The Safety and Efficacy of Oral Low-Volume Sodium Phosphate Bowel Preparation for Colonoscopy in Dogs

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THE SAFETY AND EFFICACY OF ORAL LOW-VOLUME SODIUM PHOSPHATE BOWEL PREPARATION FOR COLONOSCOPY IN DOGS

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(ABSTRACT)

Sodium phosphate (NaP) is a low-volume, hyperosmolar laxative that has been shown to be an effective bowel cleansing agent in people. The purposes of this study were to evaluate the safety and efficacy of oral NaP in dogs. Standard (NaP and enemas; NaP_1) and control preparations (polyethylene glycol [PEG] and enemas) were compared in a crossover design to determine safety and efficacy of NaP. Serial clinical and serum analytical evaluations were used to determine the safety of NaP. The efficacy of the NaP_1 preparation was compared to 3 NaP variations which excluded enema or included bisacodyl, with or without enemas in a crossover design. Eight dogs received each of 6 bowel preparations prior to colonoscopy performed one time per week. An observer blinded to the bowel preparation assigned a score of 1-4 (1 clean colon and ≥3 unacceptable preparation) to each of 5 regions of the colon. Mean total colon cleansing score (TCS), defined as the sum of scores from each region, of the control (9.4) was less than NaP_1 (13.6) ($p<0.05$). There were no significant differences in regional or TCS for the remaining 4 NaP preparations. NaP_1 resulted in moderate, but clinically occult, hyperphosphatemia and hypocalcemia, which resolved within 24 hours of initial administration. Despite the safety and ease of administration of the NaP preparations, the NaP bowel cleansing preparations used in this study cannot be recommended for routine

clinical use due to the inadequate quality of bowel preparation compared to the PEG containing bowel cleansing protocol evaluated.

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List of Abbreviations

$1,25(OH)_2D_3$……..1,25-dihydroxycholecalciferol

ANOVA…….analysis of variance

Ca^{2+} ……..……total calcium

Cl^-……..chloride

ECF……..……..extracellular fluid

HCO_3^-…….bicarbonate

IBD…….inflammatory bowel disease

iCa^{2+}…….ionized calcium

K^+……...……potassium

kg…….kilogram

Mg^+ ……magnesium

ml…….milliliter

Na^+ …… sodium

NaP……..sodium phosphate

osm ……...……osmolality

PCV …… ……...packed cell volume

PEG……polyethylene glycol

pH ……...… venous pH

phos……..……phosphorus

PTH……parathyroid hormone

pTP ……plasma total protein

RCS……...…regional colon cleansing score

SCFA…….short chain fatty acid

sTP ……...…serum total protein

tCO_2…… ……..total CO_2

TCS……total colon cleansing score

Vit D_3……..…cholecalciferol

Introduction

Colonoscopy is a widely available procedure utilized by both general and specialty practitioners for the diagnosis of chronic large bowel diarrhea and other colonic disorders in dogs and cats.[1-5] Adequate bowel preparation is necessary for complete examination of the colonic mucosa and collection of biopsies. Effective bowel cleansing preparations should clear the colon of fecal material, produce clean mucosal surfaces, and clear ileal effluent. Failure to adequately cleanse the colon decreases the diagnostic quality of examination. When inadequate bowel preparation occurs, additional methods must be utilized to remove debris, including suction and saline lavage to allow for diagnostic evaluation. These methods increase procedure time and duration of anesthesia, and may create iatrogenic mucosal lesions.

In contrast to human medicine, little research has been performed to evaluate the safety and efficacy of bowel preparation for colonoscopy in dogs. Current bowel cleansing protocols utilized in dogs and cats were extrapolated from protocols utilized in humans.[6] Veterinary bowel cleansing protocols are also based on clinical experience and the results of 2 published studies in dogs. [6,7] Burrows et al. evaluated the effect of three different doses of an orally administered polyethylene glycol (PEG) based lavage solution and determined that an 80 ml/kg dose of PEG resulted in better colon cleansing than either 60 or 100 ml/kg dose in dogs.[6] Richter et al. demonstrated that colon preparation with a polyethylene glycol based solution was superior to enema administration in dogs.[6,7] Currently, a popular veterinary protocol utilizes an isotonic PEG lavage solution in combination with administration of metoclopramide and warm water enemas. This solution flushes fecal material out of the colon, cleansing the mucosal

surfaces as it passes through the GI tract and produces a clear ileal effluent. The solution is composed primarily of PEG and electrolytes and administration results in no net movement of fluid or electrolytes across the mucosa as the solution passes through the gastrointestinal tract.[8]

The currently utilized protocol is associated with several disadvantages. Orogastric intubation is required to administer the lavage solution. In addition, the large volume of lavage fluid requires that the orogastric tube remain in place for several minutes, leading to patient discomfort, struggling, and increased stress. Large volume lavage solution also produces rapid gastric distention and discomfort, which can result in vomiting or regurgitation. In a recent review of dogs undergoing colonoscopy, vomiting occurred in at least 6.5% of dogs receiving this preparation.[9] Aspiration of PEG during administration has also been shown to be fatal.[9] If vomiting occurs, the current protocol recommends readministration of the lavage solution, thereby increasing the patient stress and discomfort, as well as risk of aspiration. Additionally, administration of enemas is time consuming, and stressful and uncomfortable for the patient.

Sodium phosphate (NaP) is a low-volume, over the counter, hyperosmolar, buffered saline laxative which cleanses the colon through its osmotic effect of drawing plasma water into the gastrointestinal tract lumen. This preparation has been shown to be as effective as PEG for bowel preparation prior to colonoscopy in people.[10-12] Varied and inconsistent derangements in hematocrit, osmolality, and serum sodium, calcium, phosphate, potassium, and magnesium have been reported in people associated with administration of NaP bowel preparation. [10,13-19] Although rare, symptomatic hypocalcemia has been reported in humans receiving NaP bowel preparations.[17-20]

The use of NaP as a low-volume oral bowel cleansing preparation for colonoscopy has not been reported in dogs. Use of NaP could simplify bowel preparation and decrease patient stress and discomfort by reducing the duration of orogastric intubation and avoiding rapid gastric distention. The objectives of this study were to evaluate the effects of NaP on selected clinicopathologic analytes, to evaluate the safety of NaP for use as a bowel cleansing agent, to determine the efficacy of NaP compared to the standard PEG bowel preparation, and to compare the efficacy of four variations of the NaP bowel preparation, including two protocols which lack enema administration, for colonoscopy in healthy adult dogs.

CHAPTER 1: Review of Literature

A. Anatomy and Physiology

a. Anatomy and physiology of the canine colon

The canine large intestine measures approximately 20 to 60 cm in length and is divided into three main regions including the ascending, transverse, and descending colon. The cecum is located at the junction of the ileum and ascending colon and measures approximately 8 to 30 cm in length in the dog. The cranial and caudal mesenteric arteries supply blood flow to the large intestine. Venous blood drains into the portal vein.[21] Approximately the first (orad) half of the colon receives parasympathetic innervation from the vagus nerves; the aborad half receives parasympathetic input from the sacral region of the spinal cord transmitted through the pelvic nerves. Parasympathetic input is important for maintenance of normal colonic function. Sympathetic input arises from several sympathetic ganglia throughout the abdominal cavity which receive fibers from the lumbar sympathetic trunk. Sympathetic stimulation inhibits activity of the gastrointestinal tract.[22] Afferent sensory nerve fibers arising from the intestinal tract may be stimulated by irritation of the mucosa, excessive distention of the intestinal lumen, or the presence of specific chemical substances. Stimulation of these neurons may result in either excitation or inhibition of intestinal motility or secretion.[22]

The mucosal surface lining the colon is flat and contains no villi. The mucosa contains straight tubular glands, crypts of Lieberkuhn, which extend from the muscularis mucosa through the entire mucosa to the surface. The deeper parts of the glands contain primarily mucous cells; the mucosal surface is composed primarily of columnar epithelial cells. Both mucous and epithelial cells comprise the central regions of the mucosal layer.

Cells multiply in the crypts, differentiating into epithelial cells as they migrate toward the mucosal surface. The submucosa lies beneath the muscularis mucosa. This layer contains blood vessels, lymphatics, and nerves surrounded by loosely arranged connective tissue. The muscularis layer, beneath the submucosa, is comprised of two layers of smooth muscle, including an inner layer of circular smooth muscle and an outer layer of longitudinal smooth muscle. This smooth muscle is capable of propagating electrical activity through a fusion of the plasma membranes of cells in areas called nexus. This cell-to-cell transmission allows intestinal smooth muscle to function as a syncytium.

The primarily functions of the colon include absorption of water and electrolytes from chyme, to form solid feces, and storage of fecal material. The orad half of the colon is principally responsible for absorption while the aborad portion functions as a reservoir for fecal storage. The motility of the colon is divided into mixing and propulsive movements. Mixing of fecal material through coordinated contractions of the circular and longitudinal smooth muscles, called rhythmic segmentation, improves absorption by retarding aborad movement and exposing all fecal material to the mucosal surface. The rate of segmentation is determined by the slow-wave activity of the colon.[21] Slow-wave activity is generated by the circular smooth muscle of the colon. This activity originates from a pacemaker in the distal region of the orad one-third of the colon. This area generates slow waves at a frequency of approximately 6 cycles per minute and results in the antiperistaltic orad movement of colonic contents in this region.[21]

Propulsive movements vary by region of the colon. As discussed above, in the orad regions, antiperistaltic contraction moves food in an orad direction which promotes mixing and delays passage until absorption is complete. In the middle region,

coordinated tonic contraction rings slowly propel colonic contents aborally. These contractions are stimulated by distention of the colon by colonic contents. The distal colon moves contents aborally with strong coordinated contractions resulting in emptying of the colon. This contractile activity results from stimulation by a prolonged burst of spikes or electrical-response activity, also called a migrating spike burst, which originates in the middle colon and progresses aborally producing mass movements and defecation.[21]

Colonic digestion occurs as a result of the activities of the normal colonic bacteria which metabolize carbohydrates, proteins, and lipids to products which are either absorbed by the colonic mucosa or excreted. Carbohydrates entering the colon include dietary fiber (non-starch polysaccharides), starch, and small amounts of sugars and oligosaccharides. These substances are metabolized or fermented by bacteria to form short-chain fatty acids (SCFAs) including acetic, propionic, and butyric acids as well as gases including hydrogen, methane, and carbon dioxide. Colonic mucosal cells rapidly absorb approximately 95 to 99% of the fatty acids produced. The mucosal cells metabolize some butyrate; the remaining butyrate and propionate are cleared by the liver and acetate is taken up and metabolized by peripheral tissues. Digestibility of fibers and polysaccharides in the colon is variable and depends on the structure and particle size of the substance, transit time, and type of gut microflora present in the colon.[21] The energy obtained through bacterial fermentation in the colon does not contribute significantly to dogs' nutritional needs. However, fermentation of polysaccharides allows the colon to remove substances which may contribute to increased fecal volume and in some cases may result in diarrhea. In addition, absorption of short chain fatty acids promotes absorption of sodium and water. SCFAs, especially butyrate, provide an energy source

for colonocytes and affect their morphology and function. Colonic mucosal atrophy resulting in reduced mucosal blood flow, mucous production, cell renewal, and sodium and fluid absorption may result from deprivation of SCFAs.

Water is passively absorbed in the colon. Water follows the energy-dependent transport of sodium across the colonocyte and is directly dependent on solute absorption.[21] Sodium is actively transported across the colonocyte's basolateral membrane against a concentration gradient by a sodium-potassium pump fueled by ATP.[21] Sodium is transported out of the cell in exchange for potassium. The basolateral membranes of the colonic mucosal cells are impermeable to sodium, preventing backflow of sodium between cells, and resulting in formation of a high concentration gradient between the luminal and serosal sides of the colonocytes. [22] Sodium moves from the lumen down a concentration gradient into the intracellular space of the colonocyte and is subsequently pumped out of the cell across the basolateral membrane into the intercellular space. Water osmotically diffuses across the colonic mucosa following sodium into the intercellular space. As hydrostatic pressure increases in the intercellular space, the fluid flows into the interstitial space and is absorbed by the microcirculation of the submucosa.[21] Sodium entry into the colonocyte is the rate-limiting step of water absorption in the colon. The basolateral membrane is permeable to potassium, allowing potassium to diffuse from the cell and resulting in passive secretion of potassium in exchange for sodium.[21]

The main secretory function of the colon is production of mucous. Mucous, secreted from mucous cells and containing moderate amounts of bicarbonate secreted by non-mucous secreting epithelial cells, forms a protective layer over the mucosal surface.

