UNDERSTANDING THE RAMIFICATIONS OF SWITCHING AMONG AEDS: WHAT ARE THE DATA?

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ABSTRACT

Historically, there have been problems with generic versions of older antiepileptic drugs (AEDs), specifically carbamazepine and phenytoin, which can be explained by 3 possible pharmacokinetic properties: low water solubility, narrow therapeutic range, and non-linear pharmacokinetics. This article discusses the historical data regarding problems with switching generic versions of older AEDs and discusses the role of dissolution rates (in vitro and in vivo) that can affect therapeutic equivalence and bioequivalence. A comparison of these properties in newer AEDs is also included. The newer AEDs do not have the same pharmaceutical or pharmacokinetic properties that often lead to problems with equivalence (bio or therapeutic), and they have proven their value in clinical practice. Finally, the financial implications of generic substitutions are discussed. For many patients, access to branded versions of these AEDs is limited by their cost. Free competition with generics based on price will lead to lower costs and greater availability of these important therapeutic options.
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There has been a history of problems with generic versions of the older antiepileptic drugs (AEDs), specifically carbamazepine and phenytoin, as summarized in several reviews.[1-3] Nuwer et al described 3 pharmacokinetic properties that predisposed the older AEDs to problems with their generic formulations: low water solubility, narrow therapeutic range, and non-linear pharmacokinetics.[1] Phenytoin is the only older AED that clearly meets all 3 criteria because of its low water solubility, dose-dependent elimination, and narrow therapeutic range. In controlled studies, increased,[4] decreased,[5] and no significant change[6] in phenytoin serum concentrations with generic switching have been reported. A difference in the effect with food for brand-name (Dilantin; Parke-Davis, Morris Plains, NJ) and generic phenytoin (Mylan Pharmaceuticals, Inc, Morgantown, WV) has been reported. There was a significant decrease in bioavailability with the generic formulation when given with food; however, there was no effect of food on the absorption of the brand-name phenytoin.[7] A retrospective chart review of developmentally challenged patients demonstrated a significant decrease in phenytoin serum concentrations and increased seizures reported in 8 patients after switching from brand to generic phenytoin.[8]

With carbamazepine, case reports of increased seizures following switching from brand to a generic[9-11] may have been because of the unanticipated effect of moisture on various carbamazepine tablets that have been approved and marketed. A study by the US Food and Drug Administration (FDA) demonstrated that the tablets can lose 33% of their effectiveness if stored in humid conditions, which exist in most bathrooms.[12] Because of the multiple polymorphic hydrous/anhydrous forms in which carbamazepine can exist, different forms result in different rates of hydration and in

vitro dissolution.[13] Similarly, a formulation of phenytoin was recalled by the manufacturer after batches of the product failed dissolution testing. Patients receiving the recalled formulation had serum phenytoin concentrations 22% to 31% lower than those who received a branded formulation.[5]

Valproate is formulated as the sodium salt and divalproex is a stable combination derived from sodium valproate and valproate in a 1:1 molar ratio. Both chemical formulations are highly water soluble. The non-linear protein-binding characteristics of valproate results in linear kinetics of the unbound or active drug, and therefore, neither formulation of valproate meets any of the characteristics suggested to predispose to problems with generics. Consistent with this prediction, no significant differences in seizure control or valproate serum concentration were found in an open-label switch study between brand-name valproate and a generic product in 64 subjects.[14] Substituting between types of chemical forms of valproate (divalproex and sodium valproate) or formulations (extended-release and immediate-release) is not a generic substitution and should not be considered in evaluating changes in adverse events and/or seizures.

The Effect of Dissolution Rates

In addition to permeability across the gastrointestinal tract, drug absorption from a solid dosage form depends on the release of the drug from the drug product (ie, dissolution). In vitro dissolution can be used to predict in vivo dissolution. Therefore, as described in FDA guidance for industry (http://www.fda.gov/cder/guidance.htm), in vitro dissolution tests are used to: (1) determine the lot-to-lot quality of a drug product; and (2) guide development of new formulations. For generic drug development, the US Pharmacopeia (USP) drug product dissolution tests are available. The most commonly used dissolution methods are the basket and the paddle methods. These methods are simple, robust, well standardized, and used worldwide. If there is a significant correlation between in vitro dissolution and in vivo performance of the drugs, the in vitro test can be used as a tool to distinguish between acceptable and unacceptable drug products.

