

Inflammatory Bowel Disease in a Diabetic Dog

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An 11-year-old neutered male Pomeranian with diabetes mellitus (well controlled for 2 years with q12h NPH insulin and a high-fiber diet) is presented with intermittent inappetence, small-bowel diarrhea, and weight loss of 2 months' duration. There is no history of diet change/indiscretion or known infectious disease exposure. Physical examination, CBC, serum chemistry profile, serum fructosamine, urinalysis, baseline cortisol, cPLI test, and abdominal imaging (radiography and ultrasonography) rule out diabetic dysregulation, pancreatitis, GI obstruction, and hypoadrenocorticism. Fecal analysis findings are unremarkable. Signs do not resolve with empiric anthelmintic (ie, fenbendazole) administration, additional dietary fiber, antibiotic administration, and an 8-week limited-antigen diet trial. Endoscopy is performed; endoscopic intestinal biopsies show lymphoplasmacytic enteritis, and inflammatory bowel disease (IBD) is diagnosed.


ACTH = adrenocorticotrophic hormone

cPLI = canine pancreatic lipase immunoreactivity

IBD = inflammatory bowel disease


































Which of the following drugs would be appropriate in the management of this patient?

Based on the information provided, how would you grade the following drugs and why?

 RED = do not use

 YELLOW = proceed with caution

 GREEN = safe

Metronidazole	 RED	 YELLOW	 GREEN
Probiotics	 RED	 YELLOW	 GREEN
Cobalamin	 RED	 YELLOW	 GREEN
NPH insulin	 RED	 YELLOW	 GREEN
Glargine insulin	 RED	 YELLOW	 GREEN
Glipizide	 RED	 YELLOW	 GREEN
Prednisone or prednisolone	 RED	 YELLOW	 GREEN
Budesonide	 RED	 YELLOW	 GREEN
Cyclosporine	 RED	 YELLOW	 GREEN
Amlodipine	 RED	 YELLOW	 GREEN
Aminopentamide	 RED	 YELLOW	 GREEN

**TURN THE PAGE TO
COMPARE YOUR RESULTS**

Did you answer?

The following represents the best responses based on drug metabolism, pharmacokinetics, species, diagnostic differentials, clinical and laboratory data, and other pertinent findings.

Metronidazole

CORRECT RESPONSE



Metronidazole is not an antidiarrheal agent, although it is sometimes misused as such. Metronidazole does, however, have antimicrobial activity against many potential GI pathogens (eg, *Clostridium* spp, *Helicobacter* spp, *Entamoeba* spp, *Balantidium* spp, *Giardia* spp). It is also used as adjunctive treatment for hepatic encephalopathy to reduce populations of gut bacteria (particularly proteolytic anaerobes) that generate ammonia and to treat GI dysbiosis, which may arise secondary to many intestinal or extraintestinal diseases. Empiric administration of metronidazole, tylosin, or tetracycline is used in patients with chronic diarrhea to assess for antibiotic-responsive diarrhea.

Metronidazole demonstrates an immunomodulating effect by suppressing cell-mediated immunity, an effect that is exploited by its use in suppressing inflammation and in treating IBD, potentially reducing the need for corticosteroids or other potent immunosuppressive agents. Metronidazole has a bitter taste to which patients may vehemently object, so administration in pill pockets or in flavored compounded suspensions may be necessary; however, flavorings and other food antigens can interfere with dietary control measures in patients being fed hypoallergenic diets and those participating in diet trials. Adverse effects include anorexia (particularly problematic in a diabetic animal), vomiting, diarrhea, and, of importance, a wide variety of neurologic abnormalities (eg, ataxia, nystagmus, head tilt, tremors, disorientation, seizures) that may be seen acutely or with chronic administration. Incidence of adverse effects may be reduced by avoiding use of higher doses or prolonged administration, but adverse neurologic effects may be seen in some patients after short-term administration of lower doses. Mutagenic effects of metronidazole administration have been demonstrated in multiple species, including humans and cats,¹ and should be considered when using the medication.

