EPILEPSY CURRENTS

It's Current
Epilepsy Resources and Updates

AES Position Statement on Generic Substitution of Antiepileptic Drugs

David G. Vossler, MD, FAAN,[1*] Gail D. Anderson, PhD,[2] and Jacquelyn Bainbridge, PharmD[3]
[1]Department of Neurology, University of Washington, Seattle, and UW Medicine, Valley Medical Center, Renton, WA
[2]Department of Pharmacy, University of Washington, Seattle
[3]Skaggs School of Pharmacy and Pharmaceutical Sciences and Department of Neurology, University of Colorado Anschutz Medical Campus, Denver
*Address correspondence to David G. Vossler, MD, Neuroscience Institute, UW Medicine | Valley Medical Center, 400 S. 43rd St., Renton, WA 98055. E-mail: david_vossler@valleymed.org

Dr. Vossler is on the speaker's or advisory boards of Eisai, Lundbeck, Sunovion, and UCB Pharmaceuticals. He conducts clinical research trials for Acorda, Marinus, Pfizer, and UCB Pharmaceuticals. Drs. Anderson and Bainbridge report no conflicts of interest.

Among the older antiepileptic drugs (AEDs), generic substitutes have been available for many years. Phenobarbital, synthesized in 1912, has long been available in generic form, and brand-name Luminal was discontinued in the United States decades ago. Phenytoin, developed in 1938, was prescribed for decades as extended-release Dilantin Kapseals (Pfizer, Inc., New York), but it has largely been replaced by generic extended-release products. After approval in the United States of carbamazepine in 1974 and valproic acid in 1978, the branded forms had many years of patent exclusivity, but generic alternatives later became available. Beginning in 1993 with felbamate, a series of approximately 20 new brand-name AEDs were approved by the U.S. Food and Drug Administration (FDA). Patent duration after FDA approval of these newer AEDs varied, but all approved before 2005 are now available as generics. Typically, generic drugs are less expensive than the branded original, which encourages, or may mandate, the substitution of generics for the brand product to reduce pharmaceutical costs.

For any drug, bioavailability is defined as the rate and extent to which the active ingredient is absorbed from a drug product and becomes available at the site of action (1). In order for a generic AED to be approved by the FDA, manufacturers are required to show pharmaceutical equivalence and to demonstrate bioequivalence of the generic form to the original brand-name product. Pharmaceutical equivalence requires that the drug product contains the same active ingredient, dosage form and strength, and route of administration. However, it may differ in inactive ingredients (e.g., binders, excipients), manufacturing process, and physical appearance (1). Bioequivalence (BE) is achieved if the product exhibits no substantial difference in the rate and extent of drug absorption. BE is tested in single-dose pharmacokinetic generally involving 24 to 36 healthy subjects under both fed and fasting conditions (1). Statistically, the BE standard requires that the entire 90% confidence interval (CI) of the log-transformed ratios of the test/reference for the maximum plasma concentration (C_{max}) and the area under the plasma concentration time curve (AUC) fall within the bounds of 80% to 125%. This is based on the judgment that a difference <20% between products would not result in a clinically-significant problem. Therefore, the test product is not significantly less than reference (T/R = 80%) and a reference product is not significantly less than test (T/R = 80%). As all data are expressed as T/R, this becomes 100/80 or 125%. In a recent analysis of 258 BE studies of AEDs the 80% to 125% BE rule resulted in <15% variability in AUC and C_{max} in 99% and 89%, respectively (2).

Epilepsy Currents, Vol. 16, No. 3 (May/June) 2016 pp. 209–211
© American Epilepsy Society

OPEN ACCESS Freely available online

Concerns

Beginning around 2005, patients, advocacy groups, and physician healthcare providers (HCPs) expressed concerns about the potential danger of generic substitution in patients with epilepsy. Generic versions of the older AEDs, specifically carbamazepine and phenytoin, had a history of problems (3). These concerns, in part, focused on the FDA's BE standard and testing methodology. First, because comparison testing typically used healthy volunteers in single-dose pharmacokinetic studies, it was thought that significant bioavailability differences in persons with epilepsy could be missed. Second, by using average BE data, it was thought that individual patients with outlier bioavailability results would be missed. Third, many believed the acceptable ratio range of 80% to 125% was too broad, and a narrower standard was indicated. Fourth, BE studies do not address concerns regarding generic-to-generic substitution.

Some of the concerns that HCPs had may have stemmed from misunderstanding of the 80% to 125% interval. Some HCPs incorrectly thought that the standard meant that the ge-

neric product was allowed to contain between 80% and 125% of the active ingredient per dose compared with the brand-name product. Others did not understand that it is the statistical 90% CI for the pharmacokinetic ratios that must be within 80% to 125%. For the entire 90% CI to meet this standard, the mean C_{max} and AUC values of the generic product should actually lie quite close to that of the reference standard (4).

