Dynamic gastrointestinal in vitro model simulating neonate, infant and toddler conditions to study the bioaccessibility of oral pediatric drugs.

Robert Havenaar, Bart Anneveld, Mans Minekus, Jeroen DeGroot and Wouter Vaes

TNO, Utrechtseweg 48; P.O. Box 360, 3700 AJ Zeist, The Netherlands
rob.havenaar@tno.nl, bart.anneveld@tno.nl

TNO innovation for life

PEDIATRIC DRUGS

Generating data (as required by regulatory authorities) on effects of drugs in children is hampered by ethical constraints regarding clinical trials in pediatric patients. Therefore, off-label drugs are used, often after manipulation of dosage forms, without exactly knowing the consequenses for bioaccessibility. It is crucial to have validated in vitro tools available to study pediatric drugs under clinically relevant conditions of the pediatric age groups.

GOAL

The goal is to develop and validate an in vitro system that simulates the conditions in GI tract of the pediatric age groups and is time/cost efficiently applicable for pediatric drug research.

METHODS

Based on literature data for GI parameters we designed hardware, software and protocols for 'TIM-pediatric' (Figure 1) to simulate the kinetic GI conditions of neonates (0-1 month of age), infants (1-6 m) and toddlers (6-24 m) (Table 1).

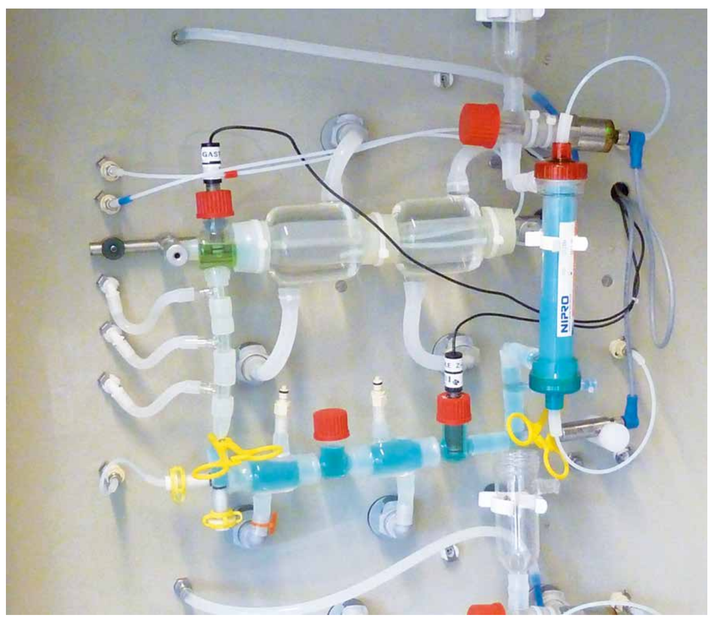

Figure 1. TIM-pediatric with compartments for stomach and small intestine, connected by a pyloric sphincter. Peristaltic mixing, stomach emptying, temperature, pH and digestion are computer controlled.

Parameter	Neonate (0-1 m)	Infant (1-6 m)	Toddler (6-24 m)
1st meal	formula milk	formula milk	milk + cereals
2nd meal	formula milk	fruit + vegetable sauce	fruit juice + cereals
gastric juice	2 mL	3 mL	5 mL
meal	90 mL	125 mL	142 mL
saliva	15 mL	20 mL	25 mL
gastric emptying	t½=60 min	t½=60 min	t½=70 min
gastric pH 0-3 h	*6.7→4.0*	*6.7→3.2*	*6.7→2.4*
3-6 h	*6.7→4.0*	*3.8→3.2*	*3.7→2.4*
intestinal pH	*6.5*	*6.5*	*6.5*
$C^{secretion}$ *0-3 h*	*50%*	*75%*	*100%*
3-6 h	*50%*	*50%*	*50%*

Table 1. Meals, volumes, set points and secretions as used in TIM-pediatric for the three age groups.

