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Full Length Research Paper

Expedited management of ulcer, colic and diarrhea in 209 horses: An open-labeled observational study of a potency-enhanced sucralfate-like elm phyto-saccharide

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A potency-enhanced polyanionic phyto-saccharide of elm mucilage (PEPPS) was prescribed in 209 horses in an open-labeled field trial. Clients provided informed consent to 32 equine veterinarians to prescribe PEPPS for low grade colic and diarrhea unresponsive to deworming. Most of the horses (n = 175/209) were presumed to have ulcers clinically, while 23/209 were confirmed by gastroscopy to have ulcers and 11/209 horses had colic related to diarrhea. A 4-day/7-dose response rate, determined by veterinarians' consensus, provided the threshold for a significant clinical outcome, and data was collected through phone interviews over period of 3.5 years. 166/198 horses with ulcer associated colic and 10/11 horses with diarrhea-associated colic responded to PEPPS within 4 days or 7 doses. Using PEPPS alone was associated with positive outcomes in 81% (29/36) of horses. PEPPS added to failed regimens of omeprazole, ranitidine and antacids was associated with positive outcomes in 85% (137/162) of horses. Accelerated healing of ulcers occurred in 8 horses within 14 to 20 days using PEPPS alone and in 15 horses using PEPPS added to failed treatment regimens of omeprazole, ranitidine and antacid. PEPPS appears useful for managing equine ulcer, diarrhea and colic. As an electronegative polyanionic saccharide with substantial muco-adherence, PEPPS was compared to sucralfate. However, a randomized blinded placebo controlled trial is needed to quantify true clinical efficacy.

Key words: Equine, ulcer, diarrhea, colic, elm, sucralfate.

INTRODUCTION

Timely management of disruptive gastrointestinal (GI) symptoms poses a challenge to veterinary physicians (Mair et al., 2002; Tams, 2003). Inappetence, ulcer colic and diarrhea in horses can lead to more severe problems. Therefore, restoration of normal GI function is paramount and management should be expedited. The problem of disruptive equine GI symptoms is fairly significant. Fifty to 92% of the 9.2 million horses in the US (American Horse Council, 2005) have gastric ulcers, depending on their breed and type of containment or athletic activity (Hammond et al., 1996; Mairs et al., 2002; Murray et al., 1996; USDA APHIS, 2001a; Vatistas et al., 1994). In "gastroscopy clinics" conducted over 12 months in 25 states in the US, 60% of 658 horses were found to have ulcerations (Knudson, 2009). Symptomatic ulcers usually present as low grade colic with food avoidance or inappetence. Inappetence is a principal sign to horse owners of colic and often serves as an early warning for the presence of ulcers. When surveyed, horse owners in Minnesota ranked ulcer colic 5th out of 25 top equine healthcares concerns (Martinson et al., 2006).

Abbreviations: GI, Gastrointestinal; **HPS,** high potency sucralfate; **PEPPS,** potency-enhanced polyanionic phyto-saccharide; **USDA,** United States Department of Agriculture; **FDA,** food and drug administration.

The USDA National Economic Cost Report on colic (2001b) reporting no geographic variation in the incidence of colic in horses, imply that this sentiment of concern for colic could be generalized to all horse owners. General prevalence positions ulcer colic as a significant disruptive GI symptom in horses and one that require effective management (Hillyer et al., 2001; Kaneene et al., 1997; Tinker et al., 1997; Traub-Dargatz et al., 2001).

Evidence-based treatment of equine diarrhea and non-surgical colic is limited. However, some published reports (Galvin et al., 2004) suggest that colic can be treated with pain medications such as xylazine (0.5 mg/kg) or butorphanol (0.01 mg/kg). The use of an anti-spasmodic is a reasonable option as well. The initial management of diarrhea entails reducing the mechanical load of the colon chiefly by elimination of large volume fiber sources. Low bulk diet is complimented by the use of psyllium, corn oil and bismuth/salicylate suspension by nasogastric tube which is a current management of equine mucosal erosions, ulcerations and resulting colic and inappetence centers on therapeutic control of acidity (Andrews, 2005; Hammond et al., 1996; Hillyer et al., 2001; Knudson, 2009; Merial, 1999). Acidity is either neutralized by antacids (Andrews, 2005), reduced by histamine-2 blockers (for example, ranitidine, cimetidine, famotidine) (Andrews, 2005) or inhibited by proton pump inhibitors (for example, omeprazole) (Anderson, 2005; Knudson, 2009; Merial, 1999). Neither of these therapeutic agents provides direct relief of colic or direct healing of the mucosa. Instead, colic relief and ulcer healing are secondary consequences of lowering acidity. There are genetically controlled mucosa-specific mechanisms unrelated to acidity that are primarily responsible for direct healing (Tarnawski et al., 1998).

