by Steven Karceski, MD

Is There a Role for Generic AEDs in the Treatment of Epilepsy?

Generic substitution is becoming an inevitability, due to the high cost of health care. But overly-broad parameters can undermine efficacy. Here's what you need to know.

The goal of epilepsy treatment is always the same: no seizures and no side effects. For the majority of patients—64 percent as reported by Kwan and Brodie[1]—this goal is met with either monotherapy or a combination of two antiseizure medications. Implicit in this is that the patient is compliant with the regimen, and therefore has consistent, steady serum anticonvulsant levels. In other words reliable serum levels, when a person is seizure-free, may reassure physicians that the patient can expect consistent, ongoing seizure control.

If a person is non-compliant and levels fall, a seizure may result. Even a single seizure can have serious consequences such as falls, injuries and possibly death (see Epilepsy Essentials, *Practical Neurology* July 2005). Other consequences of a single seizure include loss of driving privileges and occupational or recreational restrictions such as not working at heights or using machines with exposed moving parts. We are always counseling our patients about ways to maintain good seizure control: medication compliance is one example of this. When a person is taking a single brand of medication, the assumption is that there is very little batch-to-batch variability. Staying with one brand, when seizures are completely controlled, means continued seizure freedom.

Generics vs. Brand-Name Drugs

Most physicians and patients believe that generic medications and brand-name medications are the same. The generic medicine is the same molecule as the innovator drug. It is manufactured, for the most part, in the same dosage strengths as the brand-name drug. However, generics may be made from a different salt than the original drug. Generics are allowed to contain different colorants, flavors and inert materials. Although thought not to significantly impact the therapeutic effectiveness of the generic, these added components rarely may lead to unexpected reactions (such as allergy) to a medication that the patient had been taking for many.[2]

Generics are approved after they have demonstrated bioequivalence. This basically means that when given a specific dose of generic, the serum levels should be equal to what would occur if the person took the same dose of brand-name drug. To determine this, a single dose of drug is usually given to otherwise healthy adults. These individuals are usually not on other medications, and have no medical illnesses. The advantage to studying medications in this group is that the study is "clean," without interference from drug-to-drug interactions. Usually, the same person that takes the generic also takes the brand-name medication in a cross-over study design. The pharmacokinetics of the brand-name and generic medication are then calculated and compared. Parameters such as peak serum levels and amount of drug absorbed are recorded.

In order for a generic to be approved by the Food and Drug Administration, the bioavailability must be 80 to 125 percent of the innovator brand.[2] One study by the American Academy of Neurology demonstrated that the bioavailability of generic-to-branded medication was in fact 74 to 142 percent.[3]

Generics: What are the Costs?

Where do generic antiseizure medications fit in? In an era where cost-saving has become a major focus of health care systems, lower cost of medications is one reason to use generics. It has been estimated that generic medications could save billions of health care dollars. As the United States population ages, and more people are taking medication routinely, the long-term cost savings can be staggering. Interestingly, unless the individual is paying for their meds out-of-pocket, they are not likely to see this cost savings.

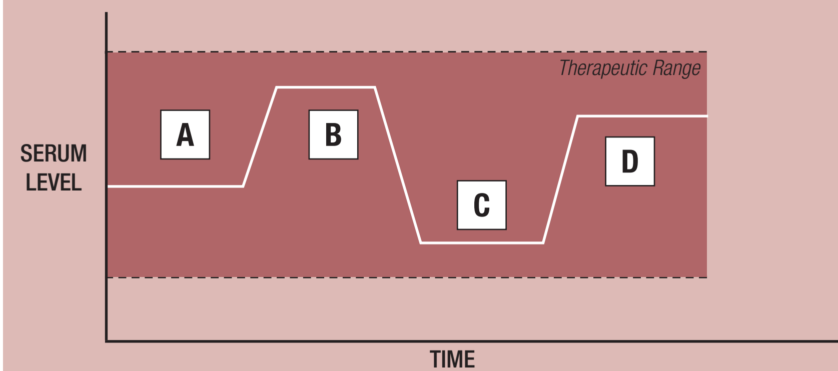
Although the cost of medication is one factor to consider, there may be other "hidden" costs to generic substitution. For instance, if a person with well-controlled epilepsy was switched to a generic and had a seizure, what is the cost of his hospitalization and lost wages? This aspect of medical costs is much more difficult to quantify. However, some authors have proposed that the cost of even one seizure outweighs the cost-savings by switching to the generic medication. It is my opinion that further study is needed in this area, using a carefully designed study that systematically evaluates both of these issues.

