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Review

Comparison of Canine and Human Gastrointestinal Physiology

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In this review, the gross physiology of the gastrointestinal tract of dogs is compared with that of humans, particularly as it pertains to drug absorption and dosage-form performance. Gastrointestinal (GI) motility and pH are the main parameters considered. Although similar motility patterns and pH profiles prevail in the two species for the most part, there are some differences that could affect the time profile and extent of drug absorption. These include slower gastric emptying in the fed state, faster small intestine transit, and higher and more variable intestinal pH in dogs compared with humans. An attempt is made to identify drug and dosage-form properties that would lead to differences in drug absorption in the two species, e.g., drug physicochemical properties, dosage-form size, and pH dependency of dosage-form release characteristics.

KEY WORDS: drug absorption; gastrointestinal tract, dogs; gastrointestinal mobility and pH; gastrointestinal drug absorption.

INTRODUCTION

Dogs have been used extensively in drug and dosage-form testing prior to the introduction of products into human subjects. The canine model is particularly popular for oral dosage-form testing since the dimensions of the gastrointestinal (GI) tract are similar enough to permit the administration of dosage forms intended for subsequent testing in humans. Added attractions of using dogs are that, in many cases, drug bioavailability is comparable to that in humans and that dogs are easier to handle than other species of similar size such as miniswine and monkeys.

The use of dogs in bioavailability studies has been reviewed by Crouthamel and Bekersy (1). Although the dog is a very useful model, a significant number of cases exist for which there is a large discrepancy between the oral bioavailability observed in dogs and that observed in humans. Underprediction of drug absorption based on canine data may lead to unnecessary formulation efforts, choice of an alternative route of administration, or even abandonment of further drug development. Overprediction is also a problem in that extra testing of reformulated drug in humans will then be required; this may add considerably to the expense of the drug development process.

The frustration for those involved in the drug development process is that the current understanding does not enable us to evaluate whether or not a particular drug/dosage-form combination will be absorbed better, less well, or about the same in humans as in dogs. There are many possible reasons for a discrepancy in oral bioavailability between dogs and humans. The drug may be less available for absorption in terms of solubility or partitioning as a function of pH, it may be absorbed by different mechanisms in the two species, it may undergo first-pass metabolism to differing extents, or it may be housed in a dosage form which is handled differently in the GI tracts of the two species.

This review focuses on two aspects of gastrointestinal (GI) physiology that may affect the availability of drug for absorption, namely, the transit time (motility) and the pH. By identifying those aspects of GI physiology that differ in the two species, it should be possible to develop a more rational method for predicting circumstances in which the time profile and/or extent of drug absorption will vary between dogs and humans.

MOTILITY

The combination of a residence time of several hours with the large surface area of the small intestine suggests that this is the major site of drug absorption in the GI tract, although clinical evidence suggests that some drugs, e.g., theophylline (2) and metoprolol (3), are also absorbed from the colon. In general, though, the more viscous contents of the colon and the lack of villi (and hence lower surface area) will tend to offset the longer colonic residence time. In the stomach both surface area and residence time are small, although it should be noted that gastric residence time may be prolonged in special circumstances. The drug contact time with the main absorptive sites therefore depends mainly on the residence time of the dosage form and its released contents in the small intestine. For those dosage forms which release drug in the stomach, one must also consider the gastric residence time. This is because during gastric residence such dosage forms will supply drug to the small intestine according to the gastric emptying pattern of released drug. Taking these factors into consideration, it appears that the upper GI residence time is the important parameter to compare between species. Residence time is of particular interest for drugs which are incompletely absorbed, as a change in the contact time with the major absorptive region

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may be expected to result in a change in the fraction absorbed.

Gastric Residence Time

The residence time of a drug in the stomach depends on several factors, e.g., whether it is administered in liquid or solid form, the volume administered in the case of liquid dosage forms, and the particle size in the case of administration of a solid dosage form. An additional complicating factor is the variation in motility pattern in the fasted versus the postprandial state, which may significantly affect the gastric residence time of certain dosage forms.

In the fasted state, there is a cyclic pattern of motility in the upper GI tract consisting of three main phases (4). The sequence consists first of a quiescent phase, accounting for about half of the fasting cycle period, during which there is little contractile activity. In the second phase, irregular contractions start to occur, which gradually increase in amplitude and frequency. When these progress into a maximal amplitude and frequency of contraction, this is designated Phase III activity. Phase III activity in the stomach is usually associated with the initiation of a migrating motility complex (mmc) in the duodenum, which then proceeds to migrate through the small intestine toward the ileum. At the end of Phase III activity, the stomach reverts to the quiescent phase. Thus, in the fasting state, contractile activity in the stomach ranges from resting to maximal amplitude and frequency. The current knowledge pertaining to fasted GI motility cycles has been thoroughly reviewed by Sarna (5). A typical cycle of human gastric contractions is shown in Fig. 1. Note that Phase III contractions are stronger than Phase II or postprandial contractions (5), having sufficient force to occlude the lumen in some cases (6), so that the contractions can expel the entire gastric content into the small intestine.

