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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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