2007 Position Statement

In 2007, the American Epilepsy Society (AES) issued a position statement on the generic substitution of AEDs that shared the concerns of patients, advocacy groups, and HCPs. It differed in some respects from the positions taken at that time by the American Academy of Neurology and advocacy groups like the Epilepsy Foundation. The AES position supported the development and completion of a valid, controlled, prospective clinical trial in people with epilepsy (with a protocol approved by the FDA) that would investigate the differences between the same AED formulations from different manufacturers. Until such data became available, the AES opposed generic substitution without physician and patient approval.

New Studies

As a result of the concerns raised by patients and the medical community, the FDA provided funding for two major studies of generic versus brand-name lamotrigine in persons with epilepsy. These real-world studies were the BioEquivalence in Epilepsy Patients (BEEP) study and the Equivalence Among Generic Antiepileptic Drugs (EQUIGEN) study (5, 6).

In the BEEP study, lamotrigine BE was examined in "generic brittle" patients with epilepsy under clinical use conditions (5). Immediate-release lamotrigine produced by the first FDA-approved generic manufacturer and brand-name Lamictal (GlaxoSmithKline, Inc., Brentford, UK) were dispensed in a blinded way as 100 mg tablets to 34 subjects at the patient's usual dose, with or without concomitant AEDs. Using a four-period crossover design, pharmacokinetic (C_{max}, AUC, C_{min}, reference-scaled average BE analysis, and within-subject variability) comparisons were made for each of the four 2-week treatment periods. The results indicated that the generic product showed BE to brand on all these measures. Indeed, the 90% CI s of the mean for steady-state AUC, C_{max}, and C_{min} for generic-to-brand average BE and reference-scaled average BE were very close to 100%.

In the EQUIGEN chronic dosing study, lamotrigine was again the AED examined (6). The study design had important differences from the BEEP study. Two marketed generic lamotrigine products with the most disparate C_{max} and AUC (based on in vitro and manufacturer data) were studied in an attempt to learn if they had substantially different BE in persons with epilepsy. Thirty-three patients taking 100 to 400 mg twice daily of immediate-release lamotrigine were randomly switched back and forth, twice, between these two generic formulations with pharmacokinetic data measured. The results showed that in chronic dosing with these two most disparate lamotrigine formulations, the 90% CIs of the ratios of the dose-normalized AUCs and C_{max} were 98% to 103% and 99% to 105%, respectively (6). In the EQUIGEN single-dose study presented in abstract form at the 69th Annual Meeting of the AES in December 2015, 48 patients taking one AED took two disparate generic forms of lamotrigine, and again, BE was shown, with no significant within-subject variability (7).

2016 Position Statement

The results of these two BE studies, done in patients with epilepsy under clinical conditions, support the validity of the FDA BE standards. As a consequence, the board of directors of the AES has approved a new position statement (Appendix) regarding generic switching of AEDs. It not only confirms that the FDA's standards for BE are appropriate for persons with epilepsy, but it also supports ongoing research and makes practical recommendations for HCPs who prescribe or dispense generic forms of AEDs.

Implications

Patients and providers can now have reasonable confidence of BE when switching from brand-name to generic, or between generic, immediate-release AEDs. When presenting this to patients, providers will likely encounter questions or concerns. Patients are usually skeptical if they previously experienced increased seizures or other adverse effects when they switched from brand-name to generic AEDs. It may be helpful to counsel them about the possible reasons for this. One explanation is that after switching to a generic AED, patients who experience increased seizure frequency, duration, or severity may attribute this to the switch even though it could be due to the natural variation of seizures. Other reasons, such as emotional stress due to switching or decreased adherence due to differences in pill appearance, could result in seizures or adverse effects. With many patients, HCPs may find it helpful to spend extra time discussing these alternative explanations for past negative experiences and how the present studies provide reassurance about the safety of switching from brand-name to generic, and between generic formulations of, immediate-release AEDs.

