RESEARCH ARTICLE

Gastric pH and Gastric Residence Time in Fasted and Fed Conscious Beagle Dogs Using the Bravo® pH System

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ABSTRACT: To further characterize the time course of gastric pH with respect to meals and gastric residence times (GRTs) in dogs, continuous pH measurements were recorded with Bravo® capsules, which were attached to the dogs' stomach mucosa or administered as free capsules, respectively. Experiments took place in home or study cages, and meals were administered at designated times. Up until 2 h prior to mealtime, the fasted gastric pH remained constantly acidic (~2.0) regardless whether the dogs were in the study or home cages. However, as feeding time became imminent, the pH was typically elevated for dogs in home cages, whereas the pH remained acidic for dogs in study cages. For both monitoring locations, the gastric pH remained acidic during meal consumption and for at least 10 h after meals. The GRT between fasted (25 ± 32 min) and fed (686 ± 352 min) conditions was significantly different with considerable inter- and intrasubject variability. Fasted gastric pH was similar to that of literature monkey and human values but differed after meals as the dog gastric pH remained acidic unlike monkey and human. In dogs, the fasted GRT was remarkably rapid and under fed conditions, longer than that observed in humans. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: gastrointestinal transit; residence time; transit time; food effects; oral absorption; Bravo® capsule; gastrointestinal pH; dog

INTRODUCTION

Dogs are one of the most frequently used species in testing human oral dosage forms. However, large discrepancies in oral bioavailability are sometimes observed between dogs and humans.[1] Differences in gross physiology between dogs and humans, such as gastric and intestinal pH, may contribute to some differences in drug absorption. Therefore, understanding the physiology of the gastrointestinal tract (GIT) will aid in making scientifically sound decisions on whether results from the dogs can be appropriately projected to humans.

There is much variability surrounding the reported gastric pH of dogs in the literature. For example, Akimoto et al.[1] reported fasted pH values from 2.7 to 8.3 (mean 6.8), whereas Youngberg et al.[2] observed fasting dog gastric pH values from 0.9 to 2.5 (mean 1.5). This can be troublesome to the pharmaceutical investigator when trying to choose the most appropriate species to study the bioavailability of new chemical entities, specifically when solubility is pH dependent.

Recently, Sagawa et al.[3] investigated fed and fasted pH and gastric residence time (GRT) in dogs with the Bravo® pH telemetry system, a catheter-free radio capsule monitoring device designed for attachment to the mucosa above the esophageal sphincter in humans to monitor esophageal pH in patients with gastroesophogeal reflux disease.[4–6] They observed large interindividual variability in pH when their colony of Beagle dogs was under fasted conditions when compared with the pH after the dogs were fed. However, because they did not attach the capsule to the stomach wall, the capsules were free to transit through the GIT. Consequently, they obtained gastric pH data only up until the time of emptying into the small

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intestine (GRT) and were unable to characterize the time course of gastric pH with respect to the time before, during, and after a meal.

The objective of this current work was to better characterize the gastric pH profile in the Beagle dog over a longer time period by attaching the Bravo® capsule to the mucosa of the stomach wall to capture any changes in pH throughout a typical day (in home cages) or during a pharmacokinetic study day (in a study room in study cages). The changes in gastric pH following administration of free Bravo® capsules were also studied, which enabled assessment of GRT in the dogs.

We have used the Bravo® pH telemetry system previously[7] as have others[3,8,9] to study intragastric pH in preclinical species. Attaching the Bravo® capsule to the gastric mucosa in the dog will allow for a direct comparison with the time course of gastric pH in the monkey,[7] and this ultimately allows for a rational selection of which preclinical species to choose for formulation/bioavailability screenings prior to human administration.

MATERIALS AND METHODS

pH Measurement System

Continuous (every 6 s) gastrointestinal pH measurements were made using the Bravo® pH system. The Bravo® pH capsule with a delivery system is a miniature radiotelemetry catheter-free capsule consisting of a battery, pH electrode, and radio transmitter enclosed in a 6 × 5.5 × 25 mm plastic housing, similar in diameter to a 00 capsule and similar in height to a 000 capsule. Prior to each use, the pH capsule was calibrated in pH 1.07 and 7.01 reference buffers (Medtronic, Shoreview, Minnesota). The Bravo® capsules were either attached to the mucosa in the GIT under endoscopic guidance or were administered orally and allowed to pass freely through the GIT. By sampling GI tract fluids and emitting a radiofrequency (433 MHz) to an external receiver in 6-s intervals over 48 h, the Bravo® capsule can measure pH between 0.5 and 9.0 with a precision of 0.01 units. After several days, the body naturally sloughs off the attached capsule, which passes unchanged through the subject's digestive tract.

A thorough *in vitro* investigation of the reproducibility, accuracy, precision, and reliability of the Bravo® pH recording device was previously completed at both 25°C and 37°C by these authors, and this work was published with the gastric pH and GRT investigations performed in the cynomolgus monkeys.[7] In brief, the Bravo® capsule recordings adjusted very rapidly (within 6 s or the equivalent of one sampling interval) when transferred from one pH buffer to another, the pH fluctuation was minimal, and the capsules slightly underestimated the pH of the commercial test buffers used in the *in vitro* experiments. Full details of the experimental design and results are reported in the publication.[7]

In Vivo Evaluation of the Bravo® pH Measuring System

Animals

Fourteen male Beagle dogs (C*anis familiaris*) with body weights between 8 and 14 kg (1–6 years old) obtained from Marshall Bio Resources (North Rose, New York) were used for these studies. The dogs were housed individually in stainless steel cages in a controlled environment (72°F ± 4°F; 50% ± 10% relative humidity) with a 12-h light/dark cycle. Filtered tap water (supplied and periodically analyzed by Philadelphia Suburban Water Company (Bryn Mawr, Pennsylvania) was available ad libitum from an automatic watering system. Prior to the study day, the animals were fasted overnight.

The gastric pH determinations were conducted in either the dog's home cage: where the dog is typically housed in a room with other dogs, or in a study cage: cages located in a room, where pharmacokinetic studies are performed. Only dogs participating in the same study would be housed in the study cages, and they are typically transferred the evening prior to studies for the ease of fasting the dogs in the morning of the study day. A major difference in the environment between these two scenarios was that the Laboratory Animal Sciences (LAS) technician was free to move in and out of the home cage room. Therefore, the normal routine of the LAS technician in the dog holding room was likely anticipated by the dogs when the light cycle started each morning. In the study cage room, the scheduled LAS technician did not enter the room because laboratory technicians of Drug Metabolism and Pharmacokinetics (not routinely in the animal facility) administered the meals.

Test meals (prepared on the day of each study) consisted of their standard meal (300 g) of dry dog food (Lab Diet #5007 made by PMI Nutrition International, St. Louis, Missouri) and wetted with 20–30 mL of tap water. The nutrient composition for this diet contained: protein 25.5%, fat (ether extract) 8.5%, fat (acid hydrolysis) 9.5%, fiber (crude) 2.8%, ash 7.1%, nitrogen-free extract 46.1%, gross energy 4.27 kcal/g, physiological fuel value 3.63 kcal/g, and metabolizable fuel value 3.40 kcal/g. The dogs were allowed 1 h to eat their meal. The amount of food each dog ate was recorded (by weight), and if no food was eaten in the allotted time window the dog was considered fasted.

All studies were conducted after review by the GlaxoSmithKline (GSK) Institutional Animal Care and Use Committee and in accordance with the GSK Policy on the Care, Welfare and Treatment of Laboratory Animals.

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