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The Effect of Promax® on Diarrhoea in Dogs

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'There was a statistically significant decrease in defecation frequency from day one to day three, suggesting that frequency is reduced following two doses of Promax®'

'Administration of Promax® can help resolve the symptoms of diarrhoea including loose faeces, increased defecation frequency, loss of appetite and lethargic behaviour, without the requirement for altering the dog's normal diet'

The Effect of Promax® on Diarrhoea in Dogs

Ian Futter BVMS MRCVS [a], Rachel Eaton BSc (Hons) [b]

[a] *Chief Veterinary Officer, Scottish SPCA, Glasgow, UK*

[b] *Research and Development, VetPlus Ltd., Lytham St Anne's, UK*

Abstract

Diarrhoea is a common complaint in small animal practice. It is indicative of disturbances in the normal gastrointestinal processes, resulting in excessive water in the large intestine, which causes loose faeces and increased urge to defecate and subsequently enhanced defecation frequency. Diarrhoea, whilst typically not having any serious implications on animal health assuming hydration status is maintained, can be distressing for pet owners who may struggle to manage the condition, resulting in increased in-house soiling incidents. A common approach is for owners to withhold food in order to reduce passage of materials through the gastrointestinal tract or to change to a bland diet. Nutraceutical products based on absorbent clays, probiotics and other gastrointestinal health-promoting ingredients, can be administered to manage the symptoms of diarrhoea and improve gastrointestinal health. The current study demonstrates that the administration of Promax® results in 85 % of animals, regardless of the root-cause of diarrhoea, having resolution of symptoms within 4 days (after 3 doses of the product), without the requirement for additional dietary management. A significant reduction in defecation frequency was also evident by day 3. Appetite and owner-perceived pet health and well-being was also improved throughout the study.

1.0 Introduction

Diarrhoea in dogs is a common complaint with owners and is in the top three reasons for consultation at first opinion veterinary clinical practices in the UK with a prevalence of 3.6 % (Robinson *et al.*, 2015). The absorption of water in the intestine is passive and secondary to the active movement of osmotically active agents or solutes such as electrolytes, carbohydrates and fatty acids. Water therefore transports across the gut in order to maintain isotonicity with the plasma. Diarrhoea occurs when there is a disturbance in the balance between the mechanisms controlling secretion and absorption of water, resulting in an excessive loss of water and subsequent liquification of the faeces (Low-Beer and Read, 1971).

There are four major mechanism of diarrhoea: 1) Osmotic diarrhoea caused by ingestion of poorly absorbed solutes. Causes include animals with food intolerance and disease conditions resulting in malabsorption or sudden dietary changes (Battersby and Harvey 2006); 2) Secretory diarrhoea occurs when fluid accumulates in the

intestinal lumen because of reduced fluid absorption. Causes of secretory diarrhoea include bacterial enterotoxins, protozoal infections (e.g. Giardiasis) and drug ingestion; 3) Exudative diarrhoea occurs when there is extensive mucosal damage caused by inflammation which prevents water absorption. This occurs in cases of colitis and inflammatory bowel disease (IBD) (Warren 1983); and 4) Dysmotility - as a primary cause of diarrhoea this is considered rare, however, many causes of diarrhoea can result in secondary alterations in motility, for example, rapid waves of contractions can occur with enterotoxigenic diarrhoea.

Dietary-related problems are the most common cause of acute diarrhoea and may be the result of dietary indiscretion, food poisoning, hypersensitivity (allergy) or intolerance. Causes of intolerance include the rapid introduction of a new diet that does not allow brush border enzymes time to adapt, or an inherent lack of a necessary enzyme such as lactase. Diarrhoea in itself is rarely life threatening and is often self-limiting, however it can be difficult and distressing for the pet owner to manage, thereby often resulting in repeated soiling incidents. A common management approach for acute diarrhoea is to apply a 24-hour period of starvation, followed by the introduction of small frequent meals of bland food (e.g. chicken and rice) (Battersby and Harvey 2006).

