Strengths and Weaknesses of Population PK Analyses for the Assessment of Bioequivalence of Complex and Locally Acting Products

Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development and Review Workshop
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Murray P. Ducharme, PharmD, FCCP, FCP
President and CEO, Learn and Confirm Inc.
And, Professeur Associé, Faculté de Pharmacie, University of Montreal, Montreal, Canada
And, Visiting Professor, Faculty of Pharmacy, Rhodes University, South Africa
• Background
• Estimating BE: Available methods and their limitations
• Utility and weaknesses of Population PK for BE
  • BE studies conducted in patients
  • Complex PK
    • Endogenous products
    • Iron products
  • « Non identical » APIs
    • Biosimilars
    • Iron products
  • Locally acting products
    • Topical products (Acyclovir cream)
    • Inhalers
• Conclusions
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• Conclusions

Only 2 examples presented today due to time constraints
How is “Bioequivalence” or “Therapeutic Interchangeability” assessed for US FDA / EMA / HC for most products?

**Pharmaceutical Equivalence**
- Identical amounts of identical medical ingredients, comparable dosage forms

**Therapeutic Equivalence / Bioequivalence**
- Rate and Extent at which the active ingredient or therapeutic ingredient is absorbed from a drug product and becomes available at the site of drug action (21CFR 505(j)(8))
  
  (By typical order of preference: PK studies, PD studies, Clinical trials, in vitro studies)

- Same route of administration
- Same conditions of use

Problem with complicated drugs such as iron products, sevelamer, Biosimilars,…
Population PK in BE

PK Methods

Noncompartmental PK
- Observed Cmax & tmax
- \( AUC_{D-t} \) via trapezoidal rule
  \( \rightarrow \) CL/F

Population PK
- PO Dose
- \( ka \) → Tlag
- \( CLd/F \) → \( Vc/F \)
- \( CL/F \) → Residual variability

PB PK
- Venous blood
- Arterial blood
- \( Q_{PB} \) → Brain
- \( Q_{LU} \) → Lung
- \( Q_{LI} \) → Heart
- \( Q_{LUS} \) → Muscle
- \( Q_{LD} \) → Kidney
- \( Q_{UR} \) → Urine
- \( Q_{LV} \) → Liver
- \( Q_{CI} \) → GI
- \( Q_{LK} \) → Bone
- \( Q_{LA} \) → Adipose
- \( Q_{SK} \) → Skin
“Bottom-Up” approach
- When no data is available
- Complicated model ("not identifiable") with most or all parameters fixed or assumed

“Top-Down” approach
- Parameters are fitted to the data, so data is needed
- Model needs to be "identifiable"
Noncompartmental approach or “Observed” PK approach in BE

• Simplest and Best approach (“reference approach”)
  • Single dose design
  • Healthy volunteers
  • > 12 concentrations per profile
  • LLOQ < 5% of Cmax

Limitations
• Endogenous substances with unstable baseline, feedback or high baseline values versus Cmax
• Substances exhibiting non linearity
• Products with API that cannot be fully characterized as being “Identical”
• Complicated Dosing in patients (nor SD nor SS, insufficient washout, …)
Population PK approach in BE

- Can help distinguish between formulation and API similarities/differences
- Can be a mechanistic model that takes into account an unstable or large baseline effect
- Can take into consideration nonlinearity whether in elimination (not formulation specific) or release (formulation specific)
- Does not need SD or SS dosing

Limitations

- Complex analysis that needs to be redone for verification by regulators
- Still an “art” type analysis where there is no cookbook recipe, and where different models and assumptions will lead to different results
- Is more (too much?) discriminative than NCPT/Observed PK approach, as “rate” differences are compared (Ka) instead of mixture of rate & Extent (Cmax)
Population PK approach in PK Equivalence ("BE")

- For Biosimilars and other Products when distinguishing between “API” and “Formulation” differences is needed?
- For Products with unstable or large baseline effect?
- For nonlinear products?
- For Topical products?

Noncompartmental approach or “Observed” PK approach in PK Equivalence ("BE")

- For the rest, but always useful as a comparison method, as “fitted” results should be in agreement with “observed” ones
Iron is and has been available commercially in many different forms:
- Iron Dextran
- Iron Gluconate
- Iron Sucrose

Iron is atypical in terms of its PK because:
- Iron is NOT eliminated per se once it is in the systemic circulation.
- Iron’s distribution is non-linear (from the RES to the Transferrin protein)
- Once injected s/c, IM or IV, the “baseline” levels in terms of TBI and ferritin will change. In addition baseline changes also because of meals.

These three violates the assumptions needed for
The noncompartmental approach to be robust
Published PK model of Iron Gluconate


• “Old” OGD recommendations (prior to 2015) for Iron gluconate, iron sucrose and others:
  – Test/Reference Ratio and 90% CI for Cmax and AUC
    • Baseline adjusted Total serum iron
    • Baseline adjusted Transferrin-bound iron

But baseline changes constantly after dosing because iron is not eliminated except for the blood loss from Sampling plus the meals affect the baseline.

