

In vitro - in vivo correlation (IVIVC) for paracetamol and caffeine in TIMpediatric simulating GI conditions of (pre-term) neonates, infants and toddlers

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Purpose

To investigate the predictive quality of in vitro TIMpediatric findings in relation to in vivo data of paracetamol and caffeine for pediatric patients.

Methods

TIMpediatric is a dynamic computer controlled in vitro system of the stomach and small intestine mimicking age and maturation-related specific physiological parameters for pre-term neonates, neonates, infants and toddlers. Among other, the post-prandial effects on transit time, pH values and digestive fluid secretion. Oral paracetamol (Calpol® suspension, 15mg/kg bw) was given concomitant with an age representative meal. Luminal filtered fractions were collected in 30 to 60 min aliquots. Oral caffeine (10 mg/ml solution in ampoules, Erasmus MC, Rotterdam) was given to TIMpediatric under a fasting state condition (water) reflecting the pre-term neonate [Siegel, 1984]. Intestinal lumen fractions were collected in 5 to 20 min aliquots. Caffeine samples were analyzed according a UV spectrophotometric method and paracetamol samples according a validated HPLC-UV method. These analysis resulted in in vitro bioaccessibility profiles for both compounds over time. Subsequently the bioaccessibility profiles were compared with published pediatric in vivo data for caffeine [Giacoia, 1989] and paracetamol [Hopkins, 1990]. De-convolution methods were applied to calculate in vivo absorption profiles. The estimated in vivo absorption profiles were compared with the in vitro bioaccessibility profiles. One of these methods was applied earlier to establish a level A IVIVC for paracetamol for adults [Souliman, 2006].

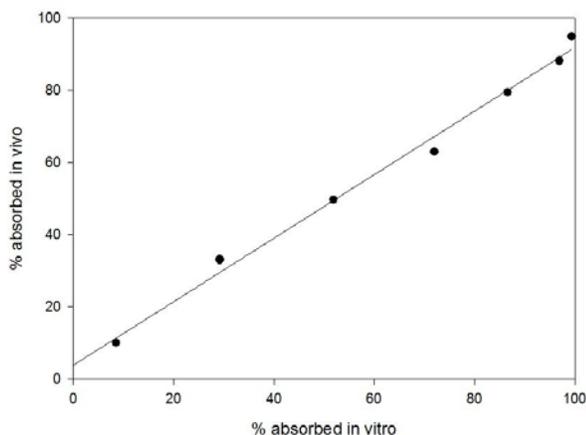
Results

An IVIVC level A was established in TIMpediatric for paracetamol for the neonate, infant and toddler population ($R^2 > 0.98$) and for caffeine for the pre-term neonate condition ($R^2 = 0.9997$).

Conclusion

Pediatric paracetamol and caffeine tested in the TIMpediatric system for the (pre-) term-neonate, infant and toddler conditions showed a good resemblance with the in vivo situation. Comparison of de-convoluted in vivo plasma profiles with in vitro absorption resulted in a level A IVIVC.

TIMpediatric infant paracetamol IVIVC



	Pre term neonate	Neonate	Infant	Toddler
age	< 0 m	0 - 1 m	1 - 6 m	6 - 24 m
1 st meal 0-3h	water	formula milk	formula milk	milk + cereals
gastric juice	1 ml	2 ml	3 ml	5 ml
saliva	5 ml	15 ml	20 ml	25 ml
meal	54 ml	93 ml	107 ml	115 ml
t _{1/2} gastric emptying	13	50	60	70
gastric pH 1 st meal	5	6.7 → 4.0	6.7 → 3.2	6.7 → 2.4
intestinal pH	6.5	6.5	6.5	6.5
GI secretion 1 st meal	-	50%	75%	100%