Pharmacogenetics and enzyme induction/inhibition properties of antiepileptic drugs

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Abstract—One of the major differences between the older antiepileptic drugs (AEDs) and the newer AEDs is the potential of the older AEDs for significant interactions with other medications. Many of the drug–drug interactions involving the older AEDs are reciprocal, i.e., both drugs affect each other. In contrast, the newer AEDs have either no or limited drug interaction potential. Despite our extensive understanding of and our ability to predict drug–drug interactions, serious drug interactions still occur. More than 30% of all new seizures occur in the elderly, and because this population may be taking a variety of other medications the addition of an AED can have profound impact on these other therapies. In women, the use of enzyme-inducing AEDs can cause significant alterations of sex hormones and can decrease the efficacy of oral contraceptives. In children and adults, the use of enzyme inducers may result in long-term endocrine effects, including bone loss and lipid, thyroid, and sex hormone abnormalities. Phenytoin and phenobarbital are metabolized by cytochrome P450 isozymes, with activity dependent on genetic polymorphism (CYP2C9, CYP2C19). The dosing of the newer AEDs is not affected by genetic polymorphism. The decreased induction and inhibition effects and the lack of significant genetic polymorphism of the newer AEDs allow increased ease of use and perhaps greater safety, especially for patients taking multiple medications.

NEUROLOGY 2004;63(Suppl 4):S3–S8

One of the major differences between the "traditional" or older antiepileptic drugs (AEDs) and the newer AEDs is in the potential of the older AEDs for significant interactions with other medications. In general, the older AEDs are broad-spectrum inducers (phenobarbital, primidone, phenytoin, and carbamazepine), whereas valproic acid is an inhibitor, of metabolic enzymes. Many of the drug–drug interactions involving older AEDs are reciprocal, i.e., each drug affects the other. In contrast, the newer AEDs have either no or limited drug interaction potential. In a recent Department of Veterans Affairs cooperative study of seizures in the elderly, Ramsay et al.[1] found that the mean number of prescription medications per patient was 6.7 (range 0 to 15). With more than 30% of all new seizures occurring in the elderly, the addition of an AED can have a profound impact on other therapies that may be concurrently prescribed. In women, use of enzyme-inducing AEDs can lead to significant alterations of sex hormones and can decrease the efficacy of oral contraceptives. In children and adults, the use of enzyme inducers may potentially result in long-term endocrine effects, including bone loss and lipid, thyroid, and sex hormone abnormalities. Despite our extensive understanding of drug interactions and our ability to predict them, serious drug interactions still occur. In addition, the effect of the older AEDs on the metabolism of endogenous substances is often underappreciated.

The function of the metabolic enzymes involved in drug metabolism is twofold: the detoxification of exogenous compounds, such as drugs, and the metabolism of endogenous compounds, such as steroids. For the AEDs, metabolic reactions are catalyzed predominantly by the cytochrome P450 (CYP) and UDP-glucuronosyltransferase (UGT) enzymes. CYP450 comprises multiple enzymes, with individual isozymes divided among three major families (CYP1, CYP2, and CYP3). Seven primary isozymes are involved in the hepatic metabolism of most drugs: CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.[2,3] The most abundant isozyme, CYP3A4, which accounts for approximately 30% of the total hepatic CYP,[2] has the broadest substrate specificity and is involved in the metabolism of more than 50% of all drugs.[3] The UGTs are a group of 16 separate isozymes consisting of two major subfamilies, UGT1 and UGT2, which are responsible for the metabolism of a wide variety of endogenous substrates, including steroids and bile acids, as well as drugs.[4,5] Recent knowledge of the specific CYP isozymes involved in the metabolism of AEDs facilitates prediction of potentially inductive and inhibitory interactions. Research that would facilitate the

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Publication of this supplement was supported by an unrestricted educational grant from GlaxoSmithKline. The sponsor has provided G.A. with an honorarium for her participation in this project. She has also received other honoraria from the sponsor during her career.