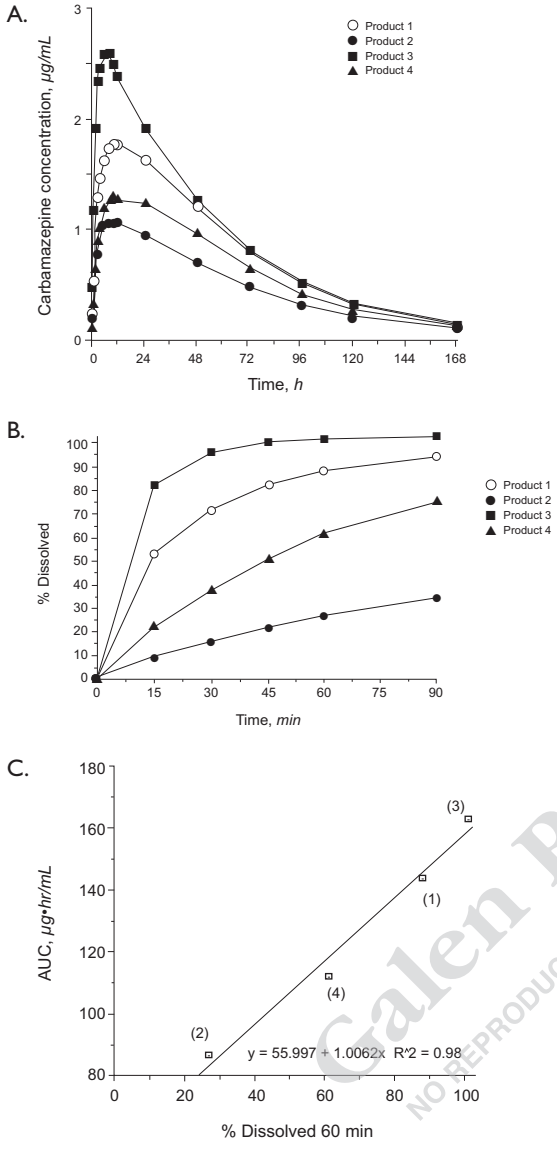
The Biopharmaceutics Classification System (BCS) was first developed by Amidon et al[15] and was designed to correlate a drug's solubility and permeability with the rate and extent of oral drug absorption. As recently reviewed by Wu and Benet[16] and Lindenberg et al,[17] a drug is considered to have high solubility when the highest dose strength is soluble in 250 mL or less of aqueous media over a pH range of 1 to 7.5 at 37°C. A drug is considered to be highly permeable when the extent of absorption (bioavailability) is at least 90%. Drugs are then classified into 4 BCS classes: high solubility/high permeability (Class I); low solubility/high permeability (Class II); high solubility/low permeability (Class III); and low solubility/low permeability (Class IV). In 2000, the FDA began using the BCS to grant a waiver of in vivo bioavailability and bioequivalence testing of immediate-release solid dosage forms for Class I drugs (http://www.fda.gov/cder/guidance/index.htm). The BCS classification also can provide estimation for the likelihood of problems with generics. The BCS classification for the old and newer AEDs is provided in Table 1.[16,18-31] Of the older drugs, carbamazepine, clonazepam, primidone, and phenytoin are not Class I drugs. However, as described above, there have been reports of problems with carbamazepine and phenytoin with regard to bioequivalence. There is very limited evidence of generic problems with primidone.[32]

Table 1. Biopharmaceutical Classification System: AEDs

AED	Solubility	Permeability	BCS Class	References
Ethosuximide*	High	High	I	20
Lamotrigine	High	High	I	24
Levetiracetam	High	High	I	25
Phenobarbital*	High	High	I	16
Pregabalin	High	High	I	18, 27
Tiagabine	High	High	I	29
Topiramate	High	High	I	30
Valproic acid*	High	High	I	16
Zonisamide	High	High	I	31
Carbamazepine*	Low	High	II	16
Clonazepam*	Low	High	II	18, 19
Felbamate	Low	High	II	21, 22
Oxcarbazepine	Low	High	II	26
Phenytoin*	Low	High	II	16
Primidone*	Low	High	II	28
Gabapentin	High	Low	III	23

*Denotes older AEDs.
AED = antiepileptic drug; BCS = Biopharmaceutics Classification System.
Data from Wu and Benet[16]; Budavari[18]; Anderson and Miller[19]; Pisani et al[20]; Kucharczyk[21]; Pellock et al[22]; Vajda[23]; Dickins et al[24]; Patsalos[25]; Bialer[26]; Ben-Menachem[27]; Fincham[28]; Sommerville and Collins[29]; Doose and Streeter[30]; and Shah et al.[31]

Figure. Bioinequivalence of Carbamazepine Tablets Withdrawn From the Market Due to Clinical Failures



The bioavailability of 3 lots of a generic 200-mg carbamazepine tablet (Products 2–4), which had been withdrawn from the market, was compared to the bioavailability of 1 lot of the innovator product (Product 1, *N* = 24 healthy volunteers). The mean maximum carbamazepine plasma concentrations for 2 of the generic lots were only 61%–74% that of the innovator product, whereas the third lot was 142% of the innovator.

