MULTIPLE AND SINGLE DOSE STUDIES (EQUIGEN) IN PATIENTS WITH EPILEPSY

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DISCLOSURES

• Consultant: Upsher-Smith, Eisai
GOALS

• Describe the design of the Equigen studies
• Present Equigen study results
• Consider implications of Equigen study results
QUESTIONS

- Are results from bioequivalence studies generalizable to patients with epilepsy taking antiepileptic drugs?
- Can a patient be switched between disparate generic products?
- What is the within-patient variability seen with the brand product and generic products?
LAMOTRIGINE CHOICE

- Reports of problems with substitution in the MedWatch program
- Commonly used newer antiepileptic drug
- Retrospective studies suggested problems with substitution
EQUIGEN STUDIES

- Chronic dose study
  - Patients with epilepsy receiving lamotrigine
  - Switch between 2 disparate generic lamotrigine products
  - Two PK analyses for each generic product
- Single dose study
  - Patients with epilepsy NOT receiving lamotrigine
  - Received 25 mg dose of brand product, generic-low, generic-high products
  - Two PK analyses for each product
DISPARATE PRODUCT SELECTION

• ANDA data from FDA files
• Dissolution and content uniformity data from independent lab testing
• Excipient composition
• Market availability of single lots
CHRONIC DOSE STUDY
CHRONIC DOSE ADHERENCE

• Careful monitoring of adherence
  • Diary
  • Tablet counts
  • Computerized prescription bottle caps

• Rigorous standards for adherence
  • 3 days prior to PK, take doses within 1 hour of scheduled time
  • No missed doses for week prior to PK
EQUIGEN Study Design: Chronic Dose

First Assessments

Second Assessments

Randomization

Inpatient

Inpatient

Inpatient

Inpatient

Follow-up

2-30 d

14d

14d

14d

14d

12-16d

Sequence 1

gLTG-high

gLTG-low

gLTG-high

gLTG-low

Sequence 2

gLTG-low

gLTG-high

gLTG-low

gLTG-high

Baseline

Period 1

Period 2

Period 3

Period 4

*19 blood levels over 12 hours at each inpatient PK visit
CHRONIC DOSE RESULTS

• 33 subjects
• 58% received other antiepileptic drugs
  • 18% on enzyme inducing drugs with known interactions with lamotrigine
  • Enzyme inhibiting drug (i.e., valproate) excluded
• No loss of seizure control
• No unexpected adverse effects
• Side effect measure scores not different between products
### CHRONIC DOSE AUC AND $C_{\text{MAX}}$

<table>
<thead>
<tr>
<th></th>
<th>Generic LTG-high</th>
<th>Generic LTG-low</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First PK (n=33)</td>
<td>Second PK (n=33)</td>
</tr>
<tr>
<td><strong>Dose-normalized $AUC_{(0-120)}$ ($\mu g$-$mL/min$)</strong></td>
<td>2723 (1145)</td>
<td>2727 (1173)</td>
</tr>
<tr>
<td><strong>Dose-normalized $C_{\text{MAX}}$ ($\mu g/mL$)</strong></td>
<td>5.03 (1.8)</td>
<td>5.02 (1.9)</td>
</tr>
<tr>
<td></td>
<td>2710 (1129)</td>
<td>2704 (1200)</td>
</tr>
<tr>
<td></td>
<td>4.96 (1.9)</td>
<td>4.95 (1.9)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or mean (SD; 95% CI). Dose normalized to 100 mg.
CHRONIC DOSE CURVES

The image shows a graph of lamotrigine level over time for different groups and sessions.

- **G1, 1st PK session** (black line with black markers)
- **G1, 2nd PK session** (light green line with light green markers)
- **G2, 1st PK session** (red line with red markers)
- **G2, 2nd PK session** (blue line with blue markers)

The x-axis represents time (hours) ranging from 0 to 12, and the y-axis represents lamotrigine level in mg/L, ranging from 0.03 to 0.05.
• No statistical difference in AUC or $C_{\text{max}}$ when switching between disparate generic products.
• Within-subject variability average <10% (2 subjects >30%).
• No change in clinical response detected.
  • Not powered for statistical comparison.
REFERENCE

SINGLE DOSE STUDY
WHY DO THIS STUDY

- More sensitive to small PK differences
- Question of variability of generic products compared to brand product
EQUIGEN Single Dose Study: 3 Treatments; 6 Periods
SINGLE DOSE RESULTS