Feeding results in a profound alteration in the GI motility pattern (7). In the stomach the cyclic contractile pattern is replaced by regular tonic contractions which propel food toward the antrum while mixing it with gastric secretions. Antropyloric contractions occur in a manner which permits fine particles and liquids to pass into the duodenum while resulting in retropulsion of larger particles into the body of the stomach (6,8). When the meal has finished emptying from the stomach, the fasting motility pattern is resumed.

These motility patterns are qualitatively followed by both dogs and humans. Several quantitive details are of importance to drug absorption. For instance, the gastric residence time of drugs given in liquid dosage forms will depend on the liquid emptying rate. Also, since large objects empty only during Phase III activity, the gastric residence time of nondisintegrating solid dosage forms will depend on the frequency of Phase III activity if given in the fasted state and the time for Phase III activity to be reestablished after a meal if given in the fed state. In contrast to large objects, the available evidence suggests that fine particles are emptied at a similar rate to digestible solids in the fed state (9). Therefore, the dependency of emptying on the dosage-form particle size in the two species is also of interest.

Frequency of Gastric Phase III Activity

Sarna *et al.* (10,11) have studied gastric motility using pressure transducers in both dogs and humans. They found that Phase III activity lasts for 18.6 ± 4 min in humans, almost identical to the duration in dogs, 19 ± 2 min. The interval between Phase III activity cycles was observed to be 106 ± 8 min in dogs. These data were corroborated by Russell and Bass (12), who observed a periodicity of 128 min. In humans, Phase III activity fronts are observed every 112.5 ± 11.4 min (mean ± SE) (13). The usual cycle period therefore appears to be about 2 hr in both species, noting that times ranging between 1 and 3 hr are quite common. Phase III activity in the stomach is usually associated with initiation of Phase III activity in the duodenum. The duration of activity in the duodenum is much shorter, however, about 3 to 5 min. The activity front is then propogated down the intestine before dying out, most commonly in the mid to distal ileum (14).

In the fasted state, Phase III activity is associated with bolus emptying of the stomach. The time of gastric emptying of monolithic dosage forms such as enteric-coated tablets and single-unit controlled-release systems should therefore be the time elapsed between the administration of the dosage form and the next Phase III activity. We have used the Heidelberg capsule as a model object (it is approximately the size of a No. 0 capsule) to compare gastric emptying times in humans and dogs after an overnight fast (15,16). A wide range of gastric emptying times was observed in both species, with the average time to empty 74 ± 27 min in dogs and 77 ± 19 min in healthy human volunteers.

In conclusion, it appears that fasted GI motility patterns are very similar in dogs and humans and that gastric residence times of indigestible monolithic dosage forms are expected to be very similar in the two species in these circumstances.

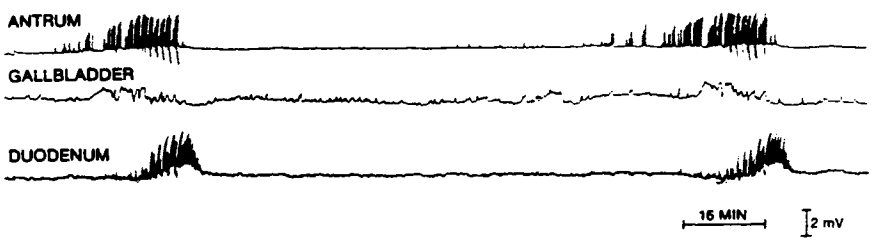

Fig. 1. Typical cyclic activity of human gastric contractions. (Reproduced from Ref. 5 with permission.)

Rate of Liquid Emptying

In considering gastric emptying of liquids, three cases are relevant—emptying of nonnutrient liquids in the fasted state, emptying of nutrient liquids, and emptying of liquids consumed with meals. When water or normal saline is ingested in the fasting state, there is usually no interruption of the fasting motility pattern (17) and emptying follows an approximately exponential pattern. The half-emptying time in humans has typically been reported in the 8- to 15-min range (18,19). Data reported for dogs are consistent with those in humans: Stephens *et al.* (20) found that about 90% of ingested fluid is emptied within 25 min, while Ehrlein and Prove (21) reported a half-emptying time of 4 to 5 min. Increasing viscosity or administering hyperosmotic solutions results in a slower gastric emptying rate (22,23).