Secretion of mucous is stimulated primarily by direct tactile stimulation of the mucous cells on the mucosal surface and by parasympathetic stimulation.[22] Mucous helps control the microenvironment of the lumen, protects the colonic wall from the bacterial activity within the feces, and neutralizes acids within the feces to prevent damage to the mucosa. Some mucins in the mucous layer bind to bacterial enterotoxins and inhibit their effects. The mucous layer also lubricates the surface of the mucosa, aiding in the passage of solid fecal material through the colon.[21]

b. Physiology of calcium and phosphorus homeostasis

Calcium plays a key role in many physiologic processes including skeletal, cardiac, and smooth muscle contraction, transmission of nerve impulses, and blood clotting. Precise control of extracellular calcium concentration is vital to maintain adequate function of these processes. The skeletal system serves as a calcium reservoir, storing calcium in times of excess and releasing calcium when extracellular fluid (ECF) concentrations decrease. Approximately 99% of total body calcium is stored in the bones with only 1% contained intracellularly, and 0.1% circulating in ECF. [22] Calcium is present in plasma in three forms. Ionized calcium accounts for approximately 50% of plasma calcium, is the biologically active form of calcium, and is able to diffuse through capillary membranes. Approximately 41% of plasma calcium is bound to plasma proteins and 9% is combined with anionic substances, such as phosphate, and can not diffuse through capillary membranes.[22] The serum total calcium is a measure of ionized calcium, protein-bound, and complex-bound calcium. Approximately 85% of the body's phosphate is stored in bones, 14% is contained intracellularly, and 1% circulates in the

ECF. Inorganic phosphate functions as a buffer in the plasma and is present in two forms: HPO_4^- and $H_2PO_4^-$. The concentrations of these substances increase or decrease as the pH of plasma fluctuates. The total quantities of both forms of plasma phosphate are measured and expressed as phosphorus. [22] Calcium and phosphorus homeostasis are important for maintenance of normal body functions, derangements may result in life threatening physiologic dysfunction. Calcium and phosphorus concentrations are regulated by many of the same factors. These factors influence absorption, storage or release from bone, and excretion; and include parathyroid hormone (PTH), vitamin D_3, and calcitonin.

Intestinal absorption and renal excretion of calcium and phosphate

Dietary calcium is poorly absorbed from the intestines in the absence of vitamin D_3. The effects of vitamin D_3 on calcium absorption are discussed below. Calcium that is not absorbed is excreted in the feces. Dietary phosphate is normally absorbed easily from the intestines. Nearly all phosphate ingested is absorbed through the intestines and only a small portion, which is bound to unabsorbed calcium, is excreted in the feces.

Calcium bound to anions, such as phosphate, and ionized calcium are filtered through the glomerular capillaries into the renal tubules. Approximately 90% of this calcium is reabsorbed in the proximal renal tubules, loops of Henle, and early distal renal tubule. The remaining 10% is selectively reabsorbed by the terminal distal tubules and collecting ducts. Calcium reabsorption in these distal segments is dependent on PTH secretion which is influenced by the calcium ion concentration of blood.

Primarily, renal phosphate excretion is controlled by an overflow mechanism. Renal tubules have a normal transport maximum for phosphate resorption of

approximately 0.1mM/min. [22] If the phosphate concentration of the glomerular filtrate falls below this amount, nearly all phosphate will be reabsorbed. If the concentration of phosphate in the filtrate is greater than this amount, excess phosphate will be excreted in urine. PTH promotes bone resorption which releases large amounts of phosphate ions into the ECF. Additionally, PTH reduces the transport maximum of phosphate by the renal tubules resulting in decreased phosphate reabsorption and increased phosphate excretion in urine.

Parathyroid hormone

Parathyroid hormone (PTH) is produced by the chief cells of the parathyroid glands. PTH has two main physiologic effects which result in increased ECF calcium concentration including: increased calcium and phosphate absorption from bone and reduced renal calcium excretion.[22] Secretion of PTH is regulated by the concentration of calcium ions in ECF. The parathyroid glands are highly sensitive to calcium ion concentration and will increase PTH secretion within minutes of detection of decreased calcium concentration. Persistent decrease in calcium ion concentration will result in hypertrophy of the parathyroid glands. In contrast, increases in extracellular fluid calcium ion concentration results in decreased PTH secretion and atrophy of the parathyroid glands.

Both rapid and slow phases of bone absorption result from the effects of PTH. The rapid phase occurs within minutes of PTH release and results from activation of membrane calcium pumps on the surface of osteocytes within the bone and osteoblasts along the bone surface. Activation results in absorption of bone (osteolysis) in the

vicinity of these cells and increased ECF calcium concentration. During the slow phase, osteoclasts become activated and formation of new osteoclasts occurs. Osteoclasts do not have membrane receptors for PTH. The process of PTH associated osteoclast activation is unclear; however, it is thought that activated osteocytes and osteoblasts may release a secondary signal which in turn activates the osteoclasts.[22]

In addition to the effects of PTH on bone, as mentioned above, PTH decreases renal calcium excretion and increases renal phosphate excretion. [22] Increased absorption of calcium occurs in the terminal distal tubule, collecting tubules, early collecting ducts and to a lesser extent the ascending loop of Henle.[22] Phosphate reabsorption in the proximal tubule is decreased by the effect of PTH on tubular epithelial cells.[22] PTH is also necessary in the activation of vitamin D in the proximal renal tubules.[22]

Vitamin D

Absorption of dietary calcium by the intestinal mucosa is mediated by 1,25-dihydroxycholecalciferol ($1,25(OH)_2D_3$), the active product of cholecalciferol (vit D_3). After ingestion, cholecalciferol is absorbed and stored in the liver until it is activated to form 25-hydroxycholecalciferol by the liver. Activation is controlled by negative feedback from 25-hydroxycholecalfiferol preventing excess formation of 25-hydroxycholecalciferol. Further activation of 25-hydroxycholecalciferol to form $1,25(OH)_2D_3$ occurs in the proximal renal tubules in the presence of PTH. $1,25(OH)_2D_3$ stimulates formation of calcium-binding protein in the intestinal epithelial cells. This protein cotransporter located on the brush border of the enterocyte actively transports calcium into the cell. Calcium leaves the enterocyte through the basolateral membrane

via facilitated diffusion. $1,25(OH)_2D_3$ also enhances the absorption of phosphate either through a direct effect or secondary to the action of $1,25(OH)_2D_3$ on calcium absorption.[22]

In addition to its effects on intestinal absorption, $1,25(OH)_2D_3$ also has a weak effect on renal tubular epithelial cells which promotes increased calcium and phosphate absorption. $1,25(OH)_2D_3$ effect on bone is dependent on the concentration of $1,25(OH)_2D_3$. In small quantities, vitamin D promotes mineralization of bone. This action may be enhanced by vitamin D mediated increase in absorption of calcium and phosphate from the intestinal tract. Excess administration of vitamin D has the opposite effect, resulting in reabsorption of calcium salts from bone. The mechanism of these effects is unknown but suspected to be a result of increased calcium transport through cellular membranes.[22]

Calcitonin

Calcitonin secretion by the C cells of the thyroid gland is stimulated by increased plasma calcium ion concentration. In general the effects of calcitonin oppose those of PTH although the magnitude of effect of calcitonin on regulation of extracellular calcium concentration is much less than that of PTH. Similar to PTH, calcitonin has both immediate and prolonged effects. The primary responsibility of calcitonin is to limit post-prandial hypercalcemia in normal mammals. The immediate effect decreases the activity of osteoclasts and possibly osteocytes to reduce bone resorption and promote deposition of bone. Calcitonin also decreases formation of new osteoclasts which in turn reduces osteolytic activity and the associated osteoblastic activity that is stimulated by increased

osteoclast activity. This results in a net reduction in both osteoclastic and osteoblastic activity and therefore minimal prolonged effect. That is, the effect of calcitonin on plasma calcium concentration is transient, lasting for a few hours to a few days.

Calcium Salts

Calcium salts, amorphous calcium phosphate compounds such as $CaHPO_4$, are found in bone and in reversible equilibrium with calcium and phosphate ions in ECF.[22] Calcium salts function as a buffer for ECF calcium and phosphate ion concentrations and are readily deposited in bone when ECF calcium and phosphate ions are in excess and are readily reabsorbed when calcium and phosphate ions in ECF are decreased.[22] This function helps maintain a stable ECF calcium ion concentration until PTH and calcitonin initiate their hormonal regulatory effects.[22]

Administration of large doses of phosphate either orally or intravenously has been shown to cause hyperphosphatemia and associated hypocalcemia.[23,24] The mechanism of action by which phosphate infusion results in reduction of serum calcium was described by Hebert et al.[23] Precipitation of calcium phosphate salts from the body fluids is initiated by the reaction $Ca^{2+} + HPO_4^{2-} \rightarrow CaHPO_4$ and occurs when the product of the serum calcium and phosphate concentrations reaches approximately 60.[23] This value represents the saturation point of serum with respect to calcium and phosphate.[23] Hebert et al. demonstrated in humans that infusion of phosphate intravenously resulted in decreased serum total calcium as a result of $CaHPO_4$ precipitation secondary to hyperphosphatemia; this effect occurred in normal healthy control subjects, as well as patients with hyperparathyroidism, hypercalcemia of malignancy, and medically treated patients with

hypoparathyroidism.[23] After discontinuation of phosphate administration, hyperphosphatemia resolved, and serum phosphorus returned to baseline values within 24 hours in each group of patients.[23] In the normal subjects, total serum calcium concentration returned to baseline within 18 hours.[23] However, in the remaining groups, serum total calcium did not return to baseline for 42, greater than 72, and greater than 96 hours for patients with hypoparathyroidism, hyperparathyroidism, and malignancy, respectively.[23] This delayed response was attributed to lack of parathyroid hormone in the hypoparathyroid patients which resulted in an inability to mobilize calcium from bone and delayed parathyroid gland response in the primary hyperparathyroidism and hypercalcemia of malignancy patients.[23] Additionally, no clinical signs associated with hypocalcemia were observed in any patient.[23]

Hypocalcemia

As ECF calcium ion concentration decreases below the normal range, the nervous system becomes progressively more excitable. This results from increased permeability of the neuronal membrane to sodium and a resulting decrease in action potential threshold. At calcium ion concentrations of approximately 50% below normal, peripheral nerve fibers may discharge spontaneously creating nerve impulses that result in tetanic muscle contraction. Increased excitability of neurons in the central nervous system (brain) may result in seizure activity.[22] Severity and onset of clinical signs associated with hypocalcemia may be influenced by the rapidity and magnitude of reduction in ECF calcium ion concentration.

B. Colonoscopy in Dogs

a. Review of colonoscopy in current veterinary literature

Colonsocopy is commonly performed during the diagnostic evaluation of chronic large bowel diarrhea, hematochezia, dyschezia, and tenesmus.[25] The colonoscopic procedure in dogs has been well described.[1,25,26] Recently, Leib et al. described complications associated with 355 flexible colonoscopic procedures in dogs.[9] In this report, the most common indications for colonoscopy included chronic large bowel diarrhea, hematochezia, tenesmus, chronic mixed bowel diarrhea, neoplasia or colitis surveillance, visible mass protruding from the anus, and excessive fecal mucus. A PEG solution (Golytely®, median dosage, 66 ml/kg) was used in 294 procedures. Major complications occurred during 0.85% of procedures and included fatal aspiration pneumonia after PEG administration, colonic perforation, and excessive bleeding after biopsy. Minor complications associated with anesthesia or colonoscopy occurred in 3.4% of procedures. Four were thought to be associated with anesthesia; the remaining eight minor complications were thought to be associated with colonoscopy and included: transient pain, abdominal distention secondary to gastric distention, vomiting which appeared to contain feces and occurred during anesthetic extubation, gastroesphageal reflux during gastroduodenoscopy which was performed prior to colonoscopy, and mild hemorrhage after resection of a leiomyosarcoma via rectal prolapse after completion of colonoscopy. Vomiting occurred in 6.5% of dogs that received PEG and after 4.6% of the total number of PEG dose administrations. Overall, major and minor complications, including vomiting occurred in 8.5% of colonoscopy procedures and mortality occurred during 0.28% of procedures.

