

Current Literature

In Clinical Science



Generic Antiepileptic Drugs: How Good Is Close Enough?

Assessing Bioequivalence of Generic Antiepilepsy Drugs.

Krauss GL, Caffo B, Chang Y-T, Hendrix CW, Chuang K. *Ann Neurol* 2011;70:221–228.

OBJECTIVE: Patients with epilepsy are often concerned that switching between brand-name and generic formulations of antiepilepsy drugs (AEDs) may cause clinically significant changes in plasma drug concentrations. We assessed bioequivalence (BE) studies for approved generic AEDs to evaluate US Food and Drug Administration claims that: (1) generic AEDs are accurate copies of reference formulations; (2) delivery of reference formulations may be as variable as generic AEDs and so provide no increased benefit; and (3) switches between generic AED formulations are safe and effective. **METHODS:** We determined differences in 90% confidence interval limits for total drug exposure (AUC_{0-t}) and peak concentration (C_{max}) ratios of generic and reference formulations during fasting and fed BE studies. We simulated BE between generic formulations after adjusting for reference values. **RESULTS:** AUC_{0-t} values of approved reference and generic formulations differed by <15% in 99% of BE studies; C_{max} differed by <15% in 89% of studies. Food affected variability of C_{max} but not AUC_{0-t} . Intersubject variability in C_{max} and AUC_{0-t} was small and similar for reference and generic products. In simulated switches between 595 pairs of generic AED formulations, estimated AUC_{0-t} differed by >15% for 17% of pairs; estimated C_{max} differed by >15% for 39%. AEDs with low bioavailability and solubility (eg, oxcarbazepine) had the greatest variability in BE. **Interpretation:** Most generic AED products provide total drug delivery (AUC) similar to reference products; differences in peak concentrations between formulations are more common. Switches between generic AED products may cause greater changes in plasma drug concentrations than generic substitutions of reference products.

Commentary

It used to be that cost was only one of the many factors that played into the therapeutic decision-making process. That was then, and this is now. Now, for many individuals, cost is the primary factor governing choice of drug treatment. There are many reasons why a patient might fail to achieve optimal seizure control, including such things as drug interactions, treatment-emergent adverse effects, medication nonadherence, and, of course, lack of drug efficacy. Many of these factors we can modify or control. Clinical experience has taught that, for many patients, optimization of treatment requires careful fine-tuning of medication, and that many antiepileptic drugs (AEDs), especially the poorly soluble ones, will display a certain amount of pharmacokinetic variability between patients. The underlying assumption is made, however, that for a given product, pharmacokinetic performance will remain relatively constant between one dose to another. This very fundamental assumption becomes a bit more tenuous, however, when patients frequently switch between different formulations of a given drug. At least, that is the concern. Skeptics will say that this is an unfounded concern and that the guidelines in place by the regulatory bodies should assure us and our patients.

Indeed, one of the most controversial areas in epilepsy therapeutics today is generic substitution. Although generic products do clearly have the potential to offer tremendous cost-savings for patients and third-party payers, this benefit is based on the assumption that a generic product displays essentially the same kinetic and dynamic profile as that of its brand-name counterpart. We ask our patients to trust that the product we are providing is equivalent in every meaningful way as the much more expensive branded product. We further try to assure them that all generic products are created equally, and yes, each prescription refill may look a little different, but it does not matter, as all the tablets are essentially copies of the same thing. It is ironic that clinicians, in an era in which many (if not most) medical organizations as well as schools of pharmacy, medicine, and nursing emphasize evidence-based evaluation of clinical data, are obliged to make these assurances with precious little evidence.

To date, most of the evidence either supporting or challenging the current practice of generic substitution has come from retrospective analysis of larger, prescription claims databases. Although these are legitimate studies, they present a number of important limitations (1). Typically, these studies use surrogate markers of therapeutic failure (e.g., emergency room visits, hospitalizations, or increased healthcare costs), and frequently contain only minimal pharmacokinetic data such as randomly obtained serum concentration measurements. When viewed through this lens, indeed most analyses

Epilepsy Currents, Vol. 12, No. 1 (January/February) 2012 pp. 32–34
© American Epilepsy Society

OPEN ACCESS Freely available online



have concluded that there really does not seem to be any conclusive association between generic substitution and either loss of seizure control or new, treatment-emergent adverse effects (2), although there clearly is a suggestion that when generic substitution occurs, expenditures of resources goes up (3, 4).

Given this overall lack of evidence that real differences do in fact exist between branded and generic products, how do we reconcile the rather widespread impression among neurologists and many patients to the contrary (5)? It seems that a piece or two of the puzzle is still missing. Fortunately, the recent study by Krauss and colleagues (6) has provided an important and clinically relevant piece of this puzzle.

