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Commentary

Similarities and Differences in Gastrointestinal Physiology Between Neonates and Adults: a Physiologically Based Pharmacokinetic Modeling Perspective

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Abstract. Physiologically based pharmacokinetic (PBPK) modeling holds great promise for anticipating the quantitative changes of pharmacokinetics in pediatric populations relative to adults, which has served as a useful tool in regulatory reviews. Although the availability of specialized software for PBPK modeling has facilitated the widespread applications of this approach in regulatory submissions, challenges in the implementation and interpretation of pediatric PBPK models remain great, for which controversies and knowledge gaps remain regarding neonatal development of the gastrointestinal tract. The commentary highlights the similarities and differences in the gastrointestinal pH and transit time between neonates and adults from a PBPK modeling prospective. Understanding the similarities and differences in these physiological parameters governing oral absorption would promote good practice in the use of pediatric PBPK modeling to assess oral exposure and pharmacokinetics in neonates.

KEY WORDS: gastric emptying; gastrointestinal pH; neonates; physiologically based pharmacokinetic modeling; small intestinal transit time.

Although physiologically based pharmacokinetic (PBPK) modeling holds great promise for facilitating pediatric drug development and regulatory review, the implementation and interpretation of pediatric PBPK models continues to face challenges, in which controversies and knowledge gaps remain regarding neonatal development of the gastrointestinal tract. In this context, we would like to offer some comments on the recent article of Khalil and Läer (1). In the work by Khalil and Läer (1), inaccurate predictions of oral pharmacokinetics of sotalol, using two PBPK models, were observed in neonates. The authors ascribed the poor predictions to factors related to the absorption rather than elimination or distribution processes and highlighted the lack of many age-specific physiological alterations in the parameterization of the used pediatric absorption models. Apart from the ontogeny of intestinal transporters and drug-metabolizing enzymes, the authors argued that gastrointestinal pH profiles and transit time should be considered as age-related physiological variables to improve the predictive power of pediatric PBPK models. In this commentary, we provide additional information to facilitate a better understanding of the similarities and differences in gastrointestinal physiology between neonates and adults, which are of critical importance when using PBPK models to simulate oral pharmacokinetics in neonates.

Despite the neutral pH in newborn stomach at delivery has been well recognized (2,3), much of the literature is replete with contradictory information on the maturation of gastric pH during the neonatal period. Some suggested that the neonatal gastric pH is greater than 5, which is quite different from the adult level (4–6); but others believed that the gastric pH of neonates stays within a more acidic range of 2–3, which is similar to that of adults (7,8). Upon careful examination of the reported neonatal gastric pH from comprehensive literature searches, many studies supported that the gastric pH under the fasted state is strongly acidic with a pH value below 3 in even healthy preterm neonates (beyond 24 weeks of gestational age) more than 2 weeks old (9–13). Sondheimer *et al.* measured the gastric pH in 23 healthy preterm neonates who were similar in gestational age and birth weight by continuous gastric pH monitoring (9). They found that the fasting gastric pH in neonates (mean gestational age 33.5 weeks, range 31–37 weeks) at 7–15 days of postnatal age was around pH 2.6 which was significantly lower than that in neonates (mean gestational age 34.0 weeks, range 32–38 weeks) at 2–6 days of postnatal age (an average pH of 4.6). Kelly *et al.* investigated the impact of gestational and postnatal age on gastric pH in 22 preterm neonates without any gastrointestinal disorders (10). Their study showed that the fasting gastric pH reached low adult values between 1.3 and 2.3 in preterm neonates beyond 2 weeks of postnatal age, regardless of gestational age (range 24–29 weeks) or birth weight (range 0.48–1.91 kg). In addition, it is interesting to note that the gastric pH of neonates is also

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Table I. Summary of the Studies of Gastrointestinal pH and Transit Time in Pediatric Populations (focused on Neonates)[a]

Gastrointestinal parameters	Ingested material	Population[b]	Postnatal age	Gestational age	Results	Method	Reference
Gastric pH	Fasted[c]	10 Preterm neonates	7–15 days	33.5 (31–37) weeks	Mean 2.6	*In situ* pH electrode	(9)
	Fasted[c]	13 Preterm neonates	2–6 days	34.0 (32–38) weeks	Mean 4.6	*In situ* pH electrode	(9)
	Fasted[d]	2 Preterm neonates	16–17 days	24–25 weeks	1.6–1.9	*In situ* pH electrode	(10)
	Fasted[d]	10 Preterm neonates	16–17 days	26–27 weeks	1.4–2.3	*In situ* pH electrode	(10)
	Fasted[d]	10 Preterm neonates	16–17 days	28–29 weeks	1.3–2.3	*In situ* pH electrode	(10)
	Fasted[d]	10 Preterm neonates	15–21 days	24–31 weeks	1.5–2.3	*In situ* pH electrode	(11)
	Fasted[e]	9 Preterm neonates	14±3 days[f]	33.1±0.4 weeks[f]	Mean 1.8	pH meter on gastric aspirates	(12)
	Fasted[g]	15 Preterm neonates and infants	N/A	36 (35–38) weeks[h]	Mean 1.9, 1.8, and 3.1[i]	*In situ* pH electrode	(13)
	Fed[j]	9 Preterm neonates	14±3 days[f]	33.1±0.4 weeks[f]	Mean pH around 6	pH meter on gastric aspirates	(12)
	Fed[j]	8 Preterm neonates	19±5 days[f]	31.1±0.9 weeks[f]	Mean pH around 6	pH meter on gastric aspirates	(12)
	Fed[j]	9 Preterm neonates and infants	25±5 days[f]	30.0±1.1 weeks[f]	Mean pH around 6	pH meter on gastric aspirates	(12)
	Fed[k]	15 Preterm neonates and infants	N/A	36 (35–38) weeks[h]	Mean 6.9, 6.0, and 5.7[i]	*In situ* pH electrode	(13)
Luminal pH of small intestine	Fasted[l]	12 Healthy children	8–14 years	N/A	Mean duodenal: 6.4 Mean proximal: 6.6 Mean middle: 7.0 Mean distal: 7.4	Radiotransmitting pH-sensitive capsule	(14)
	N/A[m]	7 Neonates and infants[n]	2 weeks to 3 months	N/A	Duodenal: 6.4±0.5 (5.8–6.9)[o] Jejunal: 6.6±0.4 (6.0–7.0)[o] Ileal: 6.9±0.7 (6.2–8.0)[o]	pH meter on enteric aspirates	(16)
	N/A[m]	8 Neonates and infants[p]	2 weeks to 3 months	N/A	Duodenal: 6.3±0.9 (5.0–7.4)[o] Jejunal: 6.0±0.5 (5.2–6.4)[o] Ileal: 6.3±0.8 (5.4–7.5)[o]	pH meter on enteric aspirates	(16)
Gastric emptying time	Calorie-containing liquid[r]	8 Preterm neonates	17±7 (15, 6–26)[s] days	29.5±2.4 (28, 27–32)[s] weeks	62±33 (54, 30–120)[s] min	Scintigraphy	(22)
	Calorie-containing liquid	Neonates	N/A	N/A	75 min[t]	Meta-analysis[u]	(24,25)

	Calorie-free liquid	Neonates	N/A	N/A	10 min[t]	Meta-analysis[u]	(24,25)
	Total diet (fed)	Neonates	N/A	N/A	75 min[t]	Meta-analysis[u]	(24,25)
Small intestinal transit time	General material[v]	Neonates	N/A	N/A	4 h[t]	Meta-analysis[u]	(24,25)

N/A not applicable
[a] Data are expressed as mean±SD, minimum-maximum, or mean±SD (minimum-maximum)
[b] All these neonates, infants, and children were free from any gastrointestinal problems
[c] At least 3-h fast before measuring
[d] All neonates were totally supported with parenteral nutrition throughout the period of the study
[e] Measured at 3 h after a formula milk feed
[f] Data are expressed as mean±SE
[g] Measured in 3–4 h after a breast milk or infant formula feed
[h] Postmenstrual age
[i] Data represent intragastric pH at 3, 6, and 9 cm below the lower oesophageal sphincter, respectively
[j] Measured immediately after a formula milk feed
[k] Measured in 0–1 h after a breast milk or infant formula feed
[l] At least 8-h fast before measuring
[m] The neonates and infants were maintained on the same feeding regimen throughout the period of the study; however, the feeding regimen was not mentioned in this report
[n] The neonates and infants were fed exclusively with breast milk
[o] Individual data were captured by computer digitization, and subsequently summarized by descriptive statistics
[p] The neonates and infants were fed exclusively with cow's milk
[r] A mixture of ^{99m}Tc (0.2–0.4 MBq, 0.5 mL) and expressed breast milk
[s] Gastric emptying half-time. Data are expressed as Mean±SD (median, minimum-maximum)
[t] Reference value
[u] Information on transit time through gastrointestinal tract published by the International Commission on Radiological Protection (ICRP) is a comprehensive meta-analysis of data derived from various techniques
[v] The reference value of small intestinal transit time is applied to all material, according to the ICRP report

susceptible to feeding schedules. After it increases immediately to a peak of roughly pH 6, the postprandial pH of stomach drops to a value of approximately pH 2 within 180 min (12,13), which is similar to that of adults.

With respect to the luminal pH of small intestine, almost identical patterns were observed between children aged 8–14 years and adults, of which the pH gradually increases along the entire small intestine from 6.4 to 7.4 (14). Another study reported the similar duodenal pH between children aged 0.5–12 years and adults (15). Limited information pertaining to the luminal pH of small intestine was reported for neonates by Barbero *et al.* (16), through our comprehensive literature searches in MEDLINE and EMBASE databases (from inception to June, 2014). In the study by Barbero *et al.* (16), the enteric fluids in various segments of small intestine were obtained from normal neonates and young infants (2 weeks to 3 months of postnatal age) by intestinal intubation combined with aspiration technique. Individual pH values reported by Barbero *et al.* (16) were captured *via* computer digitization, and subsequently summarized by descriptive statistics. Duodenal, jejunal, and ileal pH in seven neonates and infants who were exclusively breast-fed were 6.4±0.5, 6.6±0.4, and 6.9±0.7, respectively; while duodenal, jejunal, and ileal pH in eight neonates and infants who were fed solely with cow's milk were 6.3±0.9, 6.0±0.5, and 6.3±0.8, respectively. The study shows that the pattern of small intestinal pH in the breast-fed neonates and infants (postnatal age 2 weeks to 3 months) was almost the same as that of children and adults. Although the effect of gestational age and feeding schedules on the small intestinal pH profiles of neonates and young infants remains ill-defined, it is very valuable to explore the influence of changes in gastrointestinal pH on the oral absorption of clinical compounds with pH-dependent solubility by PBPK modeling in terms of "what if" scenarios during pediatric drug development, particularly for Biopharmaceutics Classification System (BCS) class II compounds. As to sotalol (a BCS class I drug) whose solubility over biologically relevant pH range is all well above dose/250 mL and independent of the pH of biorelevent media (pH range 1.0–7.5) (17), the importance of gastrointestinal pH in modeling pediatric absorption can be ruled out. More generally, the adult levels of gastrointestinal pH which are implemented in current pediatric absorption models may have little effect on the predictive performance of pediatric PBPK models for compounds with pH-independent solubility.

Various approaches are available to measure gastric emptying, but some techniques, such as 13C-octanoic acid breath test and ultrasonography, still need further validation before they can substitute for scintigraphy in research and in the clinical practice (18–20). The best quality quantitative results of gastric emptying are derived from studies conducted by scintigraphy (a radionuclide imaging technique) which has been regarded as the "gold standard" of gastric emptying studies for not only adult but also pediatric populations (18,21). Bodé *et al.* (22) determined the liquid gastric emptying half-time in eight preterm neonates without gastrointestinal diseases using scintigraphy. The radioisotopes, ^{99m}Tc (0.2–0.4 MBq, 0.5 mL), was administered at the end of a meal (expressed breast milk) *via* a nasogastric tube. One to two milliliters were repeatedly aspirated and discharged by the nasogastric tube to ensure mixing. All neonates were two to four hourly fed with expressed breast milk between scintigraphic images. The gastric emptying half-time of the caloric liquid mixture in eight preterm neonates (postnatal age 17±7 days, gestational age 29.5±2.4 weeks, birth weight 1.37±0.42 kg, mean±SD) was 62±33 min. To relate these results to adults, the average gastric half-emptying time of the skim milk in healthy adults (aged 29±8 years) was 20 min (range 10–33 min), by means of scintigraphy (23). It seems that the gastric emptying of calorie-containing liquids in preterm neonates is slower than that in adults. These findings are in accordance with the International Commission on Radiological Protection (ICRP) report on "Reference Man" (24,25) that has been one of the standard references for detailed anatomical and physiological data in PBPK modeling for many years (26–30). Information on transit time through gastrointestinal tract published by the ICRP is a comprehensive meta-analysis of data derived from various techniques, other than the hydrogen breath test for the measurement of small intestinal transit time which may yield abnormal or unreliable estimates (24,25). More important, the ICRP report provides the standard/typical value of stomach transit time from the neonatal period to adulthood, facilitating the direct comparisons of neonatal *versus* adult gastric emptying. According to the ICRP report, the typical gastric emptying time of calorie-containing liquids in neonates is longer than that in adults: 75 min in newborns compared with 45 min in adult males and 60 min in adult females, while the typical gastric emptying time of calorie-free liquids in neonates is shorter than that in adults: 10 min in newborns compared with 30 min in adults. Interestingly, however, the gastric emptying time under fed conditions (total diet) is comparable in neonates and adult men (75 min *vs.* 70 min). Given that gastric empting is often the rate-limiting step for the absorption of BCS class I compounds (17) and subject to alteration by diet and physiological conditions associated with age, it is of importance for the predictive performance of pediatric absorption models. Assessment of the impact of the gastric transit time on drug exposure in neonates is warranted, even when its variability range had been incorporated in PBPK models because the central estimate of key physiological parameters in PBPK modeling determines the central estimate of the pharmacokinetic profile while the variability range determines the variation of the pharmacokinetic profile.

Concerning the small intestinal transit time, the reference value of neonates (4 h) reported by the ICRP was the same as that of adults (4 h) (24). Furthermore, the small intestinal transit time is independent of material type and not associated with age (24,25), which concurs with those meta-analyses conducted by the developers of PK-Sim (8,31) and Simcyp (32). For a BCS class I drug with high permeability, even a slight change (increase or decrease) in the small intestinal transit time is not expected to have any significant impact on the extent of drug absorption, to say the least.

Table I summarizes the gastrointestinal pH and transit time in neonates. Taken together, when explicitly discriminating between fasted and fed conditions, the gastric pH in neonates (beyond 24 weeks of gestational age) older than 2 weeks of postnatal age is similar to that in adults; nevertheless, the gastric pH may sometimes be observed at

a relatively high value approached to neutral, given that term neonates should feed at 1- to 3-h intervals (33). Limited information on the small intestinal pH pattern indicates that it is reasonable to assume that the small intestinal pH of neonates (especially those who were breast-fed) is the same as that of adults, when parameterize absorption processes in neonates by PBPK modeling. The gastric transit time is strikingly influenced by food types. Delayed gastric emptying often be found in neonates because residual milk always present in the neonatal stomach; however, gastric emptying time in fed conditions is similar between neonates and adults. Small intestinal transit time in neonates is identical to that in adults, independently of age or material type. The commentary highlights the similarities and differences in the gastrointestinal pH and transit time between neonates and adults from a PBPK modeling viewpoint. Furthermore, we advocate that all PBPK in neonates should make an effort to take account of gestational and postnatal age in the model, when possible. Understanding the similarities and differences in these physiological parameters governing oral absorption would promote good practice in the use of pediatric PBPK modeling to assess oral exposure and pharmacokinetics in neonates.

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