Many case reports and studies have been published documenting the contributions of colonoscopy to the diagnosis, treatment, and monitoring of response to therapy of various colonic diseases. [2,5,27-30] Visualization of colonic mucosal lesions and collection of mucosal biopsies during colonoscopy has aided in the diagnosis of histiocytic ulcerative colitis in Boxer dogs and a French bulldog.[27,28,31] Additionally, colonoscopic evaluation was used to monitor response to therapy in several of these dogs.[27,31] Mucosal abnormalities and a rectal stricture were identified during colonoscopy in a young German Shepard dog with a history of protracted hemorrhagic diarrhea and tenesmus.[5] Organisms with morphologic features of Prototheca species were identified on mucosal biopsy specimens collected during colonoscopy.[5] A mixed breed dog evaluated for intestinal hemorrhage and severe anemia was diagnosed with colonic vascular ectasia upon visualization of colonic mucosa during colonoscopy.[29] In this dog, intra-operative colonoscopy was necessary to identify the extent of the vascular lesions and determine the surgical margins for resection of the affected colon.[29]

Gross colonoscopic findings or histopathologic descriptions of colonic biopsy specimens are often included in studies evaluating colonic disease processes such as inflammatory bowel disease and idiopathic large-bowel diarrhea.[2,30] Stonehewer et al. evaluated endoscopically collected colonic biopsy specimens to investigate the subpopulations of lymphocytes in the colonic mucosa of healthy dogs and dogs with inflammatory bowel disease.[30] Leib described chronic idiopathic large-bowel diarrhea in dogs in a retrospective review.[2] All 37 dogs included in the study underwent colonoscopic examination to characterize the gross appearance of the colonic mucosa and collect mucosal biopsy specimens for histopathological analysis.[2] Through evaluation of

colonic mucosal samples collected during colonoscopy, Roth et al. developed a grading system for the microscopic evaluation of endoscopically collected colonic mucosal samples in normal dogs and dogs with lymphocytic plasmacytic colitis.[32] This grading system, combined with colonoscopy, provides a method to assess disease severity and monitor response to therapy.[32]

b. Review of bowel preparations described in veterinary literature

Bowel preparation protocols for cleansing of the colon prior to colonoscopy in dogs have not been well documented in the veterinary literature. Only two studies have been published describing the effects of various bowel preparations in dogs. Richter and Cleveland compared the colon cleansing effects of an orally administered polyethylene glycol based gastrointestinal lavage solution with traditional enema administration in forty dogs undergoing rigid proctoscopy.[7] In this study, 20 dogs received 3 enemas consisting of warm water and lubricating gel at a volume of 40 ml/kg of body weight, 6 hours apart, with the last enema administered 9 to 15 hours before proctoscopy. The remaining dogs were administered the gastrointestinal lavage solution via orogastric intubation. The solution was administered twice (25 ml/kg body weight) with a 1 hour interval between dosing. The second dose was given 12 to 18 hours before proctoscopy. Food was withheld for a minimum of 24 hours prior to initiation of colon cleansing in both groups. Proctoscopy was performed using a rigid proctoscope appropriate for the size of the dog based on body weight. Colon preparation was evaluated based on the amount of feces in the colon and for the overall quality of the preparation based on amount and character of residual fecal material, ease of removal of fecal material, ease of

introduction of the scope, and ability to completely visually evaluate the entire mucosal surface during examination. Comparison of the effects of the two preparations revealed better bowel cleansing after administration of the oral gastrointestinal lavage solution. More dogs (16/20) had acceptable preparation scores associated with use of the oral lavage solution compared with scores of dogs given multiple enemas (2/20). It was noted that a few dogs in the oral lavage solution group did not voluntarily expel the large volume of liquid feces from the colon, however, it was also reported that this residual liquid was not difficult to remove through the endoscope. Additionally, adverse reaction associated with the gastrointestinal lavage solution were minimal including vomiting at the time of administration in 2 dogs and vomiting 12 hours after administration in 1 dog. Serum potassium decreased slightly, but significantly, after administration of the gastrointestinal lavage solution. This study demonstrated superior colon cleansing effects of gastrointestinal lavage over enema administration.[7] However, because examination was performed using a rigid proctoscope, only the descending colon was observed. The cleansing effect of these preparations on the orad portions of the colon was not evaluated.[7]

Burrows also evaluated the colon cleansing effects of a polyethylene glycol based gastrointestinal lavage solution.[6] In this study, 10 dogs received each of three different bowel cleansing protocols 1 week apart. Three doses (60 ml/kg body weight, 80 ml/kg, or 100 ml/kg) of a PEG (COLYTE, Reed and Carnrick, Piscataway, NJ) were evaluated. Each dose was administered via orogastric intubation in 2 equally divided doses 4-6 hours apart in the afternoon of the day preceding colonoscopy. Colonoscopy was performed to the level of the cecum in all dogs. The colon was assessed subjectively

based on the mucosal visibility and the amount of residual fluid and fecal material remaining in the colon at the time of colonoscopy. The study concluded that the 80ml/kg dose resulted in significantly better colon cleansing effect. Vomiting was observed in one dog once after administration of the lavage solution.[6]

Additional recommendations for colon preparation can be found in various veterinary textbooks.[3,25,26,33] In general, these sources recommend colon cleansing protocols which utilize a combination of PEG lavage solutions, warm water enema administration, and 24-48 hour fasting period prior to the colonoscopy procedure. These recommendations are based on the two published veterinary studies described above, current recommendations for colon cleansing in people, and on the clinical experiences of the respective authors.

C. Bowel preparation for colonoscopy in people

a. The impact of preparation quality on colonoscopy

The quality and diagnostic yield of colonoscopy is dependent on the quality of bowel preparation.[34] Froehlich et al. assessed the factors determining bowel cleansing quality and the impact of cleansing quality on the technical performance and diagnostic yield of colonoscopy in a prospective, multicenter observational study.[34] In this study, quality of bowel preparation of 5832 patients was assessed during endoscopy using a 5-point scale; a score of 5 represented a completely clean colon, score of 3 represented presence of liquid and solid stool that could be aspirated, and score of 1 represented the presence of solid stool which prevented visualization; scores of 4 and 2 were intermediate to the scores described.[34] The scores were categorized into 3 levels of cleansing quality including: high cleansing quality (scores 5 and 4), intermediate cleansing quality (score 3), and low cleansing quality (scores 2 and 1).[34] The duration of the procedure and degree of difficulty of the procedure were also reported for each patient.[34] Complete colonoscopy including intubation of the cecum was achieved in significantly greater proportion of patients in both the high and intermediate quality groups (90%) compared to the low quality group (71%). The duration of the endoscopic procedure and difficulty of performing the procedure were inversely correlated with cleansing quality.[34] Additionally, the detection of polyps was dependent on cleansing quality.[34] The authors conclude that cleansing quality critically determines quality, difficulty, speed, and completeness of colonoscopy.[34]

b. Assessment of quality of bowel preparation

A variety of bowel preparation quality scales have been used to compare different bowel preparation agents.[35] Generally, these categorical scales rate the quality of bowel preparation from excellent to poor and often use subjective terminology to describe the different levels.[35] This subjectivity may reduce inter-observer agreement and introduce bias in studies comparing the quality of different bowel preparations.[35] Rostom et al. designed a scale that evaluates the colon cleansing quality of different segments of the colon individually and generates a summary score for the entire colon.[35] In this scoring system, individual regions of the colon are assigned a numerical score based on the consistency of residual fecal material and the need for suction and/or flushing to attain adequate mucosal visualization; a numerical score is also assigned to describe the overall volume of fluid in the colon.[35] The overall quality score is determined by combining the individual regional scores and the overall fluid score.[35] This new scale was validated by comparison to a scale developed by Aronchick.[35] The Aronchick scale assessed the preparation quality of the entire colon based on a 5-point scale (1 – excellent quality; 2 – good quality, 3 – fair quality; 4 – poor quality, and 5 – inadequate quality) which requires the observer to estimate the percentage of mucosal surface observed and characterize the residual liquid and solid stool present.[35] The scoring system used in the current study evaluating the safety and efficacy of NaP bowel preparation for colonoscopy in dogs was based on these two validated scoring systems, and the 4-point numerical scoring system used by Burrows for evaluation of PEG in dogs.[6] This scoring scale utilizes the concept of assigning both individual regional scores and a summary total colon score as described by Rostom, and a 4-point scale describing the quality of preparation in each region of the

colon based on mucosal visualization and the presence of residual liquid and fecal material similar to Aronchick.[35,36]

c. Use of polyethylene glycol based gastrointestinal lavage solution in people

Research in people has shown that gastrointestinal lavage with a PEG produces adequate colon cleansing in preparation for diagnostic or surgical procedures.[37-40] Ingestion of the PEG solution results in minimal net water or electrolyte absorption or secretion across the gastrointestinal mucosa as a result of its electrical neutrality and iso-osmolality with plasma.[8,10,41] This solution flushes fecal material out of the colon, cleansing the mucosal surfaces as it passes through the GI tract and produces a clear ileal effluent. Briefly, patients are generally instructed to consume a clear liquid meal for supper and ingest 4 liters of PEG the evening prior to a morning colonoscopy.[42] Clinically significant hematologic electrolyte or metabolic abnormalities have not been reported in clinical trials evaluating PEG.[41] Reported complaints associated with PEG administration include nausea, bloating, abdominal cramps, abdominal fullness, and anal irritation, these potential adverse effects are considered to be common, yet minimal.[41] Additionally, ingestion of the large volume of fluid required is difficult for some patients and may result in inadequate colon cleansing as a result of failure to complete the preparation.[15,41,43] Complications can arise from administration of PEG. Gabel described a case of severe aspiration with subsequent aspiration bronchitis, life-threatening hypoxemia, and stroke in a senile patient after nasogastric administration of PEG solution.[44]

Early studies documented the effectiveness of PEG for colon cleansing prior to colonoscopy in people.[37,45,46] When compared to standard bowel preparations including clear liquid diets, laxatives, and enemas, or basic electrolyte solutions, PEG had equal or superior cleansing effect.[37,38,47]

Adjunctive medications have been used in combination with PEG, including metoclopramide and bisacodyl. Brady et al. compared the effect of two doses of metoclopramide administrated in combination with PEG with PEG and placebo. [48] Patient responses and were evaluated; neither dose of metoclopramide influenced adequacy of cleansing or decreased patient symptoms associated with PEG administration.[48] Additionally, metoclopramide absorption was not different based on determination of plasma concentration in patients receiving PEG when compared to normal adults not receiving PEG.

The effect of bisacodyl, an oral stimulant laxative, on colon cleansing in combination with PEG has been evaluated in people.[49-51] Pretreatment with oral administration of bisacodyl allowed for a reduction in volume of PEG needed for bowel preparation prior to colonoscopy.[49,50] Sharma et al. demonstrated superior cleansing effect in patients pretreated with a stimulant laxative and PEG compared to PEG alone.[52]

d. Use of oral sodium phosphate bowel preparation in people

Sodium phosphate is a low-volume, over the counter, hyperosmolar, buffered saline laxative which cleanses the colon through its osmotic effect of drawing plasma water into the gastrointestinal tract. Sodium phosphate bowel preparation in people generally consists of 45 ml of sodium phosphate solution (NaP) administered orally,

twice at intervals between 3 and 14 hours. Both doses may be administered the day before colonoscopy or they may be divided and administered the evening prior to and morning of colonoscopy.[42,53] One study described the use of a tablet form of NaP preparation which was comparable in dose to the oral solution.[54] The oral NaP solution contains 21.6 g monobasic monohydrate and 8.1 g dibasic heptahydrate sodium phosphate in each 45 ml dose.[53] The effects of oral sodium phosphate administration on various serum electrolytes and phosphate have been reported in people.[14-16,24,55-57] The most common electrolyte abnormalities observed after NaP administration include hypokalemia, hypocalcemia, and hyperphosphatemia.[14-16,24,55-57] However, these abnormalities are rarely associated with clinically significant symptoms. Serum potassium levels were observed to decrease after NaP administration in several studies.[14-16,24] Serum potassium values decreased below the normal range in a small number of patients, however, no patient experienced clinical sequelae due to this abnormality. [14,15] Most patients develop transient hyperphosphatemia after ingestion of the recommended dose of oral NaP.[14-16,24,56,57] Hyperphosphatemia generally resolves within 48 hours of administration of the second NaP dose.[15] However, hyperphosphatemia may result in clinically significant hypocalcemia.[17,19,20] Although a decrease in mean serum calcium levels has been observed in most trials,[14,16,24,56,57] none of 3022 people who participated in clinical trials were reported to have experienced any symptoms attributable to hypocalcemia.[53] Most studies evaluating the safety of NaP administration excluded patients with heart failure, renal failure, recent history of myocardial infarction, known electrolyte abnormalities, and/or intestinal obstruction, although the extent of exclusions

differs between studies.[53] Additionally, authors suggested these conditions were relative contraindications to administration of NaP.[53]

