Assessing Bioequivalence of Generic Antiepilepsy Drugs

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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.

The Abbreviated New Drug Application (ANDA) process permits relatively inexpensive generic drug formulations to be marketed if they provide plasma concentrations similar to corresponding reference (brand-name) formulations. This is established in small bioequivalence (BE) studies—single-dose crossover studies in healthy subjects comparing peak concentrations (C_{max}) and total drug exposure (concentration measured over time: AUC) during treatment with either reference or generic test formulations.1 For generic drug approval, the distributions of ratios of C_{max} and AUC for reference to test formulations must be between 0.80 and 1.25 (defined by upper and lower 90% confidence interval [CI]). More than 150 generic antiepilepsy drug (AED) formulations have been approved through the ANDA process in the past several years, reducing the cost per quarter (2008–2009) in the United States for AEDs to treat epilepsy from approximately $800 million to $400 million.2 Some neurologists and patients, however, report that conversion to generic formulations is occasionally associated with seizures or side effects and question the reliability of small BE studies.3–10 Consequently, it is important to determine how accurately generic AEDs copy reference brand-name formulations.11 Furthermore, although generic-generic switches are common, current regulations do not require generic-to-generic BE comparisons, and there are few data showing how similar generics are to each other.

We examined the accuracy of generic AED copies in BE studies and evaluated several key issues: (1) Are ratios of drug concentrations for generic and reference AED formulations nearly identical (geometric mean ratios [GMRs] for C_{max} and AUC near 1.0 with distributions defined by upper and lower 90% CI limits) for most subjects in the single-dose crossover BE studies, or
do many generic formulations provide concentrations near US Food and Drug Administration (FDA) 0.80 to 1.25 BE acceptance limits. The FDA supports generic drug use by noting that reference formulations may provide no more uniform drug delivery than approved generic formulations. We determined whether variability in drug delivery was comparable in groups receiving doses of reference and generic AED formulations in the BE studies. (3) Switches between generic products are not currently limited in US pharmacies and yet could potentially produce much larger shifts in drug concentration than generic substitutions for reference products. We used BE data from individual generic products to model switches between >500 potential pairs of generic AED formulations and estimated whether generic-to-generic switches could produce shifts in drug concentrations outside FDA acceptance ranges.

**Patients and Methods**

**Bioequivalence Study Data**

The FDA Center for Drug Evaluation and Research, Office of Generic Drugs provided average bioequivalence and demographic data for approved generic AED formulations following submission of Freedom of Information Act data requests. Separate fasting and fed BE studies were performed for most generic formulations. Key data for test and reference formulations were the GMRs and their 90% CIs for Cmax and for the area under the plasma concentration time curve (AUC) calculated to the last measured concentration (AUC_{0-inf}). The arithmetic means, associated coefficient of variation, and within-subject variability for AUC_{0-inf}, Cmax, and T_{max} were tabulated. Demographic data assessed were: age (mean and range), gender, ethnicity, and height and weight (mean and range). Extended phenytoin and extended-release carbamazepine formulations were not studied, because special BE assessments are required to evaluate slow-release drug delivery technology. Limited demographic data were available for several BE approval packets for older generic AEDs, particularly carbamazepine, on which fed BE studies were not performed prior to 2003.

**Analysis of AUC and Cmax Ratios for Generic and Reference AEDs**

We indexed the variability of AUC and Cmax GMRs as the maximum of the upper or lower 90% CI limit subtracted from 1.00, with absolute values and percentages displayed. For example, a BE study with upper and lower 90% CI limits for AUC_{0-inf} GMR of 0.87 and 1.05 had a maximum deviation (from 1.00) of 13%. These differences in AUC and Cmax were tabulated by AEDs and doses for all studies in 5% bands (ie, number of BE studies in which the differences were 0–5%; >5% to 10%, etc). We also determined the number and proportions of generic and reference AED products for which the 90% CI of the AUC and Cmax GMRs did not include 1.00 (ie, the Cmax and AUC ratios met BE standards but differed between reference and test formulations). These methods were also used to compare results of fasting and fed BE studies to assess food effects; fed and fasting BE studies were performed on different populations.

**Analysis of Variability of AUC and Cmax for Generic and Reference Formulations**

We determined intersubject standard deviations for AUC_{0-inf} and Cmax for generic and reference products for each BE study. We then compared standard deviations between generic and reference products and screened for major (>50%) differences in standard deviations between generic and reference formulations.

