharmacokinetics because of saturation of metabolizing enzymes (phenytoin) and autoinduction (carbamazepine). They are highly protein bound, are metabolized by the CYP450 isoenzymes,[4] and are potent inducers of metabolic enzymes.

These characteristics lead to several types of drug interactions. When enzyme inducers are given with other drugs, it causes a decrease in drug concentrations and can reduce the effectiveness of these compounds, notably lamotrigine, oxcarbazepine, topiramate, tiagabine and zonisamide. The metabolism of non-AEDs such as oral contraceptives can also be effected and increased doses may be needed. Valproic acid clearance can be accelerated by several enzyme-inducing AEDs,[5] resulting in decreases in valproic acid concentrations and requiring increases in valproic acid doses. Adding valproic acid to phenytoin may result in an increase of both total and free concentrations of phenytoin because of a weak inhibitory effect of valproic acid on phenytoin metabolism.[2] Unbound concentrations of phenytoin should be monitored when adjusting the dose when valproic acid and phenytoin are given simultaneously. Valproic acid can cause increases in drug concentration of concomitant drugs including lamotrigine[6] and phenobarbital.[7]

The amount of drug eliminated in the urine can also be affected by the co-administration of other substances. The pKa of phenobarbital is approximately 7.3; when urine (pH ~5.7) is more alkaline (such as in the presence of sodium bicarbonate) a higher percentage of phenobarbital is ionized and more phenobarbital is excreted into the urine. This results in lower blood concentrations of phenobarbital.

Drug-Drug Interactions of Newer AEDs

Since 1993, nine new AEDs have been approved in the United States: felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate and zonisamide. Most of these follow linear pharmacokinetics and exhibit fewer drug interactions than the older AEDs. A summary of the drug interactions seen with the newer AEDs is shown in Table 3.

Gabapentin depends on the L-system amino acid transporter and is a saturable process. A bioavailability of only 40 to 60 percent after oral administration of single doses (300 to 600mg) of gabapentin has been noted.[8] Antacids containing aluminum and magnesium hydroxide are also reported to decrease serum concentrations of gabapentin.[9]

Only three of the newer AEDs (felbamate, oxcarbazepine and topiramate) show a mild inducing effect on CYP3A4 and inhibition of CYP2C19. Oxcarbazepine and felbamate are CYP2C19 inhibitors, which may alter the metabolism of drugs metabolized by this enzymes, especially phenytoin.[2,4,10] Topiramate may decrease ethinyl estradiol concentrations at daily doses greater than 200mg.[11-13] Oral contraceptives have been indicated as possible inducers of lamotrigine metabolism, resulting in reduction of lamotrigine plasma concentrations.[14] Clinicians need to be aware of a patient's use of oral contracep-

Table 3. Drug Interactions of the Newer AEDs

AED	Common Drugs Affecting AED		Common Drugs Affected by AED
Felbamate	↓ *FBM*	carbamazepine, phenobarbital, phenytoin	↓ carbamazepine
Gabapentin	*none*		none
Lamotrigine	↓ *LTG*	carbamazepine, phenobarbital, phenytoin, primidone, oral contraceptives oxcarbazepine, rifampin	none
	↑ *LTG*	valproic acid	
Levetiracetam	*none*		none
Oxcarbazepine	↓ *MHD* *(active metabolite)*	carbamazepine, phenobarbital, phenytoin	↓ lamotrigine, oral contraceptives
			↑ phenytoin, phenobarbital
Pregabalin	*none*		none
Tiagabine	↓ *TGB*	carbamazepine, phenobarbital, phenytoin	none
Topiramate	↓ *TPM*	carbamazepine, phenobarbital, phenytoin, primidone	↓ oral contraceptives
Zonisamide	↓ *ZNS*	carbamazepine, phenobarbital, phenytoin	none

tives since beginning or discontinuing this medication can have a direct effect on their lamotrigine therapy. This interaction also creates an interesting challenge to those patients who take oral contraceptives that include a placebo week since this may lead to more pronounced changes in lamotrigine concentrations. Therefore, if patients are on oral contraceptives that include a placebo week they should be warned of the possibility of toxicity due to increased lamotrigine concentrations during that time. Oral contraceptives without a placebo week (monophasic) may be useful for patients who are also taking lamotrigine.