Although they occur infrequently, several case reports have described adverse events associated with NaP administration, including symptomatic hypocalcemia, hypokalemia, hypernatremia, and life-threatening hyperphosphatemia. [17-19,58,59] Life threatening complications and fatalities reported after administration of NaP have resulted from severe hyperphosphatemia and subsequent hypocalcemia, metabolic acidosis, and acute renal failure.[58,60,61] Inappropriate dosing resulting in administration of NaP in excess of the standard recommendations for NaP may have contributed to the occurrence of adverse events in some of these cases.[17,53,58] Additionally, several of the patients which experienced adverse events suffered from renal impairment or major gastrointestinal motility disturbances which may have predisposed them to complications associated with NaP administration.[17,53,58]

Colonic mucosal abnormalities suspected to be associated with NaP bowel preparation have been reported.[62-64] In one study, aphthoid-like erosions, described as small, 1 to 3 mm, shallow lesions, frequently surrounded with a reddish halo, were observed in 13 of 53 (24.5%) patients who received NaP preparation compared to only 1 of 44 (2.3%) patients who received PEG preparation.[62] Histopathologically, these lesions exhibited minimal to mild edema and superficial hemorrhage in the upper portion of the lamina propria, with variable degrees of denudation of the surface epithelium. [62] Despite their indistinguishable endoscopic appearance with lesions typical of Crohn's disease, none of the biopsies exhibited histologic features typical of inflammatory bowel disease (IBD).[62] Rejchrt et al. described similar colonic mucosal abnormalities in 24 of 730

(3.3%) patients after administration of NaP bowel preparation.[64] Focal active inflammation was observed in mucosal biopsies of 14 of these patients.[64] The authors of this study concluded that NaP associated colonic mucosal abnormalities can mimic IBD.[64] The pathogenesis of these abnormalities is not known; however it is thought that they are metabolically mediated and may result from an oxidative stress reaction in the colonic mucosa triggered by NaP.[64,65] To reduce the risk of misdiagnosis, it has been recommended that NaP bowel preparations should not be used in patients undergoing colonoscopy for evaluation of chronic diarrhea or in patients in whom IBD is suspected.[62]

e. Comparison of the efficacy of PEG and NaP bowel preparations

Greater than 500,000 colonoscopies are performed annually in the United States.[10] Because adequate preparation of the colon is essential for complete colonoscopic examination, numerous studies have evaluated the efficacy of PEG and NaP bowel preparations in people, many of which have directly compared these two methods of bowel cleansing.[10-16,66-76] In addition to efficacy, several of these studies have also evaluated patient completion of the prescribed protocol[11,13-16,67,69-76] and total number of adverse effects associated with each preparation.[11,13,15,16,66,70,71,73-76] The large number of studies evaluating PEG and NaP protocols has also been the subject of meta-analyses.[10,43] In 1998, Hsu et al. performed a meta-analysis to compare the efficacy and cost of PEG and NaP bowel preparations for colonoscopy.[10] Recently, a second meta-analysis has been performed by Tan et al. [43]

Hsu et al. pooled data from eight colonoscopist-blinded trials and compared the compliance with and efficacy of PEG and NaP as well as the cost of colonoscopy with

both methods.[10] A total of 1286 subjects were included in the meta-analysis; doses of PEG and NaP were identical among trials with only minor variability in timing of administration.[10] In 5 of 8 trials, NaP was better tolerated by patients based on either symptoms during the preparation or ability to complete the preparation.[10] Three of 8 trials concluded that NaP resulted in better quality of preparation based on colonoscopic examination; the remaining 5 of 8 trials found similar efficacy rating for PEG and NaP.[10] The direct cost associated with diagnostic colonoscopy was less when patients were prepared with NaP.[10] Based on these results, Hsu et al. concluded that NaP was as effective, less costly, and a more easily completed preparation compared to PEG.[10]

Since Hsu et al. performed the meta-analysis described above; additional studies have evaluated the efficacy and in some cases tolerance and associated adverse effects of PEG and NaP bowel preparation protocols.[11-13,66,68,70,72-76] Tan et al. performed a meta-analysis with the objective of assessing which bowel preparation agent is most effective.[43] All studies included in this analysis were randomized controlled clinical trials published between January 1990 and July 2005.[43] Eighteen articles compared PEG and NaP; 16 of these were included in the analysis.[43] PEG dose was comparable among the studies included in the analysis and the dose of NaP was uniform except for one study[54] which used sodium phosphate tablets rather than solution.[43] Nine of 16 studies concluded that the bowel cleansing ability of NaP was superior to PEG; 1 of 16 studies was in favor of PEG; the remaining 6 of 16 studies concluded that PEG and NaP were comparable in efficacy.[43] To determine patient tolerance of PEG and NaP administration as assessed by patient completion of the preparation, the reported results of 15 studies were pooled.[43] Approximately 94% of patients completed the NaP preparation compared to

approximately 71% of patients who were able to complete the PEG preparation.[43] There was no statistical difference in the total number of adverse events associated with either protocol in the 12 studies included in this analysis.[43] However, more patients in PEG groups experienced abdominal pain, and more patients in the NaP group experienced dizziness when the 2 preparations were compared.[43] There was no difference in occurrence of nausea, vomiting, or perianal pain/irritation among groups.[43] The authors concluded that NaP is more effective in bowel cleansing than PEG, however this may be partly due to the greater completion rate of the NaP preparation which would have an impact on quality of bowel cleansing.[43]

CHAPTER II: The Safety and Efficacy of Oral Low-volume Sodium Phosphate Bowel Preparation for Colonoscopy in Dogs

A. Materials and methods

Eight purpose-bred mongrel dogs (4 male and 4 female) ranging in age from 11 to 21 months were used in this study. Dogs were fed a standard ration[i] based on body weight and condition once daily. Each dog was determined to be in good health based on physical examination, packed cell volume, and biochemical profile. Fenbendazole (50 mg/kg) was administered orally for five days to each dog. A fecal sample for zinc sulfate flotation was collected from each dog after completion of treatment. Fecal consistency was assessed between 8 and 10am for 2 weeks prior to the start of and for the duration of the study using a previously described numerical scoring system.[77] Briefly, grade 1 feces was comprised of greater than two thirds liquid feces in a single defecation which had lost all form, appearing as a puddle. Grade 3 feces contained greater than two-thirds soft feces that retained enough form to pile but had lost cylindrical appearance. Grade 5 feces contained greater than two-thirds firm feces with a cylindrical shape and little flattening. Grades 2 and 4 described intermediate grades.

a. Safety study:

Every dog received each of two bowel preparations in random order 7 days apart. Biochemical parameters, including serum ionized calcium (iCa^{2+}), total calcium (Ca^{2+}), phosphorus (phos), potassium (K^{+}), sodium (Na^{+}), chloride (Cl^{-}), magnesium (Mg^{+}), anion gap, total CO_2 (TCO_2), bicarbonate (HCO_3^{-}), venous pH (pH), osmolality (osm), packed cell volume (PCV), serum total protein (sTP), plasma total protein (pTP), and

body weight were measured prior to administration of each preparation and 1, 2, 4, 5, 6, 8, and 24 hours after the initial administration. Food was withheld 15 hours prior to colon preparation.

In the standard NaP treatment group, NaP_1, each dog received 1 ml/kg NaP[ii] diluted with 2 ml/kg of water via orogastric intubation. After administration of NaP, the orogastric tube was flushed with an additional 2 ml/kg of water. Immediately after administration of NaP, a 20 ml/kg warm water enema was administered. Both the NaP and enema were repeated at the same dose four hours later. One additional warm water enema (20ml/kg) was administered the next morning prior to induction of anesthesia. For the control group, 0.3 mg/kg metoclopramide SC was given 20 minutes prior to administration PEG[iii]. Each dog received 66 ml/kg PEG via orogastric intubation. Twenty minutes after administration of PEG, a 20 ml/kg warm water enema was administered. Administration of PEG and warm water enema were repeated four hours after initial dosing. One additional warm water enema (20 ml/kg) was given the next morning prior to induction of anesthesia. Colonoscopy was performed approximately 24 hours after bowel preparation.

All blood samples were collected via jugular venipuncture. All samples except serum osmolality were processed on the day of collection. Venous blood gas samples (for ionized calcium, bicarbonate, and pH) were immediately placed on ice and analyzed within 30 minutes of sample collection. Plasma samples were stored frozen at -70ºC until osmolality was determined by the freezing point depression method[iv]. Dogs were observed for vomition and regurgitation for a minimum of 2 hours after administration of

the bowel preparations. The volume of water consumed by each dog from the beginning of bowel preparation until the administration of premedications was recorded.

Approximately 24 hours after initiation of colon preparation, premedication followed by induction of anesthesia and colonoscopy was performed on each dog. Each dog was premedicated with acepromazine (0.05 mg/kg SC) and morphine (0.5mg/kg SC). An intravenous catheter was placed in a cephalic vein. General anesthesia was induced by intravenous sodium pentothal (10 mg/kg to effect). General anesthesia was maintained by administration of isoflurane in oxygen via tracheal intubation. Pulse oximetry and electrocardiography were monitored for the duration of anesthesia. Routine colonoscopy was performed to the level of the cecum as previously described by a single endoscopist (MD) using a videoendoscopy system[v] and processor[vi].[33] An observer (ML) unaware of the bowel preparation method utilized scored the colon preparation according to the following:

1. Clean Colon: no fecal matter or nearly none seen, no residual fluid
2. Clean Colon: small amounts of thin, adherent liquid fecal matter seen, suctioned/flushed easily
3. Unacceptable Preparation: Moderate amounts of liquid to semisolid or adherent fecal matter seen, difficult to suction/flush from the colon, mucosa still visible
4. Unacceptable Preparation: Large amounts of solid or adherent fecal matter precluding adequate examination

Five regions of the colon were scored; the distal, mid-portion, and orad portion of the descending colon, the transverse colon, and the ascending colon. A total colon score (TCS) was calculated as the sum of the five regional colon scores (RCS). Still video images were recorded[vii] from each area of colon evaluated. When adherent fecal material

was present, an endo-pump[viii] was used to assess the ease by which it could be flushed away from the mucosa for adequate mucosal visualization. The volumes of water infused into the colon through the endo-pump and suctioned from the colon through the endoscope were measured.

b. Efficacy study:

Each of the eight dogs received each of four NaP preparations (table 1) once according to a Latin square crossover design to eliminate residual effects from the previous preparations. Briefly, preparation NaP_2 consisted of 1ml/kg NaP diluted with 4ml/kg water followed by an additional 4ml/kg water administered by orogastric intubation. A 20 ml/kg warm water enema, was administered immediately after NaP and water. This treatment was repeated in 4 hours. An additional enema was administered the following morning prior to induction of anesthesia. Preparation NaP-E was similar to NaP_2 except enemas were not administered. Preparation NaP/E/B was similar to NaP_2 with the addition of bisacodyl (10mg PO) administered 2 hours after each dose of NaP. Preparation NaP/B was the same as preparation NaP/E/B except that enemas were not administered. Dogs were observed for vomition and regurgitation for a minimum of 2 hours after administration and water consumption was quantitated as previously described in the safety study. Colonoscopy was performed approximately 24 hours after bowel preparation. The order in which dogs received the bowel preparations and colonoscopy was randomized weekly. Dogs were anesthetized and colonoscopy performed and scored as described in the safety section.

c. Statistical Methods

Descriptive statistics including mean and standard error based on pooled mean square for error were calculated for the data collected in the safety experiment including analytes (iCa^{2+}, Ca^{2+}, phos, K^{+}, Na^{+}, Cl^{-}, Mg^{+}, osm, HCO_3^{-}, TCO_2, pH, PCV, TP, albumin, anion gap), body weight, and volume of water consumed during preparation. Mixed effects model repeated measures analysis of variance (ANOVA) for a crossover design was used to test for effects of treatment, time and treatment by time interaction. Model adequacy was assessed using plots of standardized residuals. For the efficacy experiments a mixed effects repeated measures ANOVA was used to test for main effects of bisacodyl and enema administration as well as their interaction and to compare volume of water consumed during preparation. This model corrected for effects of period and individual dog while testing for the effect of bowel preparation on colon cleansing. A p-value less than 0.05 was considered significant. Commercial software was used to perform all calculations and statistical analyses.[ix]

B. Results

a. Safety Study

Anesthesia and colonoscopy were performed without complication in all dogs. Vomiting was not observed in any dog after administration of the control preparation. Six episodes of vomiting were observed in 5/8 dogs after administration of NaP (2/6 after administration of 1st dose, 4/6 after 2nd dose). Vomiting episodes occurred within 10-100 minutes (mean = 56) after administration of NaP. Estimated volume ranged between 10 to 50 ml (mean = 32) of vomitus per episode. Three episodes of regurgitation were observed during (1/3 dogs) or immediately after (2/3 dogs) administration of the control preparation (2/3 after 1st dose, 1/3 after 2nd dose). Estimated volume of regurgitation ranged between 170 to 200 ml (mean = 190). Any portion of the dose remaining at the time of regurgitation, and the estimated regurgitant volume of the control preparation, were administered 1 hour after regurgitation without further complication in any dog. Regurgitation was not observed in any dog after administration of the NaP. Mild hematochezia occurred in 1/8 dogs the morning after administration of the control preparation and was not observed in dogs receiving NaP. Mean water consumption during preparation was significantly greater in dogs receiving NaP than the control preparation (45 ml/kg/day and 9 ml/kg/day respectively; $p<0.0001$).