Nutraceuticals can also be employed to manage the symptoms of diarrhoea. Promax® is an absorbent paste which is designed to reduce the fluidity of the faeces and normalise stool consistency and faecal output, whilst containing several ingredients with gastrointestinal health benefits. Key ingredients in Promax® are bentonite clay, probiotic, prebiotics, β-glucans and amino acids – each of these ingredients will be discussed in turn.

Kaolin and smectites (also known as bentonite) are most commonly used in animal nutrition as growth promoters and supplements for the treatment of gastrointestinal disturbances, particularly diarrhoea. The high adsorption capacity of bentonite results from their very fine particle size, thin particle shapes and high specific surface area. Montmorillonite is the major constituent of bentonite and has the capability to bind and adsorb large organic molecules, polymers, complex ions, heavy metals, viruses, bacteria and associated endo- and exo-toxins. Clay minerals also exert a stabilising effect on the intestinal barrier through binding to and altering the rheology of mucus, increasing mucus production and via favourable effects on the morphological structure of the intestines (Slamova *et al.*, 2011). Clinical studies in humans have demonstrated that smectite can alleviate the symptoms of acute diarrhoea and shorten its duration (Szajewska *et al.*, 2006), as well as reduce the frequency of liquid stools and long-lasting diarrhoeal episodes (Madkour *et al.*, 1993), suggesting it as a useful therapeutic aid in the management of diarrhoea.

Probiotics have also been indicated in the maintenance of optimal gastrointestinal (GI) health. They are live microorganisms intended to provide health benefits by improving or restoring the gut flora. Studies in dogs and cats have indicated favourable effects on the immune system (Benvacoub *et al.*, 2003), reduced incidence of diarrhoea (Bybee *et al.*, 2011) and reduced excretion of pathogenic microorganisms in faecal samples suggesting reduced levels in the GI tract (Vahjen and Männer 2003). Promax® also contains prebiotics in the form of inulin, containing fructooligosaccharides (FOS), and mannanoligosaccharides (MOS). Prebiotics are non-digestible substrates which are fermented by the microorganisms in the gut to produce a robust microbial population that is more resistant to pathogenic and environmental challenges.

They also encourage the production of favourable molecules such as short-chain fatty acids (SFCAs) which support gut health. FOS has been demonstrated in canines to have favourable effects on stool consistency (Grieshop *et al.*, 2004) and against pathogenic challenge (Aoanavicuis *et al.*, 2007). It has also been shown to reduce numbers of pathogenic *Clostridium* in the gut (Flickinger *et al.*, 2007), encourage the growth of favourable *Bifidobacteria* and increase immune cell numbers (Grieshop *et al.*, 2004). MOS has also demonstrated benefits in canine gastrointestinal health by reducing pathogenic *E. coli* (Ferreira Gouveia *et al.*, 2006) and encouraging the growth of more favourable microbial populations (Swanson *et al.*, 2002).

Other active ingredients within Promax® include β-glucans and the amino acids L-Glutamine and L-Threonine. β-glucans are immune-stimulants which have been shown in dogs to have immune boosting effects during vaccine challenge (Altug *et al.*, 2004; Halovoa *et al.*, 2011) and raise serum IgM (Stuyven *et al.*, 2010). Additionally they have beneficial affects in inflammatory bowel disease (IBD) as demonstrated by lowering of the Canine Inflammatory Bowel Disease Activity Index value and reducing pro-inflammatory cytokine, whilst increasing anti-inflammatory mediators (Rychilik *et al.*, 2013). The amino acids within Promax®, L-Threonine and L-Glutamine have been demonstrated to have beneficial effects on mucin production and to reduce susceptibility of enterocytes and lymphocytes to apoptosis respectively, and have also been shown to help maintain mucosal structure and integrity (Wang and Qiao 2009).

The purpose of the study was to evaluate the time to resolution of diarrhoea symptoms in dogs that had been administered Promax®, whilst housed in a stressful kennel environment and maintained on a normal diet, thereby negating the need to resort to dietary management.