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Table 1 *Induction and inhibition effects of the traditional AEDs on hepatic enzymes*

AED	Induces	Inhibits
Carbamazepine	CYP1A2, CYP2C, CYP3A, UGTs	—
Ethosuximide	—	—
Phenobarbital/ primidone	CYP1A, CYP2A6, CYP2B, CYP2C, CYP3A, UGTs	—
Phenytoin	CYP2C, CYP3A, UGTs	—
Valproic acid	—	CYP2C9, UGTs, epoxide hydrolase

AED = antiepileptic drug; CYP = cytochrome P450 isozyme; UGT = UDP-glucuronosyltransferase.

prediction of drug interactions involving specific isozymes of UGT has lagged behind.

Hepatic induction. Hepatic enzyme induction is usually the result of an increase in the amount of enzyme protein. In most cases, enzyme induction leads to an increase in the rate of metabolism of the affected drug, with a consequent decrease in the serum concentration of the parent drug and possibly a loss of clinical efficacy. The older AEDs, including phenobarbital, primidone, phenytoin, and carbamazepine, have significant enzyme-inducing properties (table 1). In general, they induce a wide range of CYP450 isozymes, including CYP1A2, CYP2A6, CYP2B, CYP2C, and CYP3A, as well as the UGT isozymes. Many of the newer AEDs, such as gabapentin, levetiracetam, tiagabine, and zonisamide, either have no induction effects or induce only selected enzymes (table 2).

Hepatic inhibition. Hepatic enzyme inhibition usually occurs because of competition at the active site and leads to a decrease in the rate of metabolism of the affected drug.[6] Clinically, this is associated with an increased plasma concentration of the affected drug and the potential for an increased pharmacologic response. Valproic acid is a broad-spectrum metabolic inhibitor, inhibiting CYP2C9 (phenytoin and phenobarbital), epoxide hydrolase (carbamazepine), and several UGTs (see table 1). Valproic acid is a potent inhibitor of UGT-dependent metabolism of lamotrigine (UGT1A4),[7] zidovudine (UGT2B7),[8] and lorazepam [UGT isozyme(s) unknown].[9] There have been recent reports of coma induced by a combination of lorazepam and valproic acid[10] and of severe anemia secondary to treatment with valproic acid and zidovudine.[11] The macrolide antibiotics are also potent inhibitors of CYP3A4-catalyzed metabolism of carbamazepine. Many case reports of interactions between carbamazepine and macrolide antibiotics have been published, one with troleandomycin[12] as early as 1977 and several others with erythromycin[13,14] and clarithromycin[15] during the 1980s. Despite extensive literature establishing the serious clinical toxicity that can result from elevations in carbamazepine plasma concentrations with this combination, case reports were still being published more than 10 years later.[16,17] These examples serve to emphasize the clinical significance and potential problems of drug interactions, even when these effects are known and predictable. Of the newer AEDs, topiramate[18] and oxcarbazepine[19] selectively inhibit CYP2C19 in vitro. Common substrates of CYP2C19 include phenytoin, phenobarbital (minor), diazepam, the proton pump inhibitors (omeprazole, lansoprazole, and pantoprazole), and antidepressants (citalopram, fluoxetine, and sertraline). Only the drug interactions with phenobarbital and phenytoin have been clinically evaluated.

Table 2 *Induction and inhibition effects of the newer AEDs on hepatic enzymes*

AED	Induces	Inhibits
Felbamate	CYP3A4	CYP2C19, β-oxidation
Gabapentin	—	—
Lamotrigine	UGTs	—
Levetiracetam	—	—
Oxcarbazepine	CYP3A4, UGTs	CYP2C19
Tiagabine	—	—
Topiramate	CYP3A4,* β-oxidation	CYP2C19
Vigabatrin	—	—
Zonisamide	—	—

* Dose-dependent induction.[24]

AED = antiepileptic drug; CYP = cytochrome P450 isozyme; UGT = UDP-glucuronosyltransferase.