Noncompartment approach (baseline adjusted Cmax and AUC for Total serum iron and TBI)

- Is highly variable because baseline is not stable
- Is not directly reflective of what is administered (i.e., Iron bound to either sucrose, gluconate or dextran)

With ABE necessitates an artificially large number of subjects (>100 in a 2 way crossover)

With SBE, then passing BE may be too easy as the baseline is not stable and this will artificially make it easier to pass

• Using the proper PK model (as presented earlier and including the blood loss coming from the sampling), differences in Relative Bioavailability (Frel) can be demonstrated with a more reasonable number of subjects if the formulations are truly bioequivalent (e.g., <50 in a 2 way crossover with ABE)

• Assessment is also performed on iron administered (either bound to gluconate, sucrose or dextran) which is what is directly administered (eg, at baseline, the iron administered is ~ equal to Total serum iron – TBI)

Population PK in BE
When it could be used: Iron Products

Population PK in BE

When it could be used: Iron Products
### Population PK in BE

*When it could be used: Iron Products*

<table>
<thead>
<tr>
<th>Study</th>
<th>Analysis</th>
<th>Analyte</th>
<th>Cmax</th>
<th>AUC</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1 (n=29)</td>
<td>CPT</td>
<td>Iron gluc.</td>
<td>89.9 (86 – 94)</td>
<td>89.7 (86 – 94)</td>
<td>&gt;80%</td>
</tr>
<tr>
<td></td>
<td>NCPT</td>
<td>TI</td>
<td>104.6 (86 – 127)</td>
<td>97.1 (74 – 127)</td>
<td>&lt;40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TBI</td>
<td>95.9 (83 – 110)</td>
<td>119.7 (21 – 699)</td>
<td></td>
</tr>
<tr>
<td>#2 (n=240)</td>
<td>NCPT</td>
<td>TI</td>
<td>100.4 (97 – 105)</td>
<td>99.7 (94 – 106)</td>
<td>&gt;80%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TBI</td>
<td>86.8 (83 – 91)</td>
<td>92.4 (86 – 100)</td>
<td></td>
</tr>
</tbody>
</table>

Some Topicals contain APIs that are “locally’ acting in the skin and/or dermal regions and that are not intended for systemic action.

Preliminary data from a collaborative effort with Professor Isadore Kanfer of South Africa, an internationally recognized expert and research leader on Bioequivalence of Topical products.

Professor Kanfer has conducted a Tape Stripping Bioequivalence study on Reference (Zovirax®), Bioequivalent and Non-Bioequivalent cream formulations of Acyclovir.

My PhD student, Deniz Ozdin, presented preliminary results of a BE Population PK analysis of this data at last year’s AAPS annual meeting.

Tape Stripping – a dermatopharmacokinetic approach


- Initial TS methodology outlining the bioavailability/bioequivalence protocol for topical formulations intended for local and/or regional activity, published in a draft guideline

- subject to criticism which resulted in its withdrawal, mainly due to a number of limitations, in particular the sources of variability and control

Population PK in BE

When it could be used: Topical Products

- Dermatopharmacokinetic approach
- Determines the amount of drug permeated into the **stratum corneum**
- Utilizes adhesive tape strips Transpore, Micropore, Scotch, D-Squame tapes
- Relatively non-invasive
- Removes layers of **stratum corneum**

Population PK in BE

When it could be used: Topical Products

A Population PK model was developed to fit and characterize the amounts of Acyclovir that was absorbed in the skin using the reference Zovirax® 5% cream, in a Tape Stripping study.

The model was then used to fit the data generated by tape stripping for two different “generic” formulations of acyclovir cream: a BE 5% formulation (Adco®) and a non-BE 1.5% formulation (diluted).
Population PK in BE
When it could be used: Topical Products

- Tape stripping study conducted in Healthy volunteers
- Crossover design, 2 studies:
  - Received Zovirax cream (n=20), a BE (n=20)
  - Received Zovirax cream (n=10), and a non-BE formulation (n=10)
- Cream applied at time 0
- Cream removed after 8 Minutes (established from the ED50)
- Tape stripping conducted on 14 different layers
- Amount of acyclovir present on the different layers measured by HPLC
Population PK in BE
When it could be used: Topical Products
Acyclovir amount (mcg) in SC layers
### Estimated PK parameters of acyclovir RLD, BE and BIE formulations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Geometric Mean (CV%)</th>
<th>RLD</th>
<th>BE</th>
<th>BIE</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_{SKIN}$ (min$^{-1}$)</td>
<td>0.0016 (16.4%)</td>
<td>0.0016 (1.23%)</td>
<td>0.00044 (16.4%)</td>
<td></td>
</tr>
<tr>
<td>$F_{SKIN}$ (absolute)</td>
<td>0.87 (16%)</td>
<td>0.85 (75%)</td>
<td>0.57 (17.2%)</td>
<td></td>
</tr>
</tbody>
</table>

### Predicted results of relative bioequivalence between different acyclovir topical formulations versus the RLD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BE % Ratio of Geometric means</th>
<th>90% CI</th>
<th>BIE % Ratio of Geometric means</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$F_{SKIN}$</td>
<td>94%</td>
<td>89%-99%</td>
<td>70%</td>
<td>65%-75%</td>
</tr>
<tr>
<td>$K_{SKIN}$ (min$^{-1}$)</td>
<td>101%</td>
<td>95%-107%</td>
<td>38%</td>
<td>35%-41%</td>
</tr>
</tbody>
</table>
Thank you!

Murray.Ducharme@learnandconfirm.ca