When nutrient fluids are ingested, the fasting motility pattern is interrupted. In these circumstances feedback mechanisms in the duodenum result in a slower, approximately linear emptying pattern. The half-emptying time for a 25% glucose solution, for example, was reported to be 75 min in humans (18). The duodenal "braking" mechanism has a similar effect in dogs; the presence of tryptophan, for example, lowers the gastric emptying rate by a factor of approximately five (20).

When fluids are ingested with a solid meal, they tend to empty more slowly than when given alone. For smaller meal sizes, liquid is emptied faster than the solid fraction of the meal, and emptying follows an approximately exponential relationship. In humans, consumption of very large meals has been shown to result in convergence of the solid and liquid emptying. Half-emptying times of the order of 30 min after a small meal have been reported (24,25), whereas after a large meal this was prolonged to 3 hr (24). Figure 2 (26) shows the emptying rates of liquid and solid fractions of a meal in dogs, using radiolabeled microspheres as a marker of liquid emptying. As with humans, the liquid empties faster than the solid fraction, but the half-time of emptying is about 90 min even with a fairly small meal (100 g steak and liver). Similarly, Hinder and Kelly (27) observed a liquid half-emptying time of 60 min when given with 50 g of cubed liver. Unfortunately, no direct comparison, using identical meal and fluid, of liquid emptying rates in the two species is available (see Rate of Emptying of Solid Meals for a comparison of solids emptying). Overall, it appears that gastric handling of liquids is qualitatively very similar in dogs and humans, but while liquid emptying in the fasted state is quantitatively similar, emptying in the postprandial state may take considerably longer in dogs.

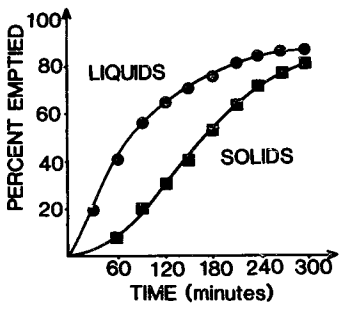

Fig. 2. Emptying of liquid and solid meal fractions from the canine stomach. (Reproduced with permission from Ref. 26.)

Rate of Emptying of Solid Meals

The rate at which meals empty from the stomach is of interest for two reasons. First, for some therapeutic actions it may be desirable for the dosage form to empty in concert with the meal, e.g., enzyme replacement therapy, bile salt replacement, and cholesterol sequestration. Alternately, for controlled-release dosage forms of some drugs, it may be desirable to delay emptying from the stomach in order to maximize the contact time of the drug with absorption sites in the upper GI tract. Typical rates of solid-meal emptying are shown in Table I. Emptying rates are quite dependent on meal size and composition (24,28) so for meaningful comparison a standard meal must be given to each species. Meyer *et al.* (31,32) studied emptying of a liver and steak meal in both dogs and humans. In both species there is substantial individual variation in the meal emptying rate, but the results clearly indicate that emptying is considerably slower in dogs than in humans.

Dosage forms intended to empty in concert with or after the meal are therefore expected to exhibit a longer gastric residence time in dogs than in humans.

Time for Phase III Activity to Return After Feeding

Since large monolithic dosage forms will remain in the stomach until Phase III activity is reestablished, studies of the delay in return of Phase III activity after feeding are also of interest. Table II lists representative data in dogs and humans.

A clear dependency of the time for return of Phase III activity on the meal size is apparent for both species. Again, the delay in return of Phase III activity after feeding is observed to be much longer in dogs than in humans. Given this information, one should be wary of extrapolating results of controlled-release dosage-form studies peformed in fed dogs to postprandial human absorption. Such extrapolation may lead to overprediction of the duration and extent of absorption from the dosage form, especially for drugs which are absorbed primarily in the upper GI tract.

