In order to more directly address some of the most common questions and concerns that impact both physicians and pharmacists who treat patients with epilepsy, the faculty also conducted a roundtable discussion. Highlights of this discussion are presented below.

INTRAVARIABILITY

Dr Berg: The issue with generic antiepileptic drugs (AEDs) is actually more fundamental than the US Food and Drug Administration (FDA) bioequivalence analysis, although that plays a role. The first question that needs to be addressed is how much variability in a drug is tolerable for a particular individual. A person who is able to maintain seizure control without side effects, with large variations in his or her AED dose, is very different from someone who has breakthrough seizures or side effects when there is a small (eg, 5%–10%) change in the dose. In the group that is sensitive to small changes in dosage, with a narrow therapeutic index, intrasubject variability (ie, how much difference there is from one to another dose of the same formulation) is a fundamental issue that needs to be determined. Then we can address the worry about a 5% or 10% difference in bioabsorption that may be present between various generic formulations in an intelligent manner.

THE FDA'S POSITION

Dr Berg: Keep in mind that the FDA's position on bioequivalence for all generics, even AEDs, may be correct. If it is not correct, it needs to be demonstrated. But if it is correct, the FDA has done a poor job of educating and demonstrating to physicians, pharmacists, and patients who are using these drugs, that the FDA's position is valid. We really should not have this issue. We should not have to think twice about whether a patient is receiving a brand medication or generic 1 or generic 2.

Dr Anderson: There is only one drug, phenytoin, that has the type of non-linear pharmacokinetics that would be affected by changes in bioavailability. Thus, changing all of the rules based on one drug does not make a lot of sense.

Dr Berg: It makes sense that phenytoin is the AED most likely to have problems with generic formulations. If it is demonstrated that the FDA rules do not ensure equivalence for the various formulations of phenytoin (ie, there are some people who, when switched from brand to generic or from one generic to another phenytoin, have a significant enough change in bioavailability to cause a clinical effect), then the FDA could specify that this drug has special pharmacokinetics and should be handled separately. They would need to reevaluate the FDA bioequivalence, and the US Pharmacopeia guidelines for it, and make those tighter. However, if there are problems with phenytoin, then there may be problems with other AEDs.

But the converse of showing that the bioequivalence criteria for phenytoin are valid is very powerful. If you demonstrate for phenytoin that, say a 10% variation in absorption is not an issue, that it does not have a meaningful clinical effect, despite its non-linear kinetics, then you have shown that there is no effect in essentially the worst case scenario. If this is the case, it might be reasonable to conclude that the FDA regulations do ensure equivalence for all generics. To the best of my knowledge, a well-designed, prospective, randomized, clinical trial on generics, including phenytoin, has not been done to demonstrate this yet.

NEW AEDS

Dr Phelps: Is switching to generics an issue for the new AEDs?

Dr Berg: The issue is present for all of the AEDs. However, the issue is one of perception: some people perceive that when they switch from a brand to a generic drug, they have a problem. Whether it is an actual pharmacologic phenomenon is not clear. The drug that has probably the biggest bioavailability problem is gabapentin.

Dr Anderson: Gabapentin has a bioavailability problem because of saturable active transport, but the saturable transport is the same for generic or branded gabapentin. Dissolution will occur before transport

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and, from a pharmaceutical perspective, gabapentin will not have a dissolution problem.

Ironically, the pharmaceutical companies have justified the higher cost of the newer AEDs by the lack of required blood level testing, because the newer AEDs have a much larger therapeutic index. Thus, based on their marketing, even for patients who are sensitive to small changes in blood concentrations, seizure control should not be a concern. However, because we do not use therapeutic drug monitoring (TDM) with the newer AEDs, we lack the concentration data to document whether there are problems.

Dr Berg: I think many clinicians would not necessarily agree with that. Blood concentrations are available for all of the new AEDs and clinicians order these tests. Most of us treat each patient as an individual, and each patient has his or her own individualized reference range. This is the debate about measuring drug concentrations. Is using a population therapeutic range applicable to the individual patient? There is some overlap, but the best use of measuring blood concentrations is to determine the individualized "therapeutic" range. The other major use for blood concentrations is to determine if the person is taking the drug (ie, adherence).

Dr Hartman: For special populations, such as children or elderly people or people who are taking a lot of other medicines, the utility of measuring drug concentrations may be less clear. The issue of TDM has been addressed by the International League Against Epilepsy.[1]

Dr Vining: Do we know how stable drug concentrations are in a patient taking a newer AED if we are sure that that patient is taking the same drug at the same time every day, under the same conditions?

