

Efficacy of a commercial hydrolysate diet in eight cats suffering from inflammatory bowel disease or adverse reaction to food

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SUMMARY

Eight of 28 cats presenting with chronic vomiting and/or diarrhoea were diagnosed as suffering from chronic enteropathy. All cats had undergone a complete diagnostic work-up, including endoscopy. Histopathology findings varied from normal, eosinophilic, to lymphoplasmacytic gastroenteritis. On the basis of findings, the cats were diagnosed with inflammatory bowel disease (IBD) or an adverse reaction to food. A hydrolysed protein diet was used as sole therapy, and clinical signs resolved within 4-8 days in all eight cats. After 2 months the cats had gained weight. A challenge trial with their previous diet resulted in recurrence of the clinical signs, which resolved in seven cats when the test diet was reintroduced. We conclude that the hydrolysed protein diet used in the current study was effective in managing these cases.

SAMENVATTING

Effectiviteit van een commercieel hydrolysaatdieet bij acht katten lijdend aan inflammatoire bowel disease (IBD) of voedselovergevoeligheid

Bij acht katten, geselecteerd uit een groep van 28 katten met chronische maagdarmproblemen, werd de diagnose chronische enteropathie gesteld (ten gevolge van hetzij voedselovergevoeligheid dan wel inflammatoire bowel disease (IBD)). Alle katten werden volledig opgewerkt, waarbij een gastroduodenoscopie onderdeel uitmaakte van het klinisch onderzoek. De histopathologie van de maagdarmbiopsieën varieerde van een normale, eosinofiele tot lymfoplasmacytaire gastroenteritis. Op basis van de resultaten van het onderzoek was de diagnose bij deze katten dat ze of leden aan IBD of een voedselovergevoeligheid hadden. Een gehydrolyseerd eiwitdieet werd bij alle katten ingezet. De klinische problemen verdwenen bij alle katten binnen vier tot

acht dagen. Na twee maanden was er een significante gewichtstoename zichtbaar. Na herintroductie van het oude dieet kregen alle katten weer maagdarmproblemen. Bij alle dieren, op een na, herstelde dit weer na herintroductie van het dieet. Wij concluderen dat een gehydrolyseerd eiwitdieet bruikbaar was bij de behandeling van deze maagdarmpatiënten.

INTRODUCTION

The diagnosis and treatment of feline chronic enteropathies can be challenging in clinical practice. While a careful gastrointestinal work-up enables most conditions to be excluded, it can still be difficult to distinguish between inflammatory bowel disease (IBD) and adverse food reactions. For this reason some recent studies have used the more global term of chronic enteropathy (2, 5). Although the results of histopathological investigations may be similar, the advised treatment may be different (10, 13).

Several clinical studies and textbooks advocate the use of antigen-limited diets, but there is limited evidence on the outcome in cases of IBD (6, 7, 10, 13). The majority of antigen-limited diets on the market are single-source protein diets, and many varieties are available. The widespread use of novel protein sources such as fish, rabbit, duck, chicken, and lamb in normal diets has limited their use in antigen-limited diets (13). In human medicine, hydrolysed protein diets were developed to partly overcome this problem (3, 22). Several hydrolysed protein diets have since been developed for veterinary use, but detailed information on their use in IBD and/or food intolerance is limited, although preliminary studies have been promising (4, 18).

A diagnosis of adverse reaction to food requires a trial with an exclusion diet and subsequent challenge with the former diet (12, 13, 17). The diagnosis can only be made if the patient responds to the exclusion diet and if clinical signs return after re-challenge with the original diet. Even so, it remains difficult to differentiate true dietary hypersensitivity from food intolerance. Suggested diagnostic tests for the former include antigen-specific immunoglobulin E (IgE) (9), gastroscopic food sensitivity testing (GFST) (11), and colonoscopic food sensitivity testing (CFST) (1). However, the use of circulating food-specific immunoglobulins is unreliable (7, 13), and both GFST and CFST are of limited use in practice (13). As both intolerance and food hypersensitivity respond in a similar manner to exclusion diets, from a clinical perspective it is usually not necessary to differentiate these conditions. Furthermore, both conditions can usually be successfully treated in the long term by continuing the exclusion diet. The aim of the

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current study was to assess the efficacy of a commercially available hydrolysed protein diet in cats that suffered from either IBD and/or an adverse reaction to food nowadays called chronic enteropathy.

