In Vitro Tools to Risk Assess the Likelihood of a Food/Vehicle Effect in Pediatric Populations

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Oral bioavailability

Drug solubility & dissolution rate in the upper GI tract

- physicochemical properties of the drug
- formulation properties
- physiological conditions in the upper GI tract at the time of dosing

subject to food effects

⇒ benefit of increased bioavailability
⇒ risk of
  - reduced efficacy
  - increased toxicity
Food effects in pediatric patients?

Dosing scenarios

• medication is administered after a meal (e.g. breakfast)
• unpleasant taste / difficulties in swallowing:

⇒ powder, tablet bits, sprinkles are admixed with soft food or fluids before administration
Food effects in pediatric patients?

Co-administration with a meal or modification of the dosage form...

• can affect physical / chemical stability of the drug / formulation
Case example: Enteric coated pellets

“In vitro stability, potency, and dissolution of duloxetine enteric-coated pellets after exposure to apple sauce, apple juice, and chocolate pudding”

- exposure of the pellets to the different foods
  - potency and impurities
  - dissolution

- enteric coating of duloxetine pellets was not negatively affected by mixing with apple sauce or apple juice

- exposing the pellets to chocolate pudding damaged the coating

Apple juice (25 °C): pH 3,5
Apple sauce (25 °C): pH 3,7
Vanilla pudding (25 °C): pH 6,5

K.A. Wells et al., Clinical Therapeutics 2008, 30 (7): 1300-1308
Food effects in pediatric patients?

Co-administration with a meal or modification of the dosage form...

- can affect physical / chemical stability of the drug
  ⇒ stability studies

- can alter the clinical performance of a drug by changing its bioavailability
  ⇒ how can we predict that?
Biorelevant *in vitro* dissolution methods

Biorelevant dissolution media

- address composition and properties of intraluminal fluids after fasted and fed dosing

Further parameters of importance

- gastric emptying time, small intestinal transit time
- GI motility and pressures

Advanced dissolution models

- dynamic gastric model, stress test device, ...
- multicompartmental models, e.g. USP 3/4, transfer model, gastroduodenal model, TIM-1...
Biorelevant *in vitro* dissolution methods

- physiologically based *in vitro* dissolution models can be helpful in establishing an IVIVC in many cases, however ...
Biorelevant *in vitro* methods for children

What is required for the test design?

- key parameters for *in vivo* drug release
  - physiological parameters
    - → fluid volume & composition in the GI sections
    - → residence times / GI passage
  - dosing conditions / manipulation
    - → co-administered food/fluid volumes & properties
    - → clinical/real dosing conditions?
- application of adult models will not work
- an universal pediatric approach is unlikely
⇒ there is need for appropriate test designs!
A possible starting point ....
Pediatric vs. adult GI physiology

⇒ the biggest differences are found in preterms and neonates

- gastric pH
- gastric emptying
- gastric acid secretion
- stomach capacity
- small intestinal pH
- small intestinal transit time
- production of digestive enzymes
- pancreatic secretion
- bile secretion
Fasted gastric fluid volumes and pH

Typical trends in healthy patients

Gastric fluid volume

<table>
<thead>
<tr>
<th></th>
<th>Newborns</th>
<th>Infants</th>
<th>Pre-school children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasted gastric fluid volume [mL]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>10</td>
<td>20</td>
<td>50</td>
</tr>
</tbody>
</table>

Fasted gastric pH

<table>
<thead>
<tr>
<th></th>
<th>Newborns</th>
<th>Infants</th>
<th>Pre-school children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasted gastric pH</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

E. Kersten, S. Klein, AAPS Annual Meeting, San Antonio, USA, 2013 (Poster)
Current practices of manipulating medicines

Occurrences of different types of soft foods/dinks appearing on administration instructions for pediatric medicines (SmPCs and PILs)