Dr Anderson: Yes. Actually, there are some data on that. Buck et al did a retrospective analysis of lamotrigine plasma concentrations in patients receiving brand only, generic only, or both generic and branded lamotrigine, and found that generic lamotrigine did not lead to changes in plasma concentration or larger variation in plasma concentrations. Unfortunately, the article is in Danish and I was unable to obtain an English version. The abstract provides only median data.[2]

Dr Berg: The FDA has thought about this and has developed a protocol to test a drug against itself for bioequivalence; it is called Individual Bioequivalence. The subject receives a dose of the reference drug, which is usually the brand drug, at 2 separate times. Both times, the concentration-time curve is generated. These curves establish the "goal posts" for the reference drug; it tells you the individual biologic variation with the same formulation. When the generic version is tested, its concentration-time curve should fall within those goal posts. That said, the Individualized Bioequivalence paradigm is not required by the FDA because, in part, when the FDA tried it, there did not seem to be an advantage over the standard Average Bioequivalence testing. There is literature on the Individualized Bioequivalence method. However, most of the studies are not published due to proprietary considerations. Unfortunately, the bioequivalence data that the FDA requires are not made available to the public, except in a summarized form.

Therefore, an Individual Bioequivalence methodology has been proposed and is available, but it has not been pursued. It makes sense that a generic should have to meet a range that is within the brand drug's variation from one dose to another dose, but that is not the way it is currently assessed.

Dr Anderson: I know clinicians commonly use generic carbamazepine and generic phenytoin. Clearly, we had problems with the generics in the 1980s or early 1990s that now can be predicted and understood based on their pharmaceutical properties. At that time, I was supporting the restriction of substitution of these drugs. However, we are no longer seeing those problems, even as case reports, possibly due to tighter controls on manufacturing and FDA regulation. Before 1990, the FDA used the 75/75 rule, the 80/20 rule, and the ±20 rule, instead of the current 80/125 rule. For example, one major difference was the past use of the 75/75 rule, which stated, "Bioequivalence is claimed if at least 75% of individual subject ratios are within the limits of 75% and 125%."[3] This rule was criticized for its poor statistical behavior.[4,5] In addition, Benet and Goyan suggested that problems that occurred in the past were due to a failure to enforce standards, not necessarily that the standards themselves were a failure. Now we have a whole new set of AEDs and new FDA regulations since the problems with carbamazepine and phenytoin generics, but the perception is still out there and many people are paranoid about using their generic versions. If we find we have the same problems with the generic versions of newer AEDs, I will have no problem restricting them in the future. But at this point, we have no data saying there should be a problem. We do have an understanding of the pharmaceutical properties of the new AEDs compared to the older AEDs suggesting that there should not be problems with generic substitution. It is inappropriate for there to be continued promotion

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of possible concerns over response with the generic forms of the newer AEDs that is based on the problems with the older AEDs.

Other Epilepsy Populations

Dr Hartman: One of my concerns, as a clinician who takes care almost exclusively of children with epilepsy, is the use of generics in patients at extremes of age: the young patients, the elderly patients, as well as the patients who have other diseases where they are taking a lot of other medications—patients in whom the concept of bioequivalence has not necessarily been "road-tested."

Dr Anderson: With the exception of gabapentin, there really are no major age-related problems with absorption once patients are older than 1 year. Similarly, with the elderly, for the drugs that have been evaluated, there has not been a difference in bioavailability. The exception may be with drugs that are affected by the increased pH that can occur in the elderly. Liver disease and renal disease affect clearance and volume of distribution, but they do not affect absorption unless at end-stage disease.

Dr Garnett: But if the absorption changed in elderly patients, there would be no reason to think it would be different between the generic or the brand, if they were bioequivalent.

Other Contributing Factors

Dr Berg: The bigger issue, in my opinion, is proper "medication hygiene." For instance, if you take phenytoin with food or without food, there can be a 50% difference in half-life. There is a change in blood concentration if the timing of the dose varies. Also, if the pills are split and one half has a little bit more than the other half, or if certain concomitant medications are taken with the morning dose but not the evening dose, blood concentrations could vary. Are we appropriately educating our patients about these issues? A missed dose has far more of an effect than any of the concerns with bioavailability between generics. If you vary a dose by several hours, the variation in blood concentrations can be much greater than with this relatively small bioequivalence concern.

Dr Garnett: I would agree. Those factors are independent of bioequivalency, and it does not matter which formulation you use, it is going to affect both of them equally.

