Chapter 21 1

Bioavailability Studies

Objectives

• Define terms related to bioavailability studies
• Understand examples of past problems
• Evaluate components of a bioavailability study
• Evaluate results from bioavailability studies

Reasons for Bioavailability Studies

• Comparison between products from different manufacturers
  – Innovator versus Generic
  – Bioequivalence determination (same ka and F ?)
• Comparison between different types of products
  – Slow release versus fast release
  – Formulation development (same F ?)
Definitions

- Bioavailability
  - Rate and Extent of Absorption
  - Therapeutic component delivered to blood
- Bioequivalent drug products
  - Pharmaceutical equivalence or alternative with rate and extent not significantly different
  - Rate change may be intentional

Definitions (contd)

- Bioequivalence requirement
  - In vitro / in vivo requirement for marketing
- Brand Name (Trade name)
- Chemical Name
- Drug product (finished dosage form)
- Generic name (common name, approved name)

Definitions (contd)²

- Pharmaceutical Alternative
  - Same therapeutic compound (or precursor)
  - Dosage form, salt, ester may vary
- Pharmaceutical Equivalent
  - Same active drug ingredient
  - Maybe different inactive excipients
- Both exhibit same in vitro / in vivo results
  - In vitro / in vivo correlation
Past Bioavailability Problems

• Examples pre-1976
  – More attention given to identifying problems
  – More extensive requirements
  – Examples
    • Chlorpropamide
    • Digoxin
    • Phenytoin
      – Acetazolamide, Aminosalicylate, Ampicillin, Aspirin,
        Ascorbic Acid, Chloramphenicol, Chlorothiazide, Diazepam,
        Furosemide, Iron, Levodopa, + 10


Chlorpropamide

One (of three) products relative $F = 0.5$

Digoxin

• 15 cases of toxicity between Oct/Dec 1975 in Israel
• Local manufacturer altered formulation
  – Improved dissolution
  – Two fold increase in absorption based on urine data
Phenytoin

- Phenytoin intoxication in 1968 and 1969 in Australia
  - Lactose substituted for calcium sulfate
  - Higher bioavailability with lactose

More Recent FDA Recalls

- FDA Web Site
- CDER Web Site
- FDA Enforcement Reports
  - Other Dissolution Problems
    - [http://www.cpb.ouhsc.edu/fda/enf/enf00375.html](http://www.cpb.ouhsc.edu/fda/enf/enf00375.html)
    - [http://www.cpb.ouhsc.edu/fda/enf/enf00367.html](http://www.cpb.ouhsc.edu/fda/enf/enf00367.html)
    - [http://www.cpb.ouhsc.edu/fda/enf/enf00366.html](http://www.cpb.ouhsc.edu/fda/enf/enf00366.html)

Bioavailability - Bioequivalence Studies

- Bioavailability Study
  - Attempt to determine absolute bioavailability
  - Compare different routes or dosage forms
- Bioequivalence Study
  - Determine if products are bioequivalent
  - Similar/same dosage form
  - Maybe required before marketing
Bioequivalence Study

- Dosage form compared with another in human bioavailability study
- Doses generally given by the same route
- Relative bioavailability determined
- If bioequivalent - no significant difference

Reasons for Bioequivalence Requirement

- Clinical results indicate varied results with different products
- Different products not bioequivalent in previous studies
- Narrow therapeutic range
- Low solubility and/or large dose
- Absorption previously shown to be somewhat less than 100%

Bioavailability Study Characteristics

- Drug
- Drug product
- Subjects
  - Health, age, weight, enzyme status, number
- Assay
- Design
- Data analysis
Drug

• Must be the same drug
  – Different kel and V make comparison impossible (with different drugs)
• Pro-drug may be an exception
  – If primary purpose is delivery of the primary drug compound
  – Must be sure that the primary drug is formed and that the pro-drug doesn’t remain in significant quantities

Drug Product

• Comparison between similar products
• Bioequivalence studies are almost always between similar dosage forms: Product A versus Product B
• Bioavailability studies may be between different dosage form types or ROA’s

Subjects

• Health
  – Healthy - less variability
• Age
  – 18 - 35 yr to reduce variability
  – Children - elderly
• Weight
  – Normal proportions - similar distribution V (Insurance tables)
Subjects ...

- Enzyme status
  - Smoking versus non-smoking
  - Diet (charcoal - barbecue), prior medication
- Number
  - Large enough to see clinically significant differences (e.g. 20%)  
  - Was commonly 10 to 20 but this may be low for high variability drugs - significant metabolism - power analysis

Methods

- Assay
  - Same assay method for all phases of the study
  - Different assays may react differently to metabolites or interfering species
  - Methods should be sensitive and specific
- Design
  - Usually complete cross-over design

Study Design

Complete cross-over: Each subject receives each product

<table>
<thead>
<tr>
<th>Two Products</th>
<th>Week 1</th>
<th>Week 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Group 2</td>
<td>B</td>
<td>A</td>
</tr>
</tbody>
</table>
Another Design

Three Products

<table>
<thead>
<tr>
<th></th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>Group 2</td>
<td>B</td>
<td>C</td>
<td>A</td>
</tr>
<tr>
<td>Group 3</td>
<td>C</td>
<td>A</td>
<td>B</td>
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<td>Group 4</td>
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<td>Group 5</td>
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</tr>
<tr>
<td>Group 6</td>
<td>B</td>
<td>A</td>
<td>C</td>
</tr>
</tbody>
</table>

Larger Designs

- May not be complete cross-over
  - Incomplete design
  - Each subject may receive 1/2 or 1/3 of the dosage forms tested

Statistical Analysis

- Determine parameters
  - $C_p$ versus time - data points
  - $C_{p_{max}}$, $t_{max}$, AUC
  - $ka$ and $F$ values
- Statistical analysis
  - t-test or ANOVA
- Confidence level - 5%
Sources of Variation

- Subject
- Week
- Treatment

Two Product Study

\[ \text{Concentration (mg/L)} \]
\[ \text{Time (hr)} \]

\[ \begin{array}{cccc}
\text{Source of Variation} & \text{d.f.} & \text{SS} & \text{MS} & \text{F} & \text{Significance Level} \\
\hline
\text{Total} & 35 & 44.6 & - & - & - \\
\text{Subject} & 11 & 28.3 & 2.58 & 10.1 & p < 0.001 \\
\text{Week} & 2 & 0.14 & 0.068 & 0.27 & \text{n.s.} \\
\text{Treatment} & 2 & 11.0 & 5.552 & 21.8 & p < 0.001 \\
\text{Residual} & 20 & 5.09 & 0.255 & - & - \\
\end{array} \]
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