

Expedited Management of Canine and Feline Vomiting and Diarrhea. Observational Study in 3952 Dogs and 2248 Cats Using Sucralfate-Like Potency-Enhanced Polyanionic Phyto-Saccharide—Elm Mucilage

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ABSTRACT

A potency-enhanced polyanionic phyto-saccharide of elm mucilage (PEPPS) was prescribed by 197 small animal veterinarians in an open-labeled field trial. Clients provided informed consent to veterinarians to prescribe PEPPS to 3952 dogs and 2248 cats. A 2 day/4 dose response rate, determined by veterinarians' consensus, provided clinical threshold for a significant clinical outcome. Data was collected through phone interviews conducted over a period of 3.5 years from June 2003 through December 2006. 82% of 1928 vomiting dogs and 77% of 1064 vomiting cats responded to PEPPS within 2 days or four doses. 93% of 2024 dogs and 79% of 1184 cats with diarrhea responded to PEPPS within 2 days or four doses. PEPPS appears useful for managing vomiting and diarrhea in dogs and cats. However, a randomized blinded placebo controlled trial is needed to quantify true clinical efficacy.

Keywords: Canine; Feline; Vomiting; Diarrhea; Slippery Elm; Sucralfate

1. Introduction

Timely management of disruptive gastrointestinal (GI) symptoms poses a challenge to both veterinary and medical physicians alike [1,2]. Restoration of normal GI function requires effective means to mitigate nausea, vomiting, diarrhea, in dogs and cats [3] as well as colicky pain and ulcerations in horses [4]. Current approaches in managing nausea (usually observed as inappetence), vomiting and diarrhea in small animals involve supportive care, bowel rest, pancreatic enzyme supplementation and/or appropriate anti-microbials [3]. Management of mucosal erosions and ulceration in small companion animals centers on control of acidity, either by neutralization with antacids, reduction with histamine-2 blockers (e.g., ranitidine, cimetidine, famotidine) or inhibition with proton pump inhibitors (e.g., omeprazole, lansoprazole, rabeprazole). A simplified approach in managing disparate GI symptoms would be useful for clinical veterinary practice were it safe, efficient and minimally burdensome [3,4].

The scale of the problem is significant. According to American Medical Veterinary Association [5] there are

150 - 197 million annual visits to small animal veterinarians in the US. Lund *et al.* [6] reported that in the US, 8.3% of veterinarian visits are for unexplained vomiting and diarrhea in dogs and cats. This translates into 12 to 16 million dog and cat visits (Appendix A) that involve diagnostic workups and treatment plans for vomiting and diarrhea. This volume however only reflects the owners who actively utilize veterinarian services. A recent survey of dog and cat owners [7] revealed that 40% of owners reported pet vomiting, diarrhea, inappetence and bloating yet only 17% of dog owners and 20% of cat owners actually consult a veterinarian. The survey implies that the estimated number of annual visits represents an undersized minority of animals that are actually affected. Given such a pervasive problem, any therapeutic intervention that improves management of disruptive GI symptoms would be a positive development.

Veterinary use of phyto-mucilages, particularly slippery elm, for gastrointestinal have been suggested by some [8,9]. A potency-enhanced version of elm USP, requiring less than 10% of suggested daily doses, has been prescribed by veterinarians since 2003. Veterinarians

were familiar with the 2002 original formulation of canine/feline Gastrafate[®] which contained 5% high potency sucralfate as the active ingredient. Following successful preliminary testing [10] high potency sucralfate was replaced in January 2003 with magnesium chelated elm mucilage. This report presents observational data from the use of polyanionic phyto-saccharide of elm mucilage (PEPPS) in practice-based settings of small animal veterinarians.

2. Materials

2.1. Potency Enhanced Polyanionic Phyto-Saccharide

Elm mucilage USP is a polyanionic phyto-saccharide [11]. Unlike sucralfate, PEPPS contains no aluminum or sulfate. Chiefly a high molecular weight mucilage (>200,000 Daltons), it is comprised of galactose-rhamnose disaccharides. Potency-enhanced elm phyto-saccharide is prepared by suspending elm mucilage in an anion-cation solution similar to that used to formulate high potency sucralfate (HPS) [12]. The resultant potency-enhanced phyto-saccharide (PEPPS) is muco-specific and capable of attaining augmented surface concentration of slippery elm. With sucralfate, potency enhancement ranges from 7 - 23 fold 3 hours post-administration, having a lower fold increase on normal GI lining and higher fold increase on inflamed or injured mucosa. The exact post-administration surface concentration of PEPPS is unknown. However, with PEPPS the concentration of elm USP administered is less than 8% the slippery elm dose recommended by holistic veterinarians [8,9]. The formulation strength of Elm USP in PEPPS for small animals is 0.9%. Administration of PEPPS was in accordance to weight. On average dogs or cats weighing less than 25 lbs received daily doses upwards of 72 mg, (b) animals between 25 - 50 lbs received 85 mg and (c) over 50 lbs received 120 mg.

