Bioequivalence of Antiepileptic Drugs: How Close is Close Enough?

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During the past few years, the use and substitution of generic antiepileptic drug products has been increasing both in the United States as well as globally. Although these less expensive products may represent an important alternative for many patients, there may be reasons for concern. Despite well-controlled regulatory studies, concerns persist regarding potential therapeutic inequivalence in some patients with epilepsy. These concerns have prompted some in the US neurology community as well as patient advocacy groups to question the current regulatory requirements for both establishing bioequivalence as well as product substitution. In addition, recent data have questioned the actual cost savings associated with generic substitution in this unique patient population. This article reviews current regulatory requirements and pharmacokinetic, biopharmaceutical, and clinical outcome issues that clinicians, pharmacists, and policymakers should consider regarding generic substitution of these complicated agents.

Introduction

Few medical issues in recent history have resulted in as much controversy, confusion, and angst as the issue of generic drug substitution [1,2•,3–5]. Both in this country and abroad, numerous surveys of neurologists and patients have suggested an increasing level of concern over the introduction of multiple generic formulations of virtually all of our current antiepileptic drug (AED) armamentarium [6–10]. In one large survey conducted in the United States, 75% of physicians and 65% of patients reported having concerns about the safety of generic AEDs. Importantly, a number of physicians subsequently reported many cases of patients with previously well-controlled epilepsy who experienced a loss of seizure control that appeared to be temporally associated with substitution to a generic formulation [11]. Concern over mandatory substitution has been expressed by patient advocacy groups such as the Epilepsy Foundation (http://www.epilepsyfoundation.org/advocacy/care/genedrev.cfm).

The arguments for an increased use and substitution of generic formulations are mainly economic. It is certainly reasonable to assume that substitution of less expensive but pharmacologically identical and pharmacokinetically similar formulations should result in reduced overall costs of care. Underlying this notion, however, is that bioequivalence (ie, pharmacokinetically similar properties) equates with therapeutic equivalence. Mounting anecdotal evidence suggests that this may not be so in all cases, and several studies have suggested that adverse patient outcomes were associated with generic substitution of AEDs. This leaves clinicians with a dilemma: how do we balance the apparent economic benefit of less expensive medication options with potential adverse therapeutic outcomes?

For clinicians as well as policymakers to understand these issues of concern, it is important to first understand the scientific methodology used to approve a generic formulation in the United States. In addition, one must examine the clinical evidence surrounding this issue.

Bioequivalence Testing Methodology

To be considered interchangeable with a brand-name drug, a generic drug product must meet a number of criteria including that the new product must contain the same amount of active drug as the innovator product and must meet United States Pharmacopeia (USP) standards for purity, strength, and quality. All drug products (both generic and brand) in the United States are required to meet USP's standards. These standards are used to conduct identification tests, tests for impurities, and analytical assays. According to USP standards, the amount of drug in a given dosage formulation can range from 98% to 102% of the stated content. All solid dosage forms will also likely contain one or more inactive ingredients, including lubricants, fillers, and dyes. These inactive ingredients must be recognized as safe but do not need to be identical to those used in the innovator product. The generic product must meet US Food and Drug Administration (FDA) requirements for adequate labeling, and

the manufacturer must be able to demonstrate to the FDA that the production facility is in compliance with Good Manufacturing Practices.

For the FDA to accept a new oral drug formulation as bioequivalent, it must be compared with the branded product in relatively small single-dose crossover studies in young, healthy volunteers. Bioequivalence is evaluated by comparison of the area under the concentration-time curve (AUC), a measure of systemic exposure, and peak plasma concentration (Cmax), a measure of absorption rate. For a generic product to be considered equivalent, the 90% confidence interval of the log-transformed ratios of AUC and Cmax between brand and generic products must fall within the range of 80% to 125%. After these criteria have been met, a product can be considered bioequivalent to the innovator formulation and therefore be interchangeable. In other words, "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study" should confer confidence that the generic product will provide identical therapeutic (efficacy or toxicity) properties and be indistinguishable from the innovator product (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=320&showFR=1&subpartNode=21:5.0.1.1.7.1). It is this assumption of equivalence that has resulted in significant controversy in the neurology community. Although the criteria are undoubtedly statistically stringent and are likely adequate for most drugs, it is arguable that this methodology may be less than optimal for certain classes of drugs (ie, those with a narrow therapeutic index) and disease states.

Numerous pharmaceutical factors can influence the oral bioavailability of a drug. For a drug to reach the systemic circulation, a number of processes must occur, including drug disintegration and dissolution, diffusion through gastrointestinal (GI) fluids, and mucosal membrane permeation and uptake into blood or lymph. Of the many factors or variables that ultimately affect drug absorption, when considering bioequivalence of drug products, water solubility is perhaps the most important [12].

