

Evaluation of selected-protein-source diets for management of dogs with adverse reactions to foods

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Objective—To evaluate 3 commercially available selected-protein-source diets as maintenance diets in dogs with pruritus caused by adverse food reactions.

Design—Randomized crossover trial.

Animals—40 dogs > 6 months of age with pruritus caused by adverse reactions to foods.

Procedure—Diagnosis was confirmed by use of diet elimination and provocation studies. Subsequently, dogs were fed 3 commercial diets for 3 weeks each in a randomized, blinded, crossover trial. Dogs were evaluated for pruritus, vomiting, diarrhea, and flatulence.

Results—Pruritus recurred in 52.5% of dogs fed a chicken-rice diet, 47.5% of dogs fed a catfish-rice diet, and 85% of dogs fed a venison-rice diet. Overall, 95% of the dogs could be managed successfully with at least 1 of the 3 diets.

Conclusions and Clinical Relevance—Results indicated that commercially available limited-allergen diets with selected protein sources may be appropriate for long-term management of pruritus caused by adverse food reactions. Testing of various protein sources is usually required. (*J Am Vet Med Assoc* 2001;219:1411–1414)

Adverse reactions to foods are unwanted and unpredictable reactions to dietary allergens. An adverse reaction to dietary ingredients is classified into 1 of 2 categories: food allergy or food intolerance. Food allergy is an immunologically based reaction to food components. Type I, III, and IV hypersensitivity reactions have been associated with food allergies.^{1,2} Immune complex formation, complement deposition, and cell-mediated immune reactions have been documented in food allergies, particularly food protein enteropathies.³ Delayed responses develop within several hours to days.⁴

Food intolerance is a nonimmunologic adverse reaction to food.^{1–3} Most food-sensitive dogs have either dermatologic or gastrointestinal tract signs. Dietary allergens are usually water-soluble glycoproteins that are stable despite heating, acids, or digestive enzymes.⁵ These allergens are usually present in a basic food ingredient, including beef, chicken, pork, horse, lamb,

fish, egg, milk, rice, wheat, oatmeal, corn, and soy.^{6,7} Commonly, exposure to food allergens occurs in the gastrointestinal tract where the allergens pass through the epithelium and enter the circulatory system, but exposure may also occur through skin contact and inhalation.⁵ These resistant proteins remain immunologically active.

Oral tolerance is failure of the immune system to respond to systemic challenge with an antigen to which it has been previously exposed via the intestine.⁸ The mechanism is poorly defined but depends upon the dose of antigen and may involve induction of antigen-specific suppressor T cells that produce transforming growth factor β and may migrate from intestine to peripheral locations. This population may be CD8⁺ or a subset of CD4⁺ cells (Th3 cells), and $\gamma\delta$ T cells may have a role in their induction, induction of clonal anergy, deletion of antigen-specific lymphocytes by apoptosis in mucosa-associated lymphoid tissue, and a shift in the Th2/Th1 immunoregulatory balance. Loss of integrity of the gastric or intestinal mucosa (eg, because of endoparasites or lack of normal intestinal microflora) may inhibit development of oral tolerance.^{8–10}

Dermatologic signs are most frequently reported, but gastrointestinal tract, respiratory tract, and neurologic signs (malaise and seizures) may also develop.^{2,4,6} In 10 to 15% of dogs with skin problems caused by adverse food reactions, concurrent gastrointestinal tract signs have been reported.^{6,11} Dogs with an adverse reaction to food initially develop a nonseasonal pruritic dermatitis.¹² Occasionally, episodic or seasonal patterns have been noticed. The severity of the pruritus is variable, and it may be regional or generalized.⁴ The distribution of the clinical signs is often indistinguishable from that of atopy; the face, feet, axillae, perineal region, inguinal region, gluteal region, and ears may be variably affected.^{12,13} A unilateral or bilateral otitis externa may develop in absence of other clinical signs.⁴

A wide variety of skin lesions may develop in food-sensitive dogs. These include papules, pustules, plaques, wheals, angioedema, erythema, ulcers, excoriation, lichenification, alopecia, scales, crusts, hyperpigmentation, and moist erosions that appear as areas of pyotraumatic dermatitis.¹⁴

No breed or sex predilections have been established for adverse reactions to foods.^{12,14} In general there is no age predisposition, but results of several studies indicate that clinical signs often appear at < 1 year of age,^{4,14} with a range of 2 months to 14 years of age.^{7,14–16} Diagnosis of adverse reactions to foods is based on history, physical examination, and dietary

