Mechanism-based modelling of gastric emptying and bile release in response to caloric intake

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• Majority of drugs administered orally
  – Convenient
  – Flexible
• However
  – Gastrointestinal system complex and not entirely understood
  – Increasing number of poorly soluble drugs*
    o Increased receptor-ligand affinity
      \textit{(i.e. potency)}
    o Associated with highly variable absorption profiles
    o Absorption affected by intestinal secretions
      \textit{(e.g. bile)}

*Biopharmaceutics Classification System (BCS) class II and IV

Williams et al., Pharmacol Rev. (2013)
Objectives

1. Establish mechanism-based models for:
   a. Gastric emptying (GE)
   b. Plasma cholecystokinin (CCK) levels
   c. Bile flow patterns to the duodenum

2. Characterize the influence of caloric intake on different system components

3. Explore the effect of Type 2 Diabetes Mellitus (T2DM)
Study design and data

**Methods**

**Total 66 subjects**

**Water study**[^1]
- 10 T2DM / 10 HV
- Water
  - 100mL of water (0 kcal)

**Glucose study**[^2]
- 8 T2DM / 8 HV
- OGGT 25g
  - 25 g of glucose in 300mL water (97 kcal)
- OGGT 75g
  - 75 g of glucose in 300mL water (290 kcal)
- OGGT 125g
  - 125 g of glucose in 300mL water (484 kcal)

**Liquid meals study**[^3]
- 15 T2DM / 15 HV
- OGGT 75g
  - 75 g of glucose in 350mL water (290 kcal)
- Low fat liquid meal
  - 2.5 g fat, 13 g prot., 107 g carb.
  - Volume of 350mL (500 kcal)
- Medium fat liquid meal
  - 10 g fat, 11 g prot., 93 g carb.
  - Volume of 350mL (500 kcal)
- High fat liquid meal
  - 40 g fat, 3 g prot., 32 g carb.
  - Volume of 350mL (500 kcal)

+ Gastric emptying marker
  - (dissolved paracetamol 1.5 g)

[^1]: Hansen et al., ClinicalTrials.gov identifier NCT01666223
[^2]: Bagger et al., JCEM. (2011)
[^3]: Sonne. et al., ADA 73 (2013)
System overview

**Methods**

**Gastric emptying model**

- **Paracetamol stomach**
  - Dose: Paracetamol
  - Paracetamol duodenum
    - Paracetamol central $V_c$
      - Q
        - Paracetamol peripheral $V_p$
          - $K_B$

- **Glucose stomach**
  - Dose: Glucose
  - Glucose duodenum
    - $K_DJ$
      - CL

- **Meal volume stomach**
  - Meal Volume

- **Signal nutrients stomach**
  - Signal nutrients duodenum
    - $K_DJ$
      - $K_JI$

**Cholecystokinin model**

- **Pool CCK_{Fast}**
  - $R_{IN}$
  - $R_{out}$
  - $K_{out_F}$

- **Blood CCK_{Fast}**
  - $R_{out}$

- **Pool CCK_{Slow}**
  - $K_{R_S}$
  - $K_{out_S}$

- **Blood CCK_{Slow}**
  - $K_{R_S}$
  - $K_{out_S}$

**Bile release model**

- **Bile in duodenum**
  - $B_{release}$
  - $K_{R_B}$

- **Gallbladder volume**
  - $R_{PROD}$

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Gastric emptying (GE) model

Methods

Key equations

\[ K_G = K_{Go} \times \left( 1 - \frac{A_{glucD}^\gamma}{I_{50}^\gamma + A_{glucD}^\gamma} \right) \]

\[ K_{DJ} = \frac{1}{MRT_{glucD}} = \frac{V_{Duodenum}}{Rate_{GE}} \]
Cholecystokinin (CCK) model