**Estimating AUC and Cmax with Switches between Generic AED Formulations**

We compared log relative pharmacokinetic (PK) measurements of paired generic to reference formulations. Specifically, we took the difference in the log ratio of the AUCs of generics to the reference across generics, and repeated this exercise for Cmax. To account for variation, we estimated changes via 90% CIs for AUC and Cmax for switches between pairs of generic AEDs tested at the same doses. GMRs of AUC and Cmax to the reference formulation were compared across generics to normalize for study-specific variation. Because of the lack of individual data, standard errors for interstudy comparisons were calculated from CIs for the test to reference comparisons. For example, if Lratio1 = 1.28 SE1 and Lratio2 = 1.28 SE2 are 90% test versus reference intervals on the natural log scale for generics 1 and 2, our interval considered the exponentiated endpoints of

\[ \text{Lratio}2 - \text{Lratio}1 \pm 1.28(\text{SE}1^2 + \text{SE}2^2)^{1/2} \]

The 90% CIs for AUC_{0-inf} and Cmax ratios for each pair of generic AED formulations were determined and tabulated as proportions of AED generic pairs in 5% bands for each AED. To consider the possibility of spurious associations due to multiple comparisons, we conducted a brief simulation study, which simulated log ratios from a normal distribution with variances given by those in the study, and replicated the analysis. This process was repeated 1,000×.

**Results**

**Subjects**

A total of 141 generic AED products were evaluated in 258 BE studies. Demographic data were available for 251 studies enrolling 7,125 subjects. Subjects were predominantly male (78.7%), with a mean age of 31.9 years (range, 19.6–82). No children (<18 years) were studied and only 44 subjects (0.71%) were elderly (>65 years). Ethnicities reflected locations of study sites and were: Caucasian, 54.4%; Asian, 25.8%; black, 9.7%; Hispanic, 3.1%. Subject demographic factors were unequally distributed in many studies: 42.1% enrolled male subjects..
Bioequivalence of Generic and Reference Formulation AEDs

Total drug delivery (AUC\(_{0-t}\)) for generic and reference AED formulations was very similar: AUC\(_{0-t}\) differed by <15% for 255 of 258 (98.8%) BE studies. In only 1 study (divalproex under a fasting condition) did the width of the 90% CI exceed 15% (2 1-sided tests procedure). Furthermore, 83.7% and 42.6% of studies differed by <10% and <5%, respectively (Fig 1). Although AUC\(_{0-t}\) met BE standards, in 45 (18.6%) of BE studies, the 90% CIs of the GMRs did not overlap (Supporting Information Fig 1). Similar numbers of generic formulations were associated with small increases and decreases in AUC\(_{0-t}\) compared to reference formulations; these small differences were distributed across most of the tested AEDs and doses.

Peak drug concentrations (Cmax) differed more between generic and reference formulations than AUC\(_{0-t}\) (Fig 2). In 28 BE studies (10.85%), the ratios of generic and reference product Cmax differed by 15 to 25%. The 90% CIs for the Cmax GMRs for generic and reference formulations did not overlap for 26% of generic formulations (see Supporting Information Fig 1).

Fasting versus Fed BE Studies

Both fasting and fed studies were performed for 111 AED formulations. The GMRs for AUC\(_{0-t}\), differed between fasting and fed states by <15% for 110 (91.8%) formulations and by 15 to 25% for 9 (8.2%) formulations (Supporting Information Table). For 4 (3.6%) of the 111 formulations, the 90% CIs for the test/reference GMRs for AUC\(_{0-t}\) did not overlap when fasting and fed values were compared. The test/reference GMRs for Cmax differed by 15 to 25% between fasting and fed studies for 29 of 111 BE studies (26%). The 90% CIs for Cmax GMRs, however, were generally wider than for AUC, reflecting the fact that Cmax tends to be more variable than AUC. Consequently, the 90% CIs for the test/reference Cmax GMR ratios in the fasting versus fed BE studies overlapped for 103 (92.3%) of the 111 formulations. Cmax for 7 of 12 (58%) oxcarbazepine BE studies differed by 15 to 25% between fasting and fed studies, a higher proportion than for other AEDs. Gabapentin and divalproex also had slightly greater proportions of BE studies in which Cmax varied by 15 to 25% compared to other AEDs.

Variability in PK Values for Reference Compared to Generic AED Formulations

Variability in the distribution of AUC\(_{0-t}\) for reference and generic formulations in BE studies was very similar; standard deviations differed markedly (>50%) between reference and generic formulations for <1% (2 of 281) of fasting and fed BE studies (Supporting Information Fig 2).
Both of these BE studies were of generic formulations with large variability in AUC0-t compared to reference formulations. Standard deviations (SD) for Cmax varied more than for AUC; however, these varied markedly (>50%) between only 4% (11 of 281) of generic and reference formulations (2 reference formulations had higher SD; 9 generic formulations had higher SD) (Fig 3). This variability is similar to standard benchmarks of variances and therefore is consistent with the possibility of statistical equality.