A, The mean areas under the plasma concentration-time curve for the 3 generic lots ranged from 60%–113% that of the innovator product. **B**, There was a wide range of dissolution rates between the generic formulations and the branded version, in addition to among the generic formulations. **C**, A good relationship was found between the in vivo parameters and the in vitro dissolution results for the 4 dosage forms. The results clearly indicate a significant difference in the rate and extent of absorption of the generic products compared to the branded drug, as well as among the generic lots.

AUC = area under the curve.

Reprinted with permission from Meyer et al. *Pharm Res.* 1992;9:1612-1616.[33]

For Class I drugs based on BCS classification alone, we can predict that in vitro dissolution testing should allow one to distinguish between acceptable and unacceptable generic drug products. Conversely, carbamazepine is a Class II drug and technically does not meet BCS criteria; hence, one would not expect a good correlation between in vitro dissolution testing and in vivo performance. However, in vitro dissolution testing was shown to be predictive in detecting unacceptable drug products (both brand and generic) for carbamazepine and phenytoin as previously described. In the 1980s, there were several reports of loss of seizure control due to generic carbamazepine.[9,10] Subsequently, the FDA determined that the problem could be attributed to a manufacturer that had changed its source of carbamazepine, resulting in a product with highly variable dissolution characteristics.[2] The in vivo bioavailability of 3 lots of generic carbamazepine that had been withdrawn from the market in 1988 were compared to Tegretol (carbamazepine; Novartis Pharmaceuticals Corporation, East Hanover, NJ).[33] For the generic products (Products 2, 3, and 4), the mean area under the concentration-time curve (AUC) ranged from 60% to 113% of the brand-name product (Product 1, Figure A). As shown in Figure B, in vitro dissolution testing also was performed on the 4 products using the standardized USP paddle method. There was a significant difference in dissolution, defined as the percent dissolved per unit time for all 4 products. An excellent linear correlation was found between the AUC and the percentage dissolved in 15, 30, 45, and 60 minutes obtained by the in vitro dissolution test (Figure C).[33] Therefore, in vitro dissolution testing can distinguish between acceptable and unacceptable generic drug products as has been demonstrated with both the recalled carbamazepine and phenytoin formulations described earlier.

Bioequivalence of Older vs Newer AEDs

Using the criteria of Nuwer et al[1] regarding the pharmacokinetic properties that predisposed the older AEDs to bioequivalence problems (ie, low water solubility, narrow therapeutic range, and non-linear), our current knowledge of the pharmacokinetic properties predicts that the new AEDs should not be predisposed to such problems. Data on therapeutic ranges of the new AEDs have not been well defined; however, many suggest that none of the new AEDs meet the criteria of a drug with a narrow therapeutic range.[34,35] The new

AEDs do not meet the second 2 criteria, as shown in Table 1. Of the new AEDs, lamotrigine, levetiracetam, pregabalin, tiagabine, topiramate, and zonisamide are all Class I drugs. Gabapentin is not a Class I drug, due to the transporter-mediated saturable absorption. However, as transport processes occur after dissolution, there is no reason to expect a difference in transporter efficiency with generic products of gabapentin, a highly soluble compound. Felbamate and oxcarbazepine are both Class II drugs.

Of the available generics on the market, there have been no documented reports of suspected, concentration-related, increased seizure rates or the occurrence of adverse events with generic gabapentin, lamotrigine, or zonisamide. Buck et al[36] performed a retrospective evaluation of lamotrigine plasma concentrations in patients receiving brand only, generic only, or both generic and branded lamotrigine corrected for defined daily dose. They found no evidence for changes in lamotrigine plasma concentrations or larger variation in lamotrigine plasma concentrations between generic and branded lamotrigine. In a case study, an unidentified impurity was suggested as a cause of a hypersensitivity reaction when a patient who had been receiving 800 mg/day branded lamotrigine for 10 years was switched to generic lamotrigine.[37,38]

Economics of Generic Substitution

Typically, generic drugs are less expensive than brand-name drugs. The potential savings from substituting generic drugs for brand-name drugs has been estimated for Medicaid beneficiaries as $229 million annually.[39] A recent study using data from the 1997–2000 Medical Expenditure Panel Survey Household Component estimated that substitution with a generic drug whenever available would save more than 10% in comparison to brand-name cost: $46 per year for adults aged younger than 65 years (interquartile range $10.35–$158.06) and $78 per year for older adults (interquartile range $19.94–$241.72).[40] As shown in Table 2, the cost saving for substituting the available generics of the new AEDs for brand name can result in substantial individual savings. The savings (cost/unit) for substitution of generic for brand name gabapentin ranged from 164% to 926%, depending on the dosage strength. For zonisamide, substitution of generic for brand name would save an individual patient 38% and 174% for the 25-mg and 100-mg dosage strengths, respectively. For lamotrigine, substitution for the 25 mg currently available generic for the brand name would save an individual patient approximately 41%.