2.2. Dosing Administration

Participating veterinarians prescribed PEPPS in accordance to weight-dose chart in label instructions. PEPPS was given twice daily with food for the majority of the patients. In the cases where vomiting and diarrhea disrupted eating and require intravenous hydration, PEPPS was given orally without food.

3. Methods

3.1. Study Design—Observational Trial

This study was an open labeled non-blinded observational trial. Information was collected regarding (a) weight of the dog or cat and (b) the nature and length of

their GI symptoms at time of adding PEPPS. The length of illness is not reported.

As an observational study, treatment intervention was not randomized. By design, differences in outcomes are observed without regard to similarities or dissimilarities of patient characteristics prior to treatment. In fact, in this type of study, treatment decisions were made by veterinarians prior to use of PEPPS, the selection of PEPPS being made by the veterinarian due to concern that pre-PEPPS treatments were ineffectual. In this trial the question addressed is not one of the efficacy of PEPPS. Instead the question addressed is one of the relative merits of PEPPS as a competing treatment or intervention. Outcome of merit is relative to the expectation of the participating veterinarians. As discussed below a clinical response of 2 days or 4 doses merited note to the veterinarians involved. This study reports the percentage of dogs and cats with vomiting and diarrhea who responded to PEPPS while on failing therapies.

3.2. Comparative Control

As an observational study, there were no control groups. To provide a comparative “control” experience, each veterinarian was asked to reflect on their respective experience and select from a choice of a clinical response times which they would deem to deviate significantly from the expectations of their clinical experience. Most of the small animal veterinarians (85%) felt that a clinical response of 2 days or 4 doses would mark a significant departure from their clinical expectations and this was based on their experience managing vomiting and diarrhea in dogs and cats. This consensus of significant departure from expected time of clinical response was used to benchmark the primary outcome and a meaningful response. In essence, expectations of past clinical experience (replete with interventions requiring more time to work) served as a “comparative control” albeit a subjective one.

3.3. Consent

All animals were privately owned and owners’ consent was obtained by veterinarians.

3.4. Veterinarians Participating in the Study

Veterinarians placing orders for commercially available PEPPS were recruited to participate in this open-labeled trial. Each had more than 5 years of professional practice. Veterinarians were recruited from June 2003 through December 2006. All veterinarians prescribing PEPPS were engaged exclusively in primary care of small companion animals. They were experienced in the standards of care in treating vomiting and diarrhea in dogs and cats. Out of 256 small animal veterinarians, 197 practicing in

48 states completed the study, the remainder lost to follow up due to their inability to complete the protocol. Veterinarians received no honorarium for their participation.

3.5. Sequential Participation

Participation in the study was sequential, determined solely by the order of spontaneous requests for product made by veterinarians responding to notification of product's availability. The veterinarians were self-selected. Information prompting orders pertain to the usefulness of PEPPS in the management of vomiting and diarrhea in small animals.

3.6. Inclusion/Exclusion Criterion for Dogs and Cats

Dogs and cats were brought to the veterinarian by clients primarily due to vomiting and/or diarrhea. Included in the trial were dogs and cats with vomiting and/or diarrhea for more than 3 days with or without bleeding and dehydration. Animal's symptoms were attributed to gastrointestinal infections from viral, bacterial and protozoan agents or to exposure to environmental toxins. Notable inclusions were animals described by veterinarians as having hemorrhagic gastroenteritis, parvovirus enterocolitis, gastritis, intestinal "flare-ups", and pancreatic "flare-ups". Cases of food intolerance were included. No cases of medication induced vomiting or diarrhea included. Excluded were animals requiring surgical intervention.

3.7. Test Population

Animals included dogs and cats of varied age, breeds and weights. The size of the test population was 3952 dogs wherein 1928 were vomiting-dominant and 2024 diarrhea-dominant. Vomiting-dominant and diarrhea-dominant was defined by the major concern of the client who initiated the visit. Also included were 2248 cats wherein 1064 were vomiting-dominant and 1184 were diarrhea-dominant. All patients were studied across multiple office-based practices. The population was also geographically diverse with input provided from 48 out of 50 states of the US.