Particle-Size Effects on Emptying in the Postprandial Phase

Multiparticulate dosage forms usually fall in the size range between very fine particles, which empty with fluid, and those which are too large to empty except in conjunction with Phase III activity. The relationship between particle size and rate of gastric emptying is of interest, as this

Table I. Gastric Emptying of Solid Meal Fraction

Species	Meal	$t_{1/2}$ (min)	Ref. No.
Human	213 g stew, 50 g liver	117	29
	208 kcal pate, lettuce, oil	130	28
	225 g stew, 30 g liver	70	30
	150 g stew, orange juice	77	24
	60 g steak, 30 g liver	115	31
Canine	60 g steak, 30 g liver	180	32
	100 g liver	180	33

Table II. Return of Phase III Activity After Meals

Species	Meal	Method[a]	Time for Phase III activity to resume (min)
Human	Breakfast	1	105–420[b]
	285 kcal, liquid	2	156 ± 54 (SD)[c]
	500 kcal, solid	2	288 ± 90 (SD)[c]
Canine	Not specified	1	>450[d]
	400 kcal, solid	2	>360[e]
	30 kcal/kg, solid	3	324 ± 23 (SE)[f]
	60 kcal/kg, solid	3	561 ± 31 (SE)[f]
	90 kcal/kg, solid	3	799 ± 33 (SE)[f]

[a] (1) Onset of drug levels; (2) pH change; (3) electrical activity.
[b] From Ref. 34.
[c] From Ref. 35.
[d] From Ref. 36.
[e] From Ref. 15.
[f] From Ref. 37.

will dictate the onset (for enteric-coated particulates) and duration of action for drugs given in these dosage forms. In the postprandial state, a pyloric sieving effect has been demonstrated in both dogs and humans. Meyer *et al.* (31,32) reported that over 97% of the meal empties as particles smaller than 1 mm in diameter, and in humans more than 80% of the chyme leaving the stomach falls in this size range. In a systematic study investigating the emptying of nondigestible spheres in dogs (26), particles of density 1 and particle size 1.6-mm diameter or less emptied faster than the meal, while particles larger than 2.4 mm in diameter emptied slower than the meal. The relationships among size, density, and emptying relative to the meal are shown in Fig. 3. Table III shows representative data for postprandial emptying of nondigestible particles in humans. The general trend is very similar to that observed by Meyer *et al.* (26) in dogs. Particles of less than 0.5 mm appear to empty with fluid, particles of 0.5–3 mm empty sometime during the course of the meal, and objects larger than 4.5 mm are usually delayed until the meal has emptied. However, a more systematic study along the lines of the canine study by Meyer *et al.* will be required

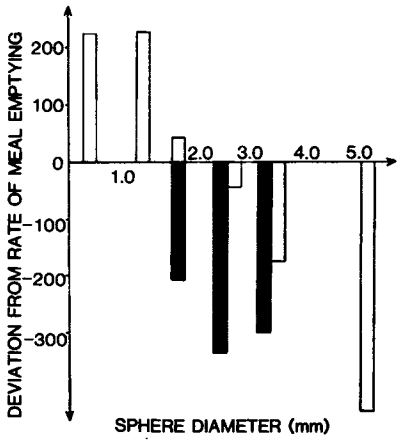

Fig. 3. Particle size and density effects on particle emptying relative to meal emptying (canine stomach). Open bars correspond to a density of 1; closed bars, to a density of 2. (Reproduced with permission from Ref. 26.)

Table III. Postprandial Gastric Emptying of Nondigestible Particles in Humans

Size	Gastric residence time (min)	Method[a]
14 mm[b]	180–>780	1
Enteric-coated tablet		
10 mm[c]	>240	2
9 mm[d]	$\bar{x}$ = 255 (105–>600)	3
3 mm[b]	$\bar{x}$ = 480 (45–>600)	1
0.7- to 1.2-mm pellet		
400 kcal	$\bar{x}$ = 119 ± 15 (SE)	1
900 kcal	$\bar{x}$ = 255 ± 45 (SE)	1
1 mm[b]	$\bar{x}$ = 160 (60–240)	1
0.16–0.4[f]	$\bar{x}$ = 58 (34–75)	1

[a] (1) Scintigraphy; (2) onset of drug level; (3) X ray.
[b] From Ref. 38.
[c] From Ref. 39.
[d] From Ref. 34.
[e] From Ref. 40.
[f] From Ref. 9.

to define the precise relationship between size and emptying in humans.

Small Intestine Transit Time

As the small intestine has a very large surface area compared with the rest of the GI tract and, additionally, is the region in which virtually all carrier-mediated uptake occurs, it is expected to be the major site of absorption for most drugs. For drugs which are poorly soluble, have a poor lipid solubility, and/or rely on carrier-mediated uptake for absorption, a change in the small intestine residence time could therefore significantly alter the extent of absorption.

