Testing Equivalence of Orally Inhaled Products: Study Designs, Subject Selection, Clinical Study Model

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Inhaled Products Commonly Used For Treatment Of Asthma

- **Short-acting beta agonists** (SABAs; terbutaline, albuterol/salbutamol)
  - First US generics approved in mid-90s
  - Precedent for other drug classes

- **Long-acting beta agonist** (LABAs; salmeterol, formoterol)

- **Corticosteroid** (ICS; beclomethasone, triamcinolone, flunisolide, budesonide, fluticasone, ciclesonide)

- **Combination products**
  - Salmeterol/fluticasone (Advair)
  - Formoterol/budesonide (Symbicort)
THE PROBLEM

Why Pharmacodynamic Studies Are Needed.

ORAL ADMINISTRATION FOR SYSTEMIC ACTION

- Rate and extent of absorption into the systemic circulation
- Useful for assessment of BIOEQUIVALENCE

PO Admin. → GI Tract

1st Pass Metabolism → Systemic Circulation

Elimination → Site(s) of Action

Site(s) of AEs
TOPICAL DRUG DELIVERY
FOR ACTION IN THE LUNGS

Assessment of drug reaching site of action in the Lung needed
PD response reflects BIOPHASE levels

Aerosol Deliver Device

Dose to Patient

Dose to Lung

Site[s] of Action (Biophase)

Other Pulmonary Sites

Dose to Oropharynx

GI Tract

Systemic Circulation

1st Pass Metabolism

(PK reflects dose to BIOPHASE?)

Study Design vs. Level of Certainty Test & Ref Delivers Equivalent Amount of Drug to Biophase

Clinical Trial
Parallel Design; One Dose Test and Ref

Dose Response
Parallel Design; Two Doses Test and Ref
“Dose Axis” Analysis

Dose Response
Cross-Over; One Dose Test and Ref
“Dose Axis” Analysis

Relative Potency
(Bioassay)
Cross-Over; One Dose Test and Ref
“Response Axis” Analysis

Level of Certainty?
LOW
HIGH
STUDY DESIGN:

1) Active Control Clinical Trial:
   - Single dose level of both test and reference.
   - Clinically relevant outcome reflecting efficacy.
   - Compare responses (to equal doses)

LOW LEVEL OF CERTAINTY
OF EQUIVALENT DRUG DELIVERY

Efficacy of CFC & HFA
BecloMethasone MDI's

Pulmonary deposition of HFA ~2X CFC

Mean and 90% C.I.

Milanowski et al, Respir Med 1999
STUDY DESIGN:

2) Dose Response to Demonstrate Sensitivity:
   - Two dose levels of both test and reference.
   - Relevant outcome reflecting efficacy.
   - Parallel Design
   - Sensitivity $\Rightarrow$ Significant Difference Between High and Low Dose Levels
   - Compare magnitude of response.

   HIGHER LEVEL OF CERTAINTY OF EQUIVALENT DRUG DELIVERY
**Potency of HFA-Beclomethasone (QVAR, 3M)**
**Relative of CFC Beclomethasone (Beclovent, GSK)**

<table>
<thead>
<tr>
<th>Dose (mcg)</th>
<th>Mean Change in FEV1</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>14</td>
</tr>
<tr>
<td>200</td>
<td>16</td>
</tr>
<tr>
<td>400</td>
<td>18</td>
</tr>
<tr>
<td>800</td>
<td>20</td>
</tr>
</tbody>
</table>

1 mcg HFA = 2.6 CFC
(95% C.I. 1.1 – 11.6)

**Busse et al, 1998**

**STUDY DESIGN:**

3) Dose Response to Demonstrate Sensitivity:
- Two dose levels of both test and reference.
- Relevant outcome reflecting efficacy.
- Cross-Over Design
- Sensitivity => Significant Difference Between High and Low Dose Levels
- Compare responses (to equal doses)

Greater Statistical Power
STUDY DESIGN:

4) BIOASSAY: Estimation of Relative Potency:
   - Two dose levels of both test and reference.
   - Relevant outcome reflecting efficacy.
   - Cross-Over Design
   - Sensitivity => Significant Difference Between High and Low Dose Levels
   - Compare DOSE needed (for RESPONSE)

HIGHEST LEVEL OF CERTAINTY

OVERALL STUDY DESIGN:
2 by 2 Bioassay

VALIDITY TESTS
- Highly Significant DRC
- Parallelism Contrast
- Preparations Contrast
Potency of Norton MDI Relative to Ventolin

Bioequivalence Criteria: 0.67 – 1.50

1 puff Norton = 0.95 puff Ventolin
(90% C.I. 0.69 - 1.40)

DOSE OF ALBUTEROL (Actuations)

Subject Selection & Clinical Study Model:

To Maximize The Steepness of the Dose-Response:

- Subjects who require higher doses to achieve response
- Choose outcome measure with sufficiently steep dose-response
- Choose best clinical circumstance under which to SEE this dose-response
FAQ

If it’s so difficult to show a dose-response relationship, doesn’t that mean that dose doesn’t really matter?

Need for Steep Dose-Response
Mean FEV1 Response to Albuterol: Daytime versus Nocturnal Awakening

Median Dose to Achieve >80% Personal Best FEV1
SUMMARY

- Demonstration of “Sensitivity”
  - \( n \Rightarrow \) Significant Dose-Response
  - \( n \) Essential
- Bioassay Study with Estimation of Relative Potency Yields the Highest Level of Certainty of Bioequivalence.