Proof of the presence of such mechanisms is found in FDA trial data on omeprazole (Merial, 1999). There was significant rate of healing observed in horses randomized to sham treatment. While acidity significantly hampered the rate of healing, nevertheless, complete healing occurred in 40% of untreated horses. This of course, was not a "mind over matter" placebo effect, but rather a genetically orchestrated phenomenon that is entirely independent of gastric pH (Jones et al., 1999; Konturek et al., 1991; Pai and Tarnawski, 1998; Skov, 1988; Tarnawski et al., 1998). Sucralfate is a polyanionic saccharide with cyto-protective properties. By composition, it is octa-sulfonated disaccharide containing glucose and fructose. The electro-negativity of its eight sulfate groups imparts charge density that favors muco-adherence to the GI lining (Dobrozsi et al., 1999; Jubeh et al., 2004; Tarnawski et al., 1987). Muco-adherent binding of sucralfate to GI lining is indifferent to gastric acidity (Steiner et al., 1982) with its strength of binding unaffected by pH (Danesh et al., 1988). Additionally, by virtue of its electro-density, sucralfate binds enteric growth factors (Jones et al., 2004; Konturek et al., 1991, 1995; Szabo, 1991; Szabo et al., 1994) and thereby facilitates immediate mucosal regeneration (Tarnawski et al., 1986).The same electro-negative density that enables it to modulate calcium channels of the gastric mucosa (Slomiany et al., 1992) may also be responsible for repolarization of voltage-gated nociceptors innervated by the vagus nerve which are known to be responsible for pain sensation from acid (Holzer, 2001, 2004), nausea and vomiting (Beyak and Grundy, 2005). The latter quality is significant and may account for the fact that in small animals, when administered in multiples of the standard 14 mg/kg per dose (that is 25 to 100 mg/kg/dose), sucralfate stops vomiting and diarrhea in 2 to 4 doses (Steiner, 1990). When suspended in a solution of cations and multi-dentate chelators, the electronegative density is multiplied through self-aggregation leading to a multifold augment-tation of surface concen-tration of sucralfate and thereby augmentation of its potency (McCullough, 2010), since the entire therapeutic effect of sucralfate is defined by the quantitative extent of its physical contact with the GI lining.

Besides positive anecdotal reports (Translational Medicine Research, 2002), there is no published data on ulcer response to potency-enhanced sucralfate. Slippery elm mucilage is a polyanionic phytosaccharide version of sucralfate. It also contains branched substituents with a high electronegative density, (galacturonic acid). When placed in a solution of cations and multi-dentate chelators, its muco-adherence is potentiated several fold (McCullough, 2010). As such, it is referred to as a potency-enhanced polyanionic phyto-saccharide or PEPPS. The clinical effects of PEPPS in humans and small animals (anti-emetic, anti-diarrhea, anti-ulcer) are indistinguish-able from that of potency-enhanced sucralfate. Therefore, it is assumed that PEPPS has physiochemical characteristics similar to sucralfate, being muco-adherent, preferentially engaging mucosa-adherent growth factors and capable of repolarization of voltage-gated nociceptors related to acid pain and nausea. Though PEPPS has been prescribed by veterinarians in the US since 2003 for equine ulcer colic and diarrhea, its use on a large scale has never been formally reported. This report presents observational data in a proof of principle study which may be useful (Dreyer et al., 2010) in prescribing PEPPS in the setting of supervised treatments in an equine practice. Of course, any therapeutic intervention positively associated with the management of inappetence, ulcer colic and diarrhea would be a constructive development.

MATERIALS AND METHODS

Potency enhanced polyanionic phyto-saccharide

Elm mucilage is a polyanionic phyto-saccharide (Upton et al., 2011). Unlike sucralfate, PEPPS contains no aluminum or sulfate. It is chiefly a high molecular weight mucilage (> 200,000 Daltons), comprising 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) (McCullough, 1995, 2010, 2012). 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 to 23 fold 3 h 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 2% of slippery elm dose recommended by equine veterinarians (Veterinary Desk Reference, 2011; Ward, 2010). The formulary strength of Elm USP for horses is 1.9%. Administration of PEPPS is in accordance to weight. On average, horses weighing less than 500 lbs received daily doses upwards of 270 mg, those between 500 to 900 lbs received 380 mg and over 900 lbs received 540 mg. PEPPS was administered separate from other medications.