Not as many data are available with respect to small intestine transit compared with gastric emptying, owing to an added degree of experimental difficulty. The use of radiopaque dosage forms/fluids and repeated X ray results in a high dose-burden of radiation, while γ-scintigraphy requires the use of either isotopes which have very short half-lives (e.g., ^{113m}In, 99 min) and must therefore be prepared very hot, creating safety problems in preparation (41), or isotopes with longer half-lives (e.g., ^{51}Cr), which have a high radiation burden in the colon. In addition, there may be problems in defining the region of interest, in assuming that the isotope remains associated with the particle of interest during transit, and in making corrections for downscatter and collimation errors. These have been discussed by Malagelada (42) and Vandeventer *et al.* (43). γ-Scintigraphy, however, is the method of choice for residence-time studies. Breath-hydrogen measurements following lactulose (44) are fraught with inaccuracy due to variable bacterial colonization of the colon and do not differentiate gastric from intestinal residence. Total GI residence time is not an accurate indicator of small intestine residence time, as the colonic residence time, which is quite variable (45), accounts for most of the total transit time.

Representative data are listed in Table IV. In the landmark study by Malagelada *et al.* (46) in humans, γ-scintigraphic data for both fluid and fiber transit were deconvoluted to determine the mean small intestine residence time in

Table IV. Intestinal Transit Times in Postprandial Phase

Species	Marker	Meal	Mean transit time (min)	Ref. No.
Human	1- to 5-mm fibers	Light	164 (same as liquid)	46
	0.7- to 1.2-mm pellets	Light	188	40
		Light	146	40
		Heavy	202	40
		Heavy	512	40
	2 × 4-mm tubing	Not documented	300	47
	Osmotic pump	Light	191	40
	Tablet	Heavy	275, >600	48
Canine	0.5 mm	Perfusion	Same as liquid	49
	2–3 mm	Perfusion	¼ liquid rate	49

the fed state. These authors found that fibers and fluid had similar residence times of just under 3 hr. Several other studies have also examined small intestine transit in humans. Overall it appears that transit consistently takes 3–5 hr, independent of particle size, when subjects are fasted (50) or have ingested a light meal. Some studies from Davis' group (40,48) indicate that transit may be prolonged after a heavy meal, although the number of subjects involved is low. The effect of meal size on intestinal transit time has not been studied in dogs. Perfusion studies have suggested that the particle size can significantly affect the transit rate in fed dogs (49), a relationship that has not been observed in humans. This effect may, however, be an artifact of the perfusion conditions (flow rates of 10 ml/min using low-viscosity solutions), since in the absence of perfusion, particle transit times were similar to those of fluid for both sizes studied (51).

Using the Heidelberg capsule technique, we have investigated small intestinal residence times in fasted dogs and humans (52). It appears that when the capsule passes into the cecum, the pH rises abruptly, then falls slowly again, subsequently fluctuating much less than in the small intestine (see Fig. 4). This pH pattern has been correlated with the entry of the capsule into the cecum/proximal colon in dogs (52). A mean small intestine residence time of 238 ± 14 min was observed in eight human subjects, consistent with transit times measured by others under fasting or light-meal conditions. The transit time in dogs was less than half as long as that in humans, 111 ± 17 min, and much more variable on a percentage basis. The range in dogs was 15 to 206 min, compared with 180 to 300 min in humans. This suggests that drug absorption is likely to be more variable and less complete in dogs. However, some poorly lipophilic compounds such as chlorothiazide, acyclovir, and phosphalinic acid are actually more extensively absorbed in dogs than in humans (53–57). These apparently anomalous findings provide an interesting subject for future research.

GASTROINTESTINAL pH

Gastrointestinal pH can affect dosage-form performance and drug absorption in several ways. For drugs that are passively absorbed, the nonionized form is generally better absorbed than the ionized species. An alteration in the effective fraction available in the nonionized form as a function of the pH may therefore dictate the rate of absorption of drugs with dissociation constraints in the physiological pH range. In the case of lipophilic compounds, extraction across the intestinal membrane may occur even when the fraction in the nonionized form is small. For these drugs, the pH of half-maximal absorption (58), rather than the pKa, should be considered. For poorly lipophilic compounds, the pH of half-maximal absorption and the pKa will be similar. If the pH of half-maximal absorption falls within the range ob-

