# Maturation of the (mini)pig's gastrointestinal tract in a paediatric drug perspective

**Steven Van Cruchten and Chris Van Ginneken**

University of Antwerp, Belgium

During prenatal and postnatal development, several morphological and physiological parameters undergo changes which can impact drug disposition. The maturation of the kidneys and the gastrointestinal (GI) system, including the liver, appears to exert the most important influence on the pharmacokinetics of most drugs.[1] When focusing on the gastrointestinal tract, several parameters such as length, diameter, surface area expansion factors, pH, transit time, enzymatic activity and, of course, biotransformation capacity can affect drug absorption.[2] In view of the current focus on paediatric drug development, detailed knowledge of these factors is a prerequisite for paediatric drug modelling, for PK/PD modelling in juvenile animals and for interpreting of juvenile toxicity studies which may be requested prior to starting clinical trials in the paediatric population.

The (mini)pig is used in (juvenile) toxicity studies and an adult animal is generally regarded as a good model for the human GI system based on morphological and physiological similarities.[3] However, comparative data during maturation are often lacking. In the tables below a comparison between man and pig is given for several GI parameters (limited to the stomach and small intestine in view of drug disposition) during perinatal and postnatal development. Rodents and dogs are also included as these two are commonly used as preclinical animal models.

The onset of gastric acid secretion differs amongst the species. In rodents, the secretion of gastric acid only becomes prominent around weaning,[4] an illustration of the relative immaturity of the GI tract at birth compared to other species.

## Stomach

| Species | | Preterm | Suckling | Weaning | Adult |
|---|---|---|---|---|---|
| Pig | pH | At 87% gestation from 7 to 3 | Linear increase in secretion 1st week | 6-7 fold more secretion | 1.6-4.3 |
| Human | | At 60 % gestation possible but minor secretion, pH below 4 (varying reports) | Increasing capacity (1st 4 months) ± 4 (varying reports!) | By 2 y = adult (level of secretion) | < 4 |
| Rodent | | At 89% gestation possible but no secretion | Maturation of gastric mucosa | By 3 weeks significant HCl secretion | Adult level reached by 6 wks of age |
| Dog | | ? | ? | ? | Fasted: 5.5 (higher than human) Fed: ± 1.9-2.6 |

| Species | | Preterm | Suckling | Weaning | Adult |
|---|---|---|---|---|---|
| Pig | Proteases | Prochymosin at 80% of gestation | Pepsinogen & progastriscin appear after birth and increase, prochymosin decreases | Response to diet (increases in pepsinogen and progastricin | |
| Human | | Low preterm | Proteolytic activity shows no big age-related differences | | |
| Rodent | | No to low preterm | No to low | Increase from 21 d pp | |
| Dog | | ? | Pepsin detectable from day 21 | Pepsin gradually increased by 63 d ~ adulthood | |

| Species | | Preterm | Suckling | Weaning | Adult |
|---|---|---|---|---|---|
| Pig | Gastric emptying | ? | Biphasic Suckling faster than weaner pig | Biphasic 3 wks post-weaning = adult | biphasic |
| Human | | 2nd trimester of gestation | biphasic | biphasic | biphasic |
| Rodent | | Maturation needed of smooth muscle cells | biphasic | biphasic | biphasic |
| Dog | | | biphasic | biphasic | biphasic |

The parietal cells in the fundic gland region are responsible for the production of proteases, of which pepsin is the most well known. Again, the rodent stomach is lagging behind that of man, pig and dog.[4] Gastric lipase (data not shown) is secreted in relatively large quantities around birth and during suckling in most species[5] to give the secretion of pancreatic lipase some time to mature.

Data about gastric motility during gestation are scarce. In humans, gastrointestinal motility is generally believed to be present before birth.[6] In all species, gastric emptying can be considered biphasic, i.e. a rapid phase during which liquid and small particles are emptied and a slower phase for the larger species. In suckling pigs and infants, gastric emptying is not influenced by osmolality.[7] No data are available for dogs.

In the small intestine, the epithelium is responsible for macromolecular transport, and mature enterocytes possess microvilli coated with brush border enzymes. The unique feature of enterocytes in newborn mammals is the presence of an apical canalicular system (ACS) leading to production of large vacuoles important for colostral macromolecule uptake. After birth this ACS gradually disappears.[8] The human intestine is generally less permeable to macromolecules compared with other species.[9]

No big difference in peptidase or dissacharidase activities is observed between the species, except that sucrase activity is seen already before birth in humans, by contrast with pigs and rodents.[10] Prenatal dog data are lacking.

In general, the data above indicate a similar pattern of GI maturation in (mini)pigs compared with humans, definitely more than rodents and possibly also more than dogs, although we need to be cautious as maturation data for the latter species are scarce. However, several "basic" data are still lacking for the GI tract of maturing minipigs as well, such as drug metabolizing capacity and transport. In our lab, we are currently compiling data on length and diameter, surface area expansion factors and pH specifically in juvenile Göttingen minipigs and fetuses. We are also investigating biotransformation capacity to better understand and predict drug disposition in this species.

## References


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**Small intestine**

| Species | | Preterm | Neonate | Weaning | Adult |
|---|---|---|---|---|---|
| Pig | Mature enterocytes | 95% gestation ACS 0.2 A/M Crypts & villi | 1 type ACS disappears 2-3 d transient 0.4 A/M | no ACS Transient lower AM Change to tongue-like villi | Tongue like villi |
| Human | | ? ACS Crypts & villi | ~ ACS | ? | ? |
| Rodent | | ACS Only villi | ACS Crypts & villi | No ACS | ? |
| Dog | | Crypts & villi | ACS (disappear around 14-21 d pn) | No ACS (after 21 d) | Stable morphology/metry at 63 d pn |

| Species | | Preterm | Suckling | Weaning | Adult |
|---|---|---|---|---|---|
| Pig | Disaccharidases | Increase final stage of gestation (lactase >>>> sucrase) | Lactase 1st week pp xx Gradual increase of others | Lactase maintenance level Transient decline of others | |
| Human | | Lactase: Increase 3rd trimester Sucrase 2nd half of gestation (lactase ~ sucrase) | Lactase xx Gradual increase of others | Lactase reduced to maintenance level (5 years) | |
| Rodent | | No sucrase activity | Lactase xx Gradual increase of others | Lactase maintenance level (reached at 4 wks) | |
| Dog | | ? | Lactase xx (gradual decrease) Gradual increase of others | At 21 d pn no lactase activity left Sucrase only from 63 d pn | |

| Species | | Preterm | Suckling | Weaning | Adult |
|---|---|---|---|---|---|
| Pig | Peptidases | Increase final stage of gestation | Gradual decrease | Transient decrease to maintenance level | |
| Human | | 2nd trimester of gestation present, End of gestation total activity = adult | No changes | No changes | |
| Rodent | | Gradual increase | Steady-state | Decrease to maintenance level (1 month of age) | |
| Dog | | Very low | Gradual increase | No changes | |