Interactions with exogenously administered drugs. An expert panel, including physicians, clinical pharmacists, and an expert on drug–drug interactions (DDIs), identified 56 DDIs.[20] The interactions were ranked on a scale of 1 to 10 in which 10 was most serious and any DDI ≥8 was considered serious. The rankings ranged from 1 to 9.2, with a mean rating of 6.6. Of the 56 DDIs listed, three involved AEDs: carbamazepine and propoxyphene (8.0), carbamazepine and macrolide antibiotics (7.6), and phenytoin and fluoxetine or fluvoxamine (7.6). In all three cases, the effect on the AED of enzyme inhibition by another commonly used drug resulted in serious drug interactions. This information is critical because health-care providers often prescribe the non-AED drugs to patients who have been prescribed an AED by another physician.

Hepatic enzyme induction by the older AEDs produces major effects on extensively metabolized drugs (>75% metabolized) with a low therapeutic index. For the drugs listed in table 3, the addition or discontinuation of an inducer could result in loss of efficacy or increased toxicity if plasma concentrations are not adjusted.[21] Dosage adjustments of approximately 50% to 100% may be necessary and require careful clinical monitoring. The effect of taking the older AEDs in addition to oral contraceptives

Table 3 *Drugs with which addition or discontinuation of a hepatic enzyme inducer could cause clinically significant effects*[21]

Drug category	Specific drugs
Antidepressant drugs	Amitriptyline, amoxapine, clomipramine, desipramine, doxepine, imipramine, nortriptyline, protriptyline, trimipramine
Antiepileptic drugs	Carbamazepine, ethosuximide, felbamate, lamotrigine, phenytoin, tiagabine, topiramate, valproic acid, zonisamide
Anti-infectious agents	Itraconazole, ketoconazole, mebendazole, voriconazole
Antipsychotic agents	Clozapine, haloperidol, risperidone, quetiapine
Antivirals	Amprenavir, atazanavir, delavirdine, indinavir, nelfinavir, ritonavir, saquinavir, zidovudine
Benzodiazepines	Alprazolam, clonazepam, diazepam, lorazepam, midazolam, triazolam
Calcium channel blockers	Amlodipine, bepridil, diltiazem, felodipine, isradipine, nisoldipine, nicardipine, nifedipine, nimodipine, nitrendipine, verapamil
Cardioactive drugs	Amiodarone, digoxin, disopyramide, procainamide, propranolol, quinidine
Corticosteroids	Cortisone, betamethasone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone
HMG-CoA reductase inhibitors	Atorvastatin, lovastatin, simvastatin
Immunosuppressants	Cyclosporine, sirolimus, tacrolimus
Oral anticoagulants	Dicumarol, warfarin
Oral contraceptives	Conjugated estrogens, ethinyl estradiol, levonorgestrel, norethindrone
Miscellaneous	Methadone, theophylline, vincristine

HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A.

(OCs) is a well-known example of a clinically significant DDI. OCs are widely used by women of childbearing age. CYP3A4 is involved in the metabolism of both endogenous and exogenously administered estrogens and progesterones. The ability of some AEDs to induce CYP3A4 results in increased clearance and corresponding decreased plasma levels of the estrogen component and also of the progestational component of the OCs. Phenytoin, phenobarbital, primidone (via phenobarbital), and carbamazepine induce CYP3A4. Of the new AEDs, topiramate, felbamate, and oxcarbazepine are weak inducers of CYP3A4. Topiramate decreases ethinyl estradiol levels only at higher doses ($\geq$400 mg/day),[22,23] consistent with studies demonstrating a dose-dependent induction of CYP3A4.[24] Valproic acid, ethosuximide, lamotrigine, gabapentin, tiagabine, and probably zonisamide do not alter the efficacy of OCs in women taking these AEDs concurrently. There has been a recent report of a reciprocal interaction whereby decreased plasma concentrations of lamotrigine were found when this AED was used in combination with an OC.[25]

Interactions with endogenous substances. Patients with epilepsy experience a wide variety of endocrine-related problems affecting pituitary, adrenal, thyroid, bone, and sexual function. Both the disease state (epilepsy) and the drug therapy have been implicated. Unfortunately, there is little or no information regarding the incidence of endocrine disorders or the effect on sexual or reproductive function with the second-generation AEDs. Because many of the endocrine effects may be due to the impact of the AED on the metabolism of endogenous hormones, the decreased propensity of the newer AEDs for drug interactions suggests that they may have less effect on the endocrine systems.[26]