Pilot studies were performed to determine bio-accessibility of various drugs from different dosage forms and to correlate these findings with clinical data in children.
To investigate consequences of real-life situations, the dosage forms were crushed and mixed with neonate, infant and toddler foods (Table 1).

RESULTS

Paracetamol showed rapid and high levels of bioaccessibility under neonate, infant and toddler GI conditions (Figure 2), with a later t_{max} for toddlers vs. neonates and infants, comparable with clinical data (Hopkins et al 1999).

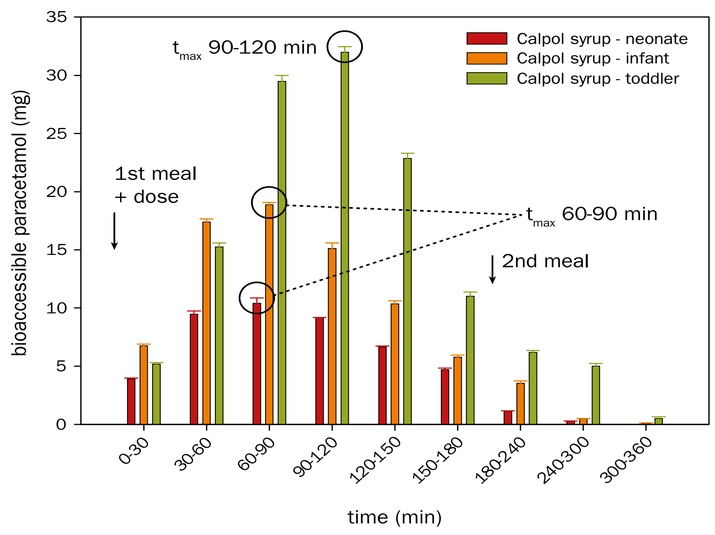

Figure 2. Mean (± range; n=2) bioaccessible paracetamol (mg) vs. time after intake of 15 mg/kg b.w. as Calpol syrup with age-related foods under physiological neonate, infant and toddler GI conditions.

Diclofenac as crushed generic tablet under physiological infant GI conditions showed a positive food matrix effect. The bioaccessibility was not influenced by gastric pH, indicating that diclofenac can be combined with a PPI (Figure 3). Diclofenac showed a slightly lower bioaccessibility under neonate vs. infant GI conditions (Figure 4).

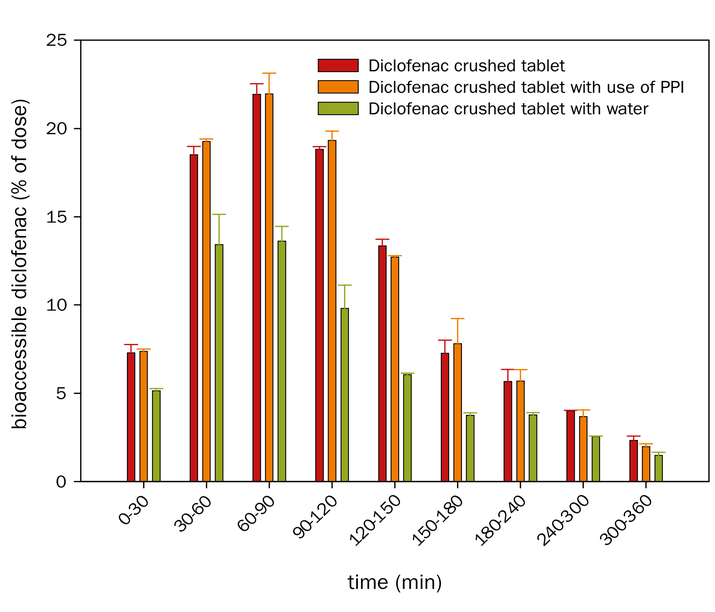

Figure 3. Mean (± range; n=2) bioaccessible amount of diclofenac (% of dose) after intake of 1.5 mg/kg b.w. as crushed tablet with age-related food or water, under physiological infant GI conditions and under high gastric pH during use of PPI.