**Methods**

**Key equations**

\[
\text{Signal Nutrients} = \frac{\text{mass}_{\text{fat}} \times \text{potency}_{\text{fat}}}{\frac{\text{mass}_{\text{carb}} \times \text{potency}_{\text{carb}}}{}}
\]

Bile release model

**Methods**

Key equations

\[
B_{\text{release}} = 1 + \frac{S_{\text{MAX}_B} \times CCK_{\text{Fast}}}{SC_{50} + CCK_{\text{Fast}}}
\]

Gastric emptying (GE) model VPCs

Results
Gastric emptying (GE) model VPCs

Results

Feedback similar to 115g of glucose
Feedback similar to 107g of glucose
Feedback similar to 107g of glucose

Water (100 mL)  Glucose 25g in 300mL of water  Glucose 75g in 300/350mL of water  Glucose 125g in 300mL of water

Low fat liquid meal (350 mL)  Medium fat liquid meal (350 mL)  High fat liquid meal (350 mL)

Observations
Median of the obs.
5th and 95th percentiles of the obs.
95% CI for the pred. 5th/95th percentiles
95% CI for the pred. median
Cholecystokinin (CCK) model VPCs

Results

<table>
<thead>
<tr>
<th>Meal Type</th>
<th>CCK Plasma Levels (pmol/L)</th>
<th>Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose 75g in 350mL of water</td>
<td>0-15</td>
<td>0-200</td>
</tr>
<tr>
<td>Low fat liquid meal (350 mL)</td>
<td>0-15</td>
<td>0-200</td>
</tr>
<tr>
<td>Medium fat liquid meal (350 mL)</td>
<td>0-15</td>
<td>0-200</td>
</tr>
<tr>
<td>High fat liquid meal (350 mL)</td>
<td>0-15</td>
<td>0-200</td>
</tr>
</tbody>
</table>

- Observations
- Median of the obs.
- 5th and 95th percentiles of the obs.
- 95% CI for the pred. 5th/95th percentiles
- 95% CI for the pred. median
Bile release model VPCs

Results

<table>
<thead>
<tr>
<th>Gallbladder volume (mL)</th>
<th>Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose 75g in 350mL of water</td>
<td>0 20 40 60</td>
</tr>
<tr>
<td>Low fat liquid meal (350 mL)</td>
<td>0 20 40 60</td>
</tr>
<tr>
<td>Medium fat liquid meal (350 mL)</td>
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</tr>
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<td>0 20 40 60</td>
</tr>
</tbody>
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- Observations
- Median of the obs.
- 5th and 95th percentiles of the obs.
- 95% CI for the pred. 5th/95th percentiles
- 95% CI for the pred. median
**Final bile release model**

**Results**

**Gastric emptying model**

- **Paracetamol stomach**: $K_G$
- **Paracetamol duodenum**: $K_a$
- **Paracetamol central $V_c$**: $Q$
- **Paracetamol peripheral $V_p$**: $CL$

**Signal Nutrients stomach**

**Signal Nutrients duodenum**

**Meal volume stomach**

**Dose Paracetamol**

**Dose Glucose**

**Meal Volume**

**Signal Nutrients**

**Key equations**

\[ Signal\; Nutrients = mass_{fat} \times \text{potency}_{fat} + mass_{prot} \times \text{potency}_{prot} + mass_{carb} \times \text{potency}_{carb} \]

\[ B_{release} = 1 + SLP_{release} \times A_{NutriD} \]

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Final bile release model VPCs

Results

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<thead>
<tr>
<th>Glucose 75g in 350mL of water</th>
<th>Low fat liquid meal (350 mL)</th>
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<td>Gallbladder volume (mL)</td>
<td>Time (min)</td>
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</tr>
<tr>
<td>0</td>
<td>0</td>
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<tr>
<td>20</td>
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<td>40</td>
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<td>60</td>
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<td>60</td>
</tr>
<tr>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
</tbody>
</table>

- Observations
- Median of the obs.
- 5th and 95th percentiles of the obs.
- 95% CI for the pred. 5th/95th percentiles
- 95% CI for the pred. median
Gastric emptying model predictions