References

1. Food and Drug Administration. Guidance for Industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs—General Considerations. March 2014. Available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm389370.pdf March 2014. Accessed February 7, 2016.
2. Krauss GL, Caffo B, Chang YT, Hendrix CW, Chuang K. Assessing bioequivalence of generic antiepilepsy drugs. *Ann Neurol* 2011;70:221–228.
3. Nuwer MR, Browne TR, Dodson WE, Dreifuss FE, Engel J Jr, Leppik IE, Mattson RH, Penry J, Treiman DM, Wilder BJ. Generic substitution for antiepileptic drugs. *Neurology* 1990;40:1647–1651.
4. Andrade C. Bioequivalence of generic drugs: A simple explanation for a US Food and Drug Administration requirement. *J Clin Psychiatry* 2015;76:e742–e744.
5. Ting TY, Jiang W, Lionberger R, Wong J, Jones JW, Kane MA, Krumholz A, Temple R, Polli JE. Generic lamotrigine versus brand-name Lamictal bioequivalence in patients with epilepsy: A field test of the FDA bioequivalence standard. *Epilepsia* 2015;56:1415–1424.
6. Privitera MD, Welty TE, Gidal BE, Diaz FJ, Krebill R, Szaflarski JP, Dworetzky BA, Pollard JR, Elder EJ Jr, Jiang W, Jiang X, Berg M.

Generic-to-generic lamotrigine switches in people with epilepsy: the ramdomized controlled EQUIGEN trial. *Lancet Neurol 2016;15:365–372.*
7. Berg M, Privitera M, Diaz F, Dsoretzky B, Elder E, Gidal B, Jiang W, Krebill R, McBee N, Pollard J, Alloway R, Paige AL, Szaflarski J, Bolger P, Welty T. EQUIvalence among GENeric AEDs (EQUIGEN): Single-dose study. Poster 2.267. Presented at the Annual Meeting of the American Epilepsy Society, Sunday, December 6, 2015, Philadelphia, Pennsylvania, USA.

Appendix

AES Position Statement on Generic Antiepileptic Drugs

The American Epilepsy Society (AES) recognizes that well-designed, prospective studies of generic antiepileptic drug (AED) substitution have been completed. Two studies demonstrated bioequivalence of generic products in patients with epilepsy taking concomitant AEDs (1, 2). Additionally, an analysis of Abbreviated New Drug Application data suggests that generic products of branded modified-release products (e.g., extended release, delayed release) are bioequivalent and safely interchangeable (3). Results from these studies have shown no difference in bioequivalence when switching from a brand product to a generic product or between multiple generic products. These studies confirm that the U.S. Food and Drug Administration (FDA) standards for bioequivalence are appropriate for patients with epilepsy.

The AES offers support of the following principles concerning the continuity of AEDs for adults and children with epilepsy:

1. The AES supports ongoing research by the FDA to study factors (e.g., extended-release products, tablet or capsule color and shape, nocebo effect) related to the generic substitution of AEDs in adults and children.

2. The AES acknowledges that drug formulation substitution with FDA-approved generic products reduces cost without compromising efficacy.

3. When dispensing medications to patients, healthcare professionals should ensure that a bioequivalent FDA-approved generic product is substituted for the brand or another generic AED. For example, an immediate-release generic product should not be dispensed as a substitute for a delayed-release or an extended-release product.

4. Based on data showing that tablet or capsule color or shape and that statements about drug products impact patient adherence and drug response, healthcare professionals should exercise the highest standards of care when substituting generic products (4, 5).

   a. Patients or caregivers should be informed when substitution of a drug product results in a change in color or shape. Drug products that differ in color or shape should not be mixed in the same prescription vial to avoid confusion by the patient or caregiver.

   b. Descriptions of generic products for patients and caregivers should indicate that generic products are equivalent to the brand product. Patient counseling should not include descriptions of generic products as being a cheaper or lower-quality version of the brand product.

References

1. Ting TY, Jiang W, Lionberger R, Wong J, Jones JW, Kane MA, Krumholz A, Temple R, Polli JE. Generic lamotrigine versus brand-name Lamictal bioequivalence in patients with epilepsy: A field test of the FDA bioequivalence standard. *Epilepsia* 2015;56:1415–1424.
2. Privitera MD, Welty TE, Gidal BE, Diaz FJ, Krebill R, Szaflarski JP, Dworetzky BA, Pollard JR, Elder EJ Jr, Jiang W, Jiang X, Berg M. Generic-to-generic lamotrigine switches in people with epilepsy: the ramdomized controlled EQUIGEN trial. *Lancet Neurol 2016;15:365–372.*
3. Johnson EL, Chang YT, Davit B, Gidal BE, Krauss GL. Assessing bioequivalence of generic modified release antiepilepsy drugs. *Neurology*. In press.
4. Kesselheim AS, Misono AS, Shrank WH, Greene JA, Doherty M, Avorn J, Choudhry NK. Variations in pill appearance of antiepileptic drugs and the risk of nonadherence. *JAMA Intern Med* 2013;173:202–208.
5. Espay AJ, Norris MM, Eliassen JC, Dwivedi A, Smith MS, Banks C, Allendorfer JB, Lang AE, Fleck DE, Linke MJ, Szaflarski JP. Placebo effect of medication cost on Parkinson disease a randomized double-blind study. *Neurology* 2015;84:794–802.