MATERIALS AND METHODS

Cats

All cases were referred to the Veterinary Specialist Centre 'The Wagenrenk' between December 2001 and January 2003. We aimed to recruit a cohort of chronic enteropathy cases similar to that of the study of Guilford et al (12). Accordingly, our inclusion criteria included signs of small intestinal disease (e.g., vomiting, small bowel diarrhoea), and a complete diagnostic investigation (see below), after which the only remaining differential diagnoses were IBD and adverse reaction to food. Further, no cats could have received corticosteroid therapy in the 3 weeks prior to this investigation. A total of 28 cats with consistent signs were seen during this period were eligible for inclusion.

Diagnostic investigations

For all 28 cats, a complete history, physical examination, complete blood count, a serum chemistry profile (urea, creatinine, alkaline phosphatase, total bilirubin, bile acids, calcium, phosphate, total protein, albumin, protein spectrum), feline leukemia virus and feline immunodeficiency virus tests, and urinalysis were performed. In all cats, two separate faecal samples were examined for *Giardia intestinalis*, *Tritrichomonas foetus*, *Cydiclomyces guttulatus*, and nematode parasites (14, 21). The faeces was also examined for digestive enzymes and the presence of fat, starch, and fatty acids; if results were abnormal (e.g., lack of digestive enzymes, food particles present), a serum sample was submitted to the GI Lab, Texas A&M University, for measurement of feline trypsin-like immunoreactivity (20) (at the time of this study the test was not available in the Netherlands). All laboratory tests were conducted either by the referring veterinarian or at the University Laboratory of the Faculty of Veterinary Medicine in Utrecht, the Netherlands. If any abnormality was found, the cat was excluded from the study. Survey abdominal radiography and abdominal ultrasonography were also performed in all cats younger than 2 years of age in which the abdominal palpation revealed abnormalities or in those animals in which the history was suggestive of a foreign body.

Three cats were excluded: one appeared to be suffering from chronic kidney disease, and two had palpable abnormalities in their abdominal cavity. Endoscopy was performed in the remaining 25 cats to exclude disease (e.g., foreign body, ulcer, neoplasm, hyperacidity, pyloric stenosis) and also to obtain tissue samples for histopathological examination. All biopsies were examined by a European board-certified pathologist. A further nine cats were excluded (five with lymphoma, two with a foreign body, one with a pyloric stenosis, and one with a duodenal tumour), leaving 16 cats with chronic gastrointestinal signs for which no other diagnosis could be made than

possible adverse reaction to food or IBD. The owners of eight cats agreed to participate in the study.

Diet

The test diet used was a commercially available diet containing hydrolysed soy protein (Table 1).

Statistics

Statistical evaluation was carried out using a computer software package (Statistix 8.0 for windows, Analytical Software, P.O. Box 12185, Tallahassee, FL 32317-2185, USA). Descriptive statistics were used to describe general data. The weight data were confirmed to be of normal distribution with a Shapiro-Wilk test and, as a consequence, a paired T-test was used to evaluate the change in weight. The level of significance was set at $P < 0.05$.

RESULTS

Cats

Six European shorthairs and two Siamese cats were included in the study. All cats were castrated males, and most were younger than 3 years (median 2.4 years, range 0.7 to 7.8 years). At first presentation, clinical signs had been present for at least 4 months (Table 2).

Presenting Signs

The median duration of signs was 6 months (range 4 to 36 months). One cat was also suffering from a linear granuloma on the ventral abdominal skin, and one cat had been diagnosed with exocrine pancreatic insufficiency (EPI) 2 years previously. Although this cat had been stable for 18 months, watery diarrhoea had developed 6 months prior to referral. Weight loss was observed in four of eight cats (median 0.2, range 0.0 to 1.5 kg). At the time of the first presentation, the cats had a mean weight of 3.6 kg (median 3.8, range 2.5 to 5.0 kg).

Treatments and investigations

All cats had received a variety of drugs prescribed by the referring veterinarian, including pancreatic enzymes, metronidazole, amoxicillin-clavulanate, trimethoprim-sulfa, cimetidine, and prednisolone as well as standard anthelmintic treatment. Six cats had also been switched to new diets, some of which were marketed as "novel protein". In two cats the diet had not yet been changed.