2.0 Materials and Methods

2.1 Animals

Seven animal centres were recruited for participation in the trial. These included Ayrshire and South West Scotland ARRC, Dunbartonshire and West Scotland ARRC, Lanarkshire ARRC, Edinburgh and Lothians ARRC, TR Centre (location undisclosed), the Three Counties Dog Rescue (Bourne) and Easterleigh Animal Sanctuary (Blackpool). Animals were recruited from each centre at the onset of diarrhoea symptoms during the 4 week trial period running from July to August 2018. 33 dogs were recruited for the study during the trial period. 4 results were excluded, resulting in 29 sets of data for analysis. Reasons for exclusion from data analysis included incomplete data sets for faecal scoring (primary study outcome), trial withdrawal and concomitant metronidazole use.

2.2 Exclusion Criteria

Puppies less than 8 weeks of age, dogs displaying severe vomiting/diarrhoea requiring other treatment and dogs showing signs of concurrent disease (cough, vomiting, anaemia, breathing problems).

2.3 Baseline Evaluation

A pre-treatment baseline questionnaire was completed for each dog by either the Chief Veterinary Officer or kennel member of staff. The questionnaire included recording the dog's weight and length of time at the centre, any known medical conditions, the use of routine medications, special dietary requirements and both worming and vaccination status.

2.4 Treatment Product

The treatment product was Promax® manufactured by VetPlus Ltd. The product contains 169500 mg/kg bentonite and Enterococcus faecium (NCIMB 10415) 2 x 10^{11} cfu/kg, together with other gut health aiding ingredients previously described.

Promax® is presented in a convenient, three dose syringe which is designed for direct administration into the dog's mouth.

2.5 Treatment Protocol

Dogs were recruited onto the trial on day 1 if they had a faecal score of 5 or greater which is consistent with diarrhoea. To determine this a faecal scoring system was used: 1=hard, dry and crumbly appearance; 2=dry but well-formed; 3=well-formed slightly moist; 4=wet appearance, beginning to lose shape; 5=soft, shapeless appearance and 6=watery appearance, no shape. Promax® syringe size was chosen based on the dog's weight (< 10kg: Small Breed, 10-25 kg: Medium Breed, >25 kg: Large Breed). There were no problems with palatability or adverse reactions recorded during the trial. Throughout the study the dogs were fed their normal diet.

The first dose of Promax® was given on day 1, with a second dose being administered at a similar time the following day (+/- 6 hours), and the third dose administered on day 3. Daily observations were recorded throughout the three-day trial period. Observations were also recorded on day 4, approximately 24 hours after the final dose of Promax® was administered. Centre staff were advised that an additional syringe of Promax® could be administered on days 4-6 following recording of day 4 observations if so desired.

2.6 Assessment Protocol

Daily observations recorded included faecal scoring (scale of 1=dry to 6=severe diarrhoea), faecal frequency (the number of defecations each day), appetite (poor, fair or good) and behaviour and well-being (scoring system used: 1=lethargic; 2=subdued; 3=restless; 4=normal and 5=high energy).

At the end of the trial a post-treatment questionnaire was completed. This included questions on product ease-of-use and palatability, coprophagy during the trial, suspected/confirmed root cause of diarrhoea and additional treatment required in the absence of diarrhoea resolution.

2.7 Data Handling and Statistics

Numeric data (faecal frequency) was assessed using the paired T-test. All other categoric data (faecal consistency, appetite and health and well-being) were assessed using the Wilcoxin paired signed rank test. A statistically significant result was considered if $p \leq 0.05$ using a two-tailed statistical test design.

3.0 Results

3.1 Faecal Scoring and Consistency

Table 1 shows the distribution of faecal scores throughout the study period and demonstrates a shift towards normalisation of faecal scores as the study progresses.

	Faecal Score			
	Dry/Firm <3	Normal 3 <5	Loose Diarrhoea ≥5	Total
Day 1	**0**	**0**	**29**	**29**
Day 2	**1**	**12**	**16**	**29**
Day 3	**1**	**20**	**8**	**29**
Day 4	**1**	**16**	**3**	**20**

Table 1: Distribution of faecal score results over the 4 day trial period. Days 1-3 n=29; day 4 n=20.