Sexual/reproductive function. Patients with epilepsy have reduced fertility and suffer from hyposexuality more frequently than the general population.[27-29] A larger number of women with epilepsy have anovulatory cycles compared with control subjects.[30,31] Because reproductive endocrine disorders are associated with temporal lobe epilepsy[32] and primarily generalized epilepsy,[33] it is difficult to determine the role of AEDs. The enzyme-inducing AEDs increase the concentration of sex hormone-binding globulin (SHBG), resulting in decreased bioactivity of estradiol and testosterone.[34,35] Valproic acid is a broad-spectrum inhibitor of UGTs, including UGT2B15, which is involved in androgen and estrogen metabolism.[36] Isojärvi et al.[37] found that valproic acid was associated with an increased incidence of polycystic ovaries and hyperandrogenism with menstrual disturbances. Women taking valproic acid had elevated plasma testosterone and dehydroepiandrosterone sulfate (DHEAS) concentrations and a trend toward a decreased estradiol concentration. When female patients with either polycystic ovaries or hyperandrogenism were switched to lamotrigine, the total number of polycystic ovaries, body mass index, and fasting serum insulin and testosterone concentrations all declined significantly.[38] In men with epilepsy, valproic acid was also associated with increased serum androstenedione concentrations.[39] Replacing carbamazepine with oxcarbazepine in male patients resulted in a decrease in SHBG concentrations and an increase in DHEAS concentrations, with no change in serum free

and total testosterone, follicle-stimulating hormone, luteinizing hormone, or prolactin, suggesting that oxcarbazepine may have less effect than carbamazepine.[40] The endocrine effects of oxcarbazepine did not occur with doses <900 mg/day in a group of men with epilepsy.[39] In addition, as reported in a review article by Morrell,[26] lamotrigine and gabapentin do not appear to alter SHBG or adrenal or gonadal steroids

Bone disorders. The risk for falls with seizures can also increase the risk for serious bone fractures. The hepatic enzyme-inducing properties of AEDs have been shown to increase the metabolism of active vitamin D to inactive metabolites. Decreased vitamin D may then lead to decreased calcium absorption in the gastrointestinal tract.[41] However, decreased bone mineral density (BMD) occurs with normal vitamin D metabolism in some patients receiving the older AEDs, suggesting that the older AEDs may also have a direct effect on bone cells.[42] In a prospective study evaluating the risk for hip fractures in women 65 years or older, women currently taking enzyme-inducing AEDs had a twofold higher risk for hip fracture.[43] A retrospective analysis of BMD studies in patients with epilepsy receiving enzyme-inducing AEDs found that lower BMD was associated with low body mass index and longer duration of AED use.[44] Patients with epilepsy receiving phenobarbital, phenytoin, and carbamazepine, but not valproic acid, have hypocalcemia, hypophosphatemia, increased serum alkaline phosphatase activity and parathyroid hormone, and decreased active vitamin D serum levels. Duration of therapy with phenytoin and/or carbamazepine correlated with the BMD at the lumbar spine and femoral neck region in 59 patients.[45] Valproic acid, which is not an enzyme inducer, was also associated with decreased BMD in children.[46,47] These studies highlight the difficulty of attributing disturbances in bone metabolism solely to the enzyme-inducing effects of AEDs. There is also little or no information on the effects of the new AEDs on bone function, although one study found no significant reduction in calcium or markers of bone resorption or bone formation in women treated with lamotrigine.[48]

