Is there a Best Recipe for Food Effect Studies?

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Current regulatory requirements (EU, HC, USA)
“Conventional” versus “Controversial” hypotheses/Assumptions
Effect of Meals on the PK of drugs
  • “Physical” effects vs. those affecting transport and metabolism
Influx and Efflux gut transporters
  • Effect of Ethnicity on gut transport and metabolism of drugs
Conclusion
**Food effect studies**

Current Fed BE Regulatory Requirements

<table>
<thead>
<tr>
<th></th>
<th>US FDA</th>
<th>HC</th>
<th>EMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR</td>
<td>Fed BE if food is specified in the label</td>
<td>No fed BE</td>
<td>No fed BE (except for microemulsions of solid dispersions)</td>
</tr>
<tr>
<td></td>
<td>(Upcoming: all drug products?)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR</td>
<td>Fed BE</td>
<td>Fed BE</td>
<td>Fed BE</td>
</tr>
<tr>
<td>Other</td>
<td>CDD</td>
<td>CDD</td>
<td>CDD</td>
</tr>
<tr>
<td></td>
<td>Non linear</td>
<td>Non linear</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Report C (highly toxic, NTR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meal</td>
<td>High fat, protein, caloric meal</td>
<td>High fat, protein, caloric meal</td>
<td>According to SmPC</td>
</tr>
<tr>
<td>Subjects</td>
<td>HV</td>
<td>HV</td>
<td>HV</td>
</tr>
<tr>
<td>Fasting</td>
<td>Min. 10 hours</td>
<td>Min. 10 hours</td>
<td>Min. 8 hours</td>
</tr>
<tr>
<td>Volume fluid to administer</td>
<td>240 ml</td>
<td>At least 150ml water room temperature</td>
<td>At least 150ml</td>
</tr>
</tbody>
</table>

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**Food effect studies**

Introduction

“Conventional” Hypotheses/Assumptions behind Food studies:

- The Gut Wall mucosa acts more like a “physical barrier”
- The effect of food/Meals is a “physical” one
- Once in solution and “absorbed”, then it does not matter what happens after (“metabolism” differences) as drug product is not coming back:

Crossover studies in any population of HV is fine, as even if there was a difference genetically in metabolism/transport, all subjects would act as their own control and BE ratio (Test/Ref) would be accurate

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Food effect studies
Effect of Meals on the PK of Drugs
Food effect studies

Introduction

Proposed “controversial” Hypotheses/Assumptions:
• Knowing that the gut wall mucosa is a major site of drug metabolism and transport
• Knowing that Food/Meals affect drug metabolism and transport activity in the gut wall

• Results of BE studies could be different between different ethnic groups because of differences in transporters expression
  Even if a crossover design is followed: Never been Proven or Disproven

Food effect studies

Effect of Meals on the PK of Drugs

• Slowed Gastric emptying
  • Decrease Cmax, delay Tmax, and no change in AUC
  • Prolonged residence time accelerate hydrolysis of acid-labile drugs (e.g., didanosine)
  • Increased solubility of poorly soluble drugs (nitrofurantoin)
• Binding to food components
  • Multivalent cations such as aluminum chelate with ciprofloxacin
• Increase blood flow (Gut and Liver)
  • Increase AUC for Propranolol
  • Increase both active transport and passive absorption
Food effect studies
Effect of Meals on the PK of Drugs

<table>
<thead>
<tr>
<th>High Solubility</th>
<th>Low Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>High permeability</td>
<td>Acetaminophen</td>
</tr>
<tr>
<td>Delayed Gastric emptying</td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>Decrease Cmax (bases), Increase Cmax (acids), increase Lipophilic drugs</td>
</tr>
<tr>
<td>Or Decr. Cmax with same AUC</td>
<td></td>
</tr>
<tr>
<td>Low permeability</td>
<td>Atenolol, ranitidine, pravastatin</td>
</tr>
<tr>
<td>No effect /Decrease</td>
<td></td>
</tr>
</tbody>
</table>