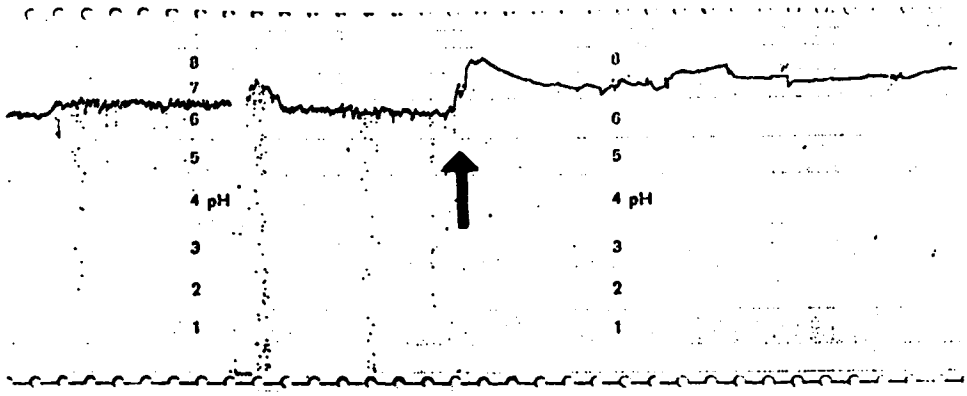

Fig. 4. Change in pH recording as the Heidelberg capsule enters the cecum (canine profile).

served in the GI tract, changes in pH due to feeding, disease state, or species difference may result in a change in bioavailability. For actively absorbed drugs, the fraction available in the ionization state which has the most affinity for the carrier is the parameter to consider, and this can be similarly influenced by variation in the GI pH. A second potential effect of a changing GI pH is that it may influence the rate of drug dissolution, an important limitation to absorption in the case of poorly soluble drugs. A third area of consideration in terms of GI pH is the release of drug from enteric-coated products. Enteric-coating polymers have dissolution profiles which are extremely pH dependent, that is, over a critical pH range, an increase in pH of 1 to 2 units results in rapid polymer dissolution and drug release versus virtually no dissolution (59). Differences in GI pH between species could therefore have a profound effect on the performance of enteric-coated products. Other dosage forms, particularly those designated for controlled release, often exhibit pH-dependent release profiles *in vitro* and so their performance may also be expected to change under different GI pH conditions.

Gastric pH

Gastric acid output has been measured in both dogs and humans in many studies. The data listed in Table V represent commonly accepted values.

Although dogs have lower basal acid secretory rates than humans, the peak gastric acid response is considerably higher in the dog. Gastric pH in the fasted state, however, is quite acid in dogs as well as in humans. Presumably this results from a small residual pool of acid and gastric debris which is usually retained in the stomach (64). Comparative pH data obtained with the Heidelberg capsule technique (52) are available for dogs and humans. The fasted gastric pH in dogs was found to be 1.5 ± 0.04 (mean ± SE), with a range of 0.9 to 2.5. In humans, the pH ranged from below pH 1 to pH 3.2, with a mean minimum gastric pH of 1.3 and a mean maximum pH of 2.1. Mean data for postprandial gastric pH in humans are shown in Fig. 5 (65). There is an initial increase in pH due to the buffering effect of food, then as gastric acid is released in response to eating, the pH gradually returns to premeal values over a period of 60 to 90 min. Similar profiles have also been observed by Malagelada *et al.* (66).

In dogs, the initial buffering effect of the food is not observed and there is no trend in pH over the first postprandial hour (15). The pH is more variable postprandially, with a range of 0.5 to 3–5 and a mean pH of 2.1. A partial explanation for the absence of an early elevation in pH due to buffering by foods may be the higher peak acid output in dogs. Also, the peak acid output in humans does not occur until about an hour after meal ingestion (66). In addition, it is possible that there is some dependency of the pH peak on the order of administration of fluids versus solids.

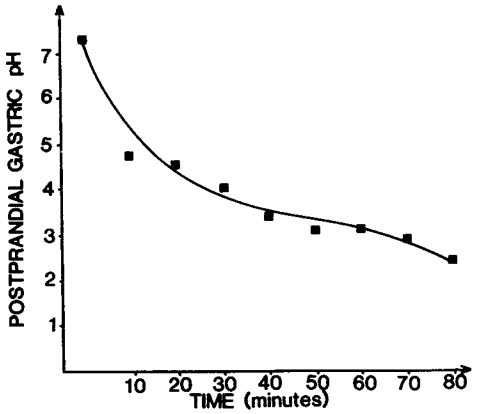

Fig. 5. Postprandial gastric pH in human subjects.

Overall results suggest that while the gastric pH in dogs and humans is very similar in the fasted state, the initial postprandial pH peak that occcurs consistently in humans appears to be absent in dogs and the pH response to meals is less predictable, ranging from no change relative to the premeal pH to a 2–3 pH unit elevation during the first postprandial hour.