On day 1 median scores across the group were 6, with a score of 4 on day 3 and 3.75 on day 4 (see figure 1). There was a statistically significant reduction in the faecal scores on each day ($p < 0.01$).

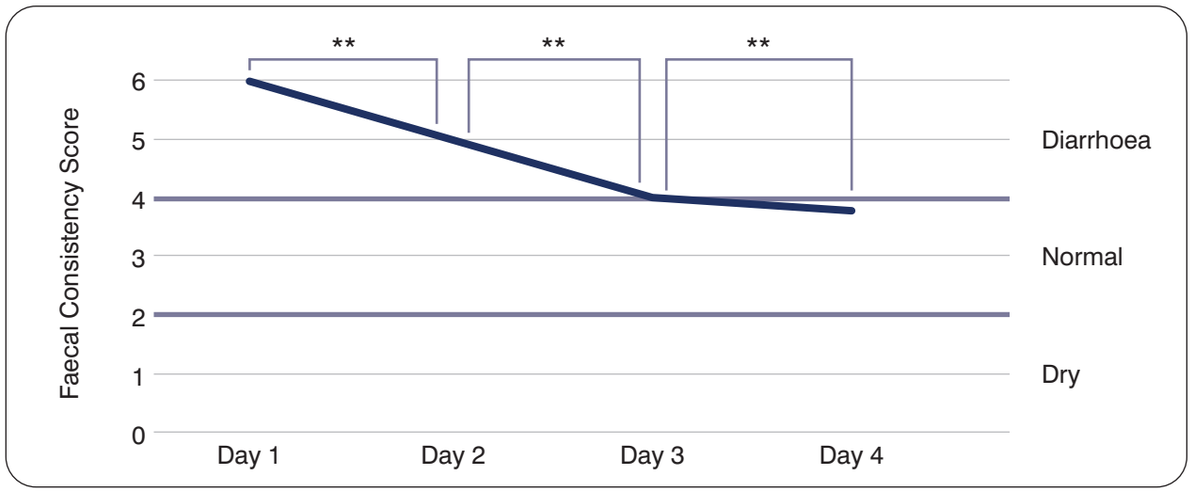

Figure 1: Changes in median faecal consistency over a four day period. Days 1-3 n=29; day 4 n=20. Interquartile ranges for days 1, 2, 3 and 4 are 1.00, 1.00, 1.75 and 1.00 respectively. **P<0.01.

A normal faecal/firm faecal score was classified as a score ≤ 4 with abnormally loose stools more consistent with gastrointestinal disturbance being indicated by scores > 4. Figure 2 shows that on trial day 1 all animals had faecal scores consistent with diarrhoea. By day 2, 38 % of dogs had achieved a normal faecal consistency, which was further increased to 69 % and 85 % on day 3 and 4 respectively.