Food effect studies
Effect of Meals on the PK of Drugs

- Carbohydrates: Increase water absorption in intestine
- Proteins:
  - Increase pancreatic secretion and increase intestinal volume
  - High protein meal increases the bioavailability of highly extracted drugs such as propranolol (could be due to increase GI blood flow and increase transport)
  - High protein diet increased Propranolol, theophylline and Antipyrine clearances
- Fat and increased bile acid release
- Increase absorption of lipophilic drugs by enhancing their solubility (Isotretinoin, CsA, Atovaquone)
- Increase Clearance of drugs (CsA IV administered)


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24/01/2012
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Effect of Meals on the PK of Drugs

• Saquinavir
  • F increase 5-10x with fatty meal
  • F increases 5x in Pgp knockout mice

• Indinavir
  • Substrate for CYP3A and Pgp
  • 60% decrease in F with high caloric meal
  • F increases 2x in Pgp knockout mice

• Potential to Induce or Inhibit Gut wall CYP metabolism
• Potential to Induce or inhibit Mucosal Efflux and Influx transport

We know already that:
• Charcoal and smoked food: Induce CYP1A1 (gut)
• Cruciferous vegetables: Induce CYPs
• Fruit juices
  • GJ Inhibit CYP3A, OATP1A2 & ABCB1 (30% increase in CsA AUC and Cmax)
  • OJ and AJ Inhibit OATP1A2 (30-40% decrease Fexofenadine Cmax and AUC)

Could it be that?
• High Fat meals decrease P-gp activity? (Saquinavir, CsA)
• High Carbohydrate meals increase P-gp/CYP3A activity? (Indinavir)
• High Protein meals decrease P-gp? (Propranolol)
• What about other nutrients?

**Food effect studies**

Effect of Meals on the PK of Drugs

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### Examples of Influx Gut Transporters

<table>
<thead>
<tr>
<th>Influx transporter genes</th>
<th>Protein names</th>
<th>Substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLC15A1</td>
<td>PEPT1</td>
<td>(Oligopeptides) Cephalosporins, penicillins, ACE inhibitors, valacyclovir</td>
</tr>
<tr>
<td>SLC15A4</td>
<td>PHT1</td>
<td>(Oligopeptides), valacyclovir</td>
</tr>
<tr>
<td>SLC15A3</td>
<td>PHT2</td>
<td>(Oligopeptide)</td>
</tr>
<tr>
<td>SLC16A1</td>
<td>MCT1</td>
<td>(Monocarboxylate), lactic acid, pyruvate, penicillins, NSAIDs, valproic acid, atorvastatin</td>
</tr>
<tr>
<td>SLC22A1</td>
<td>OCT1</td>
<td>(Organic cations) Metformin, fexofenadine, cimetidine, prazosin</td>
</tr>
<tr>
<td>SLC22A3</td>
<td>OCT3</td>
<td>(Organic cations)</td>
</tr>
<tr>
<td>SLC01A2</td>
<td>OATP1A2</td>
<td>Methotrexate, fexofenadine, steroid hormones, thyroid hormones,</td>
</tr>
<tr>
<td>SLC02A1</td>
<td>OATP2B1</td>
<td>Atorvastatin</td>
</tr>
<tr>
<td>CDH17</td>
<td>PT1</td>
<td>(Intestinal peptide)</td>
</tr>
</tbody>
</table>