With the increased number of 3-tiered pharmacy benefit plans designed to reduce overall cost by shifting increased costs to patients, it is important to understand the effects on medication-taking behavior in general. Shrank et al evaluated the implication of prescribing generics or preferred pharmaceuticals for chronic conditions (hypertension, diabetes mellitus, and hypercholesterolemia) on medication adherence.[41] Measured adherence, defined as proportion of days covered, was significantly greater for those patients initiated on generic medication versus non-preferred medications. Patients receiving generics had 62% greater odds of achieving adequate adherence compared to those receiving non-preferred medications. Surprisingly, those residents of poor areas (based on zip codes), or those least likely to be able to afford more expensive medications, were 25% more likely to receive initial treatment with branded medications.[42] If patients were enrolled in a 3-tier pharmacy plan, they were 205 times more likely to switch from branded to generic.

Table 2. Generic vs Brand-Name Prices of New AEDs

Drug	Cost/Unit: Brand Name	Generic	Savings, %*
Gabapentin/Neurontin†			
100 mg	$0.78	$0.24	225
300 mg	$1.75	$0.46	282
400 mg	$2.06	$0.78	164
600 mg	$6.18	$0.87	607
800 mg	$9.26	$0.76	926
Lamotrigine/Lamictal‡			
25 mg	$3.84	$2.72	41
Oxcarbazepine/Trileptal§			
150 mg	$1.62	$1.33	22
300 mg	$2.76	$2.08	33
600 mg	$5.19	$4.13	26
Zonisamide/Zonegran‖			
25 mg	$0.76	$0.28	174
100 mg	$2.61	$1.89	38

*Savings calculated using generic cost as reference. †Pfizer Inc, New York, NY. ‡GlaxoSmithKline, Research Triangle Park, NC. §Novartis Pharmaceuticals Corporation, East Hanover, NJ. ‖Elan Pharma International, Ltd., Dublin, Ireland.
AED = antiepileptic drug.
Data from drugstore.com, based on comparing equivalent number of tablets or capsules per bottle as of February 2008.

After a government-mandated switch from branded to generic lamotrigine in Ontario, Duh et al evaluated the economic impact of this substitution using drug cost of both AEDs and non-AEDs claims data obtained from a public-payer pharmacy claims data base from Ontario, Canada.[43] The analysis suggests that increased pharmacy utilization costs resulted in less-than-expected cost reductions after a switch to the generic formulation. For lamotrigine, the expected decrease in cost of lamotrigine was 31.9%, but the actual cost decrease was of 28.2% because of a 5.5% average increase in lamotrigine dose—overall, a significant cost savings for lamotrigine.[43,44] However, simultaneously, there was an unexpected increase in the cost of other AEDs (11%) and non-AEDs (15.6%). Because of the lack of medical claims data, there is no way to determine the significance of the relationship between the switch to generic lamotrigine and the reason for or clinical significance of the increased lamotrigine dose or the cost due to other AEDs or non-AEDs.

For carbamazepine and phenytoin, which undergo routine therapeutic drug monitoring (TDM), switching to the generic formulation could result in increased cost as a result of more frequent serum concentration testing. The new AEDs have been marketed as not requiring TDM because of their increased tolerability and larger therapeutic index (ie, ratio of toxic concentrations to therapeutic concentrations). Ironically, based on the historical concerns regarding generic AEDs, TDM may have provided a way to ensure patient safety while establishing that generic versions of the new AEDs proven to be bioequivalent in population studies are also bioequivalent in individuals. Thus, despite the cost, it may be worthwhile to reconsider performing TDM with the new AEDs.[45]

Conclusions

There are clearly large economic advantages to the use of generic AEDs. The history of problems with generic formulations of the older AEDs, carbamazepine and phenytoin, can be explained by their pharmaceutical/pharmacokinetic properties. The new AEDs do not share the same physical properties, so the concerns regarding the older AEDs are not applicable. The newer AEDs have proven their value in clinical practice. For many patients, access to branded versions of these AEDs is limited by their cost. Free competition with generics based on price will lead to lower costs and greater availability of these important therapeutic options.

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