

# Can Gluten Sensitivity Be a Multisystem Disorder?

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## In the Literature

Lowrie M, Hadjivassiliou M, Sanders DS, Garden OA. A presumptive case of gluten sensitivity in a border collie: a multisystem disorder? *Vet Rec.* 2016;179(22):573.

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## FROM THE PAGE ...

Gluten-free diets and celiac disease have garnered widespread attention in human medicine. Whereas celiac disease is generally associated with GI signs, gluten-related disorders (GRDs) affecting multiple body systems in humans have been described.<sup>1</sup>

Celiac and several other GRDs occur due to immune-mediated intolerance to proteins in gluten; the mechanism behind nonceliac gluten sensitivity has not been determined.<sup>2</sup> Gluten intolerances similar to celiac disease have been described in Irish setters.<sup>3</sup> Neurologic signs have also recently been attributed to a gluten intolerance in border terriers.<sup>4</sup>

This case report was the first to describe a potential GRD affecting multiple body systems. A 2-year-old border terrier with a history of pruritus, otitis, postprandial neurologic episodes, abdominal pain, and primarily large-bowel GI signs was evaluated. The patient was screened for pancreatitis, exocrine pancreatic insufficiency, and dysbiosis. Bile acid stimulation and fasting ammonia test results were normal. Thoracic and abdominal images were normal, but endoscopy with GI biopsy results were consistent with mild-to-moderate gastritis, enteritis, and colitis with lymphocytic, plasmacytic, and eosinophilic infiltrates.

Diagnosis of celiac disease in humans often uses serum antibody testing of antitransglutaminase 2 (TG2) and anti gliadin (AGA)<sup>5</sup>; this dog had levels approximately 5 times higher than those reported in normal dogs.<sup>4</sup> The diet history provided in the case report was vague, but the authors stated the patient had previously undergone novel protein dietary trials with no improvement. The patient was started on a gluten-free hydrolyzed diet; 14 days later, neurologic, GI, and skin-related clinical signs resolved. In addi-

## Vetmedin® (pimobendan) Chewable Tablets

Cardiac drug for oral use in dogs only

**Caution:** Federal law restricts this drug to use by or on the order of a licensed veterinarian.

**Description:** Vetmedin (pimobendan) is supplied as oblong half-scored chewable tablets containing 1.25, 2.5, 5 or 10 mg pimobendan per tablet. Pimobendan, a benzimidazole-pyridazinone derivative, is a non-sympathomimetic, non-glycoside inotropic drug with vasodilative properties. Pimobendan exerts a stimulatory myocardial effect by a dual mechanism of action consisting of an increase in calcium sensitivity of cardiac myofibrils and inhibition of phosphodiesterase (Type III). Pimobendan exhibits vasodilating activity by inhibiting phosphodiesterase III activity. The chemical name of pimobendan is 4,5-dihydro-6-[2-(4-methoxyphenyl)-1H-benzimidazole-5-yl]-5-methyl-3(2H)-pyridazinone.

**Indications:** Vetmedin (pimobendan) is indicated for the management of the signs of mild, moderate, or severe (modified NYHA Class II, III, or IV) congestive heart failure in dogs due to atrioventricular valvular insufficiency (AVVI) or dilated cardiomyopathy (DCM). Vetmedin is indicated for use with concurrent therapy for congestive heart failure (e.g., furosemide, etc.) as appropriate on a case-by-case basis.

<sup>a</sup> A dog with modified New York Heart Association (NYHA) Class II heart failure has fatigue, shortness of breath, coughing, etc. apparent when ordinary exercise is exceeded.

<sup>b</sup> A dog with modified NYHA Class III heart failure is comfortable at rest, but exercise capacity is minimal.

<sup>c</sup> A dog with modified NYHA Class IV heart failure has no capacity for exercise and disabling clinical signs are present even at rest.

**Contraindications:** Vetmedin should not be given in cases of hypertrophic cardiomyopathy, aortic stenosis, or any other clinical condition where an augmentation of cardiac output is inappropriate for functional or anatomical reasons.

**Warnings:** Only for use in dogs with clinical evidence of heart failure. At 3 and 5 times the recommended dosage, administered over a 6-month period of time, pimobendan caused an exaggerated hemodynamic response in the normal dog heart, which was associated with cardiac pathology.

**Human Warnings:** Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental ingestion by humans.

**Precautions:** The safety of Vetmedin has not been established in dogs with asymptomatic heart disease or in heart failure caused by etiologies other than AVVI or DCM. The safe use of Vetmedin has not been evaluated in dogs younger than 6 months of age, dogs with congenital heart defects, dogs with diabetes mellitus or other serious metabolic diseases, dogs used for breeding, or pregnant or lactating bitches.

**Adverse Reactions:** Clinical findings/adverse reactions were recorded in a 56-day field study of dogs with congestive heart failure (CHF) due to AVVI (256 dogs) or DCM (99 dogs). Dogs were treated with either Vetmedin (175 dogs) or the active control enalapril maleate (180 dogs). Dogs in both treatment groups received additional background cardiac therapy.

The Vetmedin group had the following prevalence (percent of dogs with at least one occurrence) of common adverse reactions/new clinical findings (not present in a dog prior to beginning study treatments): poor appetite (38%), lethargy (33%), diarrhea (30%), dyspnea (29%), azotemia (14%), weakness and ataxia (13%), pleural effusion (10%), syncope (9%), cough (7%), sudden death (6%), ascites (6%), and heart murmur (3%). Prevalence was similar in the active control group. The prevalence of renal failure was higher in the active control group (4%) compared to the Vetmedin group (1%).