3.8. Conditions Managed

Inappetence, vomiting and diarrhea fail owners' attempts to adjust the pets' diet. Following evaluation by physical exam, lab tests and in some cases x-rays the clinical impressions of veterinarian covered a broad range of diagnoses that included hemorrhagic gastroenteritis, parvovirus enterocolitis, gastritis, reflux, suspected ulcer, intestinal "flare-ups", pancreatic "flare-ups" and "stomach

issues". The severity of GI symptoms or the presence of other (non-surgical) disorders did not preclude patients' involvement in the study. Cases of food intolerance were included. There were no cases of medication induced vomiting or diarrhea in this study. Both dogs and cats were brought to the veterinarian due to vomiting and/or diarrhea.

3.9. Existing Treatment Regimens in Dogs and Cats

Methods of management for small animals were diverse. Existing treatment regimens for dogs and cats prior to PEPPS varied widely and included antibiotics, anti-emetics, acid reducers, pancreatic enzyme supplementation, bismuth preparations, plain sucralfate and dietary changes. To these diverse regimens PEPPS was added. Veterinarians in the study opted to add PEPPS to existing regimens that had been deemed inadequate or insufficient by them. There was no PEPPS only test group.

3.10. Primary Outcome Measure in Dogs and Cats

There were two symptom-related primary outcome measures for this trial—the cessation of diarrhea and the cessation of vomiting. The cessation of these symptoms within 2 days or 4 doses of PEPPS represented a positive outcome. This veterinarian-defined response to therapy was accepted as a meaningful clinical response (as described in section on Study Design) for the management of vomiting and diarrhea in dogs and cats in this study. Clinical observations made by veterinarians were reported by phone for data collection.

3.11. Hypothesis

The hypothesis is that a majority of animals with serious and disruptive GI symptoms (of non-surgical etiology) when given PEPPS will experience resolution of symptoms within a timeframe (or dose administration) significant and relevant to the collective historical experience of practicing veterinarians who routinely manage such symptoms. This was a timeframe was 2 days or 4 doses.

3.12. Analysis

Results are based on a per protocol analysis of the data. Chi-square analyses were performed to compare percent response between weight subgroups in dogs and cats at confidence level of 95% and 99% for confidence intervals and alpha level of 0.05.

3.13. Conduct of Observational Field Tests

The study was conducted from June 2003 through De-

ember 2006. Clinical observations made by veterinarians were reported by phone for data collection. Phone interviews were conducted with veterinarian staff to collect results of adding PEPPS to existing treatment regimens. Results were tabulated as either a positive or negative outcome.

4. Results

4.1. Dogs with Vomiting and Diarrhea

The were dogs grouped roughly according to five weight categories—less than 6 lbs, 6 - 14 lbs, 14.1 - 29 lbs, 29.1 - 50 lbs and greater than 50 lbs. All dogs eventually responded to PEPPS with various clinical response times extending beyond 2 days. However, **Table 1** show that 82% [CI 3.9 (CL 99%)] of 1,928 dogs with vomiting responded to PEPPS within 2 days or 4 doses, while 93% [CI 1.46 (CL 99%)] of 2024 dogs with diarrhea responded to PEPPS within 2 days or 4 doses. The collective percent response to PEPPS for vomiting and diarrhea in dogs was 88%. High percent response to PEPPS in 2 days or with 4 doses was similar across all weight classes of dogs regardless of symptom (**Table 2**). There were no weight-based differences in the percent response in dogs to PEPPS.

4.2. Cats with Vomiting and Diarrhea

Cats were grouped according to 3 weight categories—less than 6 lbs, 6 to 11 lbs, and greater than 11 lbs. All cats eventually responded to PEPPS with varying clinical response times that extended beyond 2 days. However, **Table 3** shows that 77% [CI 3.3 (CL 99%)] of 1064 cats with vomiting responded to PEPPS within 2 days or 4 doses. Similarly 79% [CI 3.05 (CL 99%)] of 1184 cats with diarrhea responded to PEPPS within 2 days or 4 doses. The ability for PEPPS to stop diarrhea and vomiting in 2 days or with 4 doses in cats was the same across all weight classes. **Table 4** shows that there were no weight-based differences in the percent response in cats to PEPPS.