Concurrent administration of metronidazole and cyclosporine may result in increased cyclosporine levels. Metronidazole has been implicated in 2 human case reports as a cause of significant increases in plasma cyclosporine levels when administered with cyclosporine.^{2,3} Mild inconsequential (6%) reduction of cyclosporine metabolism by metronidazole was identified in a study of cytochrome enzyme CYP3A activity in human liver microsomes,⁴ but there is little evidence further documenting this interaction. There are no reports of a metronidazole–cyclosporine interaction in other species; however, based on the reports in the human literature, clinicians should be aware of the potential for this interaction when considering concurrent use of these drugs in veterinary patients.

Probiotics

CORRECT RESPONSE



Probiotics are live micro-organisms that are administered orally to beneficially alter intestinal flora, improve intestinal mucosal function, and moderate intestinal immune responses. Probiotics have been beneficial in treating dogs with acute and chronic diarrheal diseases and are generally considered safe.⁵⁻⁸ Manipulation of the gut microbiome using prebiotics (ie, dietary agents that are substrates for beneficial bacteria and promote their growth) in diabetic humans has resulted in improved glucose tolerance and reduced markers of inflammation.⁹⁻¹¹ Potential benefits of manipulating gut bacterial populations in diabetic dogs have not been studied.

Cobalamin

CORRECT RESPONSE



Hypocobalaminemia may develop in patients with intestinal disease either resulting from reduced absorption of dietary cobalamin by the impaired intestine or because of increased numbers of intestinal bacteria that bind luminal cobalamin and prevent its absorption. Cobalamin deficiency may manifest clinically as a suboptimal response to treatment for intestinal disease or, less commonly, with systemic manifestations of anemia, neutropenia, or neurologic abnormalities. Commercial testing for evaluation of serum cobalamin levels is available to identify patients with hypocobalaminemia requiring supplementation. Cobalamin is most commonly administered parenterally to circumvent problems with intestinal absorption, but recent work demonstrates that oral administration may adequately correct cobalamin deficiencies in dogs.¹²

NPH insulin

CORRECT RESPONSE



Continued use of an insulin that has been effective in treating this dog's diabetes is recommended. However, if treatment with prednisone, prednisolone, or cyclosporine is initiated to manage IBD, the dose may need to be increased to overcome insulin antagonism by these drugs, and more frequent monitoring of weight, clinical signs, and parameters of glycemic control is warranted to identify changes in insulin dose requirements. The insulin dose should not be changed unless glycemic control is lost; the effect of insulin antagonist drugs may not be manifested immediately and may take weeks to months to become apparent.

Treatment for IBD may result in improved appetite, nutrient absorption, and gut motility, all of which may impact the insulin dose required to maintain control of diabetes mellitus. Diet change is key in diagnostic assessment and long-term management of chronic diarrheal diseases; any diet change will impact insulin requirements of the diabetic animal, so disruption of current glycemic control is likely in the course of evaluating and treating this patient.

Glargine insulin

CORRECT RESPONSE



No evidence exists that any particular type of insulin is less affected by the insulin antagonism of corticosteroids or cyclosporine; therefore, continued use of the current NPH insulin is recommended. Changing to another insulin type should be avoided unless diabetes mellitus becomes persistently unregulated on the current insulin despite appropriate dose adjustments and control of concurrent IBD. As compared with NPH insulin, glargine is a longer-acting insulin and may be considered if NPH's duration of action is inadequate for q12h administration or if the condition becomes refractory to NPH.¹³

IBD = inflammatory bowel disease

Glipizide

CORRECT RESPONSE



Glipizide is an oral hypoglycemic agent believed to trigger increased release of exogenous insulin from functioning pancreatic β cells. It is sometimes used to treat diabetic cats,¹⁴ in which diabetes typically parallels type 2 diabetes in humans, with a significant remaining functional β cell mass. However, it is not indicated for treating diabetic dogs.

Prednisone or prednisolone

CORRECT RESPONSE



Oral corticosteroids are widely used to control intestinal inflammation in the initial stages of IBD treatment and to treat flares. In patients with severe disease, treatment may be initiated with injectable corticosteroids to circumvent problems with absorption secondary to significantly disrupted gut function. Corticosteroids are initiated at immunosuppressive doses, followed by tapering doses over several months. Because of the high doses and extended period of administration generally followed, corticosteroid administration is expected to result in insulin antagonism and disruption of this dog's diabetic control, and adjustments in insulin doses will likely be needed. Ongoing adjustments as corticosteroid doses are sequentially reduced should also be anticipated; as a result, more intensive monitoring of this dog's diabetes will be required until IBD is controlled and corticosteroid administration is discontinued or reduced to a stable maintenance level. Although corticosteroids can complicate diabetic management, they offer an advantage in their primary appetite-stimulant effect, in addition to improvements in appetite resulting from control of intestinal inflammation from IBD; both help diabetic patients maintain an appetite, which is critical in stabilizing glycemic control.

