The Issue of Generic Substitution: A Handful of Answers, a Multitude of Questions

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Epidemiologic Highlights (US)

- 2.5 million prevalent cases
  - Point prevalence: 0.5-1%
  - 150,000 to 200,000 new cases/year
- Changing age-specific incidence over the last 3 decades
  - Decreased in younger age groups, increased over age 60

*MMWR Weekly*. November 11, 1994/43(44);810-811, 817-818.
*Data from Rochester, MN (1975-84)*
Goal of Therapy: Freedom from Seizures
Answers/Background

- Every day several million tablets of generic AEDs are taken by people with epilepsy
- Generic drugs can be an important weapon to combat health care costs
  - FDA estimated $56.7 billion per year saved in 2002 by generic substitution
- **Advocacy groups**: indiscriminate generic substitution in people with epilepsy can cause problems because FDA rules allow too much **variability** across formulations
- **FDA**: it has no **reliable** documentation of generics causing problems and formulations are **interchangeable** without additional testing
Answers: FDA Requires Rigorous Bioequivalence Testing

• Area under the plasma concentration time curve (AUC) and maximum concentration ($C_{max}$) measured

• Typically 24-36 healthy adults, single dose
  – Subjects do not have epilepsy
  – Subjects are not taking concomitant meds or have comorbid conditions common in patients with epilepsy

• Equivalence: 90% CI of the ratio of the generic to reference compound for both AUC and $C_{max}$ fall within 80-125% range
  – FDA analyzed 2000 BE studies pre-1997 and mean difference $C_{max} = 4.35\%$ and $AUC = 3.56\%$
Bioequivalency Concepts:

- AUC - area under the plasma concentration time curve
- $C_{\text{max}}$ - maximum concentration
- MTC – minimum toxic dose
- MEC – minimum effective dose
Brand v Generic (90% CI)

A. BRAND

B. EQUIVALENT

C. INEQUIVALENT: NOT APPROVED

D. INDETERMINATE: NOT APPROVED
Generic Drugs
Safe. Effective. FDA Approved.

- Consistent labeling
- Rigorous manufacturing standards
- Assured quality
- Purity check
- Performance evaluation
- Same drug

Visit www.fda.gov/cder/ or call 1-888-INFO-FDA to learn more.

U.S. Department of Health and Human Services
Food and Drug Administration
Substitution of Generic AEDs: Perceptions

- Wide-spread uncertainty regarding switching between AED branded and generic products.
  - Wilner (Epilepsy & Behavior 2004;5:995-998)
    N = 6420 neurologists surveyed. Of n = 301 responding, 67% reported breakthrough seizure, while 56% reporting increased adverse effects.
    N = 83 patients / 46 neurologists surveyed.
    - Patients generally viewed generics as safe
    - 22% unsure if they were receiving a generic product
    - 86% patients receiving generic report no problems after switch
    - Clinicians tended to overestimate patient concerns over switching
  - Crawford et al (Seizure 1996;5:1-5)
    N = 2285 patients surveyed. Of the 1330 responding, 70% reported no problems, 11% reported either increased seizure or adverse effects.
Question: How Applicable is Bioequivalence Testing?

• Area under the plasma concentration time curve (AUC) and maximum concentration ($C_{\text{max}}$) measured

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Questions: Multiple Retrospective Studies Highlighting Generic Risks (or not…)

- Generic switches associated with high switchback rate and higher costs in Canada (Andermann 2007)
- Case series follow up from survey-random blood levels (Berg 2008)
- Generic use associated with higher emergency services use (Zachry 2008)
- No effect of generic use on epilepsy related events (Devine 2010)
- Generic use associated with greater medical utilization and risk of epilepsy-related medical events, compared to brand use (Labiner, 2010)
Generic substitution

Assessing Bioequivalence of Generic Antiepilepsy Drugs

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Is Antiepileptic Drug Generic Substitution Always Safe? Slow Progress Toward Definitive Answers
Bioequivalent Study of Brand versus Generic Equivalents

Analysis of data submitted to FDA for generic drug approval.

From Krause GL et al, Ann Neurol 2011; 70:221-8.
Generic Drugs: Conclusions

- Indirect evidence that product switches with antiepileptic drugs are associated with more problems
- No prospective, adequately designed studies support this
- Three studies are planned: two chronic dosing and one single dose in people with epilepsy taking concomitant AEDs
Nonequivalence can have very serious effects. Decreased serum drug concentrations can cause breakthrough seizures, and increased concentrations can lead to toxicity......The overall cost to society of breakthrough seizures or drug toxicity may outweigh any economic incentive for mandating generic substitution”
Questions: Factors Affecting Bioequivalence

• Water solubility
  – (dissolution rate)

• Drug formulation
  – (e.g. salt form, free acid, release characteristics)

• Formulation components
  – (excipients, binders, fillers, lubricants)

• Lot to lot variability in drug content

• Storage
  – (spoilage due to temp, humidity…..importation issues)

• Multiple manufacturers
Summary

• Substitution of generic AEDs is controversial, and there are widely held views (US and abroad) that this may be undesirable due to the risk of toxicity and/or loss of seizure control.

• Most evidence supporting this is anecdotal, however. Controlled pharmacokinetic studies do not uniformly support this.
Summary

• Data does suggest that some generic products may differ between themselves. Switching between generic products may be problematic.

• Quality control of generic (and Brand) products is essential, both in manufacture and storage. In countries where GMP and quality control cannot be ensured and verified, problems may be more likely.
Conclusions

• Given the potential consequences, increased vigilance (e.g. serum drug monitoring, seizure diary) particularly in higher risk groups: pregnant, history of status epilepticus, seizure free and driving.

• Patients and pharmacies should be discouraged from frequent generic switching.

• Good communication between Physician/Pharmacist/Patient is essential.
- 64% became seizure-free

- Seizure-free rates similar between monotherapy with an older antiepileptic drug (67%) and monotherapy with a newer antiepileptic drug (69%)