5. Discussion

5.1. General Impressions

There are limited outpatient options for the treatment of acute vomiting and diarrhea in companion animals. For the most part, evidence-based guidance is drawn largely from human clinical trials, experimental studies in dogs and cats [13,14] and the collective clinical experience of small animal practitioners. Often what is recommended (and practiced) is manipulation of diet alone or concur-

Table 1. Veterinary response to PEPPS prescribed to dogs.

Wt of Dog	Vomiting	Positive Response	Negative Response	% Response to PEPPS† [CI, 99%]	Diarrhea	Positive	Negative	% Response to PEPPS† [CI, 99%]	Wt Related Response V+D
50 lb+	176	137	39	78% [8.06]	186	180	6	97% [3.23]	317/362 88%
29.1 - 50 lb	381	312	69	82% [5.08]	347	323	24	93% [3.53]	635/728 87%
14.1 - 29 lb	297	238	59	80% [5.99]	383	345	38	90% [3.95]	583/680 86%
6 - 14 lb	578	463	115	84% [3.93]	879	827	52	84% [3.19]	1290/1457 89%
<6 lb	496	432	64	87% [3.90]	232	205	29	88% [5.50]	637/728 88%
TOTAL	1928	1582	346	82% [3.90]	2024	1880	149	93% [1.46]	3462/3952 88%

Table 2. Chi-Square values comparing percent treatment response in dogs by weight.

Weight	Dogs with Vomiting		Dogs with Diarrhea	
	Chi Square Value	p Value	Chi Square Value	p Value
50 lb+	0.0009	0.976	0.0068	0.934
29.1 - 50 lb	0.0025 × 10 ⁻³	0.999	0.0012	0.972
14.1 - 29 lb	0.0003	0.986	0.0006	0.979
6 - 14 lb	0.0045	0.947	0.0017	0.967
<6 lb	0.1200	0.729	0.0330	0.856

Table 3. Veterinary response to PEPPS prescribed cats.

Wt of Cat	Vomiting	Positive Response	Negative Response	% Response to PEPPS† [CI, 99%]	Diarrhea	Positive	Negative	% Response to PEPPS† [CI, 99%]	Wt Related Response V+D
>11 lb+	186	134	52	72% [8.49]	205	160	45	78% [7.46]	294/391 75%
6 - 11 lb	426	333	93	78% [5.18]	587	464	123	78% [4.41]	797/1013 79%
<6 lb	452	357	95	79% [5.99]	392	314	78	80% [5.21]	671/844 80%
TOTAL	1064	824	240	77% [3.30]	1184	938	246	79% [3.05]	1762/2248 78%

Table 4. Chi-square values comparing percent treatment response in cats by weight.

Weight	Cats with Vomiting		Cats with Diarrhea	
	Chi Square Value	p Value	Chi Square Value	p Value
11 lb+	0.00210	0.964	0.001200	0.972
6 - 11 lb	0.00006	0.994	0.000004	0.999
<6 lb	0.00057	0.981	0.000088	0.992

rently with the use of medications [15]. Few randomized placebo controlled trials exist that offer evidence sufficient support national practice guidelines.

In this study, potency-enhanced polyanionic phyto-saccharide was prescribed to 3952 dogs and 2248 cats in the private practices of 197 small animal veterinarians in the US over a 3.5 year period. The data from this study showed an association between the use of PEPPS and the resolution of vomiting and diarrhea in dogs and cats whose symptoms had failed pre-existing therapies. Causality would require a randomized, blinded, placebo-controlled trial. As in most observational trials, a standard control group was not used. Instead, the study used as its "control" the historical experience of veterinarians whose prior management of vomiting and diarrhea did not include PEPPS. Vomiting and diarrhea resolved within 2 days or 4 doses in a majority of dogs (over 80%) and cats (nearly 80%) that received PEPPS. The data supported the original hypothesis that majority of dogs and cats with serious and disruptive GI symptoms when given PEPPS will have symptom resolution within a timeframe significantly less than anticipated from the private practice experiences of the veterinarians involved. In dogs and cats with vomiting and/or diarrhea for more than 3 days with or without bleeding and dehydration the animal's symptoms were attributable to gastrointestinal infections from viral, bacterial and protozoan agents or to environmental toxins. Notable inclusions were animals described by veterinarians as having hemorrhagic gastroenteritis, parvovirus enterocolitis, gastritis, intestinal "flare-ups", and pancreatic "flare-ups" who were on failing treatments. The majority of these animals responded to PEPPS with the cessation of symptoms between 2 to 4

days. This study does not rule out whether or not the patients would have improved otherwise. Neither does the study exclude the possibility that patients' improvement was from other causes, such as premature disqualification of existing treatment regimens or the combination of PEPPS with existing regimens led to improvement. It does support a plausible proof of principle. The study did demonstrate that PEPPS was associated with a 2 - 4 day cessation of vomiting and diarrhea in the majority of dogs and cats that received PEPPS twice daily by direct administration or with their food.

