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Managing Antiepileptic Drugs in the Oncology Setting

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Case Study

Ms. N, who resided in a region close to the Appalachian Mountains in the southeastern United States, was one of more than 1,000 local women interested in participating in the National Surgical Adjuvant Breast Project Breast Cancer Prevention Trial. The 52-year-old woman had one primary relative, her mother, with a history of breast cancer. Ms. N had a personal history of two benign breast biopsies and fibrocystic breast disease. Based on the Gail Model (National Cancer Institute, 2000), her relative risk for developing breast cancer was calculated to be 2.64% over the next five years. The normal risk is 1.7% over five years. Based on this information, Ms. N was eligible for the breast cancer prevention study. Careful review of her medical history revealed that she had been diagnosed with epilepsy 18 years earlier and had not had any seizure activity since her treatment with phenytoin began following the diagnosis. She denied other illnesses. She was 61 inches tall and weighed 138 pounds. Her blood pressure was 150/90 mmHg, and her physical examination was within normal limits. Her only medication was the antiepileptic drug phenytoin at 100 mg three times daily. Ms. N's prestudy laboratory values were normal, including albumin and total protein levels. She was accepted for study inclusion, and her treatment with either tamoxifen or placebo, based on randomization, was initiated. Two weeks later, she called the study office to report that she had been experiencing small episodes of seizure activity.

Clinical Problem Solving

What are the concerns for patients receiving antiepileptic drugs in conjunction with antiestrogen therapy?

Patients receiving antiepileptic drugs and antiestrogen therapy are at risk for altered activity of either or both drugs (Lehne, 2004). Alteration of drug activity may produce unanticipated or unwanted side effects or reactions. Two factors that may precipitate unwanted reactions in patients receiving antiepileptic drugs and antiestrogen therapy are the effects of protein binding and the cytochrome P450 (CYP) isoenzyme system (see Table 1). The interaction of two competing drugs may decrease the effectiveness of either drug, alter the blood levels of either drug, interfere with either drug's action, or cause uncomfortable side effects or adverse reactions (Mackie, 2004). Ms. N's situation emphasizes the problem of antiepileptic drugs and antiestrogen therapy. In addition, older adults have the highest incidence of new onset epilepsy of any age group (Bergey, 2004). As a result, healthcare professionals should carefully monitor the medical and medication histories of older patients with a cancer diagnosis.

How do protein-bound drugs interact, and how might this interaction have influenced Ms. N's response to the study drug?

Many drugs are bound to serum albumin, the primary carrier of protein in the blood. This means that a percentage of the drug is protein bound and a percentage is a circulating or active drug. Drugs that are bound to albumin or other carrier proteins do not diffuse across cell membranes because proteins are too large for easy cell membrane diffusion. Protein binding of drugs is a reversible process, and a balance of bound and free drugs is reached through the dosing schedule. Only free drugs can diffuse into tissue and produce effects. Drugs that are bound tightly to protein remain in the blood for a longer period of time because they are released slowly from the carrier protein, thus creating a longer duration of action.

Protein-bound drugs may interact in at least two different ways. First, depending on a drug's affinity for protein binding, the administration of a second protein-bound drug could displace the first drug, thereby increasing the blood levels of the first drug and its effects (Mackie, 2004). Second, Wainer (2004) described how some drugs, when added to human serum albumin, may cause a conformational change to albumin that increases the binding affinity of other drugs. As binding affinity increases, less of the active drug is available.

In the case of Ms. N, phenytoin and tamoxifen both are highly protein bound. Ms. N had been taking phenytoin for 18 years. Approximately 98% of phenytoin is protein bound, so only 2% of the drug actually is available to be active in the body (Deglin & Vallerand, 2004). Tamoxifen typically is 99% protein bound, leaving only 1% active (British Columbia Cancer Agency, 2004). The addition of tamoxifen to Ms. N's medication regimen may have caused a conformational change of the albumin in her blood. The conformational change could cause more phenytoin to bind to protein, leaving less active drug available and increasing seizure activity in the patient.

Levels of active drugs in the bloodstream may increase or decrease depending on the actual binding affinity of the competing drugs. All drugs have different binding abilities or "tenacity" for binding to receptors. If a highly protein-bound drug such as tamoxifen is administered, another highly protein-bound drug such as phenytoin can be displaced or have enhanced binding (Mackie, 2004; Wainer, 2004). Over time, therapeutic levels change because both medications are

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Digital Object Identifier: 10.1188/05.ONF.1094-1096

