

Fed and Fasted Gastric pH and Gastric Residence Time in Conscious Beagle Dogs

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ABSTRACT: The gastric pH values are controversial in the literature. Some suggest the dog gastric pH is higher than human and dog gastric pH after fed with particular diet is uncertain. Gastric pH in 16 male beagle dogs was measured using Bravo[®] pH telemetry system. For the fed study, the dogs received 10 or 200 g of dog dry food (5L18) 15 min before dosing the Bravo[®] pH capsule, followed by a 50 mL of water to aid in swallowing. It was surprising to find a small, but statistically significantly lower pH in the fed compared to the fasted stomach. The average gastric pH in fasted dogs was 2.05 and 1.08 and 1.26 for 10 and 200 g fed dogs. The average gastric emptying time of the capsule was 1.4, 9.4 and 20 h for fasted, 10 g fed and 200 g fed dogs, respectively. The inter-individual variability was higher in fasted dogs than in fed dogs. The results showed the gastric pH in each colony of dogs can be different from reported values in the literature. It emphasizes that the importance of measuring the pH in each colony when dogs are used to evaluate pharmacokinetics of pH sensitive drugs or formulations. © 2009 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 98:2494–2500, 2009

Keywords: gastrointestinal; intestinal absorption; food effect; physiological model; preclinical pharmacokinetics

INTRODUCTION

Beagle dogs are most commonly used to test dosage forms because of their ability to ingest human-scale dosage forms and well characterized GI physiology to predict the performance of the dosage forms in human. Gastrointestinal pH in dogs is well documented and often believed to be one unit higher than that in human.¹ Gastric pH in fasted human is reported to be ~1–2, whereas reported gastric pH in fasted dogs varies and can

be as high as 6.8.^{2,3} The pH values of 3–4 are occasionally used as a default value for *in vitro* experiments and computational simulations. Research dogs are often treated with a pharmacological agent such as pentagastrin to decrease the gastric pH to mimic human stomach pH for a precaution when they are used for pharmacokinetic studies.^{3,4} However, such H₂-receptor agonist may influence the absorption of the test drug and it is ideal if the dogs do not need to be treated with additional agents.

The gastric pH values in dogs are controversial and reported values are often inconsistent. A part of the inconsistency reports is possibly due to large inter- and intra-individual variability. A large number of subjects are required to obtain meaningful average pH value. Our preliminary study has indicated that the pH is not normally

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distributed; some dogs had low pH (<2) and only a few dogs showed pH >5. Therefore, an average value may not reflect the true meaning of gastric pH. For example, if 50% of the dogs showed the gastric pH was 1 and 50% of the dogs showed the gastric pH was 7 then the average will be 4, but it does not reflect the real pH value and it can mislead the performance of dosage forms which are pH sensitive.

There are many methods available to measure the gastric pH in *in vivo*. Among them, pH telemetry system is advantageous because it is (1) a non-invasive method so that the subject is not stressed or under the anesthesia and (2) a continuous measurement. The Medtronic Bravo[®] system is one of the pH monitoring systems which has been approved by the Food and Drug Administration (FDA) for human use. This system has been used and evaluated in research animals. The reported literatures indicate that it is a useful and reliable system.^{5,6}

The purposes of this research are (1) to establish baseline measurement of the gastric pH in our own dog colony, (2) to evaluate inter- and intra-individual variability of gastric pH, and (3) to evaluate gastric emptying time in fed and fasted dogs.

MATERIALS AND METHODS

pH Telemetry System

The pH telemetry capsules (Bravo[®] capsule) were purchased from Medtronic, Inc. (Minneapolis, MN). The capsules were calibrated about 10 min before dosing according to manufacturer's instructions. The pH values were then recorded for 24 h. The size of the capsule is approximately 6 mm × 5 mm × 25 mm.

Animals

Sixteen male beagle dogs were used for the study. The study was conducted under the approved procedure by the Institutional Animal Care and Use Committee (IACUC) at Pfizer Global Research and Development Groton Laboratory. The weight and age of these dogs are listed in Table 1. For fasted studies, the dogs were fasted the night before the study receiving only two cans of liquid diet to satisfy caloric requirements. The liquid food used was Rebound Liquid Diet

Table 1. A List of Weight and Age of the Dogs

Dog ID number	Body weight (kg)	Age (years)
38157	12.5	6
38158	9.9	6
38520	12.0	5
38522	13.1	5
38963	13.6	4
38968	14.5	4
38969	12.9	4
39174	10.4	3
38958	11.7	4
38959	10.2	4
38960	11.4	4
38961	14.5	4
38117	12.4	6
38257	9.5	6
38322	10.7	6
39034	12.2	4

(Rebound Animal Health, Atlanta GA) which contains 8 g of fat, 9 g of protein and 20 g of carbohydrate in 8 oz can (190 calories). The liquid diet was given at their normal feeding schedule around 11 am. For the fed study, the dogs received two cans of liquid diet to satisfy caloric requirements the day before around 11 am and fed with 10 or 200 g of dry food on the day of experiment at 15 min before dosing the Bravo[®] pH capsule, followed by a 50 mL of water to aid in swallowing. The dry food was 5L18 High Density Canine Diet (PMI Feeds, St Louis, MO) which contains 36% fat, 27% protein and 37% carbohydrate (percent of ration). For the fasted studies and 10 g fed studies, the animals were fed approximately 6 h post-capsule dosing. Four dogs were used for one study per day. All the studies (four study groups and 16 dogs each group) were done in approximately a 10-month period.

Statistics

When the capsule is administered in dogs, it migrates from their mouth through their esophagus where the pH is neutral. Therefore, when the capsule was swallowed, the pH generally started >4 and declines rapidly to the gastric pH of 1–2. The time when the capsule enters the stomach from the esophagus and the time that the capsule leaves the stomach were determined as pH 4 as the threshold. The pH 4 as the threshold pH was determined as “average fasted

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