Generics: Some Concerns in People with Epilepsy

The first issue that concerns many physicians who treat people with seizures is failure of the therapy. There are two phases to medical treatment: initiation of medication and maintenance of therapy. Initiation encompasses that titration of the drug to the point where the person's seizures stop. In this phase, either the brand-name or generic formulation could be used. Though there may be subtle differences between the two, regardless of the manufacturer, the goal is to arrest the seizures (without side effects, of course). Assuming the same manufacturer's drug is used through the usually short titration, consistency is maintained.

However, when a person transitions to the maintenance phase of drug therapy, the situation is different. Once the seizures are well-controlled, there is great reluctance to change therapy, as the return of seizures may be accompanied by morbidity or mortality. At this point, the concern is not whether the person started on a brand-name product or a generic, but whether he can continue to take the same manufacturer's drug from the point of seizure freedom going forward (see Figure 1). Although the differences in bioavailability may be well within the FDA criteria, these differences from one manufacturer to another might result in wide fluctuations of serum levels.

Figure 1. Variability in Bioequivalence of Generic Drugs



There are 4 manufacturers of drug "x". Depending on bioavailability, there can be wide fluctuations in levels as the person "switches" from one manufacturer to another. Although the levels are always in the "therapeutic range", level in the higher part of the range (as with drug manufacturer "B") might result in side effects while levels in the lower end of the range (as with drug manufacturer "C") may result in seizures.

Neither the physician nor the patient has control over which generic medication might be selected from a field of the drug's manufacturers. Usually, this choice occurs at the level of the pharmacy. Decisions about which manufacturer's drug to purchase are usually based on one of two issues: cost to the pharmacy, and availability of the drug. Needless to say, if the drug is less expensive to the pharmacist, he may choose this to optimize his profits. If a prescription requires immediate delivery, availability of the drug may become the most important factor in determining the selection of manufacturer. If a person has his or her prescriptions filled in more than one pharmacy, this problem is only compounded.

Generics and the Older AEDs

Little information is available regarding generic medication use and the newer antiepileptic medications, those which were approved by the FDA after 1994. However, there is some information about generics and the older AEDs. Mostly, this information comes from case reports or case series. Usually, the case reports highlight a problem that occurred as a result of a switch to generic medication. In contrast, we do not have studies which carefully evaluate the percentage of patients that do just fine on generic AEDs. Because information on the newer AEDs is limited, many physicians assume that the same problems that have been observed with the older AEDs also applies to the newer ones.

The case reports for the older AEDs follow a similar pattern: brand-name is switched to generic, resulting in seizures or side effects. Once the brand-name drug is restarted, the seizures stop (or the side effects abate). Children, adults and the elderly are susceptible to this phenomenon. Some studies have suggested that the rate of problems associated with this type of switch is 10-15 percent.[2]

Conclusions

Generic medications must be used carefully in the treatment of epilepsy. Because the cost of therapeutic failure is so high, it is important to maintain the person on the same formulation (ideally, from the same manufacturer) in order to maintain consistent serum AED levels. This may not be an easy task, especially when there are several manufacturers of the same drug. It is because of this reason that the American Academy of Neurology has issued recommendations on the use of generics in the treatment of epilepsy, encouraging pharmacies inform patients and their doctors of switches in manufacturers, and asking health organizations to evaluate problems that might arise as a result of such a switch. Unfortunately, this information remains lacking. Until it is available, physicians and their patients should be aware of the advantages and pitfalls of generic substitution in the treatment of epilepsy. **PN**

1. Kwan P and Brodie MJ. Early identification of refractory epilepsy. New England Journal of Medicine 2000;342:314-319.

2. Crawford P, M Feely, A Guberman, G Kanner. Are there potential problems with generic substitution of antiepileptic drugs? Seizure 2006;15:165-176.

3. American Academy of Neurology. Assessment: generic substitution for antiepileptic medication. Neurology 1990;40:1641-1643.

Steven Karceski, MD is Assistant Clinical Professor of Neurology at the College of Physicians & Surgeons of Columbia University and Director of the Columbia Epilepsy Center at the Atlantic Neuroscience Institute.