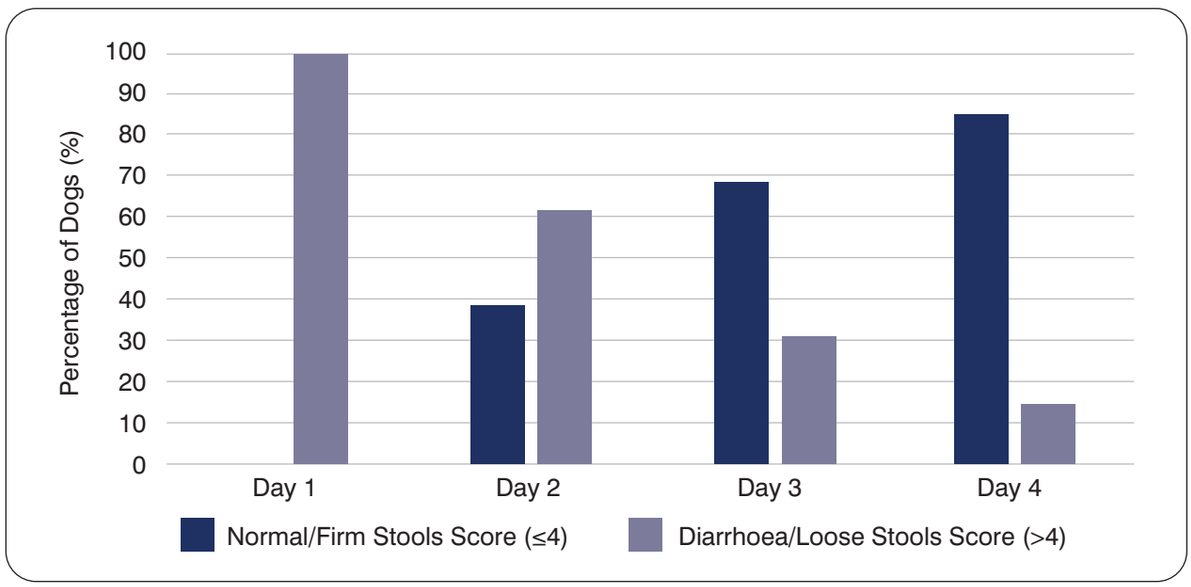

Figure 2: Distribution of normal/firm and diarrhoea/loose faeces over a four day period. Days 1-3 n=29; day 4 n=20.

3.2 Defecation Frequency

Defecation frequency (DF) decreased throughout the trial period from an average of 3.83±0.32 (standard error of the mean) on day 1 to 3.54±0.39 on day 2, 3.03±0.30 on day 3 and 2.47±0.34 on day 4 (Figures 3 and 4). The change in DF from day 1 to day 3 and day 1 to day 4 was statistically significant ($p<0.05$).

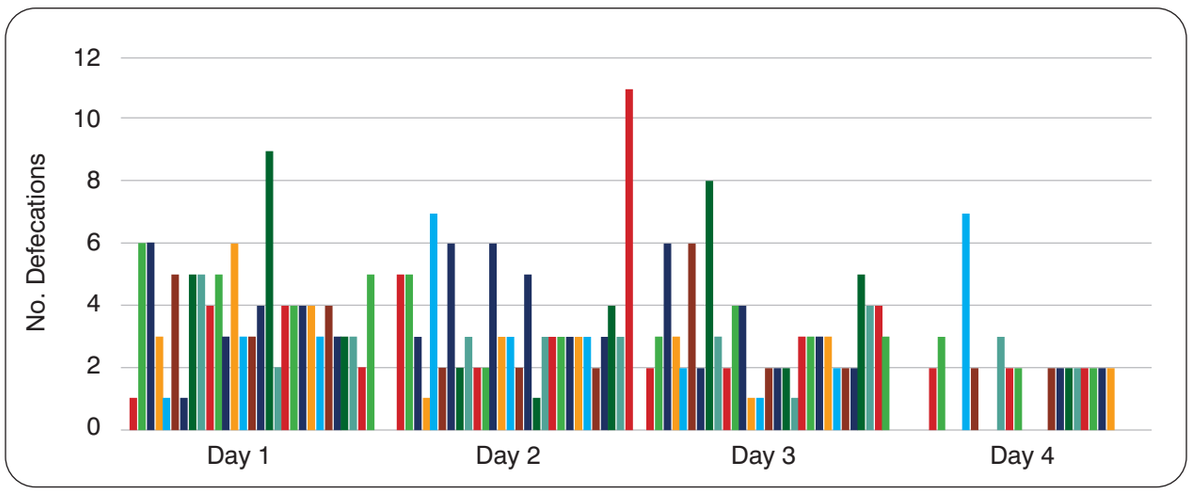

Figure 3: Distribution of the number of defecations in each trial participant over the four day trial period. Days 1 and 3 n=29, day 2 n=28 and day 4 n=15.