Hypoallergenic DR 21*

Main ingredients:

Soy protein isolate hydrolysate
Rice
Chicken fat
Fish oil
Soy and borage oil
Poultry liver hydrolysate
Beet pulp, FOS (fructo-oligosaccharide)

Royal Canin, Veterinary diet, Aimargues (France)

Table 1.

Endoscopy was unremarkable in all cats, except for a slightly increased tendency to bleed from the biopsied areas. Histopathological diagnoses included mild non-specific gastritis (n=2) and severe eosinophilic gastritis (n=1), non-specific enteritis (n=1), mild (n=1), moderate (n=3), and severe (n=1) eosinophilic enteritis, and mild lymphoplasmacytic enteritis (n=1); one cat showed no significant abnormalities in the gut. One cat, with moderate eosinophilic enteritis, also had villus atrophy. Lesional skin biopsies were taken from the cat presenting with the linear granuloma and, as expected, the diagnosis was an eosinophilic granuloma.

Outcome

All cats responded to the test diet, six within 4 days, and the remaining two after 7 and 8 days, respectively. No other treatments were given during this time. After 2 months of

dietary management, six cats were free of clinical signs, while two cats had vomited occasionally on a fortnightly basis. At this stage, the median weight of the cats was 4.6 kg (range 2.5-6.0 kg); this represented a significant increase from their weight prior to starting the diet (median 21%, range 0-43%; $P=0.0079$). The difference remained significant when the youngest cat (a growing cat) was excluded from the analysis ($P=0.015$). When cats were challenged with their former diet, gastrointestinal signs reappeared within 2 weeks. Return to the hydrolysed protein diet led to resolution of clinical signs (within 1 week) in all but one of the cats. Unfortunately, the cat was euthanized by the referring veterinarian before further investigations could be performed. Gastrointestinal signs resolved in the cat with the eosinophilic granuloma, but the granuloma did not. The cat subsequently received prednisolone¹ (1 mg/kg bodyweight once daily) and the lesion resolved completely.

A follow-up assessment was performed a median 308 days (range 112 to 509 days) after the start of this study. All

1 Prednoral® AST Farma

Cat	Breed	Age (years)	Signs at presentation	Weight Loss?	Duration of signs	Other diets tested (months)	Histopathology	Response after 2 months of diet	Weight before illness	Weight at referral	Weight at end	Difference in weight ¹
1	ESH ²	3.3	Watery diarrhoea (daily), fresh blood and mucus on stool.	Unknown	36	Novel protein (Lamb-rice)	Mild superficial gastritis	All signs resolved	4.0	4.0	4.9	0.9 (22)
2	ESH	1.6	Watery diarrhoea (daily), fresh blood and mucus on stool. Pale coloured stool.	Yes	6	Novel protein (Lamb-rice)	Moderate eosinophilic enteritis, villus atrophy	Once every 2 weeks vomiting. Pale coloured stool.	3.5	2.5	3.0	0.5 (20)
3	ESH	1.6	Diarrhoea and vomiting (daily), fresh blood and mucus on stool.	Yes	6	Other diets (R/D)	Moderate eosinophilic enteritis	Once every 2 weeks vomiting.	4.1	2.6	3.4	0.8 (31)
4	ESH	7.8	Vomiting (every week), linear granuloma	No	18	None	Severe eosinophilic gastroenteritis. Skin: eosinophilic granuloma	All gastrointestinal signs resolved; No response of skin problem	5.0	5.0	5.0	0 (0)
5	ESH	3.5	Watery diarrhoea, fresh blood on stool	No	4	None	Non-specific Enteritis (mild)	All signs resolved	4.0	4.0	4.0	0 (0)
6	ESH	0.7	Soft faeces (daily)	No	4	Other diets (Whiskas)	Mild eosinophilic enteritis	All signs resolved	3.5	3.5	5.0	1.5 (43)
7	Siamese	1.1	Vomiting (every 2 days), diarrhoea (daily), bloating.	Yes	18	Novel protein (Lamb-rice)	Mononuclear gastritis, Moderate eosinophilic enteritis	All signs resolved	4.0	3.5	4.5	1.0 (29)
8	Siamese	6.2	Watery diarrhoea (daily), abdominal/faecal pain, bloating.	Yes	6	Novel protein (Rabbit-rice)	Mild lymphoplasmacytic enteritis	All signs resolved	4.5	4.0	4.5	0.5 (12)

Table 2.

1 Difference in weight expressed in kilograms with percentage in brackets.

2 ESH = European shorthair.

cats were still on the diet, free of clinical signs, and (except for the one cat receiving prednisolone) receiving no other medication.