Dosing administration

Participating veterinarians prescribed PEPPS in accordance to weight-dose chart in label instructions. Horses weighing less than 500 lbs (227.3 kg) received 15 ml, between 500 to 900 lbs (227.3 to 409.1 kg) received 20 ml, and over 900 lbs (409.1 kg) received 30 ml. PEPPS was given by drench into cheek pouch twice daily, morning and evening. PEPPS is not absorbed systemically and act as an internal topical coating the GI lining.

Study design and controls

This study was an open labeled non-blinded observational trial. Observational trials are fundamentally distinct from a randomized controlled clinical trial, the least of which there is no control group. Merit is assessed on the basis of outcomes resulting from the introduction of an intervention into a pre-existing clinical setting (Hannan, 2008). Information was collected regarding; the age of horses, the nature of their GI symptoms (the presence of ulcer-suspected colic and diarrhea in horses), and type of treatment regimens prescribed by the practitioner 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 efficacies 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 4 days or 7 doses merited note to the veterinarians involved. This study reports the percentage of horses with ulcer related colic and diarrhea related colic who responded to PEPPS while on failing therapies.

Comparative control

As an observational study, there were no control groups (Hannan, 2008). 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 (80%) felt that a clinical response of 4 days or 7 doses would mark a significant departure from their clinical expectations, and this was based on their experience managing ulcer- and diarrhea associated colic in horses. 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.

Consent

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

Veterinarians participating in the study

Veterinarians placing orders for commercially available PEPPS were recruited to participate in this open-labeled trial. None had professional experience less than 5 years in practice. Veterinarians were familiar with using 2002 original formulation of equine Gastrafate® which contained 10% high potency sucralfate as the active ingredient. Following successful preliminary testing (Translational Medicine Research Center, 2002) high potency sucralfate was replaced in January, 2003 with calcium chelated elm mucilage in the form of PEPPS. Veterinarians were recruited from June, 2003 through December, 2006. All veterinarians prescribing PEPPS were engaged exclusively in primary care of equine animals within valid veterinarian-client-patient relationships. The combined years of practice for equine practitioners who completed the trial were 160. Each was experienced in the standards of care in treating ulcer- and diarrhea associated colic in horses. Out of 46 equine veterinarians, 32 practicing in 20 states of the US completed the study; the remainder lost to follow due to their inability to complete protocol. Veterinarians received no honorarium for their participation.

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 ulcers- and diarrhea associated colic in horses.

Inclusion/exclusion criterion for horses

Included in the observational trial were horses with low grade colic, inappetence or diarrhea for more than 5 days. These horses had failed adequate deworming therapies by owners. Horses were with and without a history of ulcers confirmed by endoscopy. Endoscopy was not required for inclusion. However, in accordance to customary practice of 8 veterinarians, 23 horses underwent endoscopy before and after treatment.

Test population

Horses of all age groups, breeds and ownership purposes were included. The size of the test population was 209 horses within a multi-practice-based study. There were 20 foals under 6 months, 38

between 6 months to a year, 33 between 1 to 2 years and 118 over age 2. The test population was geographically diverse involving input from 20 out of the top 25 states with highest horse ownership and equine population. As was the custom for 8 of the 32 equine practitioners, 23 horses with ulcer-related colic underwent endoscopy prior to and following treatment with PEPPS.

Conditions managed by equine practitioners

Conditions to be managed in the trial included low grade (non-surgical) colic, ulcer-suspected colic and diarrhea. Low grade colic was heralded by poor appetite or refusal to eat – symptoms that failed to respond to owners' use of dewormers or adjustments in feed. Ulcer-suspected colic was defined clinically as inappetence (poor feeding/drinking), poor attitude, dull coat and teeth grinding in foals. Diarrhea-associated colic was defined as symptoms identical to ulcer-suspected colic accompanied by loose stools for more than 5 days despite adequate de-wormer therapy by owners. Endoscopy in 23 horses was positive for gastric ulcers. Excluded were horses whose symptoms required surgical intervention.

Conduct of observational field tests

The study was conducted from June, 2003 through December, 2006. Participating veterinarians prescribed PEPPS in accordance to weight-dose chart in label instructions. The dose administration was three times daily for the first day then twice daily. 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.

Pre-existing treatment regimens used in study horses

Pre-existing treatment regimens for horses were fairly uniform and centered around four regimens. These were (a) omeprazole alone, (b) omeprazole + antacid, (c) histamine-2 blocker (ranitidine or cimetidine) + antacid or (d) histamine-2 blocker (ranitidine/ cimetidine) + antacid + bismuth suspension for diarrhea-associated colic. The antacid used was aluminum hydroxide/ magnesium hydroxide combination. The length of time horses had been on these regimens was not assessed, therefore unknown. When clinical results from pre-existing regimens were deemed suboptimal, participating veterinarians added the polyanionic saccharide, PEPPS.

Horses treated with PEPPS alone

This open-labeled trial was observational with no control groups of untreated horses. However, a small number of horses, 36 of 209 formed a PEPPS only treatment group. Except for a few veterinarians treating the 36 PEPPS only group, previous experience of 80% veterinarians offered no expectation of significant response to a PEPPS intervention within 4 days or 7 doses.

Primary outcome measure in horses

There were two single symptom-related primary outcome measures for this trial. Cessation of ulcer colic and diarrhea were the two single symptom outcomes, respectively. Veterinarian-defined positive responses in horses with ulcer colic and diarrhea would be the restoration normal feed habits and the return of formed stools within 4 days or 7 doses of PEPPS, respectively. This veterinarian-defined response to therapy previously discussed represented a meaningful clinical difference for the management of ulcer colic and diarrhea in horses.

Hypothesis

The hypothesis is that 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 manage such symptoms routinely. This was a timeframe of 4 days (or in 7 doses).

Analysis

The trial used a per protocol analysis of the data. Both chi-square and two-sample t-test were used to compare percent response to treatment among horses at confidence level of 95 and 99% for confidence intervals.

RESULTS

General

Horses with ulcer-related colic and diarrhea-related colic

All horses eventually responded to PEPPS with variability in the clinical response times extending beyond 4 days. However, Tables 1 and 2 showed that 85% [CI 5.47 (CL 95%)] of 198 horses with ulcer-associated colic and 91% [CI 16.91(CL 95%)] of 11 horses with diarrhea-associated colic responded to PEPPS within 4 days or 7 doses. The percent response using PEPPS alone to manage ulcer-associated colic was 81% [CI 12.9/CL 95%, n = 36]. When PEPPS was added to existing treatment regimens, the percent response was high. Percent response was 83% [CI 10.11/CL 95%] when PEPPS was added to omeprazole (n = 53), 81% (CI 12.64/CL 95%) with PEPPS added to omeprazole + antacids (n = 37), 88% (CI 7.26/CL 95%) with PEPPS added to ranitidine/ cimetidine + antacids (n = 72), and 91% (CI 16.91/CL 95%) with PEPPS added to ranitidine/ cimetidine + antacids + bismuth (n = 11).

PEPPS alone compared to PEPPS augmented treatments

Table 3 shows the results of a two-sample t-test used to compare the percent response using PEPPS alone to the percent response using PEPPS augmented treatments. In each comparison, PEPPS alone versus (PPI + PEPPS), PEPPS alone versus (PPI + AA + PEPPS), PEPPS alone versus (H2B + AA + PEPPS), or PEPPS alone versus (H2B + AA + Bismuth + PEPPS), the t-statistics was not significant at the 0.05 critical alpha levels. There was no statistically significant difference between treatment with PEPPS alone and treatment with PEPPS augmented

Table 1. Treatment response to PEPPS† stratified by GI symptoms, treatment regimens and age of horse.

Treatment regimen	< 6 months (%)	6-12 months (%)	1-2 years (%)	2-8 years (%)	> 8 years (%)	Symptom/disorder treated	Treatment related totals (%)
H2B+AA+Bismuth+PEPPS	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)	2/3 (67)	Colic-diarrhea	10/11 (91)
H2B+AA+PEPPS	2/2 (100)	11/13 (85)	9/11 (82)	25/27 (93)	17/19 (89)	Ulcer colic	64/72 (88.9)
PPI+AA+PEPPS	3/4 (75)	6/7 (86)	6/7 (86)	10/13 (77)	5/6 (83)	Ulcer colic	30/37 (81.0)
PPI alone+PEPPS	4/4 (100)	10/13 (77)	6/8 (75)	18/21 (86)	6/7 (86)	Ulcer colic	44/53 (83.0)
PEPPS† alone	7/8 (88)	3/3 (100)	4/5 (80)	10/13 (77)	5/7 (71)	Ulcer colic	29/36 (80.6)
Age Related Response	18/20 (90)	32/38 (84)	27/33 (82)	68/76 (90)	35/42 (83)	180/209 (86)	177/209 (84.7)

PEPPS, potency-enhanced polyanionic phyto-saccharide; PPI, proton pump inhibitor (omeprazole); AA, antacids; H2B, histamine-2 blocker (ranitidine or cimetidine); bismuth, bismuth preparations.

treatments. No additional clinical response was obtained over PEPPS alone by the continuance of pre-existing therapies (omeprazole, ranitidine, anti-acids or bismuth).

Endoscopy positive ulcers in horses

Of the 198 horses with ulcer-associated colic, 23 horses were endoscoped by 8 veterinarians prior to and between 14 to 20 days, following PEPPS treatment. Eight of these horses were on PEPPS alone, while the other 15 were on PEPPS augmented therapies. Table 4 shows that while horses in each treatment group had ulcers, all ulcerations were confirmed healed by second endoscopy performed between 14 to 20 days on treatment. With FDA, approved omeprazole require 28 days for a statistically significant healing effect, this observation of PEPPS healing between 14 to 20 days represented accelerated healing.

DISCUSSION

General impression

Traditionally, the treatment of ulcer coli c in horse generally centers on acid reduction (Andrews, 2005; Hammond et al., 1996) for which there are several therapeutic options. Clinical practice to treat equine diarrhea involves the use of psyllium hydrocolloids and bismuth/salicylate combination (Galvin et al., 2004). The empiric use of anti-spasmodics, analgesics and anxiolytics for colic is reasonable as well. However, simultaneous management of ulceration, diarrhea and colic by a single therapeutic agent would be preferred. Potency-enhanced polyanionic phyto-saccharide, PEPPS was prescribed to 209 horses in the private practices of 32 equine practitioners in the US. With the exception of a few cases, the equine practitioners introduced PEPPS into active treatment regimens, deemed to be failing. The study was conducted over a 3.5 year period. The data showed a positive association between the use of PEPPS and the rapid resolution of ulcers, ulcer-associated colic and diarrhea in horse whose symptoms had failed to respond to pre-existing therapies. The hypothesis that the administration of PEPPS is associated with the rapid resolution of ulcer colic, diarrhea and diarrhea associated colic in most horses was supported by the data reported here. In majority of horses on failing therapies, those symptoms resolved within 4 days (or in 7 doses) of receiving PEPPS, a timeframe significantly less than that anticipated from the private practice experiences of veterinarians participating in the trial. Additionally, all horses with ulcerations diagnosed by gastroscopy healed within 14 to 20 days using either PEPPS alone or PEPPS augmented by continuance of existing treatments. In other words, the use of PEPPS in horses with known gastric ulcers was associated with the resolution of ulcer within 14 to 20 days, which is sooner than 28 day therapy required for omeprazole (Merial, 1999) to achieve statistically significant healing effect. A more fair comparison of PEPPS to omeprazole requires evaluation of both under similar clinical restrictions. Be that as it may, 14 to 20 days for ulcer healing is far less than 28 days known to be required for omeprazole.

Limitations of this observational study

Observational study of this nature does have distinct limitations (Hannan, 2008). The absence of conventional control groups precludes any statements regarding efficacy. An observational study shows association without commentary to cause. Instead, what is known from this study is

Table 2. Percentage response to treatment in horses with CI (95%).

Parameter (Treatment regimen)	Horses with ulcer colic	
	Responsive	CI (95%)
PEPPS Alone	81% (n=36)	12.9
PPI + PEPPS	83% (n=53)	10.11
PPI + AA + PEPPS	81% (n=37)	12.64
H2B + AA + PEPPS	88% (n=72)	7.26
Ulcer colic regimens 2,3,4 collectively	85% (n=162)	5.47
	Horses with diarrhea and colic	
H2B + AA + Bismuth + PEPPS	91% (n=11)	16.91

PEPPS, potency-enhanced polyanionic phyto-saccharide; PPI, proton pump inhibitor (omeprazole); AA, antacids; H2B, histamine-2 blocker (ranitidine or cimetidine); bismuth, bismuth preparations.

Table 3. T-statistic value comparing PEPPS alone to PEPPS-enhanced treatments in horses.

Treatment with PEPPS alone compared to	t-Statistic	Degrees of freedom	2-tailed p value
PPI + PEPPS	0.289	87	0.773
PPI + AA + PEPPS	0.244	88	0.808
H2B + AA + PEPPS	1.177	106	0.242
H2B + AA + Bismuth + PEPPS	0.804	45	0.426

PEPPS, potency-enhanced polyanionic phyto-saccharide; PPI, proton pump inhibitor (omeprazole); AA, antacids; H2B, histamine-2 blocker (ranitidine or cimetidine); bismuth, bismuth preparations.

Table 4. Horses prior to treatment and day 14 to 20.

Treatment regimen	Number (%) with gastric ulcers	
	Prior to treatment	Day 14-20 on treatment
PEPPS alone treatment	8/8 (100)	0/8 (0)
PEPPS-augmented treatments	15/15 (100)	0/15 (0)

PEPPS, potency-enhanced polyanionic phyto-saccharide; Treatments augmented with PPI, proton pump inhibitor (omeprazole); AA, antacids; H2B, histamine-2 blocker (ranitidine or cimetidine); bismuth, bismuth preparations.

that a large majority of the horses were observed to improve better than 80% of the study's equine 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 points. As a result, the data offers little predictive value and is mute as to efficacy. The study design provides an affirmative proof-of-principle supporting a plausible utility of PEPPS in the management of ulcers, diarrhea and colic associated with ulcers and diarrhea.

Another 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 dysfunctional GI symptoms.

Strengths of this observational study

Despite limitations on study design, an observational study such as this can provide "real world" setting information useful in evaluating the comparative effectiveness of PEPPS (Dreyer et al., 2010). From this trial, there appear to be positive benefits associated with the use of PEPPS in managing ulcers, diarrhea and colic in horses due to ulcers and diarrhea.

Firstly, the geographic diversity of state-licensed veterinarian was a significant factor. Eighty percent of the equine regions in the US are represented in this study. The data reflected a national experience involving equine practitioners licensed in 20 of the top 25 states, with the highest horse population and ownership. The high percent response associated with PEPPS was uniform. This implies that positive association of PEPPS with symptom resolution was universal with no significant variability due to difference in region or physician practice.

Secondly, the association of a positive outcome with PEPPS demonstrated no deference to the age of the horse. All ages of horses responded similarly. The horse's age did not alter response to PEPPS. Clinical response was high across all age groups involved, with foals, yearlings and older horses responding equally well to PEPPS.

Thirdly, though horses could have improved in the same timeframe on their existing treatments, it was not likely. The continuation of pre-existing ulcer treatments, to which PEPPS was added, had no added advantage of either treatment over each other. Positive outcomes for ulcer colic in horses on PEPPS alone (81%, 29/36) was indistinguishable from the outcomes in horses treated with omeprazole, antacid and PEPPS. In this study, there did not appear to be any advantage over using PEPPS alone, as 30/37 (81%) horses had virtually the same outcome using PEPPS alone versus PEPPS with the other treatments. Prior to use of PEPPS, the other treatment regimens were failing. The time horses were on the failing treatments was not assessed, however given that the study was conducted within a practice setting, it is assumed initial treatments fail a reasonable test of time, prompting the veterinarians to prescribe PEPPS as an additional therapy.

There did not appear to be any combination of omeprazole, ranitidine or antacid that provided a discernable pre-existing advantage or disadvantage. PEPPS alone was associated with an 81% (29/36) positive outcome, not perceptibly different than omeprazole + antacids + PEPPS at 81% (30/37) or omeprazole + PEPPS at 83% (44/53). Though the positive outcome associated with ranitidine + antacid + PEPPS, 88% (63/72) was greater than that of using PEPPS alone, [81% (29/36)]; the author is unaware of any mechanism of action related to acid reduction by which ranitidine and antacids would be superior to omeprazole which was associated with lower positive outcome.

Using PEPPS alone at the onset of illness was associated with positive outcome equivalent to adding PEPPS to regimens deemed by the veterinarians to have failed. In the practice setting, failing treatments (that are not causing harm) are continued, as the practitioner does not know for sure the possible benefits that suboptimal treatments may be providing, but will prescribe an additional treatment (PEPPS) in hopes of expediting clinical improvement. There was no statistically significant difference in using PEPPS alone versus using PEPPS with omeprazole, rantidine, antacids or bismuth. This observation held true despite the diverse geographic regions of the country and the varying recreational uses of the horses. Additionally, the extended study period of 3.5 years averaged in the effects on positive outcomes, if any, attributable to seasonality.

Use of PEPPS associated with accelerated healing of ulcers without acid inhibition

Complete healing occurred within 14 to 20 days using either PEPPS alone (n = 8) or PEPPS in addition of clinically ineffective treatments (n = 15) in 23 horses with endoscopic evidence of gastric ulcers. This is 8 to 14 days sooner than the 28 days required for omeprazole to achieve statistically significant healing (Merial, 1999). Healing independent of acid treatment was reported in the Merial study (1999), wherein nearly 40% of horses on placebo either improved or were completely healed, giving support to the notion of an acid-independent ulcer-deterrent system within the mucosa. While 15 of 23 horses with ulcers were on acid reduction therapies with PEPPS, 8 of 23 were on PEPPS alone healed sooner that would otherwise be expected. Acid-mitigating therapies have no known direct interaction with mucosal mechanisms responsible for healing ulcers, but muco-adherent PEPPS does. Accelerated healing in 14 to 20 days was a positive outcome associated with the use of PEPPS alone in horses with ulcers.

Plausible mechanism of action for PEPPS

Slippery elm mucilage is a polyanionic phytosaccharide similar to sucralfate, in that it is a mult-saccharide chain that contains branched substituents with a high electro-negative density. In slippery elm, electro-negative galacturonic acid corresponds to the electro-negative sulfates of sucrose dissacharide of sucralfate. When the elm polysaccharide is placed in a solution of cations and multi-dentate chelators, it is assumed that, similar to other saccharides (and sucralfate), it polymerizes into a layered macromolecule with egg-box type configuration (DeKerchove and Elimelech, 2007; Grant et al., 1973). This layered configuration potentiates the saccharide's electronegative density, augments its muco-adherence (Dobrozsi et al., 1999; Jubeh et al., 2004) and increases its surface concentration (McCullough, 2010). It is assumed that as such a polymer, PEPPS exhibits cyto-protective characteristics reportedly existing with sucralfate. That is, similar to sucralfate, the muco-adherence of PEPPS is indifferent to gastric acidity (Steiner et al., 1982), and its strength of binding, unaffected by pH (Danesh et al., 1988).

Additionally, by virtue of its electro-density, PEPPS binds enteric growth factors as does sucralfate (Jones et al., 2004; Konturek et al., 1991, 1995) and thereby facilitates immediate mucosal regeneration (Tarnawski et al., 1986). Like sucralfate, it is supposed that the electronegative density of PEPPS enables it to modulate voltage-gated nociceptors of the enteric mucosa (Slomiany et al., 1992), thereby repolarizing neural fibers of the vagus nerve reversing colic and pain sensation from acid (Holtzer, 2001, 2004), nausea and colic (Beyak and Grundy, 2005). Just as high doses of sucralfate (25 to 100 mg/kg/dose) by some mechanism stop diarrhea in small animals in 2 to f4 doses (Steiner, 1990), so does PEPPS in the same manner relieve diarrhea in the horse. While the exact mechanism of action of PEPPS, and for that matter, of sucralfate, is not entirely clear, these comments serve as a start for discussion and future analysis. In all, the mechanism of action utilized by PEPPS allows the management of symptoms and signs via direct engagement of enteric elements responsible for mucosal integrity and normative function of the GI tract.

Conclusion

The majority of horses treated with PEPPS for colic due to ulcer and diarrhea were observed to have shortened clinical course to an extent not anticipated by experienced equine practitioners. This data was generated by veterinarians practicing in 20 out 25 most populous equine owning states. While all equine patients eventually responded to PEPPS, a majority of horses responded within 4 days or 7 doses, returning to baseline feeding habits, demeanor and bowel habits. Additionally, whenever PEPPS was used, gastroscope-positive ulcerations healed within 14 to 20 days. This was true in eight horses that healed using PEPPS alone without acid mitigating therapies. The data from this study supports the notion that PEPPS may be useful in the management of equine ulcer, colic and diarrhea. Yet blinded, randomized placebo-controlled trials are needed to assess the true efficacy of potency-enhanced phyto-saccharides.

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