Using a request under the Freedom of Information Act, the authors obtained pharmacokinetic data submitted to the agency as part of the Abbreviated New Drug Application Process (ANDA) for each of the FDA-approved generic AED formulations. This is noteworthy in that this type of pharmacokinetic data is typically not published in the peer-reviewed literature, nor is it usually available for public inspection.

In this analysis, the authors analyzed the variability of area under plasma concentration time curve (AUC) and maximal peak serum concentration (C_{max}) data submitted by generic manufacturers in support of their product. Using this data, Krauss and colleagues were able to model switches between 595 potential pairs of generic-to-generic AED formulations.

What they found was interesting. In general, virtually all of the generic AED formulations had systemic exposures (AUCs) that differed by less than 15 percent from their branded, reference counterpart. These investigators also found that peak AED serum concentrations (C_{max}) did differ by 15 to 25 percent in almost 11 percent of analyzed studies. Furthermore, generic to reference (brand formulation) ratio for AUC and C_{max} differed by 15 to 25 percent in 8.2 percent and 26 percent, respectively when fasting versus fed study conditions were compared. Together, these findings tend to support the FDA position that using current acceptance guidelines (defined as the 90% confidence interval of the log-transformed ratios of AUC and C_{max} between brand and generic products falling within 80–125% range), approved A-rated generic products should be expected to provide essentially the same performance as the branded product, at least for *most* patients. For a small subset of patients, however, variability in kinetic characteristics might be expected to result in significant changes in overall drug exposure. Although this part of the analysis does provide some assurance that in general brand to generic switching is probably acceptable, there is more to the story. An equally important question is whether we can also feel confident when patients are switched *between* generic products.

Current regulations and testing paradigms are designed to determine whether a given generic formulation is pharmacokinetically equivalent to the brand product. The assumption is made that if generic A is equal to brand and generic B is equal to brand, then it follows that generic A should equal generic B. There is no requirement that individual generic products be directly compared with each other.

In their analysis, Krauss and colleagues also compared estimates of generic with generic switches. They found that although the majority of generic-to-generic pairs had AUC

that differed by less than 15 percent 145 did differ by 15 to 25 percent, and 2 percent of generic pairs differed by greater than 25 percent. Even greater variability was seen when looking at peak serum concentrations, where differences in C_{max} of 15 to 25 percent were seen in 35 percent of drug pairs. The authors state that based upon these kinetic data, there was a 50 percent probability of seeing 14 or more changes in overall systemic drug exposure (AUC) of greater than 25 percent. The probability of seeing 25 or more changes in C_{max} of greater than 25 percent was 56 percent. Not surprisingly, variability seemed greater for the less soluble AEDs such as oxcarbazepine.

This important analysis provides, for the first time, evidence of something that many clinicians have long suspected: it is not necessarily the switch from a branded product to generic that is problematic for some of our patients. Rather, it is the switching *between* presumably equivalent formulations. Although this clearly was not an efficacy trial, it is not unreasonable to predict that serum drug concentration swings of this magnitude are likely to result in clinical symptoms, particularly in the brittle patient who perhaps is maintained at high serum concentrations in order to achieve seizure control. Interestingly, in a study evaluating healthcare service utilization, Duh and colleagues found that patients having multiple generic switches of topiramate had higher hospitalization rates as compared with brand-only users. Those patients receiving a single version of generic topiramate did not differ from brand-only recipients (7). Clearly, the analysis by Krauss and colleagues suggest that not all generics are created equal. Although substitution of a single generic product might be expected to result in only modest variability in drug exposure, multiple switches between generic products may be quite another issue.

Although these data are quite compelling, the authors correctly caution against overinterpretation of their results. They were the product of simulations. Some would advocate that current acceptance limits for assigning bioequivalence be narrowed. The question is, narrowed to what? In Denmark, AEDs are designated as narrow therapeutic index drugs, and generic products must meet a more stringent 90 to 111 percent acceptance range. Krauss suggests that this standard would have been met for AUC and C_{max} by 81 percent and 64 percent of evaluated studies, respectively. Whether this is the best approach will certainly require prospective study.

