



Di-tri-octahedral smectite for the prevention of post-operative diarrhea in equids with surgical disease of the large intestine: Results of a randomized clinical trial [☆]

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Abstract

The aim of this study was to evaluate the effects of a commercially available di-tri-octahedral (DTO) smectite product on clinical signs and prevalence of post-operative diarrhea in horses with colic associated with disease of the large intestine. Sixty-seven horses with surgical disease of the large intestine were randomly assigned to be treated with DTO smectite ($n = 37$; 0.5 kg via nasogastric intubation every 24 h for 3 days post-operatively) or a placebo ($n = 30$). The effect of treatment on fecal scores and clinical and hematological parameters, including heart rate, mucous membrane color, temperature, total white blood cell count, total neutrophil count and total plasma protein values, were determined.

Horses treated with DTO smectite had a significant reduction in the prevalence of post-operative diarrhea (10.8%), compared with controls (41.4%). A significant improvement in mucous membrane color was observed 72 h post-operatively in horses receiving treatment, compared with placebo. Administration of DTO smectite to colic patients with disease of the large intestine reduced the occurrence of diarrhea in the early post-operative period.

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Introduction

Enterocolitis is a common and potentially serious complication that may develop following celiotomy for treatment of colic. Prevalence of diarrhea in post-operative colic patients has been reported to be 26–53%, with up to 27.5% categorized as being severe (Cohen and Honnas, 1996; Parraga et al., 1997). The development of colitis poses a substantial financial burden to horse owners, and

increases the risk for several post-operative complications, including laminitis, thrombophlebitis, and death (Dolente et al., 2002). Horses with disease of the ascending colon are at higher risk for developing severe diarrhea after celiotomy for treatment of colic (Cohen and Honnas, 1996). Although *Clostridium difficile* toxins and other pathogens, such as *Salmonella* spp., are sometimes isolated, the specific cause of the enterocolitis often remains unknown, and treatment primarily consists of supportive care. Development of an effective preventive strategy would result in a marked reduction of morbidity and mortality in post-operative colic patients.

Preliminary studies using a model of lincomycin-induced colitis suggested that di-tri-octahedral (DTO) smectite, a

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natural clay material, may be useful for the treatment and prevention of colitis in horses (Herthel, 2000). Furthermore, in vitro studies have demonstrated effective neutralization of clostridial and *Bacteroides* toxins by DTO smectite (Martirosian et al., 1998; Weese et al., 2003; Lawler et al., 2008). Although the specific mechanism of action of DTO smectite in the treatment of enterocolitis is unclear, it appears to diminish the damage to the luminal surface membranes and mucous protective layer of the intestinal epithelium by pathogenic bacteria (Rateau et al., 1982).

DTO smectite can aggregate with *Escherichia coli* in vivo (Droy-Lefaix et al., 1989), and has also been demonstrated to protect the intestinal mucosa against injury induced by biliary salts (Droy-Lefaix et al., 1985). One potential mechanism for the protective effect of smectite is related to its interaction with intestinal mucus (Albengres et al., 1985). These properties may explain not only the direct therapeutic effect of DTO smectite, but also its prolonged action after withdrawal, potentially acting as a regulatory agent interacting with gastrointestinal flora and regulating intestinal secretions (Yao-Zong et al., 2004).

Several clinical trials in humans have demonstrated positive therapeutic effects of DTO smectite in the management of acute diarrhea in children (Dupont et al., 1992; Vivatvakin et al., 1992; Madkour et al., 1993; Milocco et al., 1999), chronic functional diarrhea in adults (Yao-Zong et al., 2004), and radiation-induced diarrhea in adults (Hombrink et al., 1995, 2000). Therapy with DTO smectite is a mechanical approach to capturing bacterial endotoxins and exotoxins before they escape from the intestine and reach the systemic circulation. Preventing the systemic effects of endotoxins and exotoxins may significantly reduce the severity and length of disease.