Thyroid abnormalities. Carbamazepine, phenytoin, and phenobarbital affect thyroid function, primarily by decreasing thyroid hormone concentrations.[49,50] It has been hypothesized that the enzyme-inducing properties of older AEDs are responsible for increasing the glucuronide metabolism of the thyroid hormones.[51] The thyroid gland releases the hormones tetraiodothyronine (thyroxine or T_4) and tri-iodothyronine (T_3). Regulation of T_4 and T_3 levels is under strict control of thyroid-stimulating hormone (TSH), which is influenced by negative feedback regulation by the thyroid hormone levels. T_4 is deiodinated to produce the more bioactive T_3 and is metabolized by both glucuronidation and sulfation. UGT1A2 is the isozyme primarily responsible for conjugating T_4 in the liver, with UGT1A9 also involved but to a lesser degree.[52] UGT1A2 is the primary isozyme responsible for the conjugation of bilirubin. Bilirubin glucuronidation activity is significantly increased by phenobarbital-type inducers.[53] Therefore, induction of T_4 metabolism by the broad-spectrum enzyme-inducing AEDs (carbamazepine, phenytoin, and phenobarbital) is also consistent with metabolism of T_4 by UGT1A2. Recent studies have found that T_3 is not significantly glucuronidated in the human liver or kidney, suggesting that the metabolism of T_3 is primarily due to sulfation and deiodination.[52]

Maximal decreases in thyroid hormones (T_4 and T_3) were found after 14 days of treatment with carbamazepine (400 mg/day) in healthy subjects. This time course of effect is consistent with the time course of the enzyme-inducing properties of carbamazepine. A recent study[54] evaluated thyroid function in girls (aged 8 to 18 years) with epilepsy taking carbamazepine (N = 19), oxcarbazepine (N = 18), or valproic acid (N = 41). Consistent with other studies that included male and female patients, valproic acid did not affect thyroid function.[55] Carbamazepine and oxcarbazepine resulted in equally low serum thyroid hormone (T_4 and free thyroxin) concentrations. Thyroid function normalized after withdrawal of therapy.[54] In contrast to the study in girls, when carbamazepine was replaced with oxcarbazepine in 12 male patients with epilepsy (aged 21 to 40 years), free and total thyroxin levels increased to normal.[56] Therefore, the effect of the older AEDs may be related to their UGT enzyme-inducing properties. Of the newer agents, both oxcarbazepine and lamotrigine are also inducers of the UGT enzymes, although both induce UGT to a lesser degree than the older AEDs and the specificity of the induction is not known. Except for oxcarbazepine, no long-term studies on the effect of any of the other new AEDs on thyroid hormones have been published. If the primary effect on thyroid hormone concentrations is due to induction of UGT1A2 metabolism of T_4, then we would expect the other newer AEDs to be similar to valproic acid in their lack of affect on thyroid function.

Lipid abnormalities. Epidemiologic data have linked elevated total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels and reduced high-density lipoprotein cholesterol (HDL-C) levels to the development of coronary artery disease in men and women. Epidemiologic studies have also demonstrated that mortality due to atherosclerosis-related heart disease is lower among patients with epilepsy treated with AEDs than in the general population.[57] The increase in HDL-C levels associated with phenytoin, carbamazepine, and phenobarbital has been suggested as a positive effect.[58] As with the other endocrine effects of the AEDs, the hepatic enzyme-inducing properties of the first-generation AEDs may be a factor in these lipid effects. There is a correlation between the HDL-C concentration and hepatic microsomal enzyme activity and CYP450 content in liver biopsy specimens.[59] In contrast, an increase in TC and LDL-C levels after AED therapy suggests a possible negative cardiovascular effect. Of the first-generation AEDs, only valproic acid does not increase

HDL-C. However, valproic acid does decrease TC and LDL-C.[58,60] A study of a large group of children with epilepsy[61] found that TC and LDL-C levels were high in children receiving phenobarbital (mean age 8.1 ± 3.5 years) or carbamazepine (11.4 ± 2.7 years) and low in those treated with valproic acid (9.1 ± 3.5 years). Mean apolipoprotein A-1 levels were low in all treated groups. The authors proposed that there may be an increased risk for atherosclerosis-related disease, particularly in children treated with carbamazepine or phenobarbital. No information is available about the relationship between lipid function and the newer AEDs. Given the decreased hepatic enzyme induction of the second-generation AEDs, it is possible that the effects on lipids may be significantly less

