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

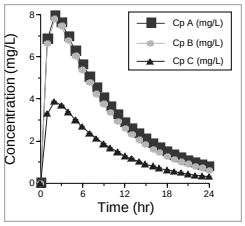
Past Bioavailability Problems

- 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

Ref: Gibaldi, M. 1984 Biopharmaceutics and Clinical Pharmacokinetics, 3rd edition, Lea & Febiger, Philadelphia, PA pp 143-152

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/enf00367.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

Two Products

	Week 1	Week 2
Group 1	A	B
Group 2	B	A

Another Design

Three Products

	Week 1	Week 2	Week 3
Group 1	A	B	C
Group 2	B	C	A
Group 3	C	A	B
Group 4	A	C	B
Group 5	C	B	A
Group 6	B	A	C

Larger Designs

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

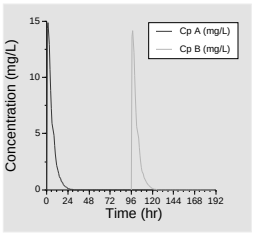
Statistical Analysis

- Determine parameters
  - Cp versus time - data points
  - Cp_{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



ANOVA

Analysis of Variance

Source of Variation	d.f.	SS	MS	F	Significance Level
Total	35	44.6	-	-	-
Subject	11	28.3	2.58	10.1	$p < 0.001$
Week	2	0.14	0.068	0.27	n.s.
Treatment	2	11.0	5.552	21.8	$p < 0.001$
Residual	20	5.09	0.255	-	-

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