Intestinal pH

The higher pH encountered in the small intestine compared with the stomach is attributable mainly to bicarbonate secretion by the pancreas, although there is also exchange for chloride ion across the intestinal wall and small amounts of bicarbonate are found in bile. Pancreatic bicarbonate secretion data are listed in Table VI.

In the fasted state, basal gastric acid secretion is lower in dogs and the concentration of bicarbonate in pancreatic secretion is similar to that in humans so that one may expect the mean intestinal pH to be higher than in humans. Also, the rate of bicarbonate secretion (200 μmol/hr) in the fasted state in dogs (69) is higher than the acid basal secretion rate (100 μmol/hr), whereas in humans the reverse is true (70) (380 μmol/hr HCO_3^- vs 3 mmol/hr H^+). In addition, the pan-

Table V. Canine and Human Gastric Acid Secretion

	Human[a]	Canine
Basal	3.7 ± 2.1 (male) mEq/hr 2.2 ± 1.8 (female) mEq/hr	0.1 mEq/hr[b]
Peak (maximal histamine response)	23 ± 7 (male) mEq/hr 18 ± 5 (female) mEq/hr	39 ± 5 mEq/hr[c] 0.5 mEq/kg/hr[d]

[a] From Ref. 60.
[b] From Ref. 61.
[c] From Ref. 62.
[d] From Ref. 63.

Table VI. Pancreatic Bicarbonate Secretion in Humans and Dogs[a]

	Humans	Dogs
Basal	20 – 25 mEq/l (minimum)[b]	23.9 ± 17.8 mEq/l[c]
Secretin test	76 ± 7 mEq/l[d]	60 ± 20.5 mEq/l
	0.2 ± 0.076 mEq/kg/hr[d]	2 ± 1.29 mEq/kg/hr

[a] Data are expressed as mean ± SD.
[b] From Ref. 64.
[c] From Ref. 68.
[d] From Ref. 67.

creatic bicarbonate output appears to be more variable in dogs than in humans. These findings are consistent with the measured intestinal pH in the fasted state (Fig. 6) (71). These data were obtained using Heidelberg capsules in both species, with the capsules allowed to move freely through the GI tract as a function of time.

Intestinal pH is consistently 1 unit higher in dogs than in humans when comparison is made at times normalized to gastric emptying of the pH measuring device.

On the basis of these results, drugs with half-maximal absorption pH in the range pH 5 to 7 may be expected to be absorbed at different rates in human and dog. Several illustrative examples have been discussed by Lui *et al.* (71). Canine intestinal pH at any given time had a wider range than the human data, so the absorption of poorly absorbed drugs with a half-maximal pH in this range may therefore also be expected to be more erratic in dogs (i.e., larger intersubject variation). An additional situation in which the elevated intestinal pH in dogs relative to humans may result in altered dosage-form performance is the testing of enteric-coated products. If the pH required for fast coating dissolution is 6–6.5, one might expect much more consistent performance in dogs than in humans. Of course, if the coating dissolves rapidly at a pH below 5.5, rapid release in the intestine would be expected in both species.

Limited data are also available for postprandial duodenal pH in both species. Table VII shows human duodenal data following a meal, with data expressed as minutes per hour in various pH ranges. Rapid pH fluctuation, caused by entry of acid chyme followed by pancreatic bicarbonate neutralization, makes definition of a mean pH value inappropriate. Overall, though, the pH decreases from a baseline value of pH 6 to about pH 5 over the course of 4 hr.

In dogs, the duodenal pH decreases more rapidly and to a greater extent than in humans. Figure 7 shows Ehrlein and Prove's canine data following a mashed potato meal (21), with chyme diverted from the duodenum via a cannula inserted at about the level of the pancreatic papilla. The mean pH decreases to a value of 3 within a 90-min interval. The chyme was sampled more proximally in dogs than in the human studies, and hence less time was available for neutralization prior to sampling for pH. Thus although a qualitative difference in postprandial pH is evident, it may not be quantitatively as great as suggested by the above data. Even

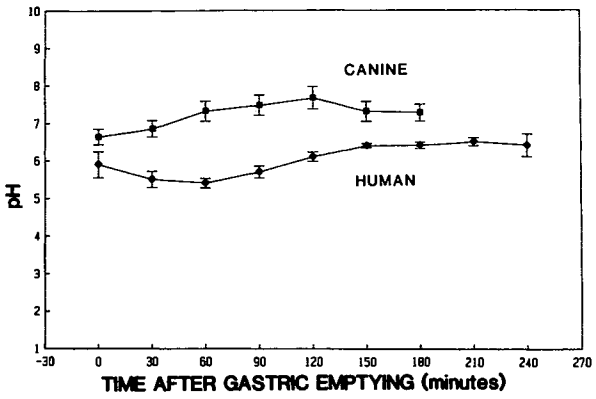

Fig. 6. Intestinal pH in fasted dogs and humans. (Reproduced with permission from Ref. 71.)