Dr Anderson: You need to then look at each individual drug, and the food effect studies that have been done for the brand-name drugs. There are very few drugs that are significantly affected by food. Food causes some delay in rate of absorption but that will not happen with most drugs.

Dr Garnett: Phenytoin has some variability in absorption when given with food. It depends on whether you give it with fat, protein, or carbohydrate. Thus, it should probably be taken in a consistent manner, probably on an empty stomach, and there may be some change in absorption, depending on the mix of the food, not just whether it is food, and it would be similar for generic and brand. But, I agree—noncompliance is probably the biggest issue.

Dr Berg: Thus, when we talk about the generic-to-brand differences, and the generic-to-generic differences, the population of concern is limited, if there even is a concern. It is in those people who are fully compliant, who take their drugs consistently, and who have an individualized narrow therapeutic index, such that the 5% or 10% variation in absorption may be an issue. For the majority of patients, I do not think it is an issue, and we need to keep that in perspective.

The Relationships Between Cost, Adherence, and Generic Drugs

Dr Hartman: Are there any data to show that lower cost might improve adherence? Cost has been discussed widely as a potential contributor to nonadherence, although the specific issue of generics has not been studied widely. One study of children in Canada showed that cost was one reason why parents did not fill prescriptions written in the emergency department—an interesting finding in light of the fact that nearly 80% of patients in that study had some form of a prescription drug plan.[6] There are some data in adults with hypertension showing a lower nonadherence rate in patients prescribed generic formulations.[7]

Dr Garnett: Several studies have shown that even small increases in the copayment can make a difference in adherence, particularly when you are taking several medications.[8,9]

Dr Phelps: A study from Canada looked at the use of generic lamotrigine and found that it did not lower the cost as much as expected. What did you conclude from these findings?[10]

Dr Anderson: The problem with that study is they only had the drug data; there were no medical outcomes. The data showed an increase in the cost of the

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other AEDs and other drugs. Without the medical data, we cannot determine why there was an increased use of other drugs and why the costs were not lowered as much in that study. I am also not sure if the cost differences between brand and generic are as large in Canada as they are in the United States.

Dr Berg: I have seen a few abstracts that associate increased health utilization with switching to generic AEDs. I am not sure how valid these data are, and I am not sure who funded the studies. I do not know if, in larger patient populations, this holds true, but it suggests that there may be an issue.

Other Possible Solutions

Dr Anderson: What would really help is if physicians and patients knew that the patients could get 1 year, for instance, of one generic—the same lot, the same manufacturer. Right now, patients pick up a prescription every month and they end up with different colored pills every month, which is obviously stressful. If patients could at least be assured of having 1 product for a longer period of time, we could start working out some of these issues.

Dr Vining: I tell my patients that if your medicine this month does not look like the pills you have been taking, question it. If they are switching generics all of the time, they are going to be questioning an awful lot of times, often feeling uncomfortable, and making the pharmacist feel uncomfortable.

Dr Phelps: Large pharmacy chains and mail-order pharmacies vary which products are stocked based on acquisition cost. The individual pharmacist has little to no control over which generic product is on the shelf from month to month.

Dr Anderson: The patient should be able to pick up 6 months' worth of pills at once. Right now, the insurance companies are controlling the number of pills they are allowed. Part of this heavy control was because patients were given a new prescription for a drug, maybe started using them, but then discontinued before the prescription ran out. But once someone is on a chronic medication, they should have the right to be able to be provided with a long-term prescription.

Dr Phelps: Some of the branded AEDs are very expensive and may cost more than $500 a month. If a patient is given a 6- to 12-month supply at one time that is $3000 to $6000—a very large cost to a payer or governmental agency if the drug is discontinued.

Dr Hartman: You would think it was in the insurance company's best interest for a patient to be on a stable medication because it would theoretically lead to better outcomes. It would also cut down on any costs associated with required or recommended testing when a patient switches drugs.

"Branded Generics"

Dr Berg: There are only 2 or 3 branded generic AEDs, out of more than 50 generic formulations of AEDs. But if you are looking for branded generics, then you are making the underlying assumption that generics are not truly equivalent, and that is the problem.

Dr Anderson: Branded generics help to make people comfortable by putting a specific brand name on something manufactured by one manufacturer. It feels one step removed from just a generic name by many generic manufacturers.

The Clinical Perspective

Dr Hartman: As practicing clinicians, what data would you accept as useful or valid for making a generic AED substitution?