Pharmacogenetics of AEDs. The activity of the metabolic enzymes is dependent on genetic, physiologic, and environmental effects. Genetic polymorphism in the expression of *N*-acetyltransferases (NAT2), CYP1A2, CYP2C9, CYP2C19, and CYP2D6 has been identified. Poor metabolizers are homozygous for the mutant gene. Extensive metabolizers are either homozygous or heterozygous for the wild-type gene, with heterozygous carriers having intermediate metabolic activity. Ultrametabolizers have multiple copies of the gene; however, this has been described only for the CYP2D6 polymorphism. There is a large interethnic variability in the proportion of poor metabolizers and ultrametabolizers. Of the AEDs, only phenytoin and phenobarbital are subject to genetic CYP450 polymorphism. Both are metabolized by CYP2C9 and CYP2C19. The CYP2C enzymes account for approximately 20% of the CYP450 in the liver. CYP2C9 is responsible for the metabolism of *S*-warfarin (the active isomer of racemic warfarin), phenytoin, tolbutamide, and several of the nonsteroidal anti-inflammatory drugs (diclofenac, piroxicam, and ibuprofen). Of the identified mutant alleles of CYP2C9, CYP2C9*2 and CYP2C9*3 have 70% and 3% to 5% enzymatic activity compared with the wild-type, CYP2C9*1. Approximately 40% of the white and 5% of the Asian or black populations are heterozygous for either CYP2C9*2 or CYP2C9*3 and demonstrate significantly decreased CYP2C9 activity compared with CYP2C9*1/*1. CYP2C19 is responsible for the metabolism of *S*-mephenytoin (the primary probe for CYP2C19), phenytoin, phenobarbital (minor), diazepam, and desmethyldiazepam, the active metabolite of diazepam. The proportion of poor metabolizers is 15% to 25% in the Asian population compared with 2% to 5% in the white[62] and black populations.[63]

There have been case reports of severe phenytoin intoxication in a patient subsequently genotyped as homozygous for CYP2C9*3 and heterozygous for the CYP2C19*2 allele[64] and in another patient who was heterozygous for both CYP2C9*1/*3 and CYP2C19*1/*3.[65] A study in patients with epilepsy found that the ratio of steady-state phenytoin concentration to dose was 35% higher in 64 heterozygous patients (CYP2C19*1/*2 or *1/*3) than in 52 with the homozygous wild-type.[66,67] Odani et al.[67] found that the maximal elimination rate (V_{max}) was 33% lower in six patients with epilepsy who were heterozygous for CYP2C9*1/*2 compared with homozygous wild-type (CYP2C*1/*1). The effect of the CYP2C9 mutation was significantly greater than was found for the CYP2C19 mutations. V_{max} was only slightly decreased (14%) in patients with the CYP2C19 mutations (*2 or *3) compared with those who had homozygous wild-type *1/*1.

The fraction of phenobarbital that is eliminated by CYP2C9- or CYP2C19-dependent oxidation is significantly smaller (~25%) than for phenytoin. Phenobarbital is eliminated by a combination of renal excretion of unchanged drug (25%), *N*-glucoside formation (25%), and CYP450 oxidation. Therefore, the effect of polymorphism is significantly less than that found with phenytoin. Mamiya et al.[66] genotyped CYP2C19 in 74 patients receiving phenobarbital. Phenobarbital total plasma clearance was only 19% less in patients with CYP2C19*2/*2 and *2/*3 than in those with CYP2C19*1/*1.

Of the new AEDs, only zonisamide is eliminated by a polymorphic metabolic pathway, NAT2.[68] Approximately 50% of whites and 10% of Asians or blacks are poor (slow) acetylators (i.e., they are homozygous carriers of NAT2 mutant alleles). Only 15% of zonisamide is metabolized by NAT2. Therefore, the acetylation pathway will effect only a fraction of the total elimination of zonisamide and should not affect the pharmacokinetics or dosing.

Conclusion. The decreased induction and inhibition effects and the lack of significant genetic polymorphism of the newer AEDs allow increased ease of use, especially for patients taking multiple medications. Very little is yet known about the long-term effects, if any, of the newer AEDs on the endocrine system. The decreased propensity of the newer AEDs for drug interactions suggests that they will have fewer endocrine effects; however, more research is needed in this area.

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