Calcium Aluminosilicate (CAS) in the Treatment of Intractable Diarrhea in Dogs with Cancer

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KEY WORDS: persistent diarrhea, calcium aluminosilicate (CAS), metronidazole, sulfasalazine

ASTRACT

Twenty-three client-owned dogs with persistent, watery diarrhea having failed conventional medical management for a period of 48 hours or longer were considered eligible for treatment were given 500 mg of calcium aluminosilicate (CAS) clay orally until they had two consecutive formed stools. Owners reported fecal consistency and the number of stools per day until resolution. Overall, 15 of the 23 dogs (65.2%) had complete resolution of symptoms within 48-72 hours after CAS administration was initiated. In the 8 dogs without complete symptom resolution, pet owners reported a decrease in the number of stools per day and symptomatic improvement within 48 hours. This case series study suggests that CAS is effective in the treatment of intractable diarrhea in the cancer bearing dog. Prospective and controlled studies are indicated to determine role of CAS in the medical management of intractable diarrhea of dogs.

INTRODUCTION

Diarrhea is a common adverse event following the administration of chemotherapy to a dog with cancer. The standard of care for the treatment of acute diarrhea is rehydration and the administration of either antibiotics, motility modifiers, synthetic prostaglandins or anti-secretory agents.[1,2] Responses are variable and most approaches fail to provide long term prevention or treatment in the dog receiving numerous treatments.[1,2]

Metronidazole, a synthetic nitroimidazole with antibacterial, anti-protozoal and anti-inflammatory properties, is commonly prescribed in the management of dogs with acute and chronic diarrhea.[1] However, because it is metabolized and excreted by the liver, care should be exercised in dogs with impaired liver function. Neurotoxicity has been associated with higher doses and chronic administration.[1]

Sulfasalazine, an antibiotic with antibacterial and anti-inflammatory properties, is also commonly prescribed to either prevent or treat diarrhea in dogs.[2] Potential adverse reactions include keratoconjuncitivitis sicca (KCS), hepatotoxicity, hemolytic anemia and leukopenia.[2] Specifically black and tan breeds are at an increased risk of adverse reactions.

Dioctahedral smectite is a naturally occurring clay composed of fine sheets of aluminomagnesium silicate. This composition has been used in human beings for the treatment of pediatric acute infectious diarrheas[3-7] and for the management of chronic diarrhea conditions such as inflammatory

bowel disease,[8] Crohn's disease and food allergies.[9] Smectite adsorbs luminal toxins, antigens and bacteria.[10] Other proposed mechanisms of action include modifications of the rheological properties of the gastrointestinal mucosa, anti-inflammatory properties, increased secretion of mucopolysaccharide 2 (MUC2), and restoration of luminal integrity.[10-13]

This study describes the use of a naturally occurring clay, calcium aluminosilicate (CAS) that resolves chemotherapy-induced intractable diarrhea in dogs that failed conventional, standard of care, medical approaches.

MATERIALS AND METHODS

Tumor-bearing dogs presenting with persistent loose watery stools without resolution, despite using standard treatment measures such as metranidazole, sulfasalazine or dietary approaches for a period of no less than 48 hours, were considered eligible for treatment with CAS. When appropriate, fecal flotation with ZnSO4 and cultures were performed. Given these inclusion criteria, intractable diarrhea unresponsive to existing standard of care, a control or placebo group was deemed inappropriate. Eligible dogs were given 500 mg sterile CS orally every six hours and followed for 14 days. The CAS tablets were free of T4 dioxin and heavy metals without binders or fillers; mean particle size was approximately 80 microns.

Owner consent was required prior to study enrollment. This study complied with the guidelines established by the Food and Drug Administration (FDA) for Good Clinical Practice. Resolution of diarrhea was defined as two consecutive formed stools. Information regarding the date and type of the most recently administered chemotherapy, the duration of diarrhea prior to starting CAS administration, and the time to resolution of diarrhea were recorded.

RESULTS

Twenty-three dogs were given CAS. Overall, 15 of the 23 dogs (65.2%) had complete resolution of symptoms within 48-72 hours after CAS administration was initiated.

Six dogs had diarrhea not considered as treatment-induced (stress colitis, 2 dogs; dietary indiscretion, 2 dogs; tumor-related, 2 dogs). Seventeen dogs had diarrhea induced following the administration of chemotherapy (doxorubicin HCL, 8 dogs; cyclophosphamide, 2 dogs; vincristine sulfate, 2 dogs; vinblastine, 2 dogs; lomustine, 1 dog; carboplatin, 1 dog; mechlorethamine HCL, 1 dog).

For the 6 dogs without chemotherapy-induced diarrhea, the average duration of symptoms prior to CAS administration was 6 days (range, 2 to 14 days). Three of these dogs had at least a 14 day history of diarrhea prior to starting CAS. Five of the 6 dogs (83.3%) had resolution of their clinical signs when treated with CAS. The mean time to resolution was 2.4 days (range, 1 to 4 days). The one non-responder in this group did experience a decrease in the number of stools per day even if though the consistency did not return to normal.