Table 1. Metabolic Pathways of Antiepileptic Drugs

Drug	Site of Metabolism	Hepatic Inducer or Inhibitor
First generation		
Carbamazepine	> 95% hepatic, cytochrome P450 (CYP) 3A4	Inducer
Phenobarbital	75% hepatic, 25% renal CYP3A4	Inducer
Phenytoin	> 90% hepatic, CYP3A4	Inducer
Primidone	Metabolized to phenobarbital	Inducer
Valproate	> 95% hepatic, CYP3A4	Inhibitor
Second generation		
Gabapentin	Mostly renal	Neither
Lamotrigine	> 95% hepatic	Neither
Levetiracetam	67% renal, 33% nonhepatic hydrolysis	Neither
Oxcarbazepine	67% hepatic	Mild inducer
Tiagabine	Mostly hepatic	Neither
Topiramate	30%–55% hepatic	Neither
Vigabatrin	Mostly renal	Neither
Zonisamide	50%–70% hepatic	Neither

Note. Based on information from French et al., 2004.

competing for binding sites on the proteins. For Ms. N, the randomized agent, which was almost certainly tamoxifen, caused more phenytoin to bind, thereby decreasing the levels of the active drug to less than 2%. In addition, more active tamoxifen was available, perhaps potentiating the side-effect profile related to that medication.

How is the cytochrome P450 enzyme system involved in drug interactions?

Biotransformation, the third step in pharmacokinetics, is comprised of two phases (see Figure 1). Phase I involves oxidation, hydrolysis, and reduction actions; phase II involves conjugation, whereby the drug or its metabolite is combined with other chemicals (e.g., sulfate, acetate). Phase I oxidation processes are the result of CYP microsomal isoenzymes (Lehne, 2004). Three of the cytochrome isoenzymes—CYP1, CYP2, and CYP3—are responsible for the majority of the oxidative reactions that cause inactivation of the drug. Each group contains subdivisions of isoenzymes that are designated by letters and numbers. In the CYP3 group, CYP3A performs more than 50% of the known oxidation reactions. CYP3A4 is a member of the subgroup that can cause drug-drug and drug-food interactions (Lehne). When an isoenzyme is induced, it increases the metabolism of the drug substrate, resulting in decreased duration of action and effectiveness. When an isoenzyme is inhibited, the metabolism of the drug substrate is reduced, resulting in increased blood levels of the drug and possible toxic effects. CYP3A4 is found in the liver as well as the intestinal mucosa, where grapefruit juice may inhibit it, limiting deactivation of certain drugs and increasing the bioavailability of the drugs and elevation of blood levels to toxic levels. Isoenzymes also may be inhibited or induced by certain drugs. A significant number of drugs and other substances have been identified as inhibitors and inducers of the CYP isoenzymes. A comprehensive and updated list of CYP isoenzyme inhibitors and inducers is available from Flockhart's (2005) work.

According to French, Lott, and Rios (2004), when using antineoplastic agents, including the antiestrogens that interact through the hepatic CYP isoenzyme system, the dose of phenytoin may need to be increased as much as 40%. Instead of titrating to the new dose, French et al. recommended switching to a nonhepatic enzyme-inducing antiepileptic drug. In addition, some enzyme-inducing agents reduce the efficacy of chemotherapeutic agents, which is another reason to select an alternate drug for seizure control.

Biotransformation: the enzymatic alteration of drug structure, most commonly taking place in the liver

Hepatic inducer or inhibitor: inducing or inhibiting as part of the hepatic microsomal enzyme system, cytochrome P450

Isoenzyme: one of a group of enzymes that catalyze the same reaction but may be differentiated by variations in physical properties such as isoelectric point, electrophoretic mobility, kinetic parameters, or modes of regulation

Pharmacogenomics: drug response based on a patient's genetic makeup

Pharmacokinetics: the study of drug movement throughout the body with four basic processes of absorption, distribution, metabolism (biotransformation), and excretion

Substrate: substance acted on and changed by an enzyme

Figure 1. Definitions

Note. Based on information from Dirckx, 1997; Lehne, 2004; U.S. Department of Energy Office of Science, 2003.

Do genetic variations in cytochrome P450 enzyme activity exist in people?

With the completion of the human genome project, single nucleotide polymorphisms now are known to be associated with what previously was termed "idiosyncratic reactions" (Roses, 2000). Research based on the human genome project has identified the genes responsible for the production of the isoenzymes in the CYP enzyme system. Genetic locations for some of the CYP isoenzymes have been identified on chromosomes 4q35.1, 7q22.1 (isoenzyme CYP3A4), 10q24.1-q24.3 (CYP2C9 and CYP2C19), 19q13.2 (CYP2A6), and 22q13.1 (CYP2D6) (Online Mendelian Inheritance in Man, n.d.). As many as 3% and 10% of Caucasians have an alteration on chromosome 10 and chromosome 22, respectively, and chromosome 10 alterations occur in as many as 20% of Asians (Roses); therefore, a thorough family history is crucial to determine familial differences in drug responses. Knowledge from the growing field of pharmacogenomics needs to be taken into account when prescribing drugs metabolized by the CYP system. In the future, drug prescribing may be based on genotypes.

What are the possible therapy choices for Ms. N?