Table VII. Time (Minutes) Spent at pH Levels Greater Than 4, 5, 5.5, and 6 in Each Postprandial Hour in Human Duodenum (From Ref. 16)

Postprandial hr	pH			
	>4	>5	>5.5	>6
1	59.8	45.0	33.8	17.9
2	56.2	31.8	23.5	6.7
3	57.7	33.6	18.4	5.1
4	55.3	28.8	16.6	2.8

so, though, there appears to be a greater change in duodenal pH on going from the fasted to the fed state in dogs than in humans. For drugs and dosage forms susceptible to pH-dependent performance, one may therefore see a greater effect of food on absorption using the dog model than would occur in humans.

SUMMARY AND CONCLUSIONS

In general, the gross physiology of the stomach in humans and dogs is very similar in the fasted state, with similar motility patterns, gastric emptying of indigestible solids and liquids, and gastric pH. The higher intestinal pH observed in dogs is the main difference between the species in the fasted state and would be of concern for those drugs with a half-maximal absorption pH in the pH 5 to 7 range and for the evaluation of enteric-coated products with a dissolution pH in this range. The shorter intestinal transit time

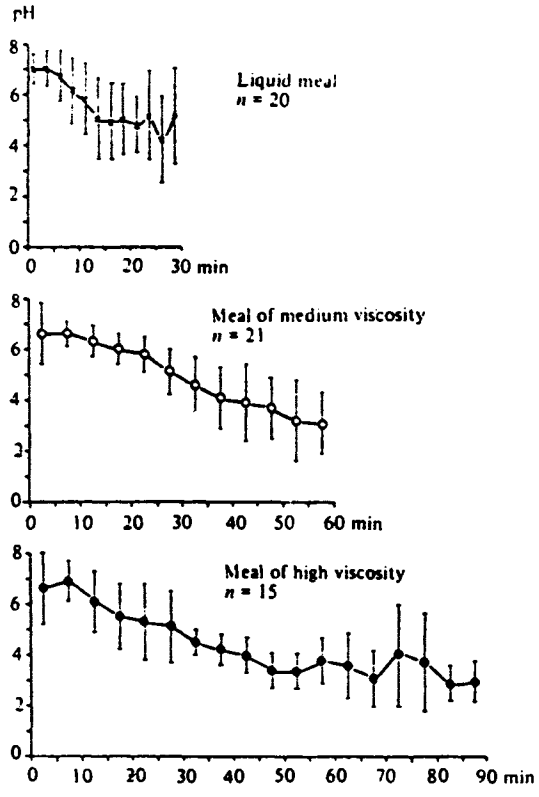

Fig. 7. Postprandial duodenal pH in dogs. (Reproduced with permission from Ref. 21.)

in dogs could conceivably result in a lower fraction absorbed for drugs which are not well absorbed in the colon and for controlled-release dosage forms of such drugs, although data to support this hypothesis are lacking.

Postprandially, differences between dogs and humans appear to occur in gastric as well as intestinal aspects of physiology. The meal emptying rate and subsequent return of the fasting motility pattern are much slower in dogs. In testing dosage forms which aim to result in a prolonged gastric residence time, canine data may lead to overoptimistic predictions for human performance. However, emptying *relative* to the meal as a function of particle size, etc., appears to correlate well between the two species, so that a dosage form which empties concomitantly with the meal in dogs will most likely empty with the meal in humans. Provided that the slower meal emptying rate in dogs is accounted for, successful extrapolation to humans should be achievable. Gastric pH and intestinal pH in the postprandial phase both appear to be more acidic in dogs than in humans. One should therefore exercise caution in predicting enteric-coated doseform performance in humans based on postprandial data from dogs. Enteric coatings which may rupture in the stomach if given too soon after a meal in humans are unlikely to do so in dogs; on the other hand, coatings that release drug adequately at postprandial duodenal pH in humans may not dissolve in the postprandial canine duodenum. The lower pH in the postprandial canine GI tract may also result in a different rate of absorption of drugs whose intestinal permeabilities are affected by a change in the fraction ionized. For these drugs, the effect of food on drug absorption may also appear to be greater than would be observed in humans, owing to the wider change in intestinal pH on going from the fasted to the fed state and also the longer period over which the drug is retained in the upper GI tract in the fed state.

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