Mean RCS were significantly greater for all regions, except transverse colon, in the NaP_1 group (table 2). The mean TCS of 13.6 for the NaP_1 group was significantly greater than the mean TCS of 9.4 for the control group ($p=0.0033$). The mean volume of water infused during colonoscopy for the NaP_1 group was significantly greater than the control group (260 ml and 114 ml, respectively; $p=0.001$).

The means for iCa^{2+}, Ca^{2+}, phos, Na^{+}, K^{+}, Cl^{-}, anion gap, TCO_2, HCO_3^{-}, and pH were significantly different between groups or fell outside of the reference interval at at least one time point (table 3). Mean values at hours 0 and 24 were not significantly different between groups for any variable evaluated. Compared to the control group, mean values for phos were significantly greater, while HCO_3^{-} and pH were significantly less in the NaP_1 group at 6/8 time points. Mean values for iCa^{2+}, K^{+}, and TCO_2 were significantly less in the NaP_1 group at 5/8 time points. Total calcium was significantly less, and anion gap, Na^{+}, and Cl^{-}, were significantly greater in the NaP_1 group at 3/8, 4/8, 2/8, and 2/8 time points respectively compared to the control group. Mean values for iCa^{2+} were greater than the reference interval in the control group at hours 8 and 24, and at hour 0 in the NaP_1 group. Mean values for Ca^{2+} were less than the reference interval in the NaP_1 group at hours 2, 4, 5, 6, and 8. Mean values for phos were greater than the reference interval at hours 1, 2, 4, 5, 6, and, 8. No dogs experienced adverse clinical effects as a result of the metabolic or electrolyte disturbances detected.

b. Efficacy Study

Vomiting was observed once after administration of both NaP_2 and NaP/E/B. Both vomiting episodes occurred approximately 20-40 minutes after administration of the second dose of NaP; estimated volumes of vomitus were 100 and 75 ml, respectively. Regurgitation was observed once immediately after administration of the second dose of both NaP/E/B and NaP/B. Estimated volumes of regurgitated fluid were 50 ml and 10ml respectively. Mild hematochezia occurred three times the morning after administration of the NaP-E (once) and NaP/E/B (twice). The mean water volume consumed during preparation was 35, 45, 30, and 40 ml/kg/day for NaP_2, NaP-E, NaP/E/B, and NaP/B

respectively. Water consumption for group NaP/E/B was significantly less than groups NaP-E and NaP/B (p=0.048 and p=0.0056; respectively).

No significant differences (p>0.05) were detected in TCS or RCS among preparations NaP_2, NaP-E, NaP/E/B, and NaP/B (table 2). Both RCS and TCS for these preparations were similar to those for NaP_1, which were significantly greater than the control group (table 2). There were no significant differences in the volume of water infused.

C. Discussion

In this study the PEG control preparation resulted in significantly better colon cleansing than the standard sodium phosphate preparation, NaP_1. Since the colon cleansing effect of NaP_2 was not significantly different from NaP-E, NaP/E/B, and NaP/B, it is likely that the control would result in a better colon cleansing effect than all of the NaP preparations evaluated. Unfortunately the results from the control and NaP_1 preparations could not be directly compared statistically with the NaP_2, NaP-E, NaP/E/B, and NaP/B groups because of the need to evaluate the safety profile of NaP_1 prior to administration of the other NaP combinations.

The safety and efficacy of oral NaP bowel preparation in people have been compared with various PEG lavage solutions.[13,14,16,57] In people, NaP has been shown to be as effective as PEG based bowel preparations. [11,12,68] In a meta-analysis and cost comparison of PEG versus NaP for colonoscopy preparation, Hsu and Imperiale concluded that bowel preparation with NaP is at least as efficacious and less costly than PEG lavage preparation.[10] In a more recent meta-analysis comparing NaP and PEG bowel preparations, Tan et al. concluded that NaP was more effective in bowel cleansing than PEG.[43] This study also demonstrated that patients are more likely to complete NaP bowel preparation than PEG, which would have an impact on quality of bowel cleansing.[43] Typically, in people, NaP is administered in two 45 ml oral doses, diluted in approximately 100 ml water or clear beverage and followed by ingestion of 600 to 800 ml water within 1 to 2 hours of NaP ingestion.[11,14,70,78] Usually, both doses are administered the day prior to a morning colonoscopy, or one dose is given in the evening prior to and one dose the morning of colonoscopy.[11,14,70,78] The standard NaP protocol

used in this study was extrapolated from the typical protocol used in people, however the timing of administration was adjusted to facilitate the technical demands of administration of the preparation to a group of dogs as well as to mimic the typical time setting for completion of bowel preparation and colonoscopy in most veterinary hospitals.

The mucosal surface in many of the dogs receiving all variations of NaP was coated with a thin layer of adherent fecal material, which was difficult to flush or suction away from the mucosal surface. Additionally, a significantly greater volume of water was instilled through the endoscope for the purpose of assessing the ease of flushing fecal material from the colonic mucosa in the NaP_1 group compared to the control group. It was speculated that decreased moisture content may have contributed to the viscous and adherent nature of the fecal material. To the authors' knowledge, this finding has not been reported with NaP bowel preparation in people. The volume of water consumed by the dogs after receiving NaP_1 was significantly greater than the controls. However, the dogs consumed less water (range 30-45 ml/kg) after NaP administration than the volume of water recommended (57 ml/kg) for people to consume during NaP preparation.[79] It is possible that inadequate water consumption may have contributed to formation of the thin adherent layer of fecal material observed after NaP preparation in this study. In people, the mean time to onset of bowel activity is 1.7 hours after the first dose of NaP and 0.7 hours after the second dose.[80] The mean duration of bowel activity was 4.6 hours after the first dose and 2.9 hours after the second dose and ceased within 4 hours in 83% of people surveyed.[80] The duration of bowel activity in dogs was not measured in this study, however, if the duration of activity in dogs is similar to that reported in people, it is possible that administration of the NaP preparations closer to the time of colonoscopy

may result in better colon cleansing effect. Delaying examination may result in drying of residual fecal material within the colon making removal of fecal material via suction and flushing less effective. Administration of one dose of NaP the evening prior to and the second dose the morning of colonoscopy may be a viable alternative to the administration schedule used in this study. In people, ingestion of NaP the evening before and morning of colonoscopy improved bowel cleansing compared to taking NaP entirely the day before the procedure.[81]

Sodium phosphate preparations rely on osmotic action to draw plasma water into the colon to soften and flush fecal material out of the colon. It is possible that the dosage of NaP used in this study was inappropriate, resulting in insufficient osmotic action to draw the necessary fluid into the colon to achieve the desired cleansing effect. Additional studies would be needed to assess the safety and efficacy of NaP if administered at a dosage greater than that used in this study.

Variations of the standard NaP protocol were evaluated to determine the effect of enema and bisacodyl on the efficacy of NaP as a colon cleansing agent. Enema administration has been a routine component of the standard PEG preparation protocol used in veterinary medicine and is a time consuming, stress producing, and messy procedure.[1] Enema administration as the sole bowel preparation for rigid colonoscopy is less effective than preparation with PEG.[7] Elimination of enemas from bowel preparation would reduce patient stress and discomfort. Unfortunately, the results of this study did not support the use of NaP preparations either with or without enema administration. Bisacodyl is a stimulant laxative which increases nitric oxide mediated epithelial cell secretion and myenteric neuronal depolarization resulting in increased mucosal secretion

and colonic propulsion.[82] Afridi et al. demonstrated that the colon cleansing effect of the standard NaP preparation with the addition of Biscodyl (10 mg, PO) 1 hour after administration of the second dose of NaP was as efficacious as the PEG preparation in people.[57] The addition of bisacodyl to the standard NaP preparation did not improve the bowel cleansing effect of NaP in the dogs of this study.

Vomiting was observed after administration of NaP, but not after administration of the PEG control. Vomiting occurred more frequently in the NaP_1 group than in the remaining NaP groups. Vomiting in the NaP_1 group was attributed to the hypertonicity of the NaP preparation and the resulting stimulation of duodenal chemoreceptors. Stimulation of these receptors can directly stimulate the vomiting center through the vagal afferent pathway.[22] For the remaining four NaP preparations, the volume of water used to dilute the NaP solution was doubled to reduce the tonicity of the solution. This resulted in reduction in the frequency of vomition after NaP administration and supports hypertonicity as the cause of vomition in the NaP_1 group.

Vomiting has been reported as a complication associated with PEG administration in 6.5% of dogs receiving PEG bowel preparation.[9] Regurgitation, but not vomiting was observed more frequently after administration of the PEG control preparation than preparations containing NaP. Regurgitation associated with the control preparation was attributed to the rapid orogastric administration of a large fluid volume which resulted in gastric distention. All episodes of regurgitation occurred during or immediately after administration of PEG. It is possible the combination of rapid gastric distention and stimulation of the gag reflex by the presence of the orogastric tube may have caused the regurgitation in these dogs. Similarly, regurgitation was observed twice after

administration of a NaP containing preparation, each time immediately after administration. In these two dogs, regurgitation was attributed to the stimulus of orogastric tube removal and moderate excitement of the dogs during administration.

Mild hematochezia was observed infrequently in association with NaP containing preparations. This may have been the result of mild trauma sustained during repeated enema administration. In people, colonic mucosal lesions, including ulceration, have been reported after NaP bowel preparation.[62,64] A report by Driman et al. indicated a 6.1% incidence of unexplained colonic mucosal abnormalities in people prepared for colonoscopy with NaP.[63] Although the exact cause of the mucosal lesions was not known, it was proposed these lesions resulted from the NaP preparation.[63] Proposed mechanisms for NaP induced mucosal lesions include oxidative stress triggered by NaP[65] and direct stimulation of crypt epithelial cell proliferation by NaP.[63] Colonic mucosal ulceration could result in mild hematochezia, however, no lesions consistent with mucosal erosion or ulceration were observed in any of the dogs in this study. Poor colon cleansing results may have prevented complete visualization of the colonic mucosa in some dogs.

Administration of NaP for bowel preparation has been associated with hyperphosphatemia, hypocalcemia, hypernatremia, hypokalemia, and hypomagnesemia in people.[17,19,55,56] Metabolic and electrolyte abnormalities occurred more commonly during preparation with NaP than PEG in people; these abnormalities were not associated with adverse clinical effects.[10] However, severe, life-threatening hyperphosphatemia and hypocalcemia have been reported after administration of NaP in people with renal insufficiency.[58,83,84] In this study, significant differences in iCa^{2+}, Ca^{2+}, phos, K^+, Na^+,

Cl^-, anion gap, TCO_2, HCO_3^-, and pH were detected in the NaP_1 group when compared to the PEG control. However, only three analytes, iCa^{2+}, Ca^{2+}, and phos, had mean values outside of the reference interval. Hyperphosphatemia and mild hypocalcemia occurred in the NaP_1 group and were significantly different from the PEG control group (table 3). However, no dog was observed exhibiting clinical signs as a result of these abnormalities and both hyperphosphatemia and hypocalcemia resolved within 24 hours after administration of the first NaP dose. Additionally, although a mild but significant decrease was noted in total calcium and ionized calcium, the ionized calcium did not fall below the normal reference interval. Thus, it is unlikely NaP will cause clinical signs associated with hypocalcemia if used at the current dosage in healthy dogs. The effects of NaP in sick dogs were not evaluated in this study. However, the use of NaP is not recommended in people with heart failure, renal failure, known electrolyte abnormalities, and/or intestinal obstruction as they may be predisposed to complications associated with administration of NaP.[53]

Although values remained within the reference interval, serum K^+ was significantly lower in the NaP_1 group compared to the PEG control group at several times. However, these differences were slight since mean values were never <3.5 mEq/L (reference interval, 3.5-4.5) and were considered clinically insignificant. Hypokalemia has been reported in people receiving NaP, especially in those receiving concurrent diuretic therapy, which can deplete total body potassium.[55] Gastrointestinal loss as a result of the osmotic diarrhea stimulated by NaP is the most likely cause of hypokalemia. Hypernatremia and hyperchloremia associated with NaP were not observed in this study, although both mean Na^+ and Cl^- concentrations were significantly greater in the NaP_1

group compared to the PEG control group 1 hour after administration of NaP and PEG. The slight increase in serum sodium concentration likely resulted from increased absorption of Na^+ from the gastrointestinal tract after administration of NaP. However, the difference in mean Cl^- appears to be the result of a slight decrease in serum chloride concentration in the control group. The significantly lower values for pH, HCO_3^-, and CO_2 suggest NaP administration may have caused a mild acidosis. This may have been due to increased gastrointestinal loss of HCO_3^- as a result of osmotic diarrhea stimulated by NaP. However, as these changes were very slight, the effect of NaP on acid base balance did not appear to be clinically important. The significantly greater anion gap in the NaP group during the 2 hours after each NaP administration corresponds to slight increase in mean Na^+ concentration and slight decreases in mean K^+ and HCO_3^- concentrations in the NaP group, and slight decreases in mean Na^+, K^+, and Cl^- in the PEG control group.