Drugs that exhibit high solubility and high permeability are generally considered to be very well absorbed. However, anything that can affect gut surface area or intestinal transit time may be expected to alter bioavailability. Drugs that display low aqueous solubility (a drug is considered to have high solubility when the highest dose strength is soluble in ≤ 250 mL of aqueous media over a pH range of 1 to 7.5 at 37°C) but high membrane permeability tend to display dissolution rate-limited oral absorption. For these drugs, increases in the rate of in vivo dissolution will tend to increase bioavailability. Drugs with low water solubility may be more likely to display variable oral absorption patterns because of variable dissolution rates. Changes in product formulation that alter (either improving or impairing) dissolution may therefore be clinically significant. For most drugs, minor variances in dissolution patterns would not be expected to be of great pharmacokinetic or ultimately clinical significance. However, when considering several commonly used AEDs (eg, carbamazepine, lamotrigine, oxcarbamazepine, and phenytoin) with relatively poor aqueous solubility [13–15], formulation changes that affect dissolution may impact oral absorption [16]. Reports of unexpected toxicity and/or seizure recurrence have been noted for phenytoin and carbamazepine [17–21].

Potential Limitations of the Current Testing Approach

Whom do we study?

As mentioned, testing to establish bioequivalence is based on single-dose crossover experiments in young, healthy volunteers. By definition, we exclude patients with coexisting medical conditions that may introduce additional variability to the pharmacokinetics of some compounds. Although this approach is certainly statistically valid, one must question whether this it is always clinically appropriate. Therefore, it is reasonable to question whether data generated from these studies can or should be generalized to other patient groups, such as the elderly, who may have altered physiology [22].

Although the GI tract shows remarkable resilience with aging, the potential impact of both healthy and nonhealthy aging may have variable impact on drug absorption. A number of physiologic changes occur within the GI tract in older patients, including delayed esophageal emptying, reduced esophageal contraction velocity, delayed gastric emptying of liquids and solids, and increased variability in gastric acid secretion.

Age-related changes also occur in the intestine. Although enterocytes are essentially unchanged in older individuals, minor changes in manometric patterns, including decreased postprandial contractions and reductions in the frequency of migrating motor complex, have been observed, raising the question as to whether GI transit times may be altered in some individuals.

In addition to these expected physiologic changes associated with aging, common comorbid disorders such as dysphagia, stroke, diabetes, congestive heart failure, and Parkinson's disease may have substantial effects on esophageal function, gastric pH, gastric emptying rates, and intestinal transit times.

Of all the potential changes in physiologic function, alterations in gastric function are most likely to influence AED absorption kinetics. Although gastric acid secretion is similar in older and younger individuals, gastric pH can display marked day-to-day as well as hour-to-hour variability. Although, on average, fasting pH is similar between younger and older individuals, the postprandial pH response may significantly differ, with older individuals requiring significantly more time to return to baseline

pH values. In addition, the incidence of achlorhydria is 10% to 20% in the elderly but less than 1% in younger subjects. Because drugs in an ionized state are typically more soluble than when un-ionized, drug dissolution can be markedly influenced by gastric pH. Increased gastric pH can decrease drug dissolution of weak bases and conversely will increase the solubility of weak acids. In addition, because drugs are more soluble when ionized, increased gastric pH can decrease drug dissolution of weak bases and increase the solubility of weakly acidic drugs. Commonly used drugs such as phenytoin and zonisamide display solubility that is pH dependent, becoming more soluble as pH increases.

Changes in the gastric emptying rate can also influence the bioavailability of certain drug products. In general, alterations would be expected to affect drugs that were either very soluble or poorly soluble. Drug products with lower solubility are less sensitive to changes in the gastric emptying rate, and delays in emptying times may in fact actually facilitate absorption of poorly soluble drugs. Might these potential changes in GI function affect AED bioequivalence (and hence interchangeability) in older patients? To date, this important question has been unexplored.

A final potential limitation to these bioavailability studies is that each generic is tested against the branded equivalent and not against other generic preparations. This practice has the potential for amplifying differences between prescriptions: if a given generic has low (but acceptable) bioequivalence and the preparation dispensed the following month from a different manufacturer has high (but also acceptable) bioequivalence, the total increase in delivered dose could be enough to result in toxic symptoms. There are more than 20 approved manufacturers of generic equivalents of some anticonvulsant drugs, with most having at least ten.

Are single doses sufficient?

Phenytoin remains one of the most commonly prescribed AEDs in the United States. This agent displays nonlinear pharmacokinetics due to saturation of the cytohrome p450 isozymes responsible for its metabolism. Practically speaking, this implies that modest changes in dose, or amount absorbed, may result in disproportionate changes in serum concentration. Although this phenomenon is well recognized, it is important to appreciate that older patients may be even more susceptible, presumably due to age-related declines in metabolic capacity. Even under optimal dosing of a brand product, significant variability can be seen in older patients [23]. This, along with the aforementioned changes in gastric physiology, suggests that very slight changes in the absorption profile may result in meaningful differences in steady-state serum concentration.

Several well-documented reports have suggested that there may be problems with previously approved generic formulations. In 1994, Rosenbaum and colleagues [24] reported that mean phenytoin serum concentrations declined by about 30% when a branded drug was replaced by an approved generic phenytoin preparation in ten patients. More recently, Burkhardt and colleagues [25] reported increased seizures in a group of 11 patients, 10 of whom had substitution of a generic formulation of phenytoin. Following substitution with the generic, phenytoin serum concentrations declined by about 30%. After patients were switched back to the brand product, serum concentrations returned to baseline values.