The purpose of this study was to evaluate the influence of a commercially available DTO smectite product (Bio-Sponge) in the prevention of post-operative diarrhea and its effect on clinical parameters in horses with surgical disease of the large intestine. We hypothesized that administration of DTO smectite in the early post-operative period would reduce the incidence of diarrhea and decrease abnormal clinical findings normally associated with endotoxemia.

Materials and methods

Study population

Between June 2001 and May 2003, eligible horses admitted to the Large Animal Clinic at the University of California, Davis were sequentially enrolled in this randomized clinical trial. Incident cases of colic undergoing ventral midline celiotomy during the specified time period were included until a minimum of 30 cases were accumulated to achieve the predetermined target sample size population based on an alpha error of 0.05 and a power of 0.90 to detect an estimated difference of 25% in development of diarrhea in the post-operative period.

Inclusion criteria included horses undergoing ventral midline celiotomy for treatment of strangulating or non-strangulating disease of the large intestine that recovered from anesthesia and survived a minimum of 24 h post-operatively. Exclusion criteria included foals <2 months of age,

horses receiving DTO smectite prior to surgery for treatment of diarrhea, horses with >4 L of gastric reflux upon passage of a nasogastric tube 4 h post-operatively, horses with a history of chronic diarrhea, patients receiving antimicrobial therapy prior to presentation for colic, patients that were euthanased or died within 24 h post-operatively, horses that had a positive fecal culture for *Salmonella* at the time of hospital admission, and horses with primary diseases of the stomach, small intestine or cecum.

All procedures were approved by the University of California, Davis, Animal Care and Use Committee and informed consent was obtained. DTO-smectite product was provided by the manufacturer.

Study protocol

A subjective assessment of risk for post-operative diarrhea was performed by the attending surgeon based on clinical appearance of intestine and type of lesion identified. A 1–3 grading scale was used: Grade 1 = unlikely to develop diarrhea; Grade 2 = mild to moderate probability of post-operative diarrhea; Grade 3 = likely to develop post-operative diarrhea. This subjective scale was incorporated to attest for the correct randomization of the individuals with regards to a potential confounding variable. Inter-observer agreement was not objectively assessed, but assessment was limited to three individuals with similar surgical training backgrounds. Selection of treatment and placebo groups took place following the risk assessment using a randomized method.

All horses underwent a similar course of perioperative antibiotic and non-steroidal therapy and received an enterotomy of the pelvic flexure, including intraluminal lavage with tap water. Using random selection with sealed envelopes, post-operative colic patients with disease of the large intestine were assigned to receive placebo or a commercially available DTO smectite clay (Bio-Sponge) per nasogastric tube at a dosage of 0.5 kg per 500 kg bodyweight (BW) in 4 L of water every 24 h for 3 days beginning 4 h post-operatively. Placebo consisted of administration of 4 L of water via nasogastric tube every 24 h for 3 days beginning 4 h post-operatively.

In an attempt to blind intensive care unit technicians to treatment group, treatment charts and daily clinician order sheets did not indicate whether the horse had been assigned to the treatment or control group. To minimize bias, technicians caring for the patients enrolled in the study were supplied with a chart to characterize fecal consistency using consistent terminology.

Data collection

The effect of treatment on fecal scores and clinical and hematological parameters including heart rate, mucous membrane color, temperature, total white blood cell (WBC) count, total neutrophil count, total plasma protein values, and fecal culture results were determined. Clinical parameters were assessed every 4 h by technicians and hematological parameters were assessed at the time of admission (baseline) and at 24 and 72 h post-operatively. Fecal scores were determined by assessment of patient charts by a single evaluator (PAS) blinded to treatment group, and took into account daily fecal consistency, volume, and frequency (value of 0–8 assigned each day with zero representing normal formed feces, and 8 representing profuse watery diarrhea), weighting for number of days post-operatively (day 1 = 0.25; day 2 = 0.5; day 3 = 1.0; day 4 = 2.0; day 5 = 4.0).