Budesonide

CORRECT RESPONSE



Budesonide is a potent glucocorticoid that, when administered orally, is well absorbed in dogs with IBD.¹⁵ It undergoes high first-pass hepatic metabolism, which reduces systemic drug levels and therefore systemic adverse effects such as insulin antagonism. Still, budesonide has systemic effects—which are reduced but not eliminated—and, like prednisone or prednisolone, there remains the potential for withdrawal effects if it is discontinued suddenly. This drug has a topical anti-inflammatory effect at the intestinal mucosa that does not require absorption and recirculation to the gut. Budesonide is more expensive than prednisone or prednisolone and is available in formulations for humans; compounding the medication for appropriate dosing in small animals can add cost and make it more difficult to taper the dose. When compounding, it is important to preserve the integrity of the enteric-coated spheres inside the capsules. Budesonide is an excellent alternative to corticosteroids for treatment of IBD in a diabetic dog.¹⁶

Cyclosporine

CORRECT RESPONSE



Cyclosporine may be used as a primary or adjunctive immunosuppressive agent in patients with IBD and has been used successfully to treat some dogs with steroid-refractory IBD.¹⁷

Cyclosporine has been shown to have toxic effects on the pancreas in several species, including dogs,¹⁸ that can cause β cell destruction, reduced insulin secretion, and insulin resistance resulting from dyslipidemia and reduced activity of genes involved in insulin action and glucose uptake. Therefore, cyclosporine likely offers no advantage over glucocorticoids for use as an immunosuppressive agent in diabetic patients. Also, addition of cyclosporine to the treatment regimen for patients already receiving glucocorticoids introduces additional insulin antagonism, with the potential to precipitate diabetes mellitus in a patient not previously diabetic as well as to further disrupt diabetic regulation in an existing diabetic patient. Concurrent use of corticosteroids, calcium-channel blockers, omeprazole, or metronidazole may increase cyclosporine levels and risk for cyclosporine toxicity. Interaction with antihypertensive drugs, including amlodipine, can result in significantly increased plasma cyclosporine levels in humans and rats and may therefore increase the risk for adverse effects of cyclosporine, such as nephrotoxicity.¹⁹⁻²² Neither of these drug–drug interactions nor cyclosporine-induced nephrotoxicity has been documented in dogs. Signs of cyclosporine toxicity in dogs (ie, inappetence, vomiting, diarrhea) may overlap with signs of poorly controlled IBD or diabetic ketoacidosis, for which this dog must be monitored. Cyclosporine is a poor choice for initial or adjunctive treatment for IBD in a diabetic dog.

Amlodipine

CORRECT RESPONSE



Systemic hypertension is a relatively common comorbidity in patients with diabetes mellitus.²³ Blood pressure should be assessed initially and monitored regularly. Hypertension may also manifest in animals with corticosteroid excess, as seen with endogenous hypercortisolism (ie, Cushing's disease) or administration of moderate-to-high doses of exogenous corticosteroids, and is associated with cyclosporine administration in humans.²⁰ In this patient, hypertension may be present as a diabetic comorbidity or may arise or worsen secondary to administration of corticosteroids or, potentially, cyclosporine. Systolic pressure should be maintained <180 mm Hg, and antihypertensive agents may be needed.

Amlodipine is a calcium-channel blocker used to treat hypertension in dogs. It is typically used as adjunctive therapy and added after use of an ACE inhibitor (eg, benazepril, enalapril) has failed to fully control blood pressure. Amlodipine may increase cyclosporine levels if cyclosporine is used to treat this patient's IBD; this effect has been well documented in humans but not reported in dogs.^{19,20} Adverse effects of amlodipine include GI signs (eg, inappetence, vomiting), which may overlap with signs of uncontrolled diabetes mellitus (eg, diabetic ketoacidosis) or IBD.