Because gabapentin, levetiracetam and pregabalin are mostly excreted unchanged in the urine, few if any drug interactions have been reported. Most of the newer AEDs that are metabolized by hepatic enzymes are sensitive to enzyme-inducing AEDs such as phenytoin and carbamazepine. Lower serum concentrations are observed when lamotrigine, oxcarbazepine, tiagabine and zonisamide are given concomitantly with other enzyme-inducing AEDs. Valproic acid can inhibit lamotrigine metabolism. Concomitant administration of valproic acid and lamotrigine reduces lamotrigine total clearance and increases the elimination half-life and area-under-the-concentration-time-curve (AUC).[5,8]

Herbal Remedies

Drug interactions with herbal medicines have not been extensively studied. There is a potential for induction of the CYP450 isoenzyme CYP3A4 by St John's wort. This causes a clinically significant interaction with several non-AEDs such as simvastatin, however, there are no data to support an interaction with an AED.[15]

Food AED interactions

Food, especially a high-fat meal, can enhance phenytoin absorption by increasing phenytoin dissolution in the stomach and saturation of first-pass metabolism. A difference in food effect has been shown between manufacturers. A 13 percent lower bioavailability was observed with a generic phenytoin formulation as compared to the branded formulation (Dilantin Kapseals).[16] This was estimated to result in a median 37 percent decrease in plasma phenytoin concentrations when the generic product is given with food as compared to the branded product given with food.

Food can also affect the newer AEDs. In the absence of food, tiagabine has a bioavailability of approximately 90 percent. The presence of food slows the absorption rate but not the extent. It is usually recommended that tiagabine be taken with food. Food can also delay the rate of absorption of lamotrigine, zonisamide, levetiracetam and topiramate with no change in the extent of absorption. High-fat and protein foods increase absorption of oxcarbazepine without changing the Tmax (time to reach maximum concentration) but these changes may not be clinically significant.[17]

Particular foods can also affect AED concentrations. Grapefruit juice has been identified as a CYP3A4 inhibitor and patients who ingest grapefruit juice experience an increase in the bioavailability of carbamazepine.[18] When grapefruit is not ingested regularly (for example, daily) it could lead to erratic

carbamazepine plasma concentrations. Clinicians may want to inform patients of this interaction.

Unique problems arise with administration of AED medications through feeding tubes. When phenytoin is administered during enteral feedings, an insoluble complex can form resulting in decreases in phenytoin serum concentrations.[19,20] In general, tube feedings should not be given within two hours of phenytoin administration. Special technical difficulties are seen when sprinkle or granular formulations are given through tubes. Gastric leakage occurs with the enteric-coated valproate sprinkle from adherence of the drug to the outer surface of the feeding tube.[21] Occlusion of feeding tubes is frequently encountered when extended-release carbamazepine granules (Carbatrol) are given.[22] This problem may be minimized by suspending the granules in water rather than milk or formula, and by using a rapid flow of the suspension.

Environmental Factors-AED interactions

Alcohol can inhibit the metabolism of drugs due to competitive inhibition and enzyme saturation, which result in a prolonged half-life. After chronic administration, alcohol has an inducer effect that can increase metabolism of AEDs including carbamazepine, phenobarbital, phenytoin and primidone.[23] It may be useful to identify chronic alcohol users when taking a medical history

Tobacco may affect the metabolism of many drugs by inducing CYP1A2. For antiepileptic drugs, smoking appears to have no effect on steady state concentrations of phenobarbital, phenytoin and carbamazepine.[24]

Pharmacodynamic Drug Interactions of AEDs

Pharmacodynamic interactions represent a change in pharmacologic response without an alteration in plasma concentration. Pharmacodynamic interactions take place at the site of action of the drug. This interaction can be beneficial, neutral, or toxic. There are limited data suggesting that using certain combinations of AEDs such as carbamazepine with valproic acid or lamotrigine with topiramate may be more effective in controlling seizures than using either of them alone.[2]

Conclusions

Clinicians need to assess the possibility of drug interactions when adding or withdrawing a medication, especially if that agent is an older antiepileptic agent since they are more likely to induce or inhibit metabolism through its effects on the CYP450 enzyme system. A full medication history needs to be taken in order to assess the potential for drug interactions. Medication histories should include prescription, over-the-counter and herbal products as well as environmental factors such as smoking or alcohol. In some cases an inquiry about certain foods may be useful (*i.e.*, grapefruit). It is equally important to assess the potential for a "reverse" drug interaction when a potentially interfering substance is removed from a drug regimen (Figure 1). **PN**

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