# Carbamazepine: Watch for Many Potential Drug Interactions

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The January 2008 edition of this column, entitled "Stopping Medications Can Cause Adverse Effects" (please visit www.PharmacyTimes.com/StopMedications), discussed the risk associated with withdrawing an enzyme inducer, carbamazepine, when coadministered with an object drug whose elimination is susceptible to induction. During concurrent administration of an inducer, the object drug dose may be titrated upward to maintain therapeutic effect. If the inducer is discontinued, the induction will slowly dissipate, and the metabolism of the object drug will return to normal. If the dose of the object drug is not reduced, toxicity may occur.

Carbamazepine is an inducer of several potential pathways of drug elimination, including CYPs 1A2, 2C9, and 3A4, as well as the active transporter P-glycoprotein. Any drug that undergoes metabolism via CYP1A2, CYP2C9, or CYP3A4 or is a substrate for the P-glycoprotein transporter, is likely to be affected by carbamazepine administration, however. The list of drugs that may potentially interact with carbamazepine is very large.[1]

The recognition of interactions resulting from the induction of elimination is usually rather poor. This is due to the slow onset of the interaction (1 to 2 weeks) and its presentation as a gradual reduction in the therapeutic efficacy of the object drug. It is typical for carbamazepine to reduce the plasma concentration of susceptible object drugs by 50%. For many drugs, this degree of reduction in plasma concentration will lead to a reduction in efficacy.

Carbamazepine is primarily metabolized by CYP3A4 to an active metabolite that has about the same efficacy as the parent compound. Drugs that inhibit the metabolism of carbamazepine frequently lead to accumulation and signs of toxicity.

Since carbamazepine has a fairly narrow therapeutic range, one should be alert for evidence of elevated plasma concentrations, such as dizziness, drowsiness, nausea, vomiting, confusion, and vision or gait disturbances when a drug that inhibits CYP3A4 is coadministered. Coadministration of inhibitors should be accompanied by careful monitoring of carbamazepine plasma concentrations and patient response. Carbamazepine side effects may be apparent within 2 to 3 days of initiating a drug that inhibits carbamazepine metabolism.

***Careful monitoring is very important if an inducer is coadministered with carbamazepine.***

Because carbamazepine is an inducer of CYP3A4 and a substrate for the enzyme, carbamazepine induces its own metabolism. Other inducers of CYP3A4 can affect carbamazepine, however, reducing its plasma concentrations.

The result of an inducer on carbamazepine would be to reduce its plasma concentrations and efficacy. While more of the active metabolite of carbamazepine is likely to be formed, the metabolism of this metabolite also appears to be inducible. This complex effect makes it very difficult to predict what net effect will be seen in a patient. Careful monitoring is very important if an inducer is coadministered with carbamazepine. Discontinuation of an inducer may result in increased carbamazepine concentrations and potential toxicity.

Oxcarbazepine (Trileptal) is a related antiepileptic drug. It too is metabolized by CYP3A4 and is an enzyme inducer; however, fewer data are available regarding its effects on other drugs. Pending further studies, it would be prudent to assume that oxcarbazepine has a similar interaction profile as carbamazepine. One comparative study on the induction effects of the 2 drugs found that carbamazepine was a more potent inducer of CYP3A4 than oxcarbazepine.[2]

Carbamazepine represents a drug with very complex drug interaction potential. Its narrow therapeutic range and potency as an inducer make it imperative to carefully monitor patients receiving carbamazepine with other drugs. It is likely to affect the elimination of a wide range of drugs and to be affected by many common therapeutic agents. Carefully review the drug profile of any patient receiving carbamazepine for potential drug interactions. PT

**online** For lists of selected drugs that interact with carbamazepine, please visit www.PharmacyTimes.com/carbamazepine.

*For a list of references, go to: www.PharmacyTimes.com.*

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## Table 1

### Selected Drugs Whose Elimination May Be Increased by Carbamazepine

Amitriptyline
Aripiprazole (Abilify)
Atorvastatin (Lipitor)
Citalopram (Celexa)
Clozapine (Clozaril)
Contraceptives, Oral
Cyclosporine (Neoral)
Felbamate (Felbatol)
Felodipine (Plendil)
Lamotrigine (Lamictal)
Lovastatin (Mevacor)
Methadone
Midazolam (Versed)
Nefazodone
Nifedipine (Procardia)
Prednisolone
Quetiapine (Seroquel)
Risperidone (Risperdal)
Simvastatin (Zocor)
Sirolimus (Rapamune)
Tacrolimus (Prograf)
Theophylline
Thyroid Hormone
Warfarin (Coumadin)
Ziprasidone (Geodon)

## Table 2

### Selected Drugs That May Increase Carbamazepine Concentrations

Amprenavir (Agenerase)
Cimetidine (Tagamet)
Clarithromycin (Biaxin)
Danazol (Danocrine)
Diltiazem (Cardizem)
Erythromycin (E-Mycin)
Fluconazole (Diflucan)
Fluoxetine (Prozac)
Fluvoxamine (Luvox)
Grapefruit Juice
Ketoconazole (Nizoral)
Itraconazole (Sporanox)
Posaconazole (Noxafil)
Propoxyphene (Darvon)
Ritonavir (Norvir)
Verapamil (Calan)
Voriconazole (Vfend)

## Table 3

### Selected Drugs That May Decrease Carbamazepine Concentrations

Efavirenz (Sustiva)
Nevirapine (Viramune)
Phenytoin (Dilantin)
Phenobarbital
Rifampin (Rifadin)
Rifapentine (Priftin)
St. John's wort