In summary, although NaP containing bowel cleansing protocols did result in moderate, transient, hyperphosphatemia and hypocalcemia, these abnormalities resolved within 24 hours of initial administration and were not associated with adverse clinical signs. Despite the apparent safety and ease of administration of the NaP preparations, the clinical use of the NaP bowel cleansing preparations evaluated in this study is not recommended due to the inadequate quality of bowel preparation as compared to the PEG containing bowel preparation. Further evaluation of the safety and efficacy of different administration schedules and dosages of NaP need to be performed before NaP preparations can be utilized in dogs undergoing colonoscopy.

CHAPTER III: Conclusions

In this study the PEG control preparation resulted in significantly better colon cleansing than the standard sodium phosphate preparation, NaP_1. Since the colon cleansing effect of NaP_2 was not significantly different from NaP-E, NaP/E/B, and NaP/B, it is likely that the control would result in a better colon cleansing effect than all of the NaP preparations evaluated. Sodium phosphate containing bowel cleansing protocols resulted in moderate, transient, hyperphosphatemia and hypocalcemia. These abnormalities resolved within 24 hours of initial administration in all dogs and were not associated with adverse clinical effects. Despite the apparent safety and ease of administration of the NaP preparations, the clinical use of the NaP bowel cleansing preparations evaluated in this study is not recommended due to the inadequate quality of bowel preparation as compared to the PEG containing bowel preparation. Further evaluation of the safety and efficacy of different administration schedules and dosages of NaP need to be performed before NaP preparations can be utilized for bowel cleansing in dogs undergoing colonoscopy.

Footnotes

[i] Hill's Science Diet® Adult Original, Hill's Pet Nutrition, INC., Topeka, KS

[ii] Fleet® Phospho-soda® Oral Saline Laxative, C.B. Fleet CO., INC. Lynchburg, VA

[iii] Golytely®, Braintree Laboratories, INC., Braintree, MA

[iv] The Advanced® Micro Osmometer, Model 3300, Advanced Instruments, INC., Norwood, MA

[v] Fujinon System Gastroscope Model EG-310HR, Fujinon, Inc., Wayne NJ

[vi] Fujinon Eve Processor Super Image Model EPX-310, Fujinon, Inc., Wayne NJ

[vii] Sony Still Video Recorder Model MVR-5300 , Sony Business Solutions & Systems Co., Park Ridge, NJ

[viii] "The Endopump" Cat # EP-1, Fujinon Inc., Wayne, NJ

[ix] SAS version 9.12, Gary, NC

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Table 1: Components of PEG and NaP bowel preparations

Groups	Treatments			
	PEG 66 ml/kg	NaP 1 ml/kg	Enema 20 ml/kg	Bisacodyl 10 mg/dog
Control	+	—	+	—
NaP_1	—	+	+	—
NaP_2	—	+	+	—
NaP-E	—	+	—	—
NaP/E/B	—	+	+	+
NaP/B	—	+	—	+

PEG – Polyethylene glycol
NaP – Sodium Phosphate

Table 2: Mean regional and total colon scores

	Ascending	Transverse	Orad Descending	Mid Descending	Distal Descending	Total Colon Score
Control	2	2.25	1.63	1.63	1.88	9.38
NaP_1	2.75	2.88	2.88	2.5	2.63	13.63
Standard Error	0.15	0.2	0.25	0.23	0.17	0.69
***p*-value**	**0.002**	0.055	**0.003**	**0.025**	**0.014**	**0.003**
NaP_2	2.25	2.63	2.5	2.63	3	13
NaP-E	2.63	2.88	2.75	2.63	2.25	13.23
NaP/E/B	2.38	2.88	2.5	2.63	2.5	12.88
NaP/B	2.63	2.88	2.88	2.75	2.75	13.88
Standard Error	0.24	0.24	0.3	0.33	0.3	0.95
***p*- value**	*0.7891*	*0.5647*	*0.8086*	*0.7687*	*0.1004*	*0.5757*

Bold indicates significant difference (*$p<0.05$*)

Table 3: Least squares means with standard error for selected analytes

Hour	Group	iCa^{2+}	Ca^{2+}	phos	K^+	Na^+	Cl^-	Anion Gap	CO_2	HCO_3^-	pH
Reference Interval		0.95-1.29 mmol/L	9.3-10.6 mg/dL	2.5-5.2 mg/dL	3.5-4.5 mEq/L	143-150 mEq/L	109-117 mEq/L	13-20	17-25 mEq/L	20-29 mEq/L	7.324-7.459
0	Control	1.29	9.5	3.7	4.1	146	113	15	22	23	7.37
0	NaP_1	**1.3**	9.6	3.7	4.1	146	113	15	22	22	7.366
1	Control	**1.3**	9.4	3.9	4	145	111	15	23	23	7.398
1	NaP_1	1.21*	9.3	**8.0***	3.8*	148*	114*	17*	21*	21*	7.353*
2	Control	1.25	9.3	3.1	3.8	146	111	15	23	23	7.4
2	NaP_1	1.19*	**8.8***	**8.1***	3.8	147	113	17*	21*	21*	7.362*
4	Control	1.29	9.5	3.8	4	146	112	15	23	23	7.392
4	NaP_1	1.24	**9**	**6.0***	3.7*	146	113	15	22	21*	7.374*
5	Control	1.26	9.4	3.6	3.9	146	110	15	25	25	7.408
5	NaP_1	1.18*	**9**	**9.4***	3.5*	148*	113*	17*	21*	21*	7.360*
6	Control	1.26	9.3	3.6	3.7	146	112	15	23	24	7.394
6	NaP_1	1.16*	**8.7***	**8.7***	3.5*	147	113	17*	21*	21*	7.360*
8	Control	**1.3**	9.5	4.3	3.9	146	112	15	23	23	7.377
8	NaP_1	1.23*	**9.0***	**6.7***	3.6*	146	113	15	22 *	22 *	7.357*
24	Control	**1.3**	9.4	4	3.8	145	112	15	22	23	7.388
24	NaP_1	1.28	9.3	3.8	3.8	144	112	15	21	22	7.383
	Std. Error	± 0.02	± 0.2	± 0.3	± 0.1	± 0	± 1	± 1	± 1	± 1	± 0.006

Bold indicates those values which fell outside the reference range ($p<0.05$)

* indicates that the difference in means of the control and NaP groups was significant at that time

Appendix 1: Safety study - least squares means for all biochemical analytes evaluated, body weight, and body temperature

		iCa^{2+}	Ca^{2+}	phos	Na^{+}	K^{+}	pTP	Mg^{+}	Cl^{-}	Anion Gap	Albumin
Reference Interval		**0.95-1.29**	**9.3-10.6**	**2.5-5.2**	**143-150**	**3.5-4.5**	**5.4-6.8**	**1.5-2.0**	**109-117**	**13-20**	**2.8-3.7**
Hour	**Group**	**mmol/L**	**mg/dL**	**mg/dL**	**mEq/L**	**mEq/L**	**g/dL**	**mg/dL**	**mEq/L**		**g/dL**
0	Control	1.29	9.5	3.7	146	4.1	5.9	1.7	113	15	3.2
0	NaP_1	1.3	9.6	3.7	146	4.1	6.1	1.8	113	15	3.2
1	Control	1.28*	9.4	3.0*	145	4	5.9	1.7	111	15	3.1
1	NaP_1	1.21	9.3	8	148	3.8	6.2	1.7	114	17	3.2
2	Control	1.25*	9.3*	3.1*	146	3.8	5.8	1.6	111	15	3.1
2	NaP_1	1.19	8.8	8.1	147	3.8	6.2	1.7	113	17	3.1
4	Control	1.29	9.5	3.8*	146	4	6	1.6	112	15	3.1
4	NaP_1	1.24	9	6	146	3.7	6.1	1.6	113	15	3.1
5	Control	1.26*	9.4	3.6*	146	3.9*	6	1.6	110*	15	3.1
5	NaP_1	1.18	9	9.4	148	3.5	6	1.6	113	17	3.2
6	Control	1.26*	9.3*	3.6*	146	3.7*	5.8	1.5	112	15	3.1
6	NaP_1	1.16	8.7	8.7	147	3.5	6.1	1.5	113	17	3.2
8	Control	1.30*	9.5*	4.3*	146	3.9*	5.8	1.6	112	15	3.1
8	NaP_1	1.23	9	6.7	146	3.6	6	1.6	113	15	3.1
24	Control	1.3	9.4	4	145	3.8	5.9	1.7	112	15	3.1
24	NaP_1	1.28	9.3	3.8	144	3.8	6	1.7	112	15	3.1
	Std.	±	±	±	±	±	±	±	±	±	±
	Error	0.02	0.2	0.3	0	0.1	0.2	0	1	1	0.1

*** denotes significant difference ($p<0.05$)**

		tCO_2	HCO_3^-	pH	Osm	sTP	PCV	Body Temp	Body Wt
Reference Interval		**17-25**	**20-29**	**7.324-**	**290-310**	**5.5-7.5**	37-55%	°F	Kg
Hour	**Group**	**mEq/L**	**mEq/L**	**7.459**	**mOsm/kg**	**g/dL**			
0	Control	22	23	7.3701	299	6	44	102.3	16.6
0	NaP_1	22	22	7.3658	300	5.9	43	102.4	16.5
1	Control	23	23	7.3977	298	5.9	45	101.5	17.2
1	NaP_1	21	21	7.3531	302	6	44	101.9	16.5
2	Control	23	23	7.4005	295	5.7	44	101.8	16.9
2	NaP_1	21	21	7.3621	300	5.8	42	102	16.6
4	Control	23	23*	7.3921	298	5.7	41	102	16.7
4	NaP_1	22	21	7.374	299	5.8	41	102	16.3
5	Control	25*	25	7.4077	301	5.7	42	101.4	17.6
5	NaP_1	21	21	7.3595	301	5.9	39	101.6	16.4
6	Control	23	24*	7.3936	299	5.6	40	101.8	17.3
6	NaP_1	21	21	7.3596	296	5.7	40	101.8	16.4
8	Control	23	23	7.3766	298	5.6	39	101.3	17
8	NaP_1	22	22	7.3566	301	5.8	40	101.5	16.2
24	Control	22	23	7.3879	299	5.8	40	101.8	16.4
24	NaP_1	21	22	7.3834	297	5.8	40	101.8	16.1
	Std.	±	±	±	±	±	±	±	±
	Error	1	1	0.0056	2	0.1	1	0.2	1.1

*** denotes significant difference (p<0.05)**

Appendix 2: Serum calcium and phosphorus values at 0, 2, and 5 hours after administration of NaP_2

		Ca2+	Phos
Reference Interval		**9.3-10.6**	**2.5-5.2**
Hour	**Dog**	**mg/dL**	**mg/dL**
0	**2143**	9.2	3.7
0	**7371**	8.9	4.3
0	**2151**	9.2	3.3
0	**8113**	9.6	4.1
0	**1326**	9.6	3.9
0	**2158**	10	3.6
0	**1852**	9.8	4.6
0	**5371**	10.2	3.1
2	**2143**	9.1	9.2
2	**7371**	8.3	8.6
2	**2151**	8.9	8.9
2	**8113**	9.3	8.5
2	**1326**	9.1	8.7
2	**2158**	9.5	8.1
2	**1852**	9.1	13.6
2	**5371**	9.8	6.8
5	**2143**	9.4	9.4
5	**7371**	8.4	10.7
5	**2151**	9.2	8.6
5	**8113**	9.5	10
5	**1326**	9	9.5
5	**2158**	10	9.2
5	**1852**	8.3	12.5
5	**5371**	9.7	8.1

To ensure that vomiting after administration of NaP_1 did not influence the systemic effects of NaP_1, total serum calcium and phosphorus were evaluated at hours 0, 2, and 5 in the NaP_2 group. These times represented the baseline and time points with the greatest magnitude of change in phosphorus in the NaP_1 group.