Food effect studies

Examples of Efflux Gut Transporters

<table>
<thead>
<tr>
<th>Efflux transporter genes</th>
<th>Protein names</th>
<th>Substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCB1 (*)</td>
<td>P-gp</td>
<td>Etoposide, Imatinib, fexofenadine, tramadol, propranolol, CsA, Tacrolimus</td>
</tr>
<tr>
<td>ABCC1 (*)</td>
<td>MRP1</td>
<td>Methotrexate, daunorubicin, doxorubicin, vincristine, Glucuronic acid or sulfate conj. compounds</td>
</tr>
<tr>
<td>ABCC2 (*)</td>
<td>MRP2</td>
<td>Doxorubicin, cisplatin, conj drug metabolites, protease inhibitors, fluoroquinolones, pravastatin</td>
</tr>
<tr>
<td>ABCC3 (*)</td>
<td>MRP3</td>
<td>Etoposide, methotrexate, bile salts</td>
</tr>
<tr>
<td>ABCC4 (*)</td>
<td>MRP4</td>
<td>Methotrexate, folic acid</td>
</tr>
<tr>
<td>ABCC5 (*)</td>
<td>MRP5</td>
<td>Adefovir, 5-FU, methotrexate</td>
</tr>
<tr>
<td>ABCG2 (*)</td>
<td>BCRP</td>
<td>Mitoxantrone, doxorubicin, Pravastatin, sulfate conjugates, irinotecan, imatinib</td>
</tr>
</tbody>
</table>


Food effect studies

Influx and Efflux Gut Transporters

-CsA increase 7X Rosuvastatin AUC (Inhibition of OATP and BCRP? + inhibition of OATP1B1 in liver)
Effect of ethnicity on activity of ABCB1 (Pgp). More than 100 mutations identified.

- C3435T polymorphism (lower activity): 50% Caucasians/Asians; 10-20% Africans
  - Africans have lower F for CsA and have 20-80% lower Tacrolimus F than in Caucasians or Latin-Americans
  - Fexofenadine 40% higher concentrations
- G2677T polymorphism: 46% Caucasians, 6.5% African-Americans
  - Fexofenadine 40% higher concentrations

Effect of ethnicity on activity of OATP1B1

- OATP1B1*5 and OATP1B1*15 alleles: increased pravastatin, pitavastatin and rosuvastatin levels
  - *15 observed in 30% Europeans/Americans, 71% Koreans. *5 observed 14% Europeans/Americans and 0% in Japanese/Koreans.
  - Europeans have higher Pravastatin Cmax and AUC than African-Americans
  - Rosuvastatin [C] higher by 2.4x in Chinese, 1.9x in Malay, 1.6x in Indians versus whites.


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Effect of Ethnicity and Food

- Tramadol (CYP3A, P-gp or other Efflux transporter)
  - Food increased Cmax and AUC by 30% in Indian population (Zydol®)
  - Food decreased Cmax and AUC by 15-30% in US population (Ultram ER®)
- Pravastatin (OATP1A2, OATP1B2, MRP2, BCRP)
  - Food decreases Cmax and AUC by 30-50% in US population
- Rosuvastatin (OATP1A2, OATP1B2, MRP2, BCRP)
  - Lower dose for asians (label specified)
- Tacrolimus (P-gp, CYP3A, OATP1A2)
  - Same PK after IV dosing African-Americans, whites and Latin Americans
  - Different PK after PO, much lower AUC and Cmax in African americans (higher P-gp activity and/or lower OATP1A2 activity?). (Label specified)
- Ropinirole XL (CYP1A2)
  - Food increases AUC and Cmax by 30% in NA population
  - Adverse events much less pronounced in Indian versus NA BE studies

Food effect studies
Would this be possible?

Ethnic group#1 for hypothetical Drug Product
Interplay between transporters, CYP3A and formulation components:
• Food effect (fast versus fed)
• More discriminative of formulation performance

Ethnic group#2
No or Less Interplay between transporters, CYP3A and formulation components:
• No or Less Food effect (fast versus fed)
• Less discriminative of formulation performance under fed

Food effect studies
Conclusion

• The “effect of food” on the PK of drugs is VERY complex.
• It is important to determine the “food effect” or verify BE under fed conditions for all drug products, similar to FDA recommendations.
• Food may affect many transporters, but very little research has been done at this time.
• Transporters activity may differ between Ethnic groups. Very little or no research has been done on this contrary to CYPs.
• Research should be done to prove or disprove the use of any Healthy Volunteers population group (versus the “targeted” one) to assess food effect and fed BE.