Adverse reactions/new clinical findings were seen in both treatment groups and were potentially related to CHF, the therapy of CHF, or both. The following adverse reactions/new clinical findings are listed according to body system and are not in order of prevalence: CHF death, sudden death, chordae tendineae rupture, left atrial tear, arrhythmias overall, tachycardia, syncope, weak pulses, irregular pulses, increased pulmonary edema, dyspnea, increased respiratory rate, coughing, gagging, pleural effusion, ascites, hepatic congestion, decreased appetite, vomiting, diarrhea, melena, weight loss, lethargy, depression, weakness, collapse, shaking, trembling, ataxia, seizures, restlessness, agitation, pruritus, increased water consumption, increased urination, urinary accidents, azotemia, dehydration, abnormal serum electrolyte, protein, and glucose values, mild increases in serum hepatic enzyme levels, and mildly decreased platelet counts.

Following the 56-day masked field study, 137 dogs in the Vetmedin group were allowed to continue on Vetmedin in an open-label extended-use study without restrictions on concurrent therapy. The adverse reactions/new clinical findings in the extended-use study were consistent with those reported in the 56-day study, with the following exception: One dog in the extended-use study developed acute cholestatic liver failure after 140 days on Vetmedin and furosemide.

In foreign post-approval drug experience reporting, the following additional suspected adverse reactions were reported in dogs treated with a capsule formulation of pimobendan: hemorrhage, petechia, anemia, hyperactivity, excited behavior, erythema, rash, drooling, constipation, and diabetes mellitus.

**Effectiveness:** In a double-masked, multi-site, 56-day field study, 355 dogs with modified NYHA Class II, III, or IV CHF due to AVVI or DCM were randomly assigned to either the active control (enalapril maleate) or the Vetmedin (pimobendan) treatment group. Of the 355 dogs, 52% were male and 48% were female; 72% were diagnosed with AVVI and 28% were diagnosed with DCM; 34% had Class II, 47% had Class III, and 19% had Class IV CHF. Dogs ranged in age and weight from 1 to 17 years and 3.3 to 191 lb, respectively. The most common breeds were mixed breed, Doberman Pinscher, Cocker Spaniel, Miniature Toy Poodle, Maltese, Chihuahua, Miniature Schnauzer, Dachshund, and Cavalier King Charles Spaniel. The 180 dogs (130 AVVI, 50 DCM) in the active control group received enalapril maleate (0.5 mg/kg once or twice daily), and all but 2 received furosemide. Per protocol, all dogs with DCM in the active control group received digoxin. The 175 dogs (126 AVVI, 49 DCM) in the Vetmedin group received pimobendan (0.5 mg/kg/day divided into 2 portions that were not necessarily equal, and the portions were administered approximately 12 hours apart), and all but 4 received furosemide. Digoxin was optional for treating supraventricular tachyarrhythmia in either treatment group, as was the addition of a  $\beta$ -adrenergic blocker if digoxin was ineffective in controlling heart rate. After initial treatment at the clinic on Day 1, dog owners were to administer the assigned product and concurrent medications for up to 56±4 days.

The determination of effectiveness (treatment success) for each case was based on improvement in at least 2 of the 3 following primary variables: modified NYHA classification, pulmonary edema score by a masked veterinary radiologist, and the investigator's overall clinical effectiveness score (based on physical examination, radiography, electrocardiography, and clinical pathology). Attitude, pleural effusion, coughing, activity level, furosemide dosage change, cardiac size, body weight, survival, and owner observations were secondary evaluations contributing information supportive to product effectiveness and safety. Based on protocol compliance and individual case integrity, 265 cases (134 Vetmedin, 131 active control) were evaluated for treatment success on Day 29. At the end of the 56-day study, dogs in the Vetmedin group were enrolled in an unmasked field study to monitor safety under extended use, without restrictions on concurrent medications.

Vetmedin was used safely in dogs concurrently receiving furosemide, digoxin, enalapril, atenolol, spironolactone, nitroglycerin, hydralazine, diltiazem, antiparasitic products (including heartworm prevention), antibiotics (metronidazole, cephalaxin, amoxicillin-clavulanate, fluoroquinolones), topical ophthalmic and otic products, famotidine, theophylline, levoroxatone sodium, diphenhydramine, hydrocodone, metoclopramide, and butorphanol, and in dogs on sodium-restricted diets.

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Revised 01/2017

tion, titers repeated 12 weeks later showed significant decreases in TG2 and AGA antibodies, although values were still higher than those seen in normal dogs.

Although these results suggest a multisystemic gluten intolerance, the hydrolyzed diet may have improved a combination of inflammatory bowel disease and food-allergic dermatitis. Gluten intolerance could have been evaluated by adding gluten to the patient's hydrolyzed diet and noting whether clinical signs returned.

## ... TO YOUR PATIENTS

Key pearls to put into practice:

- 1 Gluten-related disorders are rare in veterinary medicine. Reports describe clinical signs primarily affecting the GI tract in Irish setters and the neurologic system in border terriers.
- 2 This case suggests that gluten sensitivity cases may be presented with a combination of GI, neurologic, and pruritic skin disorders. However, more research is needed.
- 3 In patients suspected of having a gluten sensitivity, testing for TG2 and AGA antibodies should be considered.

## References

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