DISCUSSION

The current study, although preliminary in nature, demonstrated the efficacy of a hydrolysed protein diet for the management of clinical signs in these cats with chronic enteropathy (2, 5). This is the first study to examine the benefits of such diets for feline gastrointestinal disease and, as such, expands upon the recent studies using similar diets in dogs (4, 18, 19).

The study had some limitations. The owners of only 8 of 16 potentially eligible cats agreed to participate in this study, and this might have introduced some bias. The cats that were not enrolled might have been more severely affected and hence less likely to respond, leading to overestimation of the response rate. However, we did not find statistically significant differences in age, weight, sex, or histopathological findings (data not shown), which makes it less likely that selection bias influenced the outcome of the study. A further limitation is the fact that one of the cats that responded was under a year of age, and it is possible that the weight gain noted was a consequence of growth rather than of improvement in the disease process. However, the weight gain seen in the participating cats remained significant even after the data for this young cat were excluded, making it unlikely that this cat unduly influenced the results.

On the basis of the diagnostic work-up, we could not conclude whether these cats were suffering from an adverse reaction to food or IBD. The current definition of IBD is: 1) chronic (> 3 weeks) persistent or recurrent gastrointestinal signs; 2) histopathological evidence of mucosal inflammation; 3) inability to document other causes of gastrointestinal inflammation; 4) inadequate response to dietary, antibiotic, and anthelmintic therapies alone; and 5) clinical response to anti-inflammatory or immunosuppressive agents (23). On the basis of this definition, seven cats had a possible adverse reaction to food and one cat had IBD. Whether the above definition is correct is under debate. Histopathology by itself is not enough to diagnose IBD (16), because similar histopathological changes can be seen in completely different disorders (8). Moreover, although an inadequate response to antibiotics is part of the definition of IBD, antibiotics were used to treat IBD in another study by the same authors, which seems to undermine the definition (15). For this reason some recent studies have used the more global term chronic enteropathy (2, 4).

Five of eight cats showed histopathological changes suggestive of IBD, but four of the cats responded well to the diet. If we use the definition proposed by Washabau et al (23), these four cats would be considered to suffer from an adverse reaction to food rather than IBD. However, six of the eight cats had already been put on a novel protein diet and none had responded at that time. This, perhaps, suggests that hydrolysed protein diets may be more effective in managing chronic gastrointestinal disease in

cats than single-source protein diets. Whether this suggests that the hydrolysed diet can be beneficial in IBD, is not clear and, indeed, in a recent study 80 dogs with IBD were described and all dogs responded poorly to an exclusion diet trial (6). Nonetheless, the diet did not contain protein hydrolysates as a protein source. Further studies, which ideally would be randomised controlled therapeutic trial, are now recommended to determine the true efficacy of these diets.

In conclusion, the current study examined the efficacy of a hydrolysed protein diet for the management of eight cats with chronic enteropathy. All cats responded well to the diet, suggesting that these diets may be effective in helping manage cases of feline chronic enteropathy.

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CONFLICT OF INTEREST STATEMENT

Royal Canin manufactured the diet used in this study. Vincent Biourge is an employee of Royal Canin, and this company also financially supports the senior lectureship of A.J. German. However this study was not supported financially by Royal Canin.