Dr Garnett: I would like to see the data that are sent for the Abbreviated New Drug Application (ie, the bioequivalency trials) go into the package insert for the generic drug. Those data would show how many subjects were in the studies, the intravariability with the generic versus the branded drug, and the mean area under the curve and maximum blood concentration for both the brand and the generic. Having physicians and pharmacists be able to view those data would solve the problem. These are the same types of data that are published in trials of branded drugs, but nobody publishes studies comparing a generic to its branded formulation.

Dr Vining: If you had a family member who was well-controlled on a brand-name drug, what information would you use to choose whether to switch to a generic?

Dr Anderson: I trust the FDA guidelines.

Dr Berg: It depends on how hard the family member was to get seizure free and what the individual therapeutic range is for the patient. If this person has struggled to become seizure free, I would not change to the generic version of the AED. If it was a straightforward case, or the person had only 1 seizure, then yes, I would consider switching to generic.

Dr Anderson: It bothers me that so many patients are being kept on the older drugs because they cannot afford the new ones, not because it is the right drug for them. But that will all change in the next couple of years.

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Dr Vining: Yes, but that raises a difficult question. If I have a person who has done well on one of the old drugs (eg, carbamazepine), I am not looking to switch the person to a newer drug.

Dr Anderson: The issues of addressing quality of life with the old versus new AEDs are important. I had a patient with refractory epilepsy once tell me that he had been receiving AEDs so long, he was curious what person he would be without AEDs. His wife felt that his personality changed with each different AED that he tried.

Dr Hartman: Let us summarize some of the main points. We are entering a phase in AED production where there is a perceived uncertainty in terms of seizure control and adverse reactions when generic medications are used. More data are needed to help make informed decisions to guide all involved in the process of using brand-name or generic AEDs. Sources of these data might include material already on file with the FDA, as well as clinical studies. Some studies were funded by manufacturers, which invites a high level of scrutiny in terms of analyzing data.[11] Newer AEDs should not pose as many issues as older-generation drugs because of their more favorable pharmacokinetic profiles. Monitoring drug concentrations may be useful for determining whether different formulations of the same AED are effective, but seizure control and adverse reactions are the ultimate indicators. Other factors to consider include the cost of TDM and time spent by clinicians and patients ensuring that the AED is working as expected. Selecting patients who might be good candidates for generic substitution (ie, where seizure control or adverse reactions are not overly sensitive to AED concentrations) is another challenge we will face. Based on the data presented here, we would expect that most people with epilepsy would probably be able to use generic AEDs without much difficulty, although this needs better formal study.

REFERENCES

1. Patsalos PN, Berry DJ, Bourgeois BF, et al. Antiepileptic drugs—best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. *Epilepsia*. 2008. [Epub ahead of print].
2. Buck TC, Schmedes A, Brandslund I. [Does generic lamotrigine lead to larger variations in plasma concentrations?]. *Ugeskr Laeger*. 2007;169:2013-2015.
3. Federal Register. 1978:43:6965-6969.
4. Benet LZ, Goyan, JE. Bioequivalence and narrow therapeutic index drugs. *Pharmacotherapy*. 1995;15:433-440.
5. Haynes JD. Statistical simulation study of new proposed uniformity requirement for bioequivalency studies. *J Pharm Sci*. 1981;70:673-675.
6. Van Wijk BL, Klungel OH, Heerdink ER, de Boer A. Generic substitution of antihypertensive drugs: does it affect adherence? *Ann Pharmacother.* 2006;40:15-20.
7. Matsui D, Joubert GI, Dykxhoorn S, Rieder MJ. Compliance with prescription filling in the pediatric emergency department. *Arch Pediatr Adolesc Med*. 2000;154:195-198.
8. Doshi JA. Impact of prescription copayment increase on lipid lowering medication adherence in elderly patients. Presented at: 2008 American Geriatric Society Annual Scientific Meeting; April 30-May 4, 2008; Washington, DC. Abstract P8.
9. Hartung DM, Carlson MJ, Kraemer DF, et al. Impact of a Medicaid copayment policy on prescription drug and health services utilization in a fee-for-service Medicaid population. *Med Care*. 2008;46:565-572.
10. Duh MS, Andermann F, Paradis PE, et al. The economic consequences of generic substitution for antiepileptic drugs in a public payer setting: the case of lamotrigine. *Dis Manag*. 2007;10:216-225.
11. LeLorier J, Duh MS, Paradis PE, et al. Clinical consequences of generic substitution of lamotrigine for patients with epilepsy. *Neurology*. 2008;70:2179-2186.

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