5.2. Disadvantages of Observational Studies

There are obvious disadvantages to an observational study of this nature. Firstly, there are no traditional control groups, the lack of which precludes objective quantification of the efficacy. What is known from this study is that a large majority of the patients got better sooner than 85% of the study's small animal veterinarians would have thought possible based on their collective past clinical experience. The historical experience of each veterinarian and their consensus of what constitute a significant deviation from that experience are subjective. Consequently, the data offers little predictive value of efficacy. The study design, at best, provides an affirmative proof-of-concept supporting the plausible utility of PEPPS in the management of disruptive GI symptoms in dogs and cats.

A second disadvantage of this study is that the manner of recruitment gives rise to bias. Practitioners were self-selected by virtue of responding to advertisements regarding a new gastrointestinal protectant which is resold at profit if the product is prescribed to a patient. Data

obtained utilizing this method of recruitment is vulnerable to a self-selection bias that is profit driven. In general, an appropriately randomized, placebo-controlled blinded investigation would best quantify the efficacy of PEPPS and thereby provide a better basis on which to predict the benefit of PEPPS in managing vomiting and diarrhea.

5.3. Strengths of This Observational Study

Despite the aforementioned drawbacks due to design, there are a number of strengths that provide a significant context for the positive results reported here, results that imply positive benefits in using PEPPS to manage unexplained diarrhea or vomiting in small animals.

The first strength of this study is the geographic diversity of state-licensed veterinarians involved. The data reflected a nationwide experience among small animal practitioners in 48 of the 50 states. The positive findings were not a coincidence of geography but rather a reflection of generalized experience.

In addition, a study involving thousands of animals across 48 contiguous states implies that response to PEPPS was not likely influenced by geographic life-styles (rural versus urban settings) of ownership, diversity of breed, client-companion animal relationships or seasonality (having been conducted over 42 months). The majority of patients demonstrated a high PEPPS response regardless of these factors.

5.4. Implications of Findings

The positive results of this study have implications regarding the physical origin of symptom-states of the GI tract. PEPPS is a non-systemic agent. The entirety of its clinical effects is attributed solely to a topical action in coating the mucosal lining. Physical engagement of surface elements accessible to PEPPS as it layers along the gut lining results in a therapeutic effect. Similarly, sucralfate, another agent whose therapeutic effect is limited to engagement of the mucosal lining has been shown as well to reverse nausea, vomiting and diarrhea in small animals [16]. Thus the positive clinical effect of PEPPS and similar surface-active agents (e.g. sucralfate) to reverse symptom-states of vomiting and diarrhea in dogs and cats, imply that those symptom-states are controlled by or to some degree, significantly influenced by physical elements associated with the mucosa onto which these agents are layered. Causal links of mucosal elements to symptom-states of the GI tract has been mentioned elsewhere, in cases involving human patients suffering from functional bowel syndromes that present with intestinal symptoms of nausea, vomiting, diarrhea or even constipation [17,18]. The use of surface-active agents to manage symptom-states by engagement of sur-

face elements of the mucosa raises the question as to the nature of those elements so associated. Surely those elements should be targets for the design of other therapeutic agents.

6. Conclusion

The majority of 3952 dogs and 2248 cats with vomiting and diarrhea treated with PEPPS were observed to have unexpectedly shortened clinical courses unanticipated by experienced small animal veterinarians practicing in 48 out of 50 states in the US. While all patients eventually responded to PEPPS, most dogs and cats with vomiting and diarrhea responded within 2 days or 4 doses. Data from this 42-month-long observational study supports the notion that PEPPS may be useful in the practice setting to manage vomiting and diarrhea of common etiologies in small companion animals. However, blinded, randomized, placebo-controlled trials are needed to assess the true efficacy of PEPPS.

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Appendix A

Volume for office visits was calculated from data by Lund *et al.* [6] who reported that 8.3% of dog and cat visits per year for either vomiting or diarrhea. This number was multiplied by 196 million annual veterinarian visits reported in 2007 AVMA Pet ownership sourcebook, then further multiplied by 0.85 as the proportion of total small animal veterinarian visits by dogs and cats.