STRATEGY DEPENDS ON DRUG CLASS

- SABA
- LABA
- ICS
BIOEQUIVALENCE OF SABAs

Inhaled Beta Agonists: A Relatively Mature Field

To Ensure a Sufficiently Steep Dose-Response is Present:

• Protection against bronchoprovocation (methacholine, histamine)

• Bronchodilation under CAREFULLY controlled clinical circumstances
BIOEQUIVALENCE OF LABAs

- With minor modifications, methods for BE of inhaled albuterol should apply
LABA BE Studies Must Account For Differences Between LABAs & Albuterol

<table>
<thead>
<tr>
<th></th>
<th>ALBUTEROL</th>
<th>LABA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of Effect</td>
<td>15 – 30 Min minutes</td>
<td>1 – 4 Hours</td>
</tr>
<tr>
<td>Duration of Action</td>
<td>2 – 6 Hours</td>
<td>&gt; 12 Hours</td>
</tr>
<tr>
<td>Tolerance with Chronic Admin.</td>
<td>Minimal</td>
<td>Profound (bronchprotection)</td>
</tr>
</tbody>
</table>

BIOEQUIVALENCE OF ICS

Less Mature Field
This concept has not been successfully applied to inhaled corticosteroids

“… it is difficult to draw firm conclusions about the comparative efficacy of different inhaled corticosteroids.”

“…partially explained by differences between the designs of studies, the flat dose-response relationship for inhaled corticosteroids, the differences between inhalers, and the lack of control over important confounding factors in many studies.”

“Additional well-designed comparisons, perhaps examining different outcome parameters, are required before any definite conclusions can be made.”

Barnes et al. AM J RESPIR CRIT CARE MED 157;S11, 1998

FAQ

If it’s so difficult to show a dose-response relationship, doesn’t that mean that dose doesn’t really matter?
An Asthma Clinician’s Paradox

- Clinical studies with hundreds of patients show ICS dose-responses that are flat to non-existent.

- Asthma clinicians think they see ICS dose-response every day in individual patients.

Which is illusion, which is reality?

Typical ICS Study Design

Parallel Treatment Groups
1-12 Months of Treatment

Baseline
PFTs, Sx, etc.

ICS

Improvement in PFTs, Sx, PEFR

(a) high variability (S)
(b) shallow sloped DRC (B)
(c) carry-over (prevents cross-over)
Statistical Power Associated with a Bioassay Study

Related to:

- Variability of responses (S)
- Steepness of dose-response slope (B)
- S + B do not function independently, but in concert as the ratio of S/B
- The smaller S/B, the more powerful the study

Relationship Between S/B and Computed Sample Size
Asthma Stability Following Prednisone “Burst”

1. 100 and 800 mcg/d HFA-BDP
2. Cross-over

Prednisone “burst” → Baseline PFTs, Sx, etc. → ICS → Deterioration in PFTs, Sx, etc. ??

3. Multiple variables examined (58)
4. Estimate S/B for each
5. The lower S/B, the better

Relationship Between S/B and Computed Sample Size
Relationship Between Crossover and Parallel Study Designs

Asthma Stability Following High-Dose Corticosteroid “Burst”

**RUN-IN PERIOD**

- 4 weeks LOW-DOSE ICS
  (CFC-BDP 100 mcg/d)
- 2 weeks high-dose ICS
  (Budesonide DPI 1600 mcg/d)

**ENTRANCE CRITERIA:**

>7% predicted increase between HIGH and LOW-DOSE ICS
QVAR versus Flovent Diskus

- **HFA-BDP**
- **FP-Diskus**

**p-value**
- Regress.  0.01
- Parallel 0.16

1 mcg QVAR = 0.84 mcg FP  
(90% CI: 0.35 – 1.74)

Asthma Stability Following High-Dose Corticosteroid “Burst”

**RUN-IN PERIOD**

Approx. 20% of subjects met this entrance criteria
Lessons Learned From ICS Experience To Date

- “Traditional” model insensitive to dose.
- Dose DOES matter to at least some patients.
- Therefore, need a model that CAN detect differences in delivered dose.

The solution?
- Control carry-over
- Do cross-over study
- Sensitive outcome measure (at least one available)
- Select subjects most likely to show a dose-response

Number of subjects will depend on
- Design, outcome, subjects selected
- Width for BE interval (e.g. 67-150% vs 80-125%)
The Solution?
Other Outcomes?

- Exhaled nitric oxide
- Adenosine challenge
- Sputum Eosinophilia

Lessons Learned
From ICS Experience To Date

**STUDY MODEL MUST:**

- Use a clinically relevant outcome (reflect delivery to site of clinical action)
- Sufficiently steep dose-response => Sufficient statistical power.
APPLYING THESE METHODS TO COMBINATION DPIs

FACTORS ADDING TO COMPLEXITY OF EVALUATING COMBINATION DPIs

- Establishing PHARMACEUTICAL EQUIVALENCE is likely to be more difficult than:
  - Single agent inhalers
  - DPIs vs. MDIs

- Need to assess SYSTEMIC EXPOSURE for both components (r.e. potential for adverse effects)
  - PK evaluations

- Assessment of IN VIVO BE for LABA and CS
  - Different outcomes and study designs
  - => 2 separate BE studies
THANK YOU FOR YOUR ATTENTION!!

??? QUESTIONS ???