Estimates of Effects of Generic-to-Generic Formulation Switches

There were 595 potential pairs of generic AED products tested at the same doses; 496 (83.4%) had an estimated AUC0-t that differed by <15%, whereas 85 (14.3%) differed by 15 to 25%, and 14 (2.35%) differed by >25% (Fig 4). AUC0-t for a large proportion (6 of 21) of pairs of generic oxcarbazepine formulations differed by 25 to 30%. Pairs of generic formulations differed more in estimated Cmax than in AUC; 364 (61.2%) of generic pairs had Cmax that differed by 0 to 15%, 209 (35.1%) differed by 15 to 25%, and 22 (3.7%) differed by >25% (Fig 5). In a simulation study performed using variation from comparisons of generics under specific dose conditions, the number of studies of anticipated spurious results for AUC0-t and Cmax varied substantially by drug/dose group. The study estimates that the probability of seeing 14 or more changes of >25% in Cmax in a similar simulation was 56%. That is, the number of large (>25%) changes seen in the observed data is not unexpected from a study with actual equivalence between all comparisons.

Discussion

Although BE studies are designed to evaluate whether generic formulations meet ANDA standards, the small, blinded crossover studies can also provide information about how closely generic AEDs copy brand-name products. AUC values for generic and reference formulations were very similar in nearly all BE studies; mean AUC0-t values differed by <10% between generic and reference products in 83% of BE studies and differed by >15% in only 1 study. By contrast, mean Cmax values differed between generic and reference products by 15 to 25% in 11% of studies. These findings are consistent with clinical series reporting that small subgroups of patients do not tolerate conversion to generic formulations, most commonly due to central nervous system (CNS)-related side effects (eg, dizziness, drowsiness, imbalance, and diplopia)3–5 and occasionally due to seizures.7 Many patients in these clinical series were treated with relatively high doses of AEDs and appeared to be near tolerability thresholds, although some appeared sensitive to relatively small (eg, 10%) changes in AED concentrations.5

The main effect of food on AED absorption overall was to increase the variability of Cmax for both generic
and reference formulations. This variability resulted in broad CIs in BE studies, which dominated specific patterns of food effects across generic and reference drugs. Oxcarbazepine, probably due to low solubility, was particularly variable; parent oxcarbazepine and its 10-monohydroxy metabolite met BE standards, but Cmax and AUC ratios for the parent compound were near acceptance limits. The FDA notes that that reference formulations (including drugs with "narrow therapeutic indices") may have variable absorption and offer no more stable or uniform delivery than do generic formulations.\textsuperscript{13,15} Our analysis of BE studies generally supports this position; only a small number of generic formulations had large standard deviations in AUC or Cmax compared to reference drugs. Moreover, the overall variability in PK values (Cmax and AUC) across subjects for most of the BE studies was <30%. Together, these findings suggest that most patients could initiate therapy with either generic or reference AED formulations and achieve comparable AED concentrations. Repeated dosing with reference and generic formulations in 4-way individual BE studies would be needed to see whether reference drugs provide the same or decreased intrasubject variability compared to generics.

A number of drugs, including AEDs, have recently been categorized by their solubility and permeability into the Biopharmaceutics Classification System (BCS).\textsuperscript{16} Some newer AEDs are BCS I drugs that are highly soluble and permeable, and dissolve rapidly (eg, levetiracetam and lamotrigine). Several AEDs are BCS II drugs, which are poorly soluble, but highly permeable (oxcarbazepine, carbamazepine, phenytoin); gabapentin is BCS III (highly soluble and rapidly dissolving with poor permeability). Absorption for BCS I AEDs was generally more uniform (ie, narrowed 90% CI and point estimates near 1.00) compared to BCSII/III drugs in the BE studies. This supports the possibility that BE standards might best be scaled according to solubility and dissolution characteristics of AEDs.\textsuperscript{17} Due to the large number of possible generic-to-generic formulation switches (n = 595) and differences in their PK distributions, we modeled differences in AUC and Cmax, which could occur upon generic-to-generic switches. In our model, 17% of generic product switches were estimated to produce differences of >15% in estimated AUC, whereas 39% of generic pair switches had >15% differences in estimated Cmax (based on the maximum of the upper and lower 90% CI). These estimates require confirmation but nonetheless suggest that some generic-to-generic product switches could potentially produce larger differences in PK than reference-to-generic product substitutions.

Although this study confirms equivalent total exposure of generics relative to reference formulations and demonstrates potential novel findings on generic-to-generic switches, the analysis had several methodological limitations. First, no subject-level information was available to refine the BE study analyses. There was also no

\begin{figure}
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\includegraphics[width=\textwidth]{figure3}
\caption{A comparison of standard deviations of peak concentration (Cmax) for generic (test) and reference antiepilepsy drug (AED) formulations in bioequivalence (BE) studies. The standard deviations (presented in log scales) for the mean Cmax for generic (test) and reference formulations are very similar across 8 AEDs. The symbols represent standard deviations of Cmax for matched generic and reference formulations in the crossover BE studies.}
\end{figure}
crossover information between generics, as generic-to-
generic switches were not part of any study. Consequently,
all information is compared across study populations, and
generic-to-generic formulation comparisons and fasting-fed
comparisons may be influenced by differences in study pop-
ulations and in manufacturing pill lots. Our comparison of
generic formulations potentially accounts for this source of
bias by adjusting for relative absorption rates of reference
drugs; however, this correction depends heavily on log-line-
arity assumptions and adds substantial variability to the
analysis. Our simulation study also suggests caution in over-
interpreting results, as many spurious associations are likely
when studying so many possible generic combinations.

