

Can We Minimize Interaction Between AEDs and Other Common Medications?

The relative popularity of AEDs means that the potential drugs interactions is inevitable. Here's an overview of the biggest concerns.

As neurological conditions go, epilepsy is more common than many. It affects one percent or more of the population. Because epilepsy is chronic, in many people it requires long-term if not life-long treatment. Two-thirds of people with seizures will experience seizure-freedom with a single antiepileptic drug (AED) or a combination of medications.¹ The remaining one-third may require a combination of AEDs, possibly in combination with more invasive treatments such as epilepsy surgery.

Inevitably, a person with epilepsy will need to take medications for routine surgeries, the common cold, allergies or possibly a more serious medical illness. Inevitably then, there are many potential drug interactions between AEDs and the medications that might be needed in these other situations—and exponentially more when one considers the number of people taking an AED for migraine prophylaxis. This month's column will provide an overview of the most common interactions that you and your patients should be concerned with. Some are unavoidable and must simply be tolerated; others can be minimized through judicious tweaking of the regimen used for one or both drugs.

Contraceptives

As we have discussed in previous installments of Epilepsy Essentials, there are potential interactions between AEDs and steroid hormones. Sex-steroid hormones are broken down by the hepatic P450 system. Many of the older AEDs such as



phenobarbital, primidone, carbamazepine and phenytoin are inducers of this metabolic pathway. Some of the newer AEDs, such as oxcarbazepine and felbamate, are also enzyme inducers. In short, hepatic enzyme inducers accelerate the metabolism of other medications that are broken down by the P450 system.

Oral contraceptives are broken down by the cytochrome P450 enzyme. If the person with epilepsy is taking an enzyme-inducing medication, the oral contraceptive will be less effective. Although many physicians are now familiar with this interaction, it is important to counsel patients appropriately. Armed with this information, a person with epilepsy may wish to consider using another form of birth control.

Recent studies have shown that oral

contraceptives can also affect AEDs. The serum concentration of lamotrigine is reduced by these medications. In some women, the decrease in lamotrigine levels is 65 percent. If the dose of lamotrigine is not increased to compensate for this effect, seizures might occur. Most oral contraceptives are taken for three weeks. This is usually followed by one week of placebo, during which the menses occurs. Women who are taking lamotrigine might experience an increase in serum levels during this phase, and develop side effects as the lamotrigine levels rise.

Antibiotics

Some antibiotics inhibit the metabolism of AEDs, causing the serum concentration of the AED to go up. Macrolide antibiotics, such as erythromycin, are one example of this interaction. A macrolide antibiotic can potently inhibit the hepatic CYP3A4 enzyme, decreasing the metabolism of other medications, including the AEDs that are broken down through this enzymatic pathway. Carbamazepine is a good example of this. When a person who is taking carbamazepine then takes erythromycin, the carbamazepine level can increase as much as four-fold.

This could easily translate into toxicity. Isoniazid, an antituberculosis agent, can inhibit the metabolism of carbamazepine, phenytoin, ethosuximide, and valproate, resulting in toxicity. An alternative antibiotic should be selected, if possible, to avoid this interaction.

Other antibiotics are hepatic enzyme inducers, and therefore reduce the effectiveness of concomitant AEDs. For



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instance, rifampin, an antituberculosis medication, increases the metabolism of carbamazepine, phenytoin, ethosuximide, and valproate, thereby lowering the serum concentration of these AEDs. Breakthrough seizures may result.

AEDs can also affect antibiotics. Enzyme-inducing AEDs can accelerate the elimination of antibiotics, making them less effective. One example of this is doxycycline, a tetracycline antibiotic.

Antiviral Agents

Seizures occur in one out of 10 people with HIV. A person with HIV may be on any number of medications, and potential interactions with these medications and the antiseizure medication must be considered. Many of the antiretroviral medications are broken down by the CYP3A4 liver enzymes. AEDs that cause induction of the CYP3A4 system may be a problem.