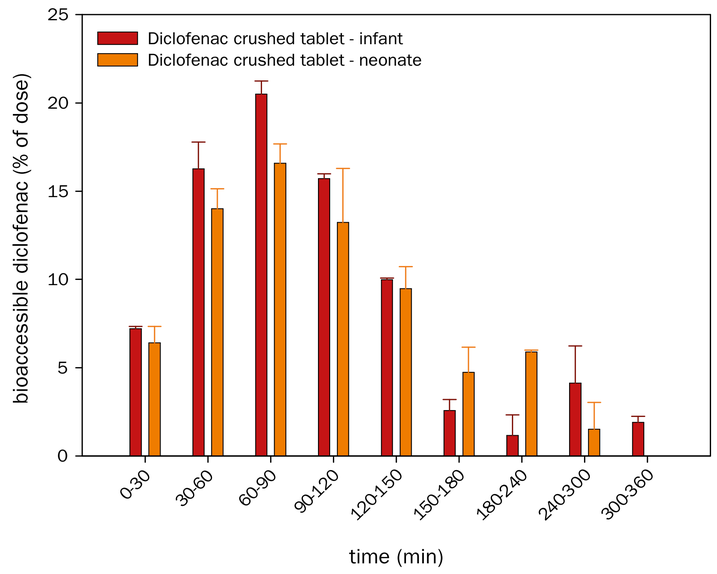

Figure 4. Mean (± range; n=2) bioaccessible amount of diclofenac (% of dose) vs. time after intake of 1.5 mg/kg b.w. as crushed tablet with age-related foods under physiological neonate and infant GI conditions.

The bioaccessibility of Esomeprazole (PPI) as crushed tablets under infants GI conditions was dependent on single vs. repeated intake (Figure 5). After repeated intake, inducing a high gastric pH, the bioaccessible amount was higher than after the first dose with a physiological (low) gastric pH. This corresponds to clinical results. Intact tablets showed variable release: before or after the 'housekeeper wave', probably due to high initial gastric pH.

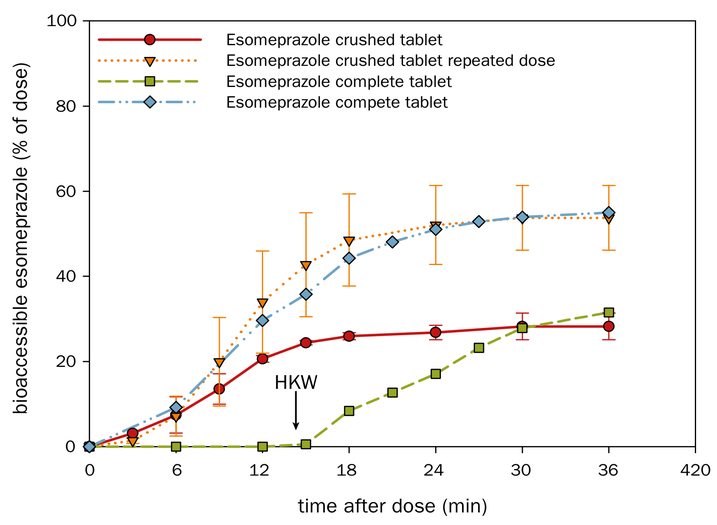

Figure 5. Cumulative bioaccessible amount of esomeprazole (% of dose) vs. time after intake of 20 mg as crushed tablet or intact tablet with age-related food, under physiological infant GI conditions and under simulation of repeated intake of esomeprazole (high gastric pH).

CONCLUSION

TIM-pediatric simulates GI conditions of neonates, infants and toddlers after the intake of drugs with age-related foods.
It can be applied for testing dosage forms for pediatric population to measure bioaccessibility under daily practice conditions.
Pilot results show a highly predictive quality.