So, where do we go from here? First, the medical community should push for greater disclosure. Clinicians should not need to resort to the Freedom of Information Act to obtain this crucial information. For physicians and pharmacists to make informed decisions, our professional organizations should insist that manufacturers of narrow therapeutic index generic drugs either publish bioequivalence studies in the literature or at least make them readily accessible. In addition, prospective studies in patients with epilepsy comparing chronic dosing of multiple generic products should be conducted. This type of study would seem necessary to either confirm or refute the observations of Krauss. Until then, it would seem prudent that frequent switching between various generic formulations be discouraged. Pharmacies should be encouraged to try, wherever possible, to purchase generic AEDs from a



single manufacturer. This is not a condemnation of generic products. Generic drugs do offer potential savings for patients and payors, and for most of our patients are an acceptable option. Rather, this is an acknowledgment that variability is a fact of biology and will always be a confounding element of pharmacotherapy. The study by Krauss is an important step toward managing the uncertainty and adds another piece of the puzzle.

by Barry E. Gidal, PharmD

References

1. Privitera M. Generic antiepileptic drugs: Current controversies and future directions. *Epilepsy Curr* 2008;8:113–117.
2. Kesselheim AS, Stedman MR, Bubrick EJ, Gagne JJ, Misono AS, Lee JL, Brookhart MA, Avorn J, Shrank WH. Seizure outcome following use of generic vs brand-name antiepileptic drugs: A systematic review and meta-analysis. *Drugs* 2010;70:605–621.
3. Labiner DM, Paradis PE, Manjunath R, Lafeuille MH, Latremouille VD, Helmers SL. Generic antiepileptic drugs and associated medical resource utilization in the United States. *Neurology* 2010;74:1566–1574.
4. Duh MS, Cahill KE, Paradis PE, Cremieux PY, Greenberg PE. The economic implications of generic substitution of antiepileptic drugs: a review of recent evidence. *Expert Opin Pharmacother* 2009;10:2317–2328.
5. Berg MJ, Gross RA, Tomaszewski KJ, Zingaro WM, Haskins LS. Generic substitution in the treatment of epilepsy: Case evidence of breakthrough seizures. *Neurology* 2008;71:525–530.
6. Krauss GL, Caffo B, Chang Y-T, Hendrix CW, Chuang K. Assessing bioequivalence of generic antiepilepsy drugs. *Ann Neurol* 2011;70:221–228.
7. Duh MS, Paradis PE, Latremouille-Viau D, et al. The risks and costs of multiple-generic substitution of topiramate. *Neurology* 2009;72:2122–2129.



American Epilepsy Society

Epilepsy Currents Journal

Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.

Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Other relationships

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.



American Epilepsy Society

Epilepsy Currents Journal

Disclosure of Potential Conflicts of Interest

Section #1 Identifying Information

1. Today's Date: 2/10/2012
2. First Name Barry Last Name Gidal Degree PharmD
3. Are you the Main Assigned Author? Yes No

If no, enter your name as co-author:

4. Manuscript/Article Title: Generic Antiepileptic Drugs: How Good Is Close Enough?
5. Journal Issue you are submitting for: 12.1

Section #2 The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship just add rows to this table.

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**
1. Grant	<input checked="" type="checkbox"/>				
2. Consulting fee or honorarium	<input type="checkbox"/>	\$0.00	\$10.00	GSK, UCB	
3. Support for travel to meetings for the study or other purposes	<input checked="" type="checkbox"/>				
4. Fees for participating in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input checked="" type="checkbox"/>				
5. Payment for writing or reviewing the manuscript	<input checked="" type="checkbox"/>				
6. Provision of writing assistance, medicines, equipment, or administrative support.	<input checked="" type="checkbox"/>				
7. Other	<input checked="" type="checkbox"/>				

* This means money that your institution received for your efforts on this study.

** Use this section to provide any needed explanation.

Section #3 Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the “Add” box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

Type of relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**
1. Board membership	<input checked="" type="checkbox"/>				
2. Consultancy	<input checked="" type="checkbox"/>				
3. Employment	<input checked="" type="checkbox"/>				
4. Expert testimony	<input checked="" type="checkbox"/>				
5. Grants/grants pending	<input checked="" type="checkbox"/>				
6. Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>	10K		GSK, UCB	
7. Payment for manuscript preparation.	<input checked="" type="checkbox"/>				
8. Patents (planned, pending or issued)	<input checked="" type="checkbox"/>				
9. Royalties	<input checked="" type="checkbox"/>				
10. Payment for development of educational presentations	<input checked="" type="checkbox"/>				
11. Stock/stock options	<input checked="" type="checkbox"/>				
12. Travel/accommodations/meeting expenses unrelated to activities listed.**	<input type="checkbox"/>				
13. Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>				

* This means money that your institution received for your efforts.

** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section #4 Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

- No other relationships/conditions/circumstances that present a potential conflict of interest.
 Yes, the following relationships/conditions/circumstances are present:

Thank you for your assistance.
Epilepsy Currents Editorial Board