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investigation, using elimination diets and challenge meals.^{6,13} In vitro serum testing and intradermal testing are helpful as aids to diagnosis in human patients but are unreliable in dogs.^{6,12,16}

In 1 study,¹ 54% of dogs with adverse reactions to foods that improved with a home-cooked elimination diet of lamb and rice developed exacerbation of clinical signs after substitution of commercially available limited-allergen diets; therefore, home-prepared diets have been recommended for diagnosis. The ingredients in the elimination diet should be selected on the basis of the individual dog's history, and it may be necessary to feed the diet for 3 to 13 weeks to achieve complete resolution of clinical signs.^{14,17} The diagnosis is confirmed by challenge with components of the original diet until signs recur, which may take 10 to 14 days, followed by resolution of clinical signs during a second feeding period with the elimination diet.¹⁴ No other foods are permitted during the test period. If other medication is required, it should be nonflavored. After the diagnosis has been confirmed, a commercially available limited-allergen diet with selected protein sources must be used for maintenance.¹⁶

The purpose of the study reported here was to evaluate 3 commercially available selected-protein-source diets as maintenance diets in dogs with dermatologic manifestations of adverse food reactions.

Materials and Methods

Fifty-one dogs referred to the Utrecht University Department of Clinical Sciences of Companion Animals with persistent nonseasonal pruritus were considered for inclusion in the study. A thorough medical history was obtained for each dog, and a general physical and dermatologic examination was conducted. Only dogs older than 6 months were included. Infectious causes of pruritus were excluded by use of routine methods, and a rigorous flea-control program with adulticidal drugs and insect growth regulators was continued throughout the study in order to avoid pruritus attributable to fleas.

An adverse reaction to food was confirmed by use of dietary elimination and challenge studies. A home-cooked elimination diet was used for this process, with the ingredients selected on the basis of each dog's dietary history. The meats used included turkey and goat and occasionally lamb or fish and were mixed with either cooked pasta or rice. The elimination diet was fed for 6 to 10 weeks pending cessation of pruritus, followed by challenge with the original diet for a maximum of 3 weeks. If pruritus recurred during the challenge, the elimination diet was again fed to the dog until clinical signs of pruritus resolved. No other foods were permitted during the elimination-challenge period except tap water. Those dogs with no pruritus after the first and second elimination diet and a relapse during the challenge period were considered to have adverse food reactions.

Informed consent was obtained from owners of dogs with confirmed food sensitivity prior to entry into the trial. Dogs entered the trial only when free of pruritus. The dogs were sequentially challenged with 3 commercial diets^{a-c} with protein and carbohydrate sources limited to chicken and rice (canned), venison and rice (canned), or catfish and rice (dry food; Table 1). Each diet was fed for 3 weeks. The order in which the diets were offered was randomized, and the diets were coded and dispensed by the faculty pharmacist so that dog owners and clinicians were unaware of the diet each dog received. The amount of food offered to each dog was calcu-

Table 1—Nutrient content of 3 commercial selected-protein-source diets fed to 40 dogs with confirmed adverse reactions to food

| Nutrient* | Diet | | |
|---------------------------------|--------------|--------------|--------------|
| | Chicken-rice | Venison-rice | Catfish-rice |
| Protein (g/MJ) | 15.7 | 22.9 | 17.0 |
| Fat (g/MJ) | 13.3 | 10.9 | 5.8 |
| Ash (g/MJ) | 4.1 | 4.8 | 5.8 |
| NFE (g/MJ) | 14.2 | 17.3 | 34.4 |
| Calcium (g/MJ) | 0.56 | 0.66 | 0.87 |
| Phosphorus (g/MJ) | 0.46 | 0.60 | 0.79 |
| Zinc (mg/MJ) | 4.4 | 7.6 | 6.9 |
| Linoleic acid (g/MJ) | 2.30 | 0.67 | 1.61 |
| α -Linolenic acid (g/MJ) | 0.17 | 0.14 | 0.06 |
| Arachidonic acid (g/MJ) | 0.11 | 0.16 | 0.02 |
| Eicosapentaenoic acid (g/MJ) | 0.01 | 0.06 | < 0.01 |
| Total n-6 PUFA (g/MJ) | 2.42 | 0.85 | 1.64 |
| Total n-3 PUFA (g/MJ) | 0.23 | 0.23 | 0.07 |
| n-6 PUFA:n-3 PUFA | 10.52 | 3.70 | 23.43 |
| Energy (MJ/100 g) | 0.59 | 0.50 | 1.38 |

*Typical analysis is represented, except for polyunsaturated fatty acids (PUFA), for which values were determined on the basis of analysis of 1 batch of each diet.
NFE = Nitrogen-free extract. MJ = Megajoule.

lated by use of the estimated energy requirement necessary to maintain body weight ($\text{kcal/d} = 110 \times \text{body weight [kg]}^{0.75}$).