- Water: 6 occurrences
- Infant formula: 5 occurrences
- Apple juice: 4 occurrences
- Milk: 4 occurrences
- Orange juice: 3 occurrences
- Juice: 2 occurrences
- Tomato juice: 2 occurrences
- Ora-sweet SF®: 2 occurrences
- Grapefruit juice: 2 occurrences
- Grape juice: 2 occurrences
- Cranberry juice: 2 occurrences
- Ora-Plus®: 2 occurrences
- Milk shake: 2 occurrences
- Breast milk: 2 occurrences
- Soy milk: 2 occurrences
- Soy formula: 2 occurrences
- Condensed milk: 2 occurrences
- Dietary supplements: 2 occurrences
- Corn syrup: 2 occurrences
- Caramel topping: 2 occurrences
- Chocolate syrup: 2 occurrences
- Light brown sugar solution: 2 occurrences
- Ginger ale: 2 occurrences
- Lemonade: 2 occurrences
- Cherry syrup (Humco®): 2 occurrences
Typical breakfasts ingested by infants (1yr)

Preparation & physicochemical characterization

A

B

C

06/06/2016 Sandra Klein, University of Greifswald
Food / fluid properties

Can affect ...
- drug / formulation stability
- drug solubility
- dissolution rate / drug release rate

 Might affect ...
- gastric emptying

Most relevant physicochemical characteristics
- pH
- buffer capacity
- osmolality
- surface tension
- viscosity

Type of food? Portion size / volume?
### Relevant physicochemical characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Temp.</th>
<th>Fluids</th>
<th>Suspension vehicles</th>
<th>Soft foods</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Water</td>
<td>Apple sauce</td>
<td>Vanilla pudding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Apple juice</td>
<td>Grape juice</td>
<td>Orange juice</td>
</tr>
<tr>
<td>pH-value (1)</td>
<td>25°C</td>
<td>7,31</td>
<td>3,47</td>
<td>3,45</td>
</tr>
<tr>
<td></td>
<td>37°C</td>
<td>7,89</td>
<td>3,49</td>
<td>3,43</td>
</tr>
<tr>
<td>Buffer capacity [mEq/pH/L]</td>
<td>25°C</td>
<td>0,11</td>
<td>(0,00)</td>
<td>33,4</td>
</tr>
<tr>
<td></td>
<td>37°C</td>
<td>0,06</td>
<td>(0,0)</td>
<td>33,9</td>
</tr>
<tr>
<td>Osmolality [mOsmol/kg]</td>
<td></td>
<td>4</td>
<td>(1)</td>
<td>677</td>
</tr>
<tr>
<td>Surface tension [mN/m]</td>
<td>25°C</td>
<td>70,2</td>
<td>(0,36)</td>
<td>64,17</td>
</tr>
<tr>
<td></td>
<td>37°C</td>
<td>68,74</td>
<td>(0,46)</td>
<td>62,51</td>
</tr>
<tr>
<td>Viscosity [mPa*s]</td>
<td>25°C</td>
<td>0,91</td>
<td>(0,00)</td>
<td>1,26</td>
</tr>
<tr>
<td></td>
<td>37°C</td>
<td>0,72</td>
<td>(0,00)</td>
<td>0,96</td>
</tr>
</tbody>
</table>

† mean of n=18 calculated from measuring surface tension a set of 3 dilutions at concentrations above the critical micelle concentration (CMC) – see 5.2.4 for more details

‡ measured with the rotational viscometer (see figures 1-4 for viscosity profiles)

* to ensure complete pulp removal, orange juice was filtered through a 12 µm cellulose nitrate filter (Schleicher & Schuell, Dassel, Germany) using a vacuum filtration device before measuring viscosity

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Sandra Klein, University of Greifswald

E. Kersten, A. Barry, S. Klein, DiePharmazie, 2016; 71 (3): 122-127(6)
Case example

Ibuprofen

- used in children of all age groups
- adults: BCS class 2 → pediatric BCS class?
- food-effect?

How can the drinking volumes, fluid and food properties affect *in vivo* dissolution in neonates and infants?
Test design – gastric dissolution

Resting gastric fluid pH
1.8; 2.5; 3.5; 4.0; 5.0; 7.0

Mini Paddle
200 mL, 75 rpm
Predictive test methods for newborns

Simulating drug release in the fasted stomach of a 3 kg newborn

<table>
<thead>
<tr>
<th></th>
<th>Furosemide</th>
<th>Ibuprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing recommendation</td>
<td>2 mg/kg</td>
<td>20 mg/kg</td>
</tr>
<tr>
<td>Test dose</td>
<td>6 mg</td>
<td>60 mg</td>
</tr>
</tbody>
</table>