If Ms. N is committed to continuing with antiestrogen therapy in an attempt to prevent breast cancer, her dose of phenytoin can be adjusted by phenytoin levels. Based on the literature and the suggestion that phenytoin can result in poor seizure control when given in conjunction with a variety of drugs, a different type of antiepileptic drug could be given to Ms. N. In patients with cancer receiving chemotherapy, removing an enzyme-inducing agent such as phenytoin may cause a sudden increase in toxicity as a result of the rapid loss of metabolic enzyme induction or reduced clearance of the chemotherapy (French et al., 2004). In this case, switching from phenytoin to a nonisoenzyme-inducing agent is preferable. Doing so would include decreasing the dose of phenytoin while increasing the dose of the new agent prior to beginning antineoplastic therapy. Because second-generation antiepileptic drugs have minimal, if any, ability to induce or inhibit enzymes, they have no effect on the hepatic metabolism of other drugs. This is an attractive feature for patients with cancer, especially those with liver involvement. Of the antiepileptic drugs in Table 1, gabapentin, oxcarbazepine, and levetiracetam can be initiated at a therapeutic dose when patients must attain an effect as rapidly as possible.

What was Ms. N's clinical outcome?

Ms. N stopped the prevention study medication and was started on a low but increasing dose of gabapentin with decreasing doses of phenytoin. When she reached

Clinical Highlights: Antiepileptic Drug Interactions in the Oncology Setting

Definition: Drug interactions occur when a desired drug action is amplified or decreased or a new result occurs that neither drug produces alone.

Incidence: The incidence of drug interactions increases with age, when the number of medications administered increases, and when individuals are taking highly protein-bound drugs, such as first-generation antiepileptic drugs. Because the incidence of epilepsy (3:100) and cancer (1:4) increases with age, the probability that older adults being treated for these concomitant conditions can develop drug interactions increases (American Cancer Society, 2005; Epilepsy Foundation, 2005; French, Lott, & Rios, 2004).

Pathophysiology: The pharmacokinetics of medications taken by the older population differ from those in younger patients. Atrophy of the gastric mucosa, altered gastric motility, and decreased concentration of serum albumin are some of the usual age-related physiologic changes in older adults that can affect the pharmacokinetics of antiepileptic drugs. These can result from changes in fluid distribution, altered metabolism of the liver, lower protein binding, diminished enzyme activity, and decreased elimination by the kidneys (Stolarek, Brodie, & Brodie, 1995). In addition, the cytochrome P450 (CYP) isoenzyme system can interact with drugs, causing competition for binding at the receptor site (inhibition) or an increase in the enzyme synthesis and metabolic capability (induction). Genetic variations of the CYP isoenzymes are responsible for idiosyncratic drug reactions (Roses, 2000).

Risk factors: Drug interactions with antiepileptic drugs can cause serious side effects and adverse reactions. Older adults with cancer who are taking first-generation antiepileptic drugs are especially at risk. Asians and Caucasians with family histories of altered CYP isoenzyme function also may be at risk (French et al., 2004; Roses, 2000). Some chemotherapeutic agents commonly use the CYP isoenzyme pathways and can interact with first-generation antiepileptic drugs. They include busulfan, cisplatin, corticosteroids, cyclophosphamide, doxorubicin, toposide, irinotecan, methotrexate, nitrosureas, tamoxifen, taxanes, and vinca alkaloids (French et al.).

Differential diagnoses: New or worsening malignancy, especially hepatic involvement, may occur.

Prevention of drug-drug interactions: Asians and Caucasians should be questioned carefully about family histories of differences in drug responses. Thorough drug and medical histories are important to identify patients with epilepsy who are taking antiepileptic drugs prior to the initiation of antineoplastic therapy.

Management of drug-drug interactions: The preferred treatment is to begin second-generation antiepileptic drugs prior to initiating antineoplastic therapy. The dose of the first-generation antiepileptic drug is decreased while the dose of the new agent is increased prior to beginning cancer treatment. Because second-generation antiepileptic drugs have minimal, if any, ability to induce or inhibit enzymes, hepatic metabolism of other drugs is not affected, which is especially attractive for patients with liver cancer or metastatic hepatic involvement. If achieving a rapid effect is important, gabapentin, oxcarbazepine, and levetiracetam can be initiated at a therapeutic dose (French et al., 2004).

Patient education: Patients receiving antiepileptic drugs should be monitored and instructed to watch for enhanced known side effects or new and unusual side effects after taking new medications. In addition, new seizure activity should be assessed carefully.

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a stable dose of gabapentin and was no longer taking phenytoin, the study drug was restarted. She tolerated both medications well and did not experience any other seizure activity.

The authors gratefully acknowledge Julie Martin, FNP, AOCN®, in the Clinical Research Unit at Greenville Hospital System and Jeffrey Giguere, MD, at Cancer Centers of the Carolinas, both in Greenville, SC.

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