Clinically Significant Pharmacokinetic Drug Interactions with Carbamazepine: An Update

Edoardo Spina,1 Franco Pisani2 and Emilio Perucca3

1 Institute of Pharmacology, University of Messina, Messina, Italy
2 Institute of Neurological and Neurosurgical Sciences, University of Messina, Messina, Italy
3 Clinical Pharmacology Unit, Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy

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Summary

Carbamazepine is one of the most commonly prescribed antiepileptic drugs and is also used in the treatment of trigeminal neuralgia and psychiatric disorders, particularly bipolar depression. Because of its widespread and long term use, carbamazepine is frequently prescribed in combination with other drugs, leading to the possibility of drug interactions.

The most important interactions affecting carbamazepine pharmacokinetics are those resulting in induction or inhibition of its metabolism. Phenytoin, phenobarbital (phenobarbitone) and primidone accelerate the elimination of carbamazepine, probably by stimulating cytochrome P450 (CYP) 3A4, and reduce plasma carbamazepine concentrations to a clinically important extent.
Inhibition of carbamazepine metabolism and elevation of plasma carbamazepine to potentially toxic concentrations can be caused by stiripentol, remacemide, acetazolamide, macrolide antibiotics, isoniazid, metronidazole, certain antidepressants, verapamil, diltiazem, cimetidine, danazol and (dextropropoxyphene) propoxyphene. In other cases, toxic symptoms may result from elevated plasma concentrations of the active metabolite carbamazepine-10,11-epoxide, due to the inhibition of epoxide hydrolase by valproic acid (sodium valproate), valpromide, valnoctamide and progabide.

Carbamazepine is a potent inducer of CYP3A4 and other oxidative enzyme system in the liver, and it may also increase glucuronyltransferase activity. This results in the acceleration of the metabolism of concurrently prescribed anticonvulsants, particularly valproic acid, clonazepam, ethosuximide, lamotrigine, topiramate, tiagabine and remacemide.

The metabolism of many other drugs such as tricyclic antidepressants, antipsychotics, steroid oral contraceptives, glucocorticoids, oral anticoagulants, cyclosporin, theophylline, chemotherapeutic agents and cardiovascular drugs can also be induced, leading to a number of clinically relevant drug interactions.

Interactions with carbamazepine can usually be predicted on the basis of the pharmacological properties of the combined drug, particularly with respect to its therapeutic index, site of metabolism and ability to affect specific drug metabolising isoenzymes. Avoidance of unnecessary polypharmacy, selection of alternative agents with lower interaction potential, and careful dosage adjustments based on serum drug concentration monitoring and clinical observation represent the mainstays for the minimisation of risks associated with these interactions.

Carbamazepine is one of the most commonly prescribed drugs for epilepsy; it is also widely used in the treatment of trigeminal neuralgia and psychiatric disorders, particularly bipolar depression. Since these conditions often require long term therapy, there is a high likelihood that at some stage in treatment other drugs will be given in combination with carbamazepine to enhance the therapeutic benefit or to manage associated or intercurrent diseases. Use of combination therapy, in turn, may expose the patient to the risk of drug interactions.

Carbamazepine has a high propensity to be involved in clinically relevant drug interactions for a number of reasons: first, carbamazepine has a low therapeutic index and a relatively small change in its plasma concentration (due to induction or inhibition of metabolism) may easily result in loss of efficacy or signs of intoxication; secondly, carbamazepine is a potent inducer of several cytochrome P450 (CYP) isoenzymes and may, therefore, stimulate the metabolism of concurrently administered drugs. Finally, carbamazepine has an active metabolite, carbamazepine-10,11-epoxide (CBZ-E), whose concentration may be modified to a clinically important extent by concomitant medications.

The purpose of this article is to provide an updated review on pharmacokinetic drug interactions in patients taking carbamazepine. Attention will be focused on those interactions which have the greatest clinical relevance, particularly with respect to those medications which are most likely to be prescribed in combination with carbamazepine. Pharmacodynamic interactions, though important, will not be discussed, but may be mentioned in selected cases when they are relevant to the interpretation of clinical findings.

1. Pharmacokinetic Properties of Carbamazepine

The clinical pharmacokinetics of carbamazepine has been reviewed in previous issues of this journal. The rate of carbamazepine absorption