How can these observations be explained? One possible explanation is that, given the nonlinear, saturable elimination of phenytoin, extrapolating results from single-dose studies in fasting subjects may not necessarily predict outcomes when the medication is given chronically. To illustrate this, Wilder and colleagues [26] evaluated a group of healthy subjects after they took single doses of an approved phenytoin generic or branded Dilantin (Pfizer, New York, NY) in a crossover pharmacokinetics study. Bioequivalence was assessed using accepted FDA study design, except that in this study subjects were given the drug with a high-fat meal. Under these conditions, the AUC was only about 13% lower for the generic product than with the brand, suggesting that both formulations were quite similar. Interestingly, however, when pharmacokinetic parameters derived from this study were modeled to simulate chronic dosing, the authors found that a mere 13% decrease in bioavailability would likely result in a 37% reduction in mean serum concentration if this formulation was given with food. The implications of these observations are that extrapolation of data from single-dose studies to chronic multiple dosing situations may be problematic for a nonlinear medication such as phenytoin.

Clinical Consequence of Generic Substitution: Are We Really Saving That Much?

Although a number of anecdotal reports have hinted that differences in bioavailability might translate into meaningful clinical outcomes, few data were available to substantiate this until recently. In a retrospective claims database analysis, Zachry and colleagues [27] questioned the association between a recent (previous 6 months) substitution of an A-rated generic product and emergent care for a seizure-related event. In this analysis, patients requiring urgent care had 81% greater odds of having an generic AED formulation switch in the previous 6 months than controls (11.3 vs 6.2%).

In a retrospective analysis based on data from an Ontario database, Anderman and coworkers [28•] evaluated switchback rates of several classes of drugs, including AEDs (lamotrigine, clobazam, and valproic acid) as well as several antidepressants and cholesterol-lowering drugs. In Ontario, a physician letter of medical necessity is required before switchback from a generic formulation to the original brand product can be allowed. In this analysis, a high switchback from generic to brand (12.9%–20.9%) was seen for AEDs as compared with non-AED classes of drugs, such as antidepressants or statins (1.5%–2.9%).

Similar findings were noted by LeLorier and colleagues [29•], who found markedly higher switchback rates for AEDs than for antihypertensive or lipid-lowering drugs. During the period when patients were receiving the generic AED, significantly higher rates of medical service utilization and longer hospital stays were noted.

Although the design of these studies does not allow delineation of the reasons for apparently high switchback rates, the data do clearly suggest that patients, physicians, or perhaps both are feeling compelled to return to using higher-cost branded medications for epilepsy.

Finally, an important element that must be included in any discussion of generic substitution is economics. Several recent analyses [30,31] have centered on the potential cost implications of generic substitution. Using health claims data from Quebec's provincial health plan, LeLorier and colleagues [31] identified 671 patients with epilepsy who were being treated with branded lamotrigine. Time periods during which branded or generic formulations of lamotrigine were used were compared for total health care costs, stratified by prescription drugs and inpatient and outpatient services. Despite the lower cost of the generic product, total projected health care costs significantly *increased* when patients were receiving the generic product (US $1750–$2500 per person-year). This study suggests that the potential savings associated with a switch to a generic AED may not be as great as one might expect. A higher overall cost of care (as opposed to simply the cost of the medication) is likely—because of increased physician visits, hospitalizations, and use of medical or pharmacy services. Although these observations clearly require confirmation, they do suggest that, whether due to anticipated or actual untoward clinical consequences, generic substitution may be increasing the overall cost of patient care.

Conclusions

Mandatory substitution of generic AEDs is clearly a controversial subject even though there is little doubt that generic drugs offer an opportunity not only for individual patient savings but cost savings for the greater health care system as well. Although FDA guidelines are very sound for most medications, it is not unreasonable to question whether current assessment strategies and regulatory guidelines are appropriate for all patients in all situations. For many patients, optimization of pharmaceutical care requires careful adjustments of their antiepileptic medications. In these patients, even modest additional variability in AED kinetics might be enough to result in loss of seizure control or the emergence of new or more intense adverse effects. Does this mean that generic equivalents should never be used? Certainly, substitution may be quite appropriate for most patients. There may, however, be "vulnerable" patients or patient groups for which product substitution may not only prove detrimental but, as recent studies suggest, may even be costing us money.

Given the potential consequences of nontherapeutic equivalence, at the very least, increased vigilance when switching between formulations would seem prudent. Patients should be encouraged to discuss this issue with their physician. They also should discuss their prescription with their pharmacist and, if there is a concern, ask the pharmacist to provide the name of the product distributor and lot number. Ultimately, well-conducted prospective trials should be designed to address the adequacy of current regulatory guidelines and acceptance limits for patients as well as healthy individuals. It is hoped that efforts directed toward identifying "vulnerable" patient groups will lead to greater confidence by both clinicians and patients.

Disclosure

No potential conflict of interest relevant to this article was reported.

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