• 50 subjects randomized
  • 46 completed all 6 periods
• No outliers in accordance with statistical analysis in replicate studies
  ¹
• No serious adverse events


Unpublished data, manuscript submitted.
# Single Dose Relative Bioavailability Data

<table>
<thead>
<tr>
<th></th>
<th>$C_{max}$ Estimate mean (90% CI)</th>
<th>$AUC_{(0-\infty)}$ Estimate mean (90% CI)</th>
<th>$AUC_{(0-96)}$ Estimate mean (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 vs Brand</td>
<td>102.2% (98.7 to 105.8)</td>
<td>97.8% (94.9 to 100.8)</td>
<td>99% (96.9 to 101.2)</td>
</tr>
<tr>
<td>G2 vs Brand</td>
<td>96% (92.6 to 99.6)</td>
<td>98.5% (95.9 to 101.2)</td>
<td>99.4% (97.6 to 101.2)</td>
</tr>
<tr>
<td>G1 vs G2</td>
<td>106.4% (102.6 to 110.4)</td>
<td>99.3% (96.6 to 102)</td>
<td>99.6% (97.3 to 101.9)</td>
</tr>
</tbody>
</table>
SINGLE DOSE CURVES

Unpublished data, manuscript submitted.
## SINGLE DOSE WITHIN-SUBJECT VARIABILITY

<table>
<thead>
<tr>
<th></th>
<th>Brand (N=49)</th>
<th>gLTG-high (N=49)</th>
<th>gLTG-low (N=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC(_{(0-96)})</strong> (mg·mL/min)</td>
<td>7.0% (5.8 to 8.3)</td>
<td>8.7% (7.3 to 10.3)</td>
<td>7.9% (6.7 to 9.3)</td>
</tr>
<tr>
<td><strong>AUC(_{(0-∞)})</strong> (mg·mL/min)</td>
<td>12.1% (10.3 to 14.2)</td>
<td>12.9% (10.8 to 15.3)</td>
<td>9.9% (8.3 to 11.9)</td>
</tr>
<tr>
<td><strong>C(_{max})</strong> (mg/mL)</td>
<td>14.6% (12.2 to 17.4)</td>
<td>14.7% (12.4 to 17.6)</td>
<td>16.0% (13.5 to 18.9)</td>
</tr>
</tbody>
</table>

Data are presented as percent coefficient of variation (95% CI). Unpublished data, manuscript submitted.
• No difference in bioavailability
• Within-subject variability similar for brand and generic products
IMPLICATIONS FOR PRACTICE

- Generic products meet bioequivalence standards in patients with epilepsy, therefore can be safely interchanged for brand product.

- Disparate generic products meet bioequivalence standards in patients with epilepsy, therefore switches between generic products can be practiced safely.
  - Resulted in change of American Epilepsy Society position statement on generic substitution.

- Same amount of variability is seen with brand product compared to generic products.
FUTURE CONSIDERATIONS: VARIABILITY

• Lower the bioavailability, higher the inter-subject variability.\(^1\) Is the same true for within-subject variability?

• What within-patient variability is seen in clinical practice, given the following observations in ideal conditions?
  • BEEP: 6-13%
  • Equigen Chronic: <10%, 2 subjects >30% (maximum of 58% for AUC and 45% for \(C_{\text{max}}\))
  • Equigen Single: 7-16%

• How does the issue of within-patient variability impact patient response?
  • Retrospective studies?
  • Non-bioequivalence factors?

CONCLUSION

• No bioequivalence differences
  • Disparate generic product switches
  • Brand to generic switches
• FDA bioequivalence standards are applicable to patients with epilepsy
• Variability needs to be further investigated
STUDY TEAM

- Michael Privitera MD: University of Cincinnati
- Michel Berg MD: University of Rochester
- Timothy Welty PharmD: Drake University
- Barry Gidal PharmD: University of Wisconsin
- Ron Krebill MPH: University of Kansas Medical Center
- Francisco Diaz PhD: University of Kansas Medical Center
- Barbara Dworetzky MD: Brigham and Women's Hospital Harvard Medical School
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- John Pollard MD: University of Pennsylvania
- LeBron Paige MD: University of Iowa
- Edmund Elder PhD: University of Wisconsin
- Wenlei Jiang PhD: Food and Drug Administration
- Xiaohui Jiang PhD: Food and Drug Administration
- Multiple study site coordinators