REFERENCES

- Allenspach K, Rufenacht S, Sauter S, Grone A, Steffan J, Strehlau G, et al. Pharmacokinetics and clinical efficacy of cyclosporine treatment of dogs with steroid-refractory inflammatory bowel disease. *J Vet Intern Med* 2006; Mar 20 (2): 239-244.
- Allenspach et al. Chronic enteropathies in dogs: evaluation of risk factors for a negative outcome. *J Vet Intern* 2007; 21; 700-708.
- Berg A von, Koletzko S, Grubl A, Filipiak-Pittroff B, Wichmann HE, Bauer CP, et al. The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention Study, a randomized double-blind trial. *J Allergy Clin Immunol* 2003; Mar 111 (3): 533-540.
- Biourge VC, Fontaine J and Vroom MW. Diagnosis of adverse reactions to food in dogs: efficacy of a soy-isolate hydrolyzate-based diet. *J Nutr* 2004; Aug 134 (8 Suppl): 2062S-2064S.
- Burgener IA, König A, Allenspach K, et al. Upregulation of toll-like receptors in chronic enteropathies in dogs. *J Vet Intern Med* 2008; 22: 553-560.
- Craven M, Simpson JW, Ridyard AE and Chandler ML. Canine inflammatory bowel disease: retrospective analysis of diagnosis and outcome in 80 cases (1995-2002). *J Small Anim Pract* 2004; Jul 45 (7): 336-342.
- Day MJ. The canine model of dietary hypersensitivity. *Proc Nutr Soc* 2005; Nov 64 (4): 458-464.
- Day MJ, Bilzer T, Mansell J, Wilcock B, Hall EJ, Jergens A, et al. Histopathological standards for the diagnosis of gastrointestinal inflammation in endoscopic biopsy samples from the dog and cat: a report from the World Small Animal Veterinary Association Gastrointestinal Standardization Group. *J Comp Pathol* 2008; Feb 138 Suppl 1: S1-S43.
- Foster AP, Knowles TG, Moore AH, Cousins PD, Day MJ and Hall EJ. Serum IgE and IgG responses to food antigens in normal and atopic dogs, and dogs with gastrointestinal disease. *Vet Immunol Immunopathol* 2003; May 12 92 (3-4): 113-124.
- German AJ, Hall EJ and Day MJ. Chronic intestinal inflammation and intestinal disease in dogs. *J Vet Intern Med* 2003 Jan; 17 (1): 8-20.
- Guilford WG, Strombeck DR, Rogers Q, Frick OL and Lawoko C. Development of gastroscopic food sensitivity testing in dogs. *J Vet*

- Intern Med 1994; Nov 8 (6): 414-422.
12. Guilford WG, Jones BR, Markwell PJ, Arthur DG, Collett MG and Harte JG. Food sensitivity in cats with chronic idiopathic gastrointestinal problems. *J Vet Intern Med* 2001; Jan 15 (1): 7-13.
 13. Hall EJ. Dietary sensitivity. In: Bonagura JD, editor. *Kirk's Current Veterinary Therapy XIII*. XIII ed. Philadelphia: WB Saunders; 2000: p. 632-637.
 14. Houwers DJ and Blankenstein B. *Cyniclomycetes guttulatus* and diarrhea in dogs. *Tijdschr Diergeneeskd* 2001; Jul 15 126 (14-15): 502.
 15. Jergens AE, Crandell J, Morrison JA, Deitz K, Pressel M, Ackermann M, et al. Comparison of oral prednisone and prednisone combined with metronidazole for induction therapy of canine inflammatory bowel disease: a randomized-controlled trial. *J Vet Intern Med* 2010; Mar 24(2): 269-277.
 16. Jergens AE, Crandell JM, Evans R, Ackermann M, Miles KG and Wang C. A Clinical Index for Disease Activity in Cats with Chronic Enteropathy. *J Vet Intern Med* 2010; Jun 24.
 17. Leistra M and Willemse T. Double-blind evaluation of two commercial hypoallergenic diets in cats with adverse food reactions. *J Feline Med Surg* 2002; Dec 4 (4): 185-188.
 18. Loeffler A, Lloyd DH, Bond R, Kim JY and Pfeiffer DU. Dietary trials with a commercial chicken hydrolysate diet in 63 pruritic dogs. *Vet Rec* 2004; 154: 519-522.
 19. Mandigers PJJ and Biourge V. Efficacy of a Soy Hydrolysate Based diet in the management of chronic Canine Gastroenteritis: A controlled Study. *Symposium of the ESVCN* 2004; 8 (8): 128-129.
 20. Steiner JM and Williams DA. Serum feline trypsin-like immunoreactivity in cats with exocrine pancreatic insufficiency. *J Vet Intern Med* 2000; Nov 14 (6): 627-629.
 21. Tolbert MK and Gookin J. *Trichostrongylus axei*: A New Agent of Feline Diarrhea. *Compend Contin Educ Vet* 2009; 31 (8): 374-381.
 22. Walker-Smith J. Hypoallergenic formulas: are they really hypoallergenic? *Ann Allergy Asthma Immunol* 2003; Jun 90 (6 Suppl 3): 112-114.
 23. Washabau RJ, Day MJ, Willard MD, Hall EJ, Jergens AE, Mansell J, et al. Endoscopic, biopsy, and histopathologic guidelines for the evaluation of gastrointestinal inflammation in companion animals. *J Vet Intern Med* 2010; Jan 24 (1): 10-26.

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