For the 17 dogs with chemotherapy-induced diarrhea, the average duration of symptoms prior to CAS administration was 6.8 days (range 2 to 30 days). Ten of the 17 dogs (58.8%) had resolution of their diarrhea. Two additional animals had a decrease in the number of stools per day even if the fecal consistency did not improve. The mean time to resolution of the diarrhea was 2.9 days (range, 2 to 8 days). Of the 10 dogs that responded, most pet owners reported symptomatic improvement within 48 hours. One dog experienced constipation as a result of treatment with CAS. No other adverse reactions were reported during the study period.

Overall, 15 of the 23 dogs (65.2%) had complete resolution of symptoms within 48-72 hours after CAS administration was initiated.

DISCUSSION

This study demonstrates that CAS is effective in resolving signs and symptoms associated with intractable diarrhea in cancer bearing dogs. Diarrhea is a common com-

plication of both cancer and its treatment. In the canine patient, diarrhea may be the result of dietary indiscretion, neoplastic disease, or treatment related (due to chemotherapy or radiation therapy). Dosages of chemotherapy are limited by toxicity and patients are given chemotherapy based on the maximally tolerated dose. A common dose limiting toxicity is diarrhea (both large and small bowel). Chemotherapy agents, such as doxorubicin HCL, have a high incidence of inducing diarrhea and colitis.[14] Gastrointestinal toxicity is named as the dose limiting toxicity for doxorubicin.[14] Seventeen dogs in this trial had chemotherapy as the inciting cause of their diarrhea, of which 8 (47.1%) were induced by doxorubicin administration. While most cases of diarrhea are self limiting or respond to minimal treatment. However, most protocols require repeated exposure to cytotoxic chemotherapy or radiation therapy and treatment intervention is eventually warranted. Continued treatment with anti-secretory agents, such as Loperamide, or antibiotics, such as metronidazole, is not without the potential risk of serious complications.[1,2] Loperamide can result in dry mouth and nausea and can in the long term setting can lead to dependence.[15] Metronidazole, when given long term, carries an increased risk of neurological complications.[1,2] Agents such as CAS, which are not absorbed through the gastrointestinal tract, may provide a safer option for chronic administration.[15]

CAS is chemically distinct from other clays that have been investigated to control diarrhea.[16] The CAS physical structure consists of microscopically large flat plates of aluminosilicate separated by calcium ions that produces a distinct highly charged equidistance inner layer (between the plates) that has the ability to attract and trap toxins in the inner layer as opposed to electrostatic surface binding as is the case with other clays that have been studied to prevent or treat diarrhea.[17-18]

In the rat model, smectite clay down-regulates the inflammatory response; and reduces the levels of myeloperoxidases and IL-1β, which indicates decreased infiltration and activity of neutrophils and monocytes in the intestinal tissue samples.[11,13,19,20] Smectite clay also increases the secretion of MUC2 in the colon thus providing an improved barrier to luminal contents.[16,21] Additionally, smectite clay inhibits the basolateral secretion IL-8 in a dose dependant manner. These results suggest that smectite clay is as effective as sulfasalazine in an experimental model of chronic colitis.[10,16,21]

In the rabbit model for experimental infectious diarrhea, smectite clay was shown to decrease bacterial mucolysis and the destruction of the luminal surface membranes by pathogenic bacteria.[22] *Escherichia coli* 0128B12 was used to create an invasive and toxigenic situation to attempt to determine the mechanism of action of smectite clay. Smectite clay was shown to favor absorption and counteracts the excretion of water while at the same time maintaining absorption of luminal electrolytes. In addition, membrane enzymes levels of disaccharidase and alkaline phosphatase were both elevated in the smectite clay model which is consistent with protective effects on the luminal surface in the presence of an invasive, toxigenic bacteria.[22,23]

In the pediatric model, smectite clay has been used to treat acute infectious diarrhea.[24] In an open, randomized, multi-center trial in Lithuania, the duration of diarrhea was significantly shorter when smectite clay was used in combination with an oral rehydration solution then when treated with an oral rehydration solution alone (42.3+/- 24.7 hours versus 61.8 +/-33.9 hours).[24] A similar double blinded placebo controlled study in Egypt found that although smectite clay did not impact the initial volume of stool; it decreased the duration of diarrhea from 73 hours to 53 hours when used in combination with oral rehydration.[25]

Diarrhea in the canine patient not only affects the dog, but also the family unit. Diarrhea results in increased stress on the caretaker, by requiring additional work

such as additional trips outside for bowel movements, cleanup of fecal accidents, and administration of medication, rehydration solutions and food preparation. Smectite clays in the pediatric model have been shown to decrease the duration of watery stools; therefore, decreasing the work load and strain on the family unit.[18,23] Decreasing the strain on the family unit promotes greater compliance and willingness to treat. Quality of life for the patient is also improved by decreasing the duration of a post therapy diarrhea episode.[18]

CONCLUSION

In this evaluation of 23 dogs with intractable diarrhea, CAS administration was effective (overall response rate 65.2%) and well tolerated. One dog experienced constipation and this quickly resolved upon discontinuation. This case series study suggests that CAS is effective in the treatment of intractable diarrhea in the cancer bearing dog. Prospective and controlled studies are indicated to determine role of CAS in the medical management of intractable diarrhea of dogs.

ACKNOWLEDGEMENTS

The authors acknowledge the contributions of Dr. Robert Newman, Dr. Glen King, and Dr. Melissa Endicott.

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