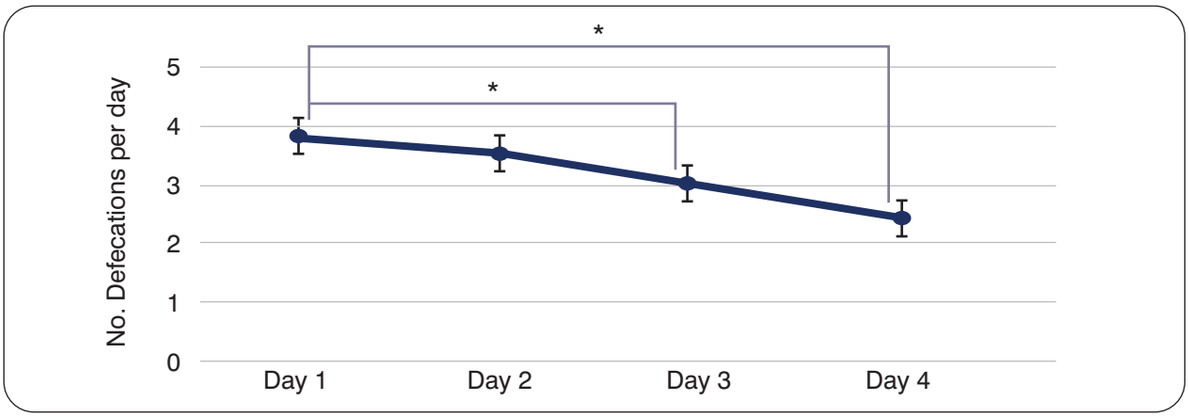

Figure 4: Mean defecation frequency over the four day trial period. * p<0.05.

3.3 Appetite

Appetite was recorded each day as either poor, fair or good. On day 1, 38 % of dogs were scored as having poor appetite. On day 3, only 10 % had a poor appetite and on day 4 this was reduced further to 0 %. The improvement in appetite was statistically significant from day 1 to day 2 and from day 1 to day 3 (p=0.05) and from day 1 to day 4 (p=0.01). Figure 5 shows the split in appetite scores over 4 days.

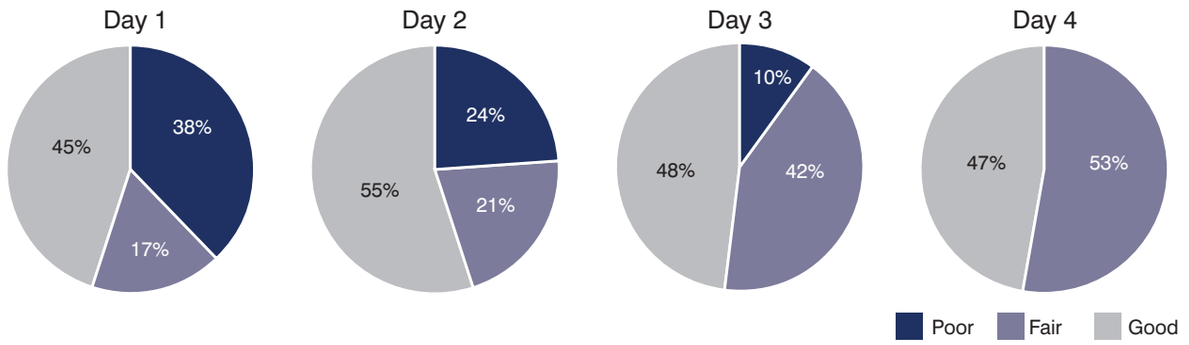

Figure 5: Charts demonstrating the percentage split between poor, fair and good appetite over the four day trial period. Days 1-3 n=29 and Day 4 n=15.

3.4 Health and Well-Being

Table 2 shows the distribution of health and well-being scores throughout the trial. Results were further split into suboptimal behaviour (scores ≤ 3) and average or above behaviour (≥ 4). On day 1, 28 % of dogs were classed as displaying sub-optimal overall health, this was reduced to 14 % and 0 % on days 3 and 4 respectively (Figure 6). There was a significant difference in scores from day 1 to day 4 (p=0.01).