A general physical and dermatologic examination was performed by a clinician at the beginning and end of each phase of the trial. Information on alterations in fecal consistency (normal or abnormal [consistency and frequency of defecation]), flatulence (frequency), vomiting (frequency), and apparent diet palatability (excellent, good, moderate, or poor) were sought from the owner and scored on a daily basis. If pruritus developed after introduction of a test diet, the next test diet was introduced only if pruritus was again alleviated by feeding the home-cooked diet. At the completion of the trial and after evaluation of the data, the diets were decoded.

Results

Forty of the 51 dogs met inclusion criteria. Pruritus resolved in 11 of the 51 dogs when fed the elimination diet but did not recur when they were fed their previous diet during the 3-week challenge period. Sixteen of the 40 dogs were male, and 24 were female.

A wide variety of breeds were represented, with none considered to be overrepresented in comparison to the hospital population. Age at onset of pruritus varied from 7 weeks to 8 years, and 21 (53%) dogs were < 1 year of age.

Locations of pruritic regions at the time of referral varied and were detected in various combinations: limbs ($n = 20$ dogs), gluteal region (caudal back-perineum-tailhead [13]), abdomen (10), back (8), inguinal area (8), head (6), ears (6), axillae (5), thorax (4), flanks (3), and scrotum-vulva (2). Generalized pruritus was detected in 8 dogs. In only 1 dog was a single location (scrotum) affected. Six dogs had a history of concurrent pruritus and gastrointestinal tract signs, and 1 dog had a history of concurrent pruritus and sneezing.

Nineteen (47.5%) dogs had an excellent response after being fed the elimination diet for a 6-week period. Twenty-one (52.5%) dogs required a longer period (6 to 10 weeks) to attain the same degree of improve-

Table 2—No. of dogs with clinical signs after challenge with 3 commercial selected-protein-source diets in 40 dogs with confirmed adverse reactions to food

| Clinical sign | Diet | | |
|---------------|--------------|--------------|--------------|
| | Chicken-rice | Catfish-rice | Venison-rice |
| Pruritus | 21 | 19 | 34 |
| Vomiting | 0 | 1 | 3 |
| Flatulence | 5 | 2 | 10 |
| Diarrhea | 6 | 3 | 8 |

Table 3—No. of dogs that developed pruritus in various time periods among 40 food sensitive dogs that were fed 3 selected-protein-source diets

| Diet | Time period (d) | | | |
|--------------|-----------------|-----|------|-------|
| | ≤ 1 | 2-7 | 8-14 | 15-21 |
| Chicken-rice | 2 | 9 | 9 | 1 |
| Catfish-rice | 1 | 10 | 8 | 0 |
| Venison-rice | 2 | 14 | 18 | 0 |

ment. Time required for a subsequent recurrence of clinical signs during challenge with the original food varied between 1 day and 3 weeks; 3 dogs had recurrence of pruritus within 1 day, 24 dogs had recurrence in 2 to 7 days, 11 dogs had recurrence in 8 to 14 days, and 2 dogs had recurrence in 15 to 21 days. Cessation of pruritus occurred between 6 and 28 days after resubstitution of the elimination diet.

Recurrence of pruritus with feeding of the 3 selected-protein-source test diets varied, with recurrences detected in 47.5 to 85% of the dogs, depending on the protein source (Table 2). Relapse developed within 1 to 21 days independent of the protein source (Table 3). Pruritus recurred in association with feeding only 1 test diet in 30 of 40 dogs and in association with feeding 2 of the 3 diets in 8 dogs. Palatability was judged to be good to excellent for all 3 diets, and the body weight of all dogs was maintained during the trial. At follow-up 6 months after finishing the study, all dogs were still doing well on the chosen maintenance diet.

Discussion

Forty of 51 (78%) dogs considered for inclusion were confirmed as food-sensitive by use of dietary challenge studies. This apparently high prevalence among a group of dogs with nonseasonal pruritus probably reflects a degree of selection bias prior to referral of the dogs. It is unclear why the remaining 11 dogs had improvement in pruritus while receiving the elimination diet without recrudescence when rechallenged with their original diets. Similar observations have been made in a study¹⁸ of cats that received a commercial diet with selected protein sources. It is possible that the dietary histories of these dogs were incomplete, and thus they were not challenged with the food item to which they were sensitive. Alternative explanations are that they may have recovered spontaneously or that another feature of the elimination diet may have helped recovery.