Results

Simulated rate of GE following different caloric intakes (typical individual)

\[ K_G = K_{G_0} \times \left( 1 - \frac{A_{glucD}^\gamma}{I_{50}^\gamma + A_{glucD}^\gamma} \right) \]

with:
- Half-life of \( K_{G_0} \): 5.3 min
- \( I_{50} \): 4.9 gluc. gram equivalent
- \( \gamma \): 4.8

<table>
<thead>
<tr>
<th>Meal (g of glucose)</th>
<th>Time to 50% emptying</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5.3 min</td>
</tr>
<tr>
<td>25</td>
<td>8.0 min</td>
</tr>
<tr>
<td>75</td>
<td>44 min</td>
</tr>
<tr>
<td>125</td>
<td>86 min</td>
</tr>
</tbody>
</table>

*Assuming a meal volume of 300mL*
Results

Simulated rate of gastric emptying following different caloric intakes (HV vs. T2DM)

\[ K_G = K_{G0} \times \left( 1 - \frac{A_{glucD}^\gamma}{I_{50}^\gamma + A_{glucD}^\gamma} \right) \]

with:
- Half-life of \( K_{G0} \): 5.3 min
- \( I_{50} \): 4.9 gluc. gram equivalent
- \( \gamma \): 4.8
- T2DM on \( I_{50} \): +29%

<table>
<thead>
<tr>
<th>Meal (g of glucose)</th>
<th>Time to 50% emptying (HV)</th>
<th>Time difference (T2DM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5.3 min</td>
<td>0 min</td>
</tr>
<tr>
<td>25</td>
<td>8.0 min</td>
<td>-3 min</td>
</tr>
<tr>
<td>75</td>
<td>44 min</td>
<td>-10 min</td>
</tr>
<tr>
<td>125</td>
<td>86 min</td>
<td>-14 min</td>
</tr>
</tbody>
</table>

**T2DM:** Type 2 Diabetes Mellitus
**HV:** Healthy Volunteers (matched on BMI, gender, age)
Bile release model predictions

**Results**

*Assuming a meal volume of 300mL and the same gastric emptying rate*
**T2DM effects on bile release**

**Results**

**Signal Nutrients** = \( \text{mass}_{fat} \times \text{potency}_{fat} + \text{mass}_{prot} \times \text{potency}_{prot} + \text{mass}_{carb} \times \text{potency}_{carb} \)

with:
- \( \text{potency}_{fat} \) = 1.0 fixed
- \( \text{potency}_{prot} \) = 1.1
- \( \text{potency}_{carb} \) = 0.028

**T2DM on \( \text{potency}_{carb} \) = +12%**

**Simulated gallbladder emptying following different caloric intakes (HV vs. T2DM)**

**Subject**
- HV
- T2DM

**Meal**
- 50 g of glucose
- 50 g of protein
- 50 g of fat
- 10 g fat/11 g prot/93 g carb

**T2DM**: Type 2 Diabetes Mellitus

**HV**: Healthy Volunteers (*matched on BMI, gender, age*)
Conclusions

• Gastric emptying was found to be controlled by a feedback mechanism of caloric content in duodenum

• CCK kinetics was not sufficient on its own to describe bile release

• An alternative approach connecting the bile release to nutrients in duodenum was preferred

• T2DM was found to affect gastric emptying and bile release through changes in sensitivity to carbohydrates

• The final model demonstrated to be predictive of gastric emptying, plasma CCK levels and bile release across a wide range of liquid meals
Future Directions

• Use new data to correlate gallbladder volume to bile concentration in duodenum and study recirculation of bile acids

• Explore correlation between plasma biomarkers and bile acid concentration in duodenum

• Integrate findings in systems pharmacology models (PBPK) to improve prediction of oral absorption
The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking (http://www.imi.europa.eu) under Grant Agreement No. 115369, resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution.