Variability in Gastric pH and Delayed Gastric Emptying in Yucatan Miniature Pigs

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INTRODUCTION

Oral drug absorption is commonly studied in the dog. Although the dog model is predictive of bioavailability in man for certain drugs, the agreement is poor for others, especially oral sustained-release formulations (1–3). The physiology of the pig resembles that of man in areas such as cardiovascular, gastrointestinal, renal, and neonatal (4–5), and therefore, the pig may be a promising animal model for the study of human physiology and disease. Recently, miniature swine were used successfully for studying oral drug absorption and metabolism (6–8). In addition, breeding to a smaller size and the development of effective and gentle handling techniques have made the pig a more useful animal model.

The selection of an appropriate animal model in oral dosage form design should be based on similarities in gastrointestinal anatomy and physiology between man and the animal species, including gastrointestinal motility and transit, secretions, pH, fluid volume, gastric emptying, food composition, gut wall or bacterial metabolism, membrane permeability and morphology, and site-specific absorption. Further studies of gastrointestinal physiology are necessary if the pig is to become a useful large animal model for oral drug absorption. Gastrointestinal pH was determined in the fasted state and after a meal in three Yucatan miniature pigs. Results were compared to pH values obtained in humans.

METHODS

Animals

Three healthy male miniature swine of the Yucatan strain were obtained from Charles River Inc. (Wilmington, MA). The animals were individually housed in pens with rubber-coated metal mesh gratings, at a temperature of 68–70°F and approximately 50% relative humidity. The animals were exposed to automated 12-hr lighting cycles. They were fed once daily with minipig chow (Purina Mills) and given water ad libitum. The animals were 1–2 years in age and ranged in weight from 19 to 40 kg (mean, 29 kg) at the time of the studies. The animals were individually conditioned with regard to handling, restraint, and dosing.

Procedure

The pH of the gastrointestinal tract was monitored continuously in three pigs by radiotelemetry, using a Heidelberg pH capsule system (Heidelberg International Inc., Atlanta, GA). This method has been described previously and successfully used in man and dogs (9,10). Briefly, the capsule consists of a battery, a pH electrode, and a high-frequency transmitter enclosed in a 7-mm-diameter and 20-mm-long plastic housing and emits a radio signal according to pH. The pH is activated and calibrated with reference buffers at pH 1.0 and 7.0. Once the calibrated capsule is swallowed, an antenna strapped around the pig's abdomen receives the transmitter output signal, which is then converted to pH and continuously recorded for the duration of the study.

The pigs had been acclimated for several months prior to initiating the pH studies. After fasting for 24 hr, pH capsules followed by 50 mL of water were administered orally by hand between 8 and 10 AM and pH was recorded for approximately 5–8 hr. Results were determined from a strip-chart recording. Gastric emptying of the capsule was defined as the time of rapid change in pH at least 3 units from a low value typical of the stomach to a high value that is maintained for at least 60 min. Meals were given during these studies at approximately 2–6 hr after capsule administration to note the response of pH to food. After initiating the study, water was not given until the meal. During pH recordings, the pigs were allowed to remain in cages of restricted area. Profiles of pH versus time were measured on two occasions separated by at least 2 weeks in each of three miniature pigs. Data are expressed as the mean ±1 SD. The protocol was reviewed and approved by the Ciba-Geigy Animal Care Committee.

RESULTS AND DISCUSSION

A total of six pH profiles was obtained in three fasted miniature pigs. A typical pH profile exhibited two distinct values of gastric pH (Fig. 1). Initially, the pH was high, ranging from 4 to 7 (mean, 6.3 ± 1.6) for 20 min to 4 hr after dosing, at which time the pH decreased within 1 min to a typically low stomach pH, ranging from 0.3 to 1.7 (mean, 1.3 ± 0.7) (Fig. 1, Table I). This type of profile was found in four of six cases. In the fifth case, the pH was initially high (8.6 ± 0.2) but, after a meal at 2.5 hr, drifted lower, to a mean of 5.5 ± 0.5. The pH was perturbed by a meal given during the above studies, indicating the probable presence of the capsule in the stomach. The mean pH in the stomach after the meal was 3.6 ± 1.1 (n = 5). The capsule did not empty from the stomach during the 5–8 hr of pH measurements in these five studies. The pH was still low (0.8–1.2) at 24 hr postdosing during one of these studies in pig 1. In the other four studies, data at 24 hr were unreliable and are not reported. In the other study in pig 1, the capsule still resided in the stomach at the time of necropsy, 54 hr after dosing.

In the sixth case, the capsule emptied from the stomach at 1.3 hr after an initial mean pH of 1.4 ± 0.4 (pig 3A, Fig. 2).

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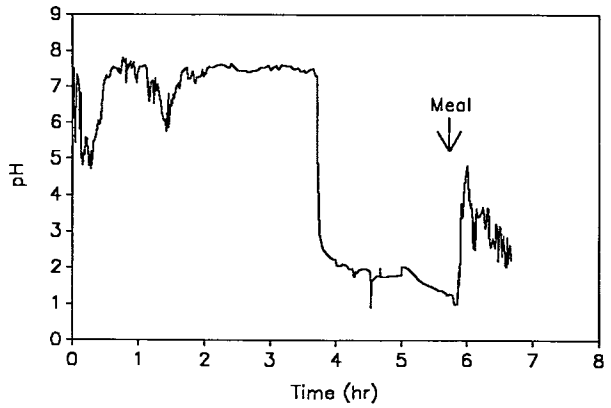

Fig. 1. Gastric pH profile in pig 3A. A meal was given at 5.8 hr. Four of six profiles exhibited this pattern.

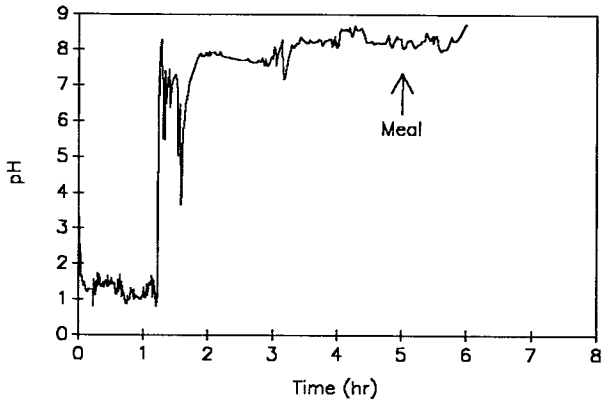

Fig. 2. Gastrointestinal profile in pig 2A. Gastric emptying of the capsule occurred at 1.3 hr. A meal at 5 hr did not alter the pH profile.

A meal given at 5 hr did not perturb the pH values, indicating that the capsule had emptied from the stomach and entered the small intestine. The small intestinal pH was quite high, at approximately 7 initially, drifting higher, to 8.5, over the 6-hr period. The results of these studies are summarized in Table I.

Gastrointestinal pH affects the nonionized fraction and the rate of dissolution and release from enteric-coated and controlled-release formulations and, therefore, can have a significant effect on drug absorption. The gastrointestinal pH values in miniature pig demonstrated several differences from results in man. Although the pig shows no anatomical divisions of the stomach into compartments, considerable differences between the anterior (pH 4.3) and the posterior (pH 2.2) portions of the stomach have been reported in pigs fed ad libitum (11). In the present study, similar results were found in fasted animals using the Heidelberg capsule. Previously reported values of stomach pH in both the miniature and the domestic pig have ranged from 1.2 to 5.0 (11,12). Most of these values were obtained shortly after a meal and/or after euthanizing the animal, which may account for the large observed variability. Although the capsule position was not confirmed in these studies, the abrupt variation in stomach pH may be due to the fact that there is a large cardiac region, composed of mucus cells and devoid of chief (pepsinogen-secreting) and oxyntic (acid-secreting) cells, in the stomach of the pig. The pig has by far the largest cardiac gland region of all species, covering more than a third of the interior surface of the stomach (13). In contrast, a relatively small zone of cardiac glands, 0.5–4 cm in radius, surrounds the esophageal opening in man (14). Gastric pH values are also variable in man, with values ranging from 0.4 to 4.0 (15). However, the pattern of abrupt change in pH from high to low values, where these values are maintained after administration, has not been reported in man or dogs using radiotelemetry. Transit of the capsule through the esophagus can cause initially high pH readings in man and dogs; however, esophageal transit is probably 5–10 min at most (10,15) and is unlikely to account for those profiles where the pH was high for 1–4 hr after dosing.

Table I. Fasted and Fed Gastric pH and Emptying Time in Yucatan Minipigs[a]

Pig	Initial pH (premeal)	Final pH (premeal)	Meal pH	Gastric emptying time (hr)
1A	4.1 ± 1.8 (0–0.9)	0.3 ± 0.2 (0.9–6.0)	2.9 ± 0.8 (6–7.5)	>24
1B	6.2 ± 1.6 (0–0.3)	1.8 ± 0.3 (0.3–6.0)	3.4 ± 1.1 (6–7)	>54
2A	1.4 ± 0.4 (0–1.3)	7.7 ± 1.0 (1.3–6.0)	—[b]	1.3
2B	5.8 ± 1.2 (0–2.2)	1.2 ± 0.4 (2.2–6.0)	3.2 ± 0.9 (6–7.5)	>7.5
3A	6.8 ± 1.1 (0–3.9)	1.7 ± 0.3 (3.9–5.8)	3.0 ± 0.7 (5.8–6.8)	>6.8
3C	8.6 ± 0.2 (0–2.5)	—	5.5 ± 0.5 (2.5–5)	>5

[a] Data are expressed as mean ± SD. Time (hr) after capsule administration in parentheses.

[b] Gastric pH after a meal could not be recorded due to gastric emptying of the capsule.

These results have several implications with regard to the use of the pig as an animal model for evaluation of drug absorption. Premature dissolution of enteric coated dosage forms in the stomach of this species may occur, as pH values greater than 6 were recorded in the stomach. Evaluation of other pH-sensitive controlled-release dosage forms such as hydrogels using the minipig model may not be predictive of their performance in man.

Fasting GI motility is characterized by cyclical fluctuations in contractions called the interdigestive migrating motor complex (IMMC) in man, dog, and pig. In humans, mean IMMC cycle lengths of 90–150 min have been reported (16–18). The cycle length in dogs is quite comparable, ranging from 90 to 110 min (19). Upon feeding, the IMMC is interrupted and replaced by continuous contractions of medium intensity in man and dogs (20). If pigs are fed once or twice per day, they have an IMMC pattern of 75–80 min in length that, as in dogs and humans, is interrupted by feeding. However, if pigs are fed ad libitum, the motility pattern resembles ruminants, where the MMC pattern persists in spite of feeding (21). Emptying of large-unit dosage forms occurs during phase III of the IMMC in man and dogs (20,22). The Heidelberg capsule empties from the stomach of both man and dog in approximately 60–100 min after dosing and appears to correspond to the random occurrence of phase III in relation

to dosing (3,15). In the current study, the capsule did not empty from the stomach during the entire study period of approximately 6 hr in five of six cases. In two of these cases, the capsule remained in the stomach for at least 24 hr. In the sixth case, the capsule emptied from the stomach at a time comparable to that seen in man and dogs, 1.25 hr. Although fasted motor activity in pigs resembles that in man and dogs, the mechanism of gastric emptying of large objects appears to be unrelated to the presumed phasic activity in pigs. Hossain *et al.* recently reported gastric residence times in excess of 7 days for the Heidelberg capsule and large nondisintegrating dosage forms in young adult white Yorkshire pigs (45 kg) (23). The current findings in minipigs confirm their results in domestic pigs. Delayed gastric emptying and high variability in gastric pH may preclude the use of minipigs for evaluation of drug formulations, particularly controlled or delayed-release and enteric-coated dosage forms.

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REFERENCES

1. W. A. Cressman and D. Sumner. The dog as a quantitative model for evaluation on non-disintegrating sustained-release tablets. *J. Pharm. Sci.* 60:132–134 (1971).
2. W. Crouthamel and A. C. Sarapu. *Animals Models for Oral Drug Delivery in Man: In Situ and in Vivo Approaches,* American Pharmaceutical Association, Washington, DC, 1980.
3. J. B. Dressman. Comparison of canine and human gastrointestinal physiology. *Pharm. Res.* 3:123–131 (1986).
4. W. G. Pond and K. A. Houpt. *The Biology of the Pig,* Comstock, Ithaca, NY, 1978.
5. M. E. Tumbleson (ed.). *Swine in Biomedical Research,* Plenum Press, New York, 1985.
6. H. Souhaili-El Amri, A. M. Batt, and G. Siest. Comparison of cytochrome P450 content and activities in liver microsomes of seven animal species, including man. *Xenobiotica* 16:351–358 (1986).
7. C. L. Litterst, T. E. Gram, E. G. Mimnaugh, P. Leber, D. Emmerling, and R. I. Freudenthal. A comprehensive study of *in vitro* drug metabolism in several laboratory species. *Drug Metab. Disp.* 4:203–207 (1976).
8. E. Harboe, C. Larsen, M. Johansen, and H. P. Olesen. Macromolecular prodrugs. XIV. Absorption characteristics of naproxen after oral administration of a dextran T70-naproxen ester prodrug in pigs. *Int. J. Pharm.* 53:157–165 (1989).
9. J. B. Dressman and G. L. Amidon. Radiotelemetric method for evaluating enteric coatings *in vivo*. *J. Pharm. Sci.* 73:935–938 (1984).
10. C. A. Youngberg, J. Wlodyga, S. Schmaltz, and J. B. Dressman. Radiotelemetric determination of gastrointestinal pH in four healthy beagles. *Am. J. Vet. Res.* 46:1516–1521 (1985).
11. H. W. Smith. Observations on the flora of the alimentary tract of animals and factors affecting its composition. *J. Pathol. Bacteriol.* 89:95–122 (1965).
12. W. G. Huber and R. F. Wallin. *Swine in Biomedical Research,* Frayn, Seattle, 1966.
13. W. O. Sack. *Essentials of Pig Anatomy,* Veterinary Textbooks, Ithaca, NY, 1982.
14. H. W. Davenport. *Physiology of the Digestive Tract,* 5th ed., Year Book Medical, Chicago, 1982.
15. C. Y. Lui, G. L. Amidon, R. R. Berardi, D. Fleisher, C. A. Youngberg, and J. B. Dressman. Comparison of gastrointestinal pH in dogs and humans: Implications on the use of the beagle dog as a model for oral absorption in humans. *J. Pharm. Sci.* 74:271–274 (1986).
16. P. Kerlin and S. Phillips. Variability of motility of the ileum and jejunum in healthy humans. *Gastroenterology* 82:694–700 (1982).
17. P. Fleckenstein. Migrating electrical spike activity in the fasting human small intestine. *Digest. Dis.* 23:769–775 (1978).
18. P. Fleckenstein and A. Oigaard. Electrical spike activity in the human small intestine. A multiple study of fasting diurnal variations. *Digest. Dis.* 23:776–780.
19. C. F. Code and J. Schlegel. The gastrointestinal interdigestive housekeeper: Motor correlation of the interdigestive myoelectric complex of the dog. In E. E. Daniel (ed.), *Proceedings of the Fourth International Symposium on GI Motility,* Mitchell Press, Vancouver, 1973.
20. K. A. Kelly. Motility of the stomach and gastroduodenal junction. In L. R. Johnson (ed.), *Physiology of the Gastrointestinal Tract,* Raven, New York, 1981.
21. Y. Ruckebusch and L. Bueno. The effect of feeding on the motility of the stomach and small intestine in the pig. *Br. J. Nutr.* 35:397 (1976).
22. R. Khosla and S. S. Davis. The effect of tablet size on the gastric emptying of non-disintegrating tablets. *Int. J. Pharm.* 62:R9–R11 (1990).
23. M. Hossain, W. Abramowitz, B. J. Watrous, G. J. Szpunar, and J. W. Ayres. Gastrointestinal transit of non-disintegrating nonerodible oral dosage forms in pigs. *Pharm. Res.* 7:1099–1012 (1990).