BE studies are not clinical efficacy or safety studies
and cannot be used to evaluate whether changes in AED
centrations might be associated with side effects or
seizures in individual patients. The FDA, however,
describes approved generic formulations as being “bioe-
quivalent” and “therapeutically equivalent” to brand
name drugs, and BE studies are the current standard for
approving generic formulations. Drug concentration
ratios differed significantly between many generic and
reference formulations (with nonoverlapping CIs) despite
meeting BE standards, suggesting that many patients are
likely to have small to moderate (5–15%) changes in
drug concentrations with generic conversion; a small
number of patients in the large epilepsy treatment popu-
lation are likely to experience greater shifts.

This is consistent with larger clinical series identifying small subgroups of patients who do not tolerate or
develop seizures with generic conversion. In a Canadian
survey, 10% of patients with epilepsy switched back from
generic to reference lamotrigine due to unspecified clinical
problems, a proportion much higher than the 2% switchback for other common drug classes. Another
study found that a large proportion of patients seen in
an emergency department for seizures or drug toxicity
had recently been switched to generic AED formulations. The FDA, however, emphasizes that no large
objective studies have demonstrated increased seizures or side effects with generic switches. It cites 2 small,
blinded crossover studies that showed no significant
increase in seizures or side effects in patients treated with
several different carbamazepine formulations (though car-
bamazepine concentrations varied up to 40% for individ-
ual patients). A more recent study, however, showed
that conversion to generic carbamazepine formulations
caued both side effects and increases in Cmax in some
patients. A recent pilot study verified that some
patients with seizures or side effects during conversion to
generic lamotrigine have concentration changes that are
outside the BE limits.

FIGURE 4: Estimated differences in limits of total drug expo-
sure (AUC0-t) between 595 pairs of generic antiepilepsy drug
(AED) formulations: maximum limits of 90% confidence inter-
vals (upper limit = 100%, 100% – lower limit) for AUC ratios
are plotted for 8 AEDs by doses. AUC0-t is estimated to differ
by >15% between many pairs of the same doses of generic
AED formulations. AED abbreviations: CBZ = carbamazepine;
VPA = divalproex; GBP = gabapentin; LTG = lamotrigine; LEV
= levetiracetam; OXC = oxcarbazepine; TOP = topiramate;
ZON = zonisamide. [Color figure can be viewed in the online
issue, which is available at annalsofneurology.org.]

FIGURE 5: Estimated differences in peak concentration
(Cmax) between 595 pairs of generic antiepilepsy drug (AED)
formulations: maximum limits of 90% confidence intervals
(upper limit = 100%, 100% – lower limit) for ratios of Cmax
are plotted for 8 AEDs by doses. Cmax is estimated to differ
by >20% between many pairs of the same doses of generic
AED formulations. AED abbreviations: CBZ = carbamazepine;
VPA = divalproex; GBP = gabapentin; LTG = lamotrigine; LEV
= levetiracetam; OXC = oxcarbazepine; TOP = topiramate;
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Partially due to limited safety data regarding generic drug conversion, there has been a good deal of caution and controversy regarding the use of AED generic products; neurology societies recommend physicians be permitted to continue brand-name medications for individual patients, for example, for patients requiring high AED doses with plasma concentrations near tolerability thresholds, for patients sensitive to CNS-related side effects of AEDs, and for patients whose seizures were initially difficult to control. It is suggested that BE studies are also criticized for not evaluating AED absorption in young or elderly subjects and in patients receiving polytherapy. In the absence of gastric disorders, there has been no clear evidence, however, that absorption of AEDs varies in special populations. The limited number of objective studies and publications on generic AEDs may be related to differing marketing and advocacy positions of drug manufacturers, regulators, and clinical groups.

Finally, although our simulations suggesting that switches between generics could potentially be associated with greater changes in AED concentrations than reference-to-generic switches, this possibility should be explored further in clinical PK studies. It is not market practice to maintain patients on single generic formulations, and such studies could help interpret findings, such as those of a recent survey showing increased seizures, and such studies could help interpret findings, such as those of a recent survey showing increased seizures,
to differing marketing and advocacy positions of drug manufacturers, regulators, and clinical groups.

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Potential Conflicts of Interest


References


Authorship

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