Appendix 3: Volume of water consumed by each dog during bowel preparation

A. Safety

Dog	Group	H2O ml/kg/d
2143	Control	7
1326	Control	7
2151	Control	31
7371	Control	5
2158	Control	8
5371	Control	4
8113	Control	4
1852	Control	4
2143	NaP_1	56
1326	NaP_1	48
2151	NaP_1	66
7371	NaP_1	57
2158	NaP_1	23
5371	NaP_1	51
8113	NaP_1	28
1852	NaP_1	32

B. Efficacy

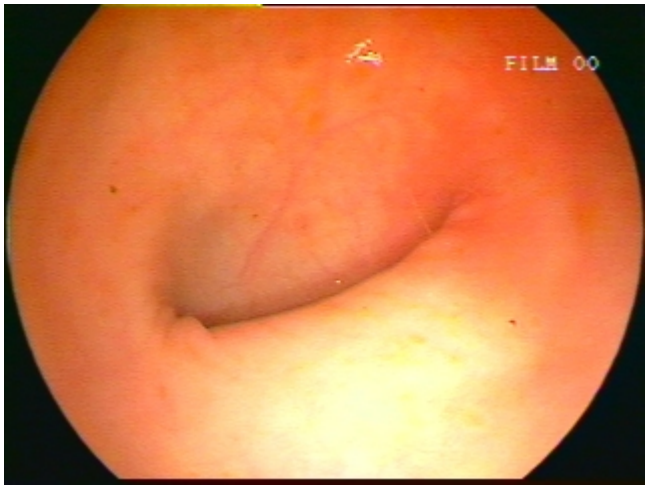
Dog	Group	H2O ml/kg/d
2143	NaP_2	38
1326	NaP_2	24
2151	NaP_2	59
7371	NaP_2	39
2158	NaP_2	47
5371	NaP_2	26
8113	NaP_2	34
1852	NaP_2	9
2143	NaP-E	50
1326	NaP-E	40
2151	NaP-E	44
7371	NaP-E	42
2158	NaP-E	39
5371	NaP-E	31
8113	NaP-E	33
1852	NaP-E	14

Dog	Group	H2O ml/kg/d
2143	NaP/E/B	36
1326	NaP/E/B	32
2151	NaP/E/B	35
7371	NaP/E/B	43
2158	NaP/E/B	40
5371	NaP/E/B	29
8113	NaP/E/B	7
1852	NaP/E/B	19
2143	NaP/B	45
1326	NaP/B	36
2151	NaP/B	58
7371	NaP/B	48
2158	NaP/B	46
5371	NaP/B	39
8113	NaP/B	35
1852	NaP/B	11

Appendix 4: Endoscopic images demonstrating bowel cleansing scoring system

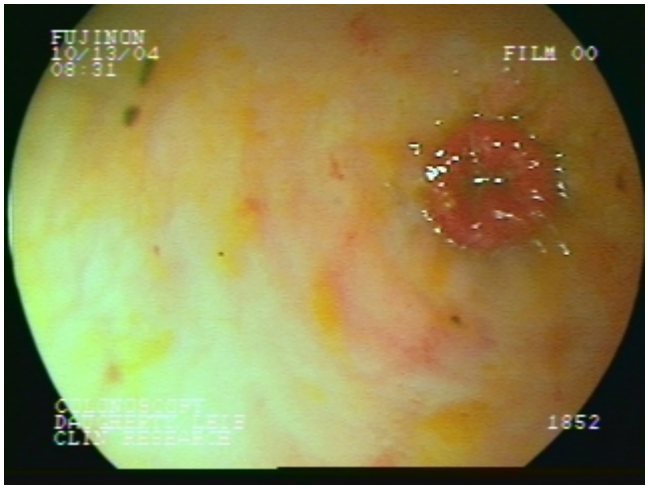
A. Score 1

Clean Colon: no fecal matter or nearly none seen, no residual fluid



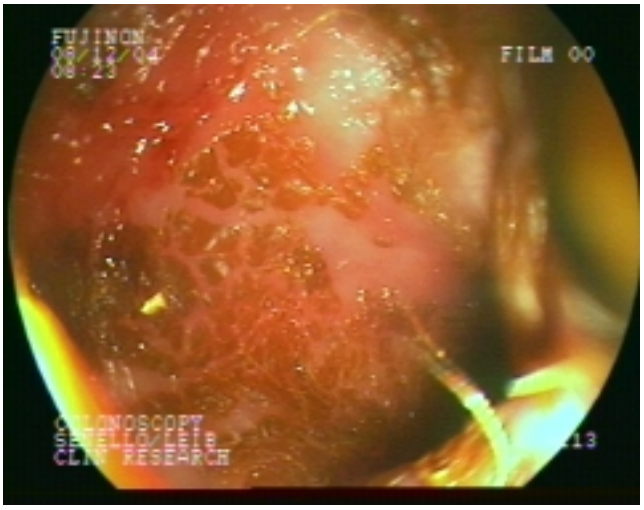
B. Score 2

Clean Colon: small amounts of thin, adherent liquid fecal matter seen, suctioned/flushed easily



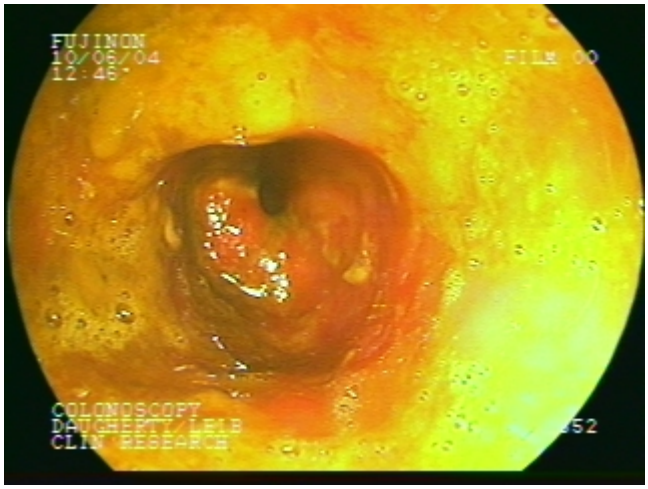
C. Score 3

Unacceptable preparation: Moderate amounts of liquid to semisolid or adherent fecal matter seen, difficult to suction/flush from the colon, mucosa still visible



D. Score 4

Unacceptable Preparation: Large amounts of solid or adherent fecal matter precluding adequate examination



Appendix 5: Regional and Total Colon Scores

A. Safety

Dog	Group	Ascending Colon	Transverse Colon	Orad Descending Colon	Mid-Descending Colon	Distal Descending Colon	Total Colon Score
2143	Control	2	2	1	1	2	8
1326	Control	2	3	2	2	1	10
2151	Control	2	2	3	2	2	11
7371	Control	2	3	2	2	2	11
2158	Control	2	2	1	1	2	8
5371	Control	2	2	1	1	2	8
8113	Control	2	2	2	2	2	10
1852	Control	2	2	1	2	2	9
2143	NaP_1	3	3	2	2	3	13
1326	NaP_1	3	3	3	3	3	15
2151	NaP_1	3	3	3	2	3	14
7371	NaP_1	2	3	3	2	2	12
2158	NaP_1	3	2	3	2	2	12
5371	NaP_1	3	3	3	3	3	15
8113	NaP_1	3	4	4	4	3	18
1852	NaP_1	2	2	2	2	2	10

B. Efficacy

Dog	Group	Ascending Colon	Transverse Colon	Orad Descending Colon	Mid-Descending Colon	Distal Descending Colon	Total Colon Score
2143	NaP_2	2	3	1	2	3	11
1326	NaP_2	2	3	3	3	3	14
2151	NaP_2	3	3	2	2	3	13
7371	NaP_2	2	2	2	1	3	10
2158	NaP_2	2	3	3	3	3	14
5371	NaP_2	2	2	3	3	3	13
8113	NaP_2	3	3	4	4	3	17
1852	NaP_2	2	2	2	3	3	12
2143	NaP-E	3	4	4	3	1	15
1326	NaP-E	3	3	2	3	2	13
2151	NaP-E	3	3	2	1	1	10
7371	NaP-E	2	2	2	2	4	12
2158	NaP-E	3	3	2	2	2	12
5371	NaP-E	3	3	3	3	2	14
8113	NaP-E	3	4	4	4	3	18
1852	NaP-E	1	1	3	3	3	11
2143	NaP/E/B	3	3	3	3	3	15
1326	NaP/E/B	3	3	3	3	4	16
2151	NaP/E/B	3	3	2	2	3	13
7371	NaP/E/B	3	3	2	3	3	14
2158	NaP/E/B	2	3	3	2	2	12
5371	NaP/E/B	2	2	3	3	2	12
8113	NaP/E/B	2	3	2	2	1	10
1852	NaP/E/B	1	3	2	3	2	11
2143	NaP/B	3	3	3	3	1	13
1326	NaP/B	2	3	3	3	3	14
2151	NaP/B	2	3	2	2	3	12
7371	NaP/B	3	4	4	4	4	19
2158	NaP/B	2	2	2	2	2	10
5371	NaP/B	2	3	3	2	2	12
8113	NaP/B	4	3	4	4	3	18
1852	NaP/B	3	2	2	2	4	13

Appendix 6: Time to complete endoscopy, Volume of water instilled and suctioned during endoscopy, Occurrence of vomiting and regurgitation

A. Safety

Dog	Group	Endoscopy Time (minutes)	Volume Instilled (ml)	Volume Suctioned (ml)	Episodes of Vomiting	Episodes of Regurgitation
2143	Control	13	120	84	0	1
1326	Control	26	220	144	0	0
2151	Control	14	95	66	0	1
7371	Control	22	210	142	0	0
2158	Control	8	55	63	0	0
5371	Control	20	40	43	0	0
8113	Control	24	105	90	0	1
1852	Control	22	65	84	0	0
2143	NaP_1	15	390	181	0	0
1326	NaP_1	26	325	198	0	0
2151	NaP_1	22	255	46	0	0
7371	NaP_1	14	340	158	2	0
2158	NaP_1	17	53	47	1	0
5371	NaP_1	17	255	95	1	0
8113	NaP_1	19	250	340	1	0
1852	NaP_1	14	210	139	1	0

B. Efficacy

Dog	Group	Endoscopy Time (minutes)	Volume Instilled (ml)	Volume Suctioned (ml)	Episodes of Vomiting	Episodes of Regurgitation
2143	NaP_2	28	400	140	0	0
1326	NaP_2	9	225	97	0	0
2151	NaP_2	12	400	76	0	0
7371	NaP_2	10	230	67	0	0
2158	NaP_2	12	260	228	0	0
5371	NaP_2	13	245	119	0	0
8113	NaP_2	15	315	194	1	0
1852	NaP_2	11	230	131	0	0
2143	NaP-E	12	330	80	0	0
1326	NaP-E	14	440	288	0	0
2151	NaP-E	12	200	51	0	0
7371	NaP-E	17	230	66	0	0
2158	NaP-E	8	210	108	0	0
5371	NaP-E	17	260	142	0	0
8113	NaP-E	13	245	113	0	0
1852	NaP-E	20	400	230	0	0
2143	NaP/E/B	14	310	244	0	0
1326	NaP/E/B	21	410	78	0	0
2151	NaP/E/B	15	340	88	0	0
7371	NaP/E/B	13	235	153	0	1
2158	NaP/E/B	10	220	60	0	0
5371	NaP/E/B	12	235	126	0	0
8113	NaP/E/B	20	240	92	1	0
1852	NaP/E/B	18	374	166	0	0
2143	NaP/B	14	235	87	0	0
1326	NaP/B	20	405	209	0	1
2151	NaP/B	27	310	178	0	0
7371	NaP/B	13	170	132	0	0
2158	NaP/B	13	255	63	0	0
5371	NaP/B	16	325	184	0	0
8113	NaP/B	12	210	76	0	0
1852	NaP/B	10	305	83	0	0

