

## THE FAR-REACHING INFLUENCE OF HEPATIC ENZYME-INDUCING ANTIEPILEPTIC DRUGS

**Effects of Antiepileptic Drugs on Lipids, Homocysteine, and C-Reactive Protein.** Mintzer S, Skidmore CT, Abidin CJ, Morales MC, Chervoneva I, Capuzzi DM, Sperling MR. *Ann Neurol* 2009;65:448–456. **OBJECTIVE:** The widely prescribed anticonvulsants phenytoin and carbamazepine are potent inducers of cytochrome P450 enzymes, which are involved in cholesterol synthesis. We sought to determine whether these drugs have an effect on cholesterol and other serological markers of vascular risk. **METHODS:** We recruited 34 epilepsy patients taking carbamazepine or phenytoin in monotherapy whose physicians had elected to change treatment to one of the noninducing anticonvulsants lamotrigine or levetiracetam. Fasting blood samples were obtained both before and 6 weeks after the switch to measure serum lipid fractions, lipoprotein(a), C-reactive protein, and homocysteine. A comparator group of 16 healthy subjects underwent the same serial studies. **RESULTS:** In the epilepsy patients, switch from either phenytoin or carbamazepine produced significant declines in total cholesterol (–24.8 mg/dL), atherogenic (non-high-density lipoprotein) cholesterol (–19.9 mg/dL), triglycerides (–47.1 mg/dL) (all  $p < 0.0001$ ), and C-reactive protein (–31.4%;  $p = 0.027$ ). Patients who stopped taking carbamazepine also had a 31.2% decline in lipoprotein(a) level ( $p = 0.0004$ ), whereas those taken off phenytoin had a decrease in homocysteine level (–1.7  $\mu\text{mol/L}$ ;  $p = 0.005$ ). All of these changes were significant when compared with those seen in healthy subjects ( $p < 0.05$ ). Results were similar whether patients were switched to lamotrigine or levetiracetam. **INTERPRETATION:** Switching epilepsy patients from the enzyme-inducers carbamazepine or phenytoin to the noninducing drugs levetiracetam or lamotrigine produces rapid and clinically significant amelioration in several serological markers of vascular risk. These findings suggest that phenytoin and carbamazepine may substantially increase the risk for cardiovascular and cerebrovascular disease.

### COMMENTARY

One major distinctive feature of most new antiepileptic drugs is that they do not interact with cytochrome P450 (CYP450) liver enzymes, while in contrast, the classic antiepileptic drugs carbamazepine, phenytoin, phenobarbital, and primidone are potent inducers and valproate is an inhibitor of these enzymes. The most recognized disadvantage of enzyme induction or inhibition is interaction with other pharmacological therapies. In particular, enzyme inducers can decrease serum concentrations and the therapeutic efficacy of medications metabolized by the CYP450 enzymes. The list of influenced medications includes antiepileptic drugs as well as various nonseizure medications, including anticoagulants, antibiotics, antineoplastic agents, immunosuppressants, and statins. For example, when carbamazepine is initiated for a patient also receiving warfarin for anticoagulation, the warfarin metabolism is augmented and its therapeutic efficacy is reduced to the point that the dose of warfarin must be increased to maintain the same level of anticoagulation. Similarly, carbamazepine and phenytoin increase the metabolism of valproate to the extent that it can be very difficult

to reach the target valproate serum level, even with very high doses. The increased breakdown of medications not only elevates inactive metabolites but occasionally also may add to the production of toxic byproducts. For instance, the concomitant use of carbamazepine and valproate increases valproate toxic metabolites and may play a role in the onset of idiosyncratic hepatitis and pancreatitis (1).

As more has become known about the CYP450 enzyme system, it is apparent that the system has a multitude of other functions, including the synthesis and breakdown of endogenous substances, such as vitamin D, steroid sex hormones, cholesterol, and other lipids (2); accordingly, the chronic use of enzyme-inducing antiepileptic drugs has been associated with reduced bone density (3,4), altered sex hormone levels (5,6), and changes in lipid profile (7).

The current study by Mintzer and colleagues focused on the lipid profile as well as other markers of vascular disease, including C-reactive protein and homocysteine levels, and evaluated the effect of switching from the enzyme-inducers, carbamazepine and phenytoin, to the non-enzyme-inducers, lamotrigine, and levetiracetam. The observation that total cholesterol, atherogenic non-high-density cholesterol, triglycerides, and C-reactive protein were all lowered by switching from either of the enzyme-inducing to the noninducing

medications strongly suggests that reversal of enzyme induction is the mechanism underlying this improvement. However, carbamazepine and phenytoin also had distinct effects on lipoprotein(a) and homocysteine, indicating that nonspecific enzyme induction alone is not responsible for all the changes.

One important observation in the study by Mintzer et al. is that there was considerable heterogeneity among individuals with respect to changes in lipid profile after switching to lamotrigine or levetiracetam. Among the 36 patients, 3 had an increase in total cholesterol and 6 had an increase in atherogenic cholesterol after stopping enzyme-inducing medications. Furthermore, Mintzer and colleagues point out that studies of Finnish populations failed to show that enzyme-inducing antiepileptic drugs increased cholesterol at all (8). Mintzer et al. speculated that this finding reflects pharmacogenetic heterogeneity as a result of allelic variants of the CYP450 genes. Just as certain individuals are genetically predisposed to the toxicity of certain medications, others may be predisposed to unfavorable changes in lipid profile from induction of the CYP450 enzymes. With advances in pharmacogenetics, individuals at risk for adverse changes in lipid profile potentially may be identified with genetic testing.

Mintzer et al. argue that treatment with phenytoin and carbamazepine may increase the risk for cardiovascular and cerebrovascular disease. In support of their contention, they cited epidemiological data indicating a greater prevalence of cardiovascular and cerebrovascular disease in epilepsy patients than in the general population. The authors recommended that epilepsy treatment start with a non-enzyme-inducing drug. While there are many reasons to select a non-enzyme-inducing antiepileptic drug as first-line therapy, it seems advisable to await additional evidence for a link between enzyme induction and cardiovascular risk before excluding enzyme-inducing drugs on that basis alone. As a result of the complexity and extensive role of the CYP450 system, enzyme induction may have additional unforeseen influences. In addition, it also is not known if the new non-enzyme-inducing antiepileptic drugs affect cardiovascular risk through mechanisms other than the CYP450 system. Caution can be engendered from the unpredictable relationship between enzyme induction and alteration of bone metabolism. Use of an enzyme-inducing antiepileptic drug was expected to be associated with reduced bone density, as a result of hypermetabolism of vitamin D. Yet, when a careful study was done, bone den-

sity also was reduced by the non-enzyme-inducing antiepileptic drug valproate (9), and there was surprisingly no difference between carbamazepine and the much less enzyme-inducing drug, oxcarbazepine, with respect to vitamin D level and measures of bone turnover (10). The link between enzyme induction and cardiovascular risk will need to be explored further, with direct assessment of cardiovascular risk of patient groups receiving either enzyme-inducing or non-enzyme-inducing antiepileptic drugs in monotherapy. If enzyme-inducing antiepileptic drugs indeed, are associated with increased cardiovascular risk, their first-line use in epilepsy therapy will need to be strongly reassessed.

by Bassel W. Abou-Khalil, MD

## References

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