These commercial diets are not a viable alternative to a home-cooked elimination diet for the diagnosis of food sensitivity. It is apparent that no single diet could fulfill this role. Even sequential testing with all 3 diets

would not have been as effective as use of home-cooked diets, because only 38 of 40 (95%) food-sensitive dogs would have been identified.

The purpose of this study was to establish whether most dogs with confirmed dietary sensitivity could be managed successfully with 1 of 3 commercially available selected-protein-source diets; this goal was achieved in 95% of the dogs. Challenge with the test diets resulted in recurrence of pruritus in 73 of 120 instances (3 diets tested in 40 dogs) within 14 days; only in 1 instance was recurrence of pruritus detected after 15 to 21 days. For this reason, and because recurrence of pruritus did not develop in any of the dogs during a 6-month follow-up period during which they were fed a maintenance diet, a challenge period of 3 weeks seems adequate.

Apart from pruritus, challenge diets caused gastrointestinal tract signs in 32 to 62% of the dogs. It is of interest that these percentages are substantially higher than expected, because only 6 of the 40 (15%) dogs originally had gastrointestinal tract signs in addition to pruritus. An explanation for this observation was not apparent.

The chicken and rice diet was tolerated by nearly as many dogs as the catfish and rice diet was (19 vs 21, respectively), despite the latter representing a novel protein source for all of the dogs. The limited number of dogs that tolerated the venison and rice diet was surprising, given that this was also a novel protein source for all tested dogs. Sensitivity to commercial diets based on the same ingredients as home-prepared diets has been noted in 3 studies.¹⁸⁻²⁰ Suggested explanations for these results included leaching of metal from the can or that heat treatment may alter the antigenicity of the proteins in the diet. Neither of these explanations appears likely to account for the observations in the study reported here, unless the effects are specific to certain protein sources (ie, venison). It has also been suggested that additives in commercial foods may be responsible for dietary sensitivities in companion animals; however, documented cases are extremely rare. Additives are also unlikely to have accounted for the small number of dogs that were tolerant of the venison and rice diet, because only minerals and vitamins were added, and these were added to the other diets as well. Immunologic cross-reactivity of venison proteins with other unidentified allergens in the dogs' original food is another explanation for the recurrence of pruritus associated with the venison diet.

Another difference between the chicken and venison diets was the polyunsaturated fatty acid (PUFA) content (Table 1). The competition between the long-chain PUFA, arachidonic acid (AA [n-6 PUFA]) and eicosapentaenoic acid (EPA [n-3 PUFA]), determines incorporation into cell membranes. Hence, cell structure and function can be influenced by the PUFA type and content in the diet.^{21,22} Arachidonic acid metabolites such as prostaglandins and leukotrienes are believed to function as primary mediators of hypersensitivity and inflammatory reactions. In addition to this direct competitive effect, the metabolic products of the actions of cyclooxygenase and lipoxygenase on

EPA are considered less pro-inflammatory than the products of AA metabolism.²³

It appears unlikely, however, that the n-3 PUFA contents of these diets accounted for the differences in tolerance observed in this study, because the chicken- and venison-based diets had similar total n-3 content, most of which was derived from α -linolenic acid. Indeed, the 2 varieties (chicken and catfish) with the higher n-6 PUFA content and the highest n-6 to n-3 ratio were the most efficacious in this study. Results of a study²⁴ in dogs indicate that decreased inflammation may be expected with use of diets with n-6 to n-3 ratios between 5:1 and 20:1 because of lower concentrations of pro-inflammatory mediators. For the chicken and rice diet, our observations were in accordance with the latter study, but the n-6 to n-3 ratio of the venison-based diet was in contrast to those findings.

Results of the study reported here indicate that commercial limited-allergen diets with selected protein sources may be appropriate for at least 6 months and may be useful for long-term management of pruritus caused by adverse food reactions. Testing of various protein sources is usually required.

^aWaltham veterinary diet, Pedigree selected protein: chicken and rice, Waltham, UK.

^bWaltham veterinary diet, Pedigree selected protein: venison and rice, Waltham, UK.

^cWaltham veterinary diet, Pedigree selected protein: catfish and rice, Waltham, UK.

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