GI transfer
May 13 2014
In silico (PBPK) models
Integration of the gastrointestinal transit into different *in vitro* models

Evaluation of the gastrointestinal transit by using a non-absorbable marker
Integration of the gastrointestinal transit into different *in vitro* models

- **Non-absorbable marker:**
  - Paromomycin Sulfate: Gabbroral®: Antibiotic
  - Site of action: infections of the GI tract
    - Not transported to the blood compartment (confirmed by Caco-2 experiment)
    - Candidate compound to evaluate the GI transit
Analysis: HPLC-FLUO

- Derivatisation by Fluorenlymethylxycarbonyl chloride (FMOC-Cl) to make it possible to detect
Method validation

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mobile Phase</th>
<th>Detection</th>
<th>Wavelength (Ex/Em)</th>
<th>Flow Rate (mL/min)</th>
<th>Retention Time (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paromomycin Sulfate</td>
<td>Acn:H₂O (87:13)</td>
<td>FLUO</td>
<td>260/315</td>
<td>1</td>
<td>7.5</td>
</tr>
</tbody>
</table>

**INTRADAY**

- FaHIF
- FeHIF
- FaHGF

**INTERDAY**

- FaHIF
- FeHIF
- FaHGF
Setup Clinical Trial

– 5 healthy volunteers:
  • Drinking 250mL of water, pre-dissolved with one tablet of Gabbroral®
  • Aspirating stomach & duodenal fluids
Setup Clinical Trial

- **4 different conditions:**

1. Fasted State
2. Fed State
3. Fed State + Domperidon (Motilium®) (transit stimulating effect)
4. Fed State + Loperamide HCl (Imodium®) (transit inhibiting effect)
Clinical Trial

• **Results:**
  
  – **Fasted State:**

![Graph showing pH changes over time for Stomach and Duodenum Fasted State.](image)

![Graph showing paromomycin levels over time for Stomach and Duodenum Fasted State.](image)
Clinical Trial

– Fed State:
Fed State + Domperidone

![Motilium Instant box]

Graph showing the effect of Motilium on Paromomycin Cmax in the duodenum.

- **Fed State**: Blue line for Stomach, Red line for Duodenum.
- **Fed State + Domperidone**: Blue line for Stomach, Red line for Duodenum.

Volunteers:
- Volunteer 1
- Volunteer 2
- Volunteer 3
- Volunteer 4
- Volunteer 5
Integration of the gastrointestinal transit into different *in vitro* models

- Implementation to *in vitro/ in silico*:

  1. Psachoulas et al. 2012
  2. Tiny TIM and TIM-1
Integration of the gastrointestinal transit into different *in vitro* models

- Implementation to *in vitro*/*in silico*:

Psachoulias et al. 2012

Tiny TIM and TIM-1
Integration of the gastrointestinal transit into different *in vitro* models

- Implementation to *in vitro/ in silico*:

Psachoulias et al. 2012:

Simulated duodenal concentration-time profiles of paromomycin, using the three-compartmental model in both the original mode (Psachoulias et al. 2012) (■) and the modified mode (Symillides et al. 2013) (---). Reference data is given by the mean (± SEM) *in vivo* duodenal concentration-time profile (▲).
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Psachoulias et al. 2012

Tiny TIM and TIM-1
Integration of the gastrointestinal transit into different *in vitro* models

- Implementation to *in vitro/ in silico*:

  TNO Intestinal Model (TIM-1):

  **TIM-1 fasted state experiment 1 & 2:** Mean concentration-time profiles and pH profiles of the stomach (▲) and duodenum (●) compartment of TIM-1 compared with the mean concentration-time profile of the *in vivo* duodenum (■) (n=3; mean ± SEM). The arrow indicates the difference between the gastric emptying time for the TIM-1 (0.55 hour) and the *in vivo* data (0.125 hour).
Integration of the gastrointestinal transit into different in vitro models

• Implementation to in vitro/ in silico:

Psachoulia et al. 2012

Tiny TIM and TIM-1
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• Implementation to *in vitro*/*in silico*:

Simcyp® Simulation model:

Simulations of duodenal paromomycin concentrations using Simcyp® (varying gastric emptying time (GET), from 0.4 h to 0.101 h) in a “virtual population”. Mean duodenal concentration-time profile in the fasted state in humans is also shown (mean ± SEM) (■).
Conclusions

**In Vivo:**
- For drugs in solution, a fast transfer from stomach to small intestine (observed mean GET 0.125 h) results in a dilution of less than 1:2 in fasting conditions.
- Delayed gastric emptying time in the fed state (observed mean GET 0.8 h) is not influenced by the administration of domperidone or loperamide, a transit-stimulating and inhibiting agent, respectively.

**In Vitro & In Silico:**
- Using the human data as reference, it was demonstrated that current *in vitro* and *in silico* tools tend to overestimate the gastric emptying time for drugs in solution.
- Nevertheless, adaptation of model parameters allows for a better simulation of the *in vivo* situation.