The assigned fecal consistency value was multiplied by the value for the number of days post-operatively, and the sum of the 5 post-operative days was calculated as the fecal score. Because soft manure is commonly seen perioperatively following enterotomy and colonic lavage, this grading system was developed to allow for higher scores in horses developing diarrhea further from the time of surgery. For example, a horse who had normal feces for 3 days post-operatively followed by 'cow pie' consistency feces on day 4 and profuse watery diarrhea on day 5 post-operatively would receive a score of: $0(0.25) + 0(0.5) + 0(1.0) + 4(2.0) + 8(4.0) = 40$. In contrast, a horse that had cow pie consistency feces for 3 days post-

operatively, followed by normal feces would obtain the following score: $4(0.25) + 4(0.5) + 4(1.0) + 0(2.0) + 0(4.0) = 7$.

Development and validation of this fecal scoring scheme occurred via assessment of numerous post-operative colic medical records by the authors (PAS, DMH), encompassing a wide range of clinical disease. Application of the scoring scheme occurred following an overall clinical assessment of the entire patient record with subjective determination of whether a patient should or should not be characterized as having developed post-operative diarrhea. Based on these evaluations, a cut-off value of 10 (range 0–50) was established for fecal scores to create a dichotomous outcome for presence or absence of post-operative diarrhea.

Fecal cultures for *Salmonella* spp. were performed daily at admission and throughout hospitalization for all horses ($n = 67$). Culture for *C. difficile* was performed when clinically indicated ($n = 6$).

Statistical analysis

The relationship of treatment and diarrhea with rectal temperature, heart rate, mucous membrane color, total WBC count, neutrophil count, and total plasma proteins was evaluated by repeated measures ANOVA. Baseline comparisons were carried out to identify potential confounders. The variables assessed for homogeneity between treatment groups were age, breed, sex, subjective grading of probability of post-operative colitis as determined by the surgeon, and results of fecal cultures. Mann–Whitney tests, Pearson Chi-square or Fisher's exact tests were used, correspondingly with the variable type. For baseline comparisons only, α was set at 0.1. The outcome was evaluated as a dichotomous variable (presence or absence of diarrhea) and as a continuous variable (\log_{10} of diarrhea score).

The effect of treatment on occurrence of diarrhea was assessed by Pearson Chi-square tests for significance, and by odds ratio (OR) with 95% confidence intervals (95% CI) for magnitude. The analysis was stratified by potential confounders if they were significant in the baseline comparisons.

The relationship of diarrhea scores and treatment group was assessed by generalized linear model, including the potential confounders if significant in the baseline comparisons. Results were considered significant if $P < 0.05$.

Results

Sixty-seven horses were enrolled in the study. Of these, 37 were randomly assigned to the DTO smectite group and 30 to the placebo group. There were a larger number of treated horses ($n = 37$) than controls ($n = 30$) as a consequence of random selection from a pool of 100 envelopes used for selection of treatment group. Descriptive statistics for each of the parameters of interest are included in Table 1. Surgical lesions included enterolith obstruction ($n = 20$), large colon displacement ($n = 14$), sand impaction with or without large colon displacement ($n = 4$), large colon volvulus ($n = 17$), large colon feed or fecolith impaction ($n = 5$), small colon impaction ($n = 2$), or non-specific enteritis or gas ($n = 5$). There were no significant differences in baseline values between the treatment group and controls for age, sex, breed, clinical parameters, or grading of likelihood of development of post-operative diarrhea by surgeons.

Administration of DTO smectite was associated with a significant reduction in mean post-operative fecal score ($P = 0.01$). Using a fecal score of >10.0 as positive for diarrhea, 41.4% of controls (12/29) and 10.8% of the treated group (4/37) developed diarrhea in the 5 day post-operative

period ($P = 0.003$). The odds of developing diarrhea given no treatment with DTO smectite were 6.0 times greater than the odds of diarrhea when the horse received treatment with DTO smectite (OR, [95% confidence interval] = 6.0 [1.7, 21.3]). There was no significant effect of treatment on rectal temperature during the 3 days post-operatively, but horses that developed diarrhea (fecal score >10 ; $n = 16$) had significantly higher rectal temperatures both at admission (average \pm SEM = 38.1 ± 0.1) and 24 h post-operatively (38.3 ± 0.1 ; $P = 0.017$).

There was no significant effect of treatment or diarrhea on heart rate ($P = 0.726, 0.156$), total WBC count ($P = 0.524, 0.270$), neutrophil count ($P = 0.759, 0.528$), and total plasma proteins ($P = 0.788, 0.431$). Mucous membrane color was more likely to be toxic or injected in controls at 72 h post-operatively compared with horses treated with DTO smectite ($P = 0.01$). Similarly, horses with diarrhea, irrespective of whether they were within the treatment or control group, were more likely to have a toxic or injected mucous membrane color at 72 h post-operatively, compared with horses that did not develop post-operative diarrhea ($P = 0.003$).

Discussion

The results of the present study suggested that, when compared with a placebo, administration of DTO smectite in the early post-operative period to horses with surgical disease of the large intestine significantly reduced their likelihood of developing post-operative diarrhea. Horses with surgical disorders of the large intestine that undergo an enterotomy are at high risk for development of diarrhea in the post-operative period (Cohen and Honnas, 1996), which is likely to contribute to prolonged hospitalization, increased occurrence of complications and higher client costs.

The prevalence of post-operative diarrhea in the control population in this study was higher than that previously reported (Mair and Smith, 2005; Puotunen-Reinert and Huskamp, 1986). This may be a result of the inclusion criteria of receiving a pelvic flexure enterotomy with intraluminal lavage and evacuation of colonic contents using tap water. Evacuating the normal intestinal flora and volatile fatty acids from the colon while concurrently flooding the mucosa with a hypotonic solution may in part be responsible for the high prevalence of post-operative diarrhea. A marked reduction in post-operative fecal score was observed when treated with DTO smectite. These findings are consistent with results of other clinical and research studies in horses (Herthel, 2000), dogs (Fioramonti et al., 1987), and people (Dupont et al., 1992; Vivatvakin et al., 1992; Madkour et al., 1993; Hombrink et al., 1995, 2000; Milocco et al., 1999; Yao-Zong et al., 2004).

Positive fecal cultures for *C. difficile* ($n = 2$) were identified in two horses within the placebo group after 4 and 10 days of hospitalization, and no positive cultures were

Table 1
Mean (SEM) values for fecal scores and clinical parameters in horses with colic treated post-operatively with di-tri-octahedral smectite (treatment; $n = 37$) or placebo (controls; $n = 30$)

	Treatment	Control
Fecal score	3.9 (0.67)*	10.6 (2.26)
Diarrhea	4/37*	13/30
Positive fecal culture	0/37	3/30
<i>Body temperature (°C)</i>		
Baseline	38.0 (0.09)	37.9 (0.08)
24 h post-op	38.1 (0.08)	38.2 (0.06)
72 h post-op	37.9 (0.06)	38.0 (0.09)
<i>Heart rate (bpm)</i>		
Baseline	51 (1.93)	49 (2.50)
24 h post-op	42 (1.57)	42 (1.79)
72 h post-op	37 (1.09)	37 (1.77)
<i>Total WBC count (cells/μL)</i>		
Baseline	6.93 (0.42)	7.14 (0.56)
24 h post-op	4.83 (0.37)	4.64 (0.32)
72 h post-op	5.70 (0.76)	4.43 (0.25)
<i>Total neutrophils (cells/μL)</i>		
Baseline	4.5 (0.38)	4.9 (0.52)
24 h post-op	4.6 (0.63)	3.2 (0.36)
72 h post-op	3.2 (0.60)	2.5 (0.24)
<i>Total plasma protein (g/dL)</i>		
Baseline	6.5 (0.13)	6.4 (0.17)
24 h post-op	5.9 (0.09)	5.8 (0.14)
72 h post-op	6.3 (0.10)	6.3 (0.14)
<i>Mucous membrane color</i>		
Baseline vs. 24 h	Normalized*	NS
Baseline vs. 72 h	Normalized*	NS
24 h vs. 72 h	NS	NS

NS = no improvement seen.

* Values are significantly different ($P < 0.05$) between treatment and control groups.

observed in the treatment groups. *C. difficile* cultures were not performed on all horses within the study and were more likely to be performed in association with clinically significant diarrhea. Therefore, drawing conclusions regarding the effect of DTO smectite on reducing the prevalence of positive fecal cultures is difficult. However, clostridia are known important etiologic agents of diarrhea in horses and changes in intestinal flora of horses with colic may allow for proliferation of clostridia and elaboration of enterotoxins regardless of whether diarrhea develops (Donaldson and Palmer, 1999). Administration of DTO smectite in horses with *C. difficile* colitis may help ameliorate some of the associated clinical signs by binding luminal enterotoxins, as has been demonstrated in vitro (Martirosian et al., 1998; Weese et al., 2003).

Although significant improvements in clinical parameters compared to baseline were not observed in horses receiving DTO smectite compared to controls, the population of horses studied had only minor abnormalities in clinical parameters (Table 1). Survival was not assessed as an outcome parameter, as all but two horses survived. This high survival was in part a consequence of the exclu-

sion of those horses not surviving 24 h post-surgically. If treatment were to influence survival, a much larger scale study would be required to identify this effect of treatment.

A mild, but statistically significant increase in body temperature was observed pre-operatively and 24 h post-operatively in horses that developed diarrhea. Subjective assessment of mucous membrane color in horses with diarrhea compared to those that did not develop diarrhea indicated an increased likelihood of having mucous membrane color abnormalities 72 h post-operatively. The same observation was made for placebo-treated horses compared with the treatment group. Toxic or injected mucous membranes are a common clinical finding in horses with endotoxemia (Morris et al., 1990). Considering the findings in this study combined with results of in vitro testing (Lawler et al., 2008; Martirosian et al., 1998; Weese et al., 2003), it is possible that DTO smectite reduced the absorptive load of endotoxins and exotoxins in horses undergoing surgical correction of disease of the large intestine.

Water was selected as the placebo in the group of control animals since this was the method of dilution used to administer the DTO smectite. A similar volume of fluid was administered to treatment and control groups, but marked differences in osmolality of the fluid administered exists. Water, as a hypo-osmotic fluid administered in a small volume (4 L orally, once daily), should be rapidly absorbed by the small intestine and contribute little to colonic hydration, and therefore development of diarrhea. In a recent study, administration of 60 L of water to adult horses over 12 h via nasogastric tube resulted in no significant increases in fecal water content, and mild and transient increases in water content in the right dorsal colon (Lopes et al., 2004). Considering these findings, administration of a 4 L volume is unlikely to have a substantial impact on fecal water content and induce diarrhea. However, the effect of oral administration of fluids in horses that have undergone celiotomy for colic has not been studied, and it is possible the small volume of water administered to controls may have played a minor role in affecting fecal consistency.

A blinded study represents the ideal scenario for clinical trials to remove observational biases, but it was difficult to achieve 100% blinding during patient hospitalization. Fecal scoring and clinical data collection from records was performed in a blinded fashion by a single individual (PAS). Technicians were responsible for documenting clinical parameters and fecal output and were blinded to treatment group as they did not administer the treatment or placebo. Also, treatment charts and clinician order forms did not indicate whether a patient belonged to the treatment or placebo group. However, it is likely that some technicians could identify to which group a patient belonged (i.e. if they were present at the time of administration of treatment or placebo). The majority of technicians who recorded fecal output and consistency were unaware of the treatment group.

Conclusions

These results support the use of DTO smectite as a preventative treatment for post-operative diarrhea in horses with surgical disease of the large intestine. Administration of DTO smectite to colic patients in the early post-operative period reduced the occurrence of diarrhea.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.

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