**Scenario 1**

<table>
<thead>
<tr>
<th></th>
<th>Fluid volume available for dissolution</th>
<th>Dose:gastric volume ratio</th>
<th>Upscaled dose:volume ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 mL residual gastric fluid + 25 mL co-ingested fluid</td>
<td>6 mg/30 mL</td>
<td>40 mg/200 mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60 mg/30 mL</td>
<td>66.7 mg/200 mL</td>
</tr>
</tbody>
</table>
Ibuprofen – newborns

5 mL
pH 7.0
pH 5.0
pH 4.0
pH 3.5
pH 2.5
pH 1.8

60 mg + 25 mL water

60 mg + 25 mL formula milk

PREMATURE NEWBORNS, PRO PRE, PRO 1

Buffer capacity [mEq/pH/L]
Ibuprofen – newborns

Combining gastric and small intestinal compartment

- use of physiologically relevant test volumes
- transfer of gastric contents into the small intestine

Ibuprofen – newborns

5 mL
- pH 7.0
- pH 5.0
- pH 4.0
- pH 1.8

100 mL
- pH 7.0 → pH 6.8
- pH 5.0 → pH 6.8
- pH 4.0 → pH 6.8
- pH 1.8 → pH 6.8
Ibuprofen – infants

10 mL
pH 4.0
pH 3.5
pH 2.5
pH 1.8

Scenario 1 - 50 mL water

Scenario 3 - 300 mL water
Properties of co-administered fluid

<table>
<thead>
<tr>
<th>Fluid Type</th>
<th>pH</th>
<th>Buffer Capacity [mEq/pH/L]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apple juice</td>
<td>3.5</td>
<td>30</td>
</tr>
<tr>
<td>Apple spritzer (1:2)</td>
<td>3.5</td>
<td>30</td>
</tr>
<tr>
<td>Carrot juice</td>
<td>3.5</td>
<td>30</td>
</tr>
<tr>
<td>Grape juice</td>
<td>3.5</td>
<td>30</td>
</tr>
<tr>
<td>Grape juice spritzer (1:5)</td>
<td>3.5</td>
<td>30</td>
</tr>
<tr>
<td>Orange juice</td>
<td>3.5</td>
<td>30</td>
</tr>
<tr>
<td>Orange spritzer (1:2)</td>
<td>3.5</td>
<td>30</td>
</tr>
<tr>
<td>Whole milk (3.5%)</td>
<td>3.5</td>
<td>30</td>
</tr>
<tr>
<td>Cocoa</td>
<td>3.5</td>
<td>30</td>
</tr>
<tr>
<td>Vanilla milk</td>
<td>3.5</td>
<td>30</td>
</tr>
<tr>
<td>Formula milk (Beba 1)</td>
<td>3.5</td>
<td>30</td>
</tr>
</tbody>
</table>
Ibuprofen – infants

10 mL + 100 mg + 150 mL

- Whole milk (3.5%)
- Grape juice spritzer (1:5)

pH 4.0 + water
pH 3.5 + water
pH 2.5 + water
pH 1.8 + water

% dose dissolved

0 10 20 30 40 50 60 70 80 90 100

time [min]

0 5 10 15 20 25 30

% dose dissolved

0 10 20 30 40 50 60 70 80 90 100

time [min]
Ibuprofen – infants

Simulating postprandial gastric conditions in infants – ibuprofen (1 year)

- design & application of individual, but reproducible postprandial gastric media
  - carbohydrates
  - proteins
  - fat
  - pH
  - volume
Predicting food effects in children ...

- a safe dosing recommendation requires fundamental background information on drug/formulation, food/fluid properties, co-administered food/fluid portions and GI physiology

- with this information, it should be possible to design appropriate *in vitro* tools to risk assess the likelihood of a food/vehicle effect in pediatric populations

Current status

+ we have a lot of experience for adults

- both *in vitro* and *in vivo* test methods cannot simply be downscaled from adult designs
Predicting food effects in children ...

Where are the needs?

- new *in vitro* methods with pediatric relevance including apparatus, test settings and media
- appropriate *in vivo* screening methods to compare with

>a lot of gaps to fill on GI features of the pediatric population

> this is only possible with international collaboration and sufficient support

- modern and biopredictive pediatric *in vitro tools* will hopefully help to reduce the number of clinical studies required for releasing safe pediatric drug products to the market
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AAF - Modification of Dosage Forms Required for Children Workstream
Thank you

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