	Health and Well-Being Score			
	1-2	>2 to 3	4-5	Total
Day 1	**1**	**7**	**21**	**29**
Day 2	**1**	**5**	**22**	**28**
Day 3	**1**	**3**	**25**	**29**
Day 4	**0**	**0**	**16**	**16**

Table 2: Distribution of health and well-being score results over the four day trial period. Days 1 and 3 n=29, day 2 n=28 and day 4 n=16.

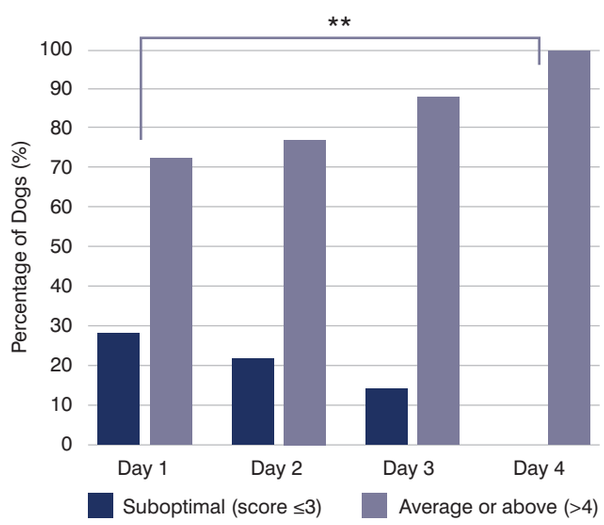

Figure 6: Health and well-being over the 4 day trial period. **p<0.01.

4.0 Discussion

Diarrhoea is an obvious clinical sign of gastrointestinal disturbance and indicates an imbalance of the absorptive and resorptive activities in the gut (Low-Beer and Read, 1971). Results of the faecal scoring show that faecal consistency became firmer throughout the trial period with a statistically significant decline in scores being observed each day. When examining the results in context of resolution of diarrhoea symptoms, data was grouped into those of normal faecal consistency (obtaining a score ≤ 4) and scores descriptive of looser faeces and diarrhoea (>4). On day 1, 100 % of dogs had faecal scores consistent with diarrhoea as expected given the trial enrolment criteria. On day 2, after a single dose of Promax®, 38 % had resolution of diarrhoea symptoms. This was further increased to 69 % on day 3. At the end of the 4-day trial period, 85 % of dogs had resolution of diarrhoea symptoms. It is a common approach in the treatment of diarrhoea in pets that food is either withheld or alternatively the diet is changed to a typically bland meal such as chicken and rice in order to hasten resolution of diarrhoea symptoms (Battersby and Harvey 2006). During this trial, dogs remained on their typical diet throughout. Results therefore suggest that at onset of diarrhoea symptoms, the administration of 3 doses of Promax®, 24 hours apart will be associated with normalisation of faecal consistency and resolution of diarrhoea symptoms within four days for 85 % of cases. Although almost 4 in 10 will expect resolution after a single dose and nearly two thirds after 2 doses without the need to resort to dietary management.

The increase in fluid in the large bowel due to suboptimal absorption of water, results in watery faeces consistent with diarrhoea and pressure build-up (Low-Beer and Read, 1971). This causes an increased urge to defecate, hence resulting in an increase in defecation frequency which can be difficult for pet owners to manage without indoor soiling incidents occurring.

Helping to normalise defecation frequency is therefore a desirable end-point in the treatment of diarrhoea symptoms in pets. There was a statistically significant decrease in defecation frequency from day 1 to day 3, suggesting that frequency is reduced following two doses of Promax®. A further reduction in frequency was seen on day 4, after the full 3 doses of Promax® had been administered and time permitted for the final dose to take effect.