Carbamazepine, phenytoin and phenobarbital induce this system of metabolism. If given to someone taking nevirapine, efavirenz, delavirdine, indinavir, ritonavir or saquinavir, the effectiveness of the antiviral drug will be reduced. In order to avoid this interaction, one of the newer AEDs should be selected; many of these do not affect the hepatic enzyme system of drug metabolism.

Antineoplastic Medications

Many people with brain tumors will experience seizures. An antiseizure medication is likely to be initiated. Whether primary brain tumors or metastases, chemotherapy may also be needed. Many chemotherapeutic agents are hepatically metabolized. Enzyme inducing AEDs can reduce the effectiveness of medications like cyclophosphamide, etoposide, methotrexate, and busulfan.

Some anticancer medications, like fluorouracil and tamoxifen, are enzyme inhibitors. As a result, they increase serum concentrations of the hepatically metabolized AEDs. As we have seen, this results

in higher serum concentrations of these medications and therefore toxicity.

Cholesterol-lowering Medications

Referred to as “statins” (simvastatin, atorvastatin, lovastatin), lipid-lowering medications are broken down by CYP3A4 hepatic enzymes. In the presence of an enzyme-inducing AED, the effectiveness of these medications is reduced.

Anticoagulants

Warfarin metabolism is accelerated by hepatic enzyme-inducing AEDs. When given together, the dose of warfarin must be increased to maintain a therapeutic INR. Similarly, if the hepatic enzyme inducer is eliminated, the dose of warfarin must be reduced in order to prevent a dangerous increase in anticoagulation. Valproate, a hepatic enzyme inhibitor, has the opposite effect: its presence will cause an increase in the INR. The dose of warfarin must be lowered accordingly.

Immunosuppressants

Cyclosporine is broken down by CYP3A4. If an enzyme-inducing AED is given to a patient taking cyclosporine, the serum concentration of this drug will decrease. If the enzyme-inducing AED is withdrawn during cyclosporine administration, the dose must be lowered to avoid toxicity.

Strategies to Avoid Interactions

Many other drugs interact with the AEDs in similar ways. Physicians must be aware of this in order to select an optimal combination of medications. Fortunately, many AEDs are now available. Many are not metabolized by the P450 or CYP3A4 systems, and therefore would have little or no impact on the metabolism of drugs that pass through this pathway. When possible, a physician should select one of these antiseizure agents in order to avoid these interactions.

However, this may not always be possible. There are many instances when an

enzyme-inducing medication is needed. One example would be a person with a brain tumor who now presents to the Emergency Department in status epilepticus. An intravenous medication will be needed. Phenytoin (or fosphenytoin) is a good choice. If phenytoin is continued as the maintenance AED, the dose of the coexisting chemotherapy may need to be adjusted. If levels of the chemotherapeutic drug are available, by monitoring the plasma concentration of the drug, adjustments can be made to maintain the drug within a therapeutic range.

Careful monitoring of side effects is needed whenever medications are combined. This is especially true when certain AEDs are combined with other medications. Toxicity may result from changes in the serum concentration of the AED. They may also be a result of changes in the plasma level of the coexisting drug.

Conclusions

Epilepsy patients often require long-term AED therapy. At some point, another medication may be needed. Physicians must be careful about possible drug interactions. AEDs may reduce the effectiveness of co-administered medications by inducing their metabolism. Some AEDs may inhibit the metabolism of other drugs, increasing serum levels and causing toxicity. The opposite may occur: coexisting drug can reduce AED levels, causing breakthrough seizures, or increase levels, causing side effects. By understanding these interactions and selecting drugs which do not share common metabolic pathways, the physician can optimize the treatment of both illnesses. **PN**

1. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *New England Journal of Medicine* 2000;342(5):314-9.

2. Patsalos P, Perruca E. Clinically important drug interactions in epilepsy: interactions between antiepileptic drugs and other drugs. *Lancet Neurology* August 2003;2:473-477.

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