Appendix 7: Daily Fecal Scores and Fecal Scoring System

		Dog Identification Number							
Day	**Date**	**8113**	**1326**	**7371**	**2158**	**1852**	**2143**	**5371**	**2151**
Mon	30-Aug	4.0	4.0	4.0	4.0	4.0	4.0	4.0	5.0
Tues	31-Aug	4.0	nf	4.0	4.0	4.0	5.0	4.0	4.0
Wed	1-Sep	4.0	4.0	4.0	4.5	4.0	5.0	4.0	5.0
Thurs	2-Sep	4.0	nf	4.0	nf	5.0	5.0	4.0	nf
Fri	3-Sep	4.0	nf	4.0	5.0	5.0	3.5	4.0	5.0
Sat	4-Sep	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Sun	5-Sep	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Mon	6-Sep	4.0	3.0	4.0	4.0	4.0	nf	5.0	4.0
Tues	7-Sep	4.0	3.5	nf	nf	5.0	4.0	5.0	nf
Wed	8-Sep	4.0	4.0	nf	2.0	4.0	4.0	4.5	3.0
Thurs	9-Sep	4.0	3.5	3.5	3.0	5.0	4.0	4.0	3.0
Fri	10-Sep	4.0	nf	4.0	4.0	5.0	4.0	4.0	5.0
Sat	11-Sep	4.0	5.0	2.0	3.0	5.0	4.0	4.0	5.0
Sun	12-Sep	5.0	4.0	3.0	3.0	5.0	4.0	4.0	4.0
Mon	13-Sep	4.5	5.0	3.5	4.0	5.0	4.0	4.0	4.0
Tues	14-Sep	4.0	nf	3.5	4.0	5.0	5.0	4.5	4.0
Wed	15-Sep	1.0	2.0	1.0	1.0	1.0	1.0	1.0	2.0
Thurs	16-Sep	1.5	2.0	nf	1.0	2.0	nf	1.0	1.5
Fri	17-Sep	3.0	3.0	4.0	4.0	4.0	3.5	4.5	3.0
Sat	18-Sep	4.0	3.0	3.0	4.0	4.0	4.0	5.0	3.0
Sun	19-Sep	4.0	3.0	3.0	4.0	4.0	4.0	5.0	3.0
Mon	20-Sep	4.0	3.5	5.0	3.5	5.0	5.0	5.0	4.0
Tues	21-Sep	4.0	4.0	4.0	4.0	5.0	5.0	4.5	4.5
Wed	22-Sep	1.0	1.0	1.0	1.0	2.0	1.0	1.0	1.0
Thurs	23-Sep	1.0	2.0	2.0	nf	2.0	1.0	2.0	2.5
Fri	24-Sep	3.5	4.0	3.0	4.0	4.0	3.5	4.0	4.5
Sat	25-Sep	4.0	3.0	3.5	4.0	4.0	4.0	4.0	3.5
Sun	26-Sep	3.5	4.0	3.5	4.0	4.5	5.0	4.0	4.0
Mon	27-Sep	4.0	4.0	5.0	5.0	5.0	5.0	5.0	5.0
Tues	28-Sep	4.5	4.0	4.5	4.0	5.0	5.0	5.0	5.0
Wed	29-Sep	1.0	1.5	1.0	1.0	1.5	nf	nf	2.0
Thurs	30-Sep	3.0	3.0	2.5	3.0	3.0	2.5	1.0	3.0
Fri	1-Oct	5.0	3.0	4.5	4.0	4.0	4.0	5.0	3.0
Sat	2-Oct	4.0	4.0	4.5	3.0	4.5	4.0	4.0	3.0
Sun	3-Oct	4.5	4.0	4.5	4.0	4.5	4.5	4.0	3.0
Mon	4-Oct	4.0	5.0	5.0	5.0	5.0	5.0	4.0	4.0
Tues	5-Oct	5.0	5.0	5.0	4.0	5.0	5.0	4.5	4.0
Wed	6-Oct	1.0	1.5	1.0	1.0	1.0	1.0	1.0	1.0
Thurs	7-Oct	4.0	4.0	4.0	2.0	4.0	4.0	1.0	4.0
Fri	8-Oct	5.0	4.0	4.0	5.0	3.0	4.0	5.0	4.0
Sat	9-Oct	3.0	3.5	3.0	2.5	4.0	4.0	3.5	3.0
Sun	10-Oct	4.0	3.0	3.0	4.0	3.5	4.5	4.0	3.0
Mon	11-Oct	4.0	4.0	3.5	5.0	5.0	4.5	5.0	4.0
Tues	12-Oct	5.0	4.0	4.0	5.0	4.5	5.0	4.0	5.0

Wed	13-Oct	1.0	1.5	1.0	1.0	1.0	1.0	1.0	2.0
Thurs	14-Oct	2.5	3.0	3.0	1.0	3.5	1.5	2.0	1.0
Fri	15-Oct	4.0	4.0	4.0	4.0	4.5	3.0	4.0	4.0
Sat	16-Oct	4.0	4.0	4.5	3.5	4.0	4.0	4.5	4.0
Sun	17-Oct	5.0	3.5	4.5	4.0	3.5	4.5	3.5	5.0
Mon	18-Oct	5.0	4.5	4.5	4.0	4.0	4.0	5.0	4.5
Tues	19-Oct	4.5	5.0	4.5	4.0	5.0	4.0	5.0	4.0
Wed	20-Oct	1.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0
Thurs	21-Oct	2.0	1.5	2.5	3.5	1.5	2.0	3.0	1.5
Fri	22-Oct	4.5	4.5	4.0	4.5	3.0	2.5	5.0	3.5
Sat	23-Oct	4.5	3.0	4.0	3.5	4.0	3.5	4.0	4.0
Sun	24-Oct	4.0	4.5	4.0	4.0	4.0	4.5	4.0	4.5
Mon	25-Oct	4.5	5.0	4.5	4.0	5.0	4.0	5.0	5.0

nf – no feces available to assess

n/a – fecal scores were not recorded on these days due to an error in communication with animal care staff

Fecal Scoring System

Grade 1: Greater than two-thirds of the feces in a defecation are liquid. Feces have lost all form, appearing as a puddle.

Grade 2: Soft-liquid feces are an intermediate between soft and liquid feces.

Grade 3: Greater than two-thirds of the feces in a defecation are soft. The feces retain enough form to pile but have lost cylindrical appearance.

Grade 4: Firm-soft feces are an intermediate between the grades of firm and soft.

Grade 5: Greater than two-thirds of feces in a defecation are firm. They have cylindrical shape with little flattening.

Appendix 8: Summary of results of pilot study evaluating NaP

A pilot study was performed prior to initiation of this study to determine the dose of NaP to be evaluated in dogs. Three dogs given three doses of NaP. A standard dose (0.65 ml/kg) was determined by extrapolation of the standard NaP dose used in people. On a ml/kg basis, the other two pilot doses were 1.3 ml/kg (double the standard dose) and 0.33 ml/kg (half the standard dose). Each dog received one bowel preparation protocol one time. Food was withheld from each dog for 15 hours prior to bowel preparation. During preparation, each dog received two doses of NaP diluted in 2 ml/kg water (doses listed in the table below) administered by orogastric intubation 4 hours apart. An additional 2 ml/kg water was administered after NaP to flush the orogastric tube to ensure complete administration of NaP. A warm water enema (20 ml/kg) was administered immediately after each NaP dose. Dogs were allowed free access to water until the time of premedication for anesthesia, approximately 24 hours after initiation of bowel preparation. Blood samples were collected via jugular venipuncture immediately prior to initial NaP administration (0 hour) and 1, 2, 4, and 24 hours after NaP administration. Appendix 10 lists the results for the biochemical parameters evaluated at each of these times. Approximately 24 hours after initiation of bowel preparation, dogs were routinely anesthetized and colonoscopy performed to the level of the cecum in each dog as previously described.[1,25,26] Bowel cleansing effect was subjectively determined by observation by the endoscopist and one observer.

The quality of bowel cleansing effect subjectively improved as the dose of NaP increased. The half-standard NaP dose had poor bowel cleansing effect. The cleansing effect of the standard and double-standard NaP doses was subjectively determined to be

fair to good. The double-standard dose resulted in greater hyperphosphatemia and hypocalcemia than the standard dose, although clinical signs resulting from these metabolic derangements were not observed, and abnormalities resolved within 24 hours. Based on the bowel cleansing effect and metabolic abnormalities observed in these three dogs, a standard dose of 1 ml/kg was chosen for evaluation of NaP as a bowel cleansing preparation in dogs.

Individual NaP doses used

Dog	NaP (ml/kg)
2151	0.65
7371	1.3
2158	0.33

Appendix 9: Results of biochemical parameters evaluated during pilot study

		iCa^{2+}	Ca^{2+}	phos	Na^{+}	K^{+}	pTP	Mg^{+}
Reference Interval		**0.95-1.29**	**9.3-10.6**	**2.5-5.2**	**143-150**	**3.5-4.5**	**5.4-6.8**	**1.5-2.0**
Hour	**Dog**	**mmol/L**	**mg/dL**	**mg/dL**	**mEq/L**	**mEq/L**	**g/dL**	**mg/dL**
0	**2151**	1.29	9.9	3.7	146	3.9	6	1.6
0	**7371**	1.26	10	5	148	4.2	6.7	1.9
0	**2158**	1.26	10.3	4.4	148	4	6.5	1.7
1	**2151**	1.18	9.8	7.3	149	3.6	5.8	1.7
1	**7371**	1.18	9.1	9.5	148	3.8	6.2	1.8
1	**2158**	1.3	9.7	7.6	147	4.5	6.4	1.7
2	**2151**	1.22	9.2	7.9	149	3.6	5.9	1.6
2	**7371**	1.07	8.3	10.1	146	3.8	6.4	1.6
2	**2158**	1.32	9.6	5.9	147	3.7	6.9	1.5
4	**2151**	1.27	9.4	5.7	148	3.5	5.8	1.6
4	**7371**	1.19	8.6	7.1	146	3.6	6.5	1.7
4	**2158**	1.4	10.2	5.4	147	4	6.3	1.6
24	**2151**	1.3	9.6	4	147	3.7	5.8	1.7
24	**7371**	1.19	9.1	4	146	3.5	6	1.7
24	**2158**	1.33	9.9	4.6	145	3.7	6.9	1.6

		Cl^{-}	Anion Gap	Albumin	tCO_2	HCO_3^{-}	pH	sTP	PCV
Reference Interval		**109-117**	**13-20**	**2.8-3.7**	**17-25**	**20-29**	**7.324-**	**5.5-7.5**	**37-55%**
Hour	**Dog**	**mEq/L**		**g/dL**	**mEq/L**	**mEq/L**	**7.459**	**g/dL**	
0	**2151**	113	14.9	3.4	22	21.5	7.372	6	47
0	**7371**	112	17.2	3.2	23	22.6	7.340	6	52
0	**2158**	113	18	3.4	21	20.5	7.346	6.2	49
1	**2151**	113	19.6	3.5	20	21.4	7.354	5.8	50
1	**7371**	113	17.8	3.2	21	23.6	7.339	5.9	49
1	**2158**	112	18.5	3.3	21	21.5	7.330	5.7	47
2	**2151**	113	20.6	3.5	19	20.6	7.360	5.9	47
2	**7371**	110	20.8	3	19	21.9	7.360	5.8	48
2	**2158**	113	17.7	3.3	20	20.7	7.328	6.2	45
4	**2151**	115	17.5	3.5	19	19.9	7.350	5.8	46
4	**7371**	111	14.6	3.1	24	23.3	7.350	5.8	48
4	**2158**	114	16	3.3	21	21.4	7.337	6	45
24	**2151**	114	16.7	3.3	20	20.7	7.346	5.8	46
24	**7371**	111	13.5	3	25	24.7	7.401	5.8	43
24	**2158**	113	15.7	3.3	20	21.5	7.365	6	45

VITA

Megen A. Daugherty was raised in Weirton, West Virginia. She attended Michigan State University and received a Bachelor of Science degree in Veterinary Science in 2000. She graduated from the Michigan State University College of Veterinary Medicine earning her Doctor of Veterinary Medicine degree with honors in 2002.

After graduation, Megen completed a rotating internship in small animal medicine and surgery at the Veterinary Teaching Hospital at Purdue University. Megen is currently completing the requirements of a residency in small animal internal medicine and a Master of Science in Biomedical and Veterinary Sciences at the Virginia-Maryland Regional College of Veterinary Medicine. Upon completion of these requirements, Megen will join the faculty and staff of the Cornell University Hospital for Animals as a clinical instructor.