An initial sign of pets being unwell is often a change in typical feeding behaviour and loss of appetite, suggesting pain and discomfort in the animal. Promax® administration was associated with improved appetite scores, with 90 % and 100 % of dogs having a fair or good appetite on day 3 and 4 respectively, compared to only 62 % on day 1. This change in appetite from study start (day 1) to end (day 4) was statistically significant, suggesting that three doses of Promax® helps to improve appetite. It is suggested that this improvement is due to a reduction in the symptoms of diarrhoea and therefore improved gastrointestinal comfort, resulting in normalisation of feeding behaviour, since loss of appetite often accompanies diarrhoea (Leib. 2000).

Similar to humans, pets show changes in their overall demeanour when unwell which can serve as an observational measurement of the pet's overall health and well-being. Over the course of the trial the percentage of animals with a suboptimal score for health and well-being decreased from 28 % on day 1 to 0 % by day 4, suggesting that Promax® can help to improve pet health and well-being.

It should be noted that a placebo group was not used in this study as the animals enrolled were shelter animals under stressful conditions, in animal centres where it was common practice to actively manage animals on the presentation of diarrhoea in order to manage symptoms. Decreasing the prevalence of diarrhoea in animal shelters helps to improve the welfare of animals kept in naturally stressful environments, as well as accelerate their recovery from symptoms. Animals with diarrhoea are likely to be quarantined and exempt from adoption during their convalescence, therefore any hastening in the resolution of the symptoms is in both the individual animal's and the shelter's best interest. It was therefore considered unethical to withhold treatment for certain animals in the chosen sample population. Whilst without a placebo group within the study, we cannot confirm the outcome of these various parameters without treatment, meta-analysis of studies in humans (n=1076) examining the effects of montmorillonite clay in diarrhoea against placebo have shown a significant reduction in diarrhoea duration compared to untreated groups. The reduction was approximately 1 day less for the treatment group (Swajewska *et al.*, 2006). Another study employing a placebo group also demonstrated a reduction in defecation frequency of approximately 20 % after 3 days (Madkour *et al.*, 1993). It may therefore be considered likely that Promax® would produce more favourable clinical outcomes than withholding treatment based on the presence of the clay component alone, although the additional nutraceutical ingredients within the product including probiotics, prebiotics, β-glucans and amino acids are also expected to have additional beneficial effect on gastrointestinal health.

5.0 Conclusion

Diarrhoea in dogs is a common complaint and can be distressing for both owners and the animal. Having an effective option that is easy to administer and works quickly to resolve symptoms is important. Results from this study demonstrate that the administration of Promax® can help resolve the symptoms of diarrhoea including loose faeces, increased defecation frequency, loss of appetite and lethargic behaviour without the requirement for altering the dog's normal diet. If Promax® is administered on day 1 of diarrhoea, the pet owner can expect to see a reduction in defecation frequency by day 3 of treatment.

In 85 % of cases, resolution will occur within 4 days and 3 doses of Promax®, suggesting that there is only a relatively short period of time that the owner will need to manage their pet's diarrhoeal symptoms. The convenience and potential time and cost-saving of the use of Promax® to manage symptoms of canine diarrhoea has been shown in this study.

6.0 Acknowledgements

The authors would like to thank the animal centre staff involved in the trial, including SSPCA centres, Ayrshire and South West Scotland ARRC, Dunbartonshire and West Scotland ARRC, Lanarkshire ARRC, Edinburgh and Lothians ARRC, TR Centre (location undisclosed), the Three Counties Dog Rescue (Bourne) and Easterleigh Animal Sanctuary (Blackpool), whom independently ran the trial and provided independent data for assessment by VetPlus Ltd.

The Scottish SPCA are committed to the care and welfare of animals and routinely use Promax® for the treatment of animals in their care. Therefore the aim of this trial involved the SSPCA looking at the effectiveness of their current nutraceutical treatment regime with Promax®. There was no potential harm to animals during the trial and their welfare was monitored throughout.

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VetPlus Ltd
'Animal House', Boundary Road, Lytham, United Kingdom FY8 5LT.

Customer Services
+44 1253 797 400

Fax
+44 1253 797 409

E-mail
customer.services@vetplus.co.uk

91440