IBD = inflammatory bowel disease

Aminopentamide

CORRECT RESPONSE



Aminopentamide is an anticholinergic agent that blocks activation of smooth muscle contraction, thereby reducing GI motility. In most patients with diarrhea, GI motility is already reduced, and further suppression of motility with an anticholinergic agent is contraindicated. GI motility is also reduced in diabetic patients; further reduction caused by an anticholinergic agent is contraindicated and may complicate glycemic control by altering the rate of delivery and absorption of nutrients. ■■■

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See page 108 for references.

Loxicom® (meloxicam)

1.5 mg/mL Oral Suspension

Non-steroidal anti-inflammatory drug for oral use in dogs only

Warning: Repeated use of meloxicam in cats has been associated with acute renal failure and death. Do not administer additional injectable or oral meloxicam to cats. See Contraindications, Warnings, and Precautions for detailed information.

Brief Summary: Before using Loxicom Oral Suspension, consult the product insert, a summary of which follows.

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

Description: Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class.

Indications: Loxicom Oral Suspension is indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

Contraindications: Dogs with known hypersensitivity to meloxicam should not receive Loxicom Oral Suspension.

Do not use Loxicom Oral Suspension in cats. Acute renal failure and death have been associated with the use of meloxicam in cats.

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. **For oral use in dogs only.** As with any NSAID all dogs should undergo a thorough history and physical examination before the initiation of NSAID therapy. Appropriate laboratory testing to establish hematological and serum biochemical baseline data is recommended prior to and periodically during administration.

To report suspected adverse reactions, to obtain a Material Safety Data Sheet, or for technical assistance, call Norbrook at 1-866-591-5777.

Precautions: The safe use of Loxicom Oral Suspension in dogs younger than 6 months of age, dogs used for breeding, or in pregnant or lactating dogs has not been evaluated. As a class, cyclo-oxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the individual patient.

Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be carefully approached. NSAIDs may inhibit the prostaglandins that maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease that has not been previously diagnosed. Since NSAIDs possess the potential to induce gastrointestinal ulcerations and/or perforations, concomitant use with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided or closely monitored. The use of concomitantly protein-bound drugs with Loxicom Oral Suspension has not been studied in dogs. Commonly used protein-bound drugs include cardiac, anticonvulsant and behavioral medications. The influence of concomitant drugs that may inhibit metabolism of Loxicom Oral Suspension has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy.

Adverse Reactions: Field safety was evaluated in 306 dogs. Based on the results of two studies, GI abnormalities (vomiting, soft stools, diarrhea, and inappetence) were the most common adverse reactions associated with the administration of meloxicam. Of the dogs that took meloxicam (n=157), forty experienced vomiting, nineteen experienced diarrhea/soft stool, five experienced inappetence, and one each experienced bloody stool, bleeding gums after dental procedure, lethargy/swollen carpus, and epiphora. Of the dogs that took the placebo (n=149), twenty-three experienced vomiting, eleven experienced diarrhea/soft stool, and one experienced inappetence.

In foreign suspected adverse drug reaction (SADR) reporting over a 9 year period, incidences of adverse reactions related to meloxicam administration included: auto-immune hemolytic

anemia (1 dog), thrombocytopenia (1 dog), polyarthritis (1 dog), nursing puppy lethargy (1 dog), and pyoderma (1 dog).

Effectiveness: The effectiveness of meloxicam was demonstrated in two field studies involving a total of 277 dogs representing various breeds, between six months and sixteen years of age, all diagnosed with osteoarthritis. Both of the placebo-controlled, masked studies were conducted for 14 days. All dogs received 0.2 mg/kg on day 1. All dogs were maintained on 0.1 mg/kg oral meloxicam from days 2 through 14 of both studies. Parameters evaluated by veterinarians included lameness, weight-bearing, pain on palpation, and overall improvement. Parameters assessed by owners included mobility, ability to rise, limping, and overall improvement. In the first field study (n=109), dogs showed clinical improvement with statistical significance after 14 days of meloxicam treatment for all parameters. In the second field study (n=48), dogs receiving meloxicam showed a clinical improvement after 14 days of therapy for all parameters; however, statistical significance was demonstrated only for the overall investigator evaluation on day 7, and for the owner evaluation on day 14.

How Supplied:

Loxicom Oral Suspension 1.5 mg/mL: 10, 32 and 100 mL bottles with small and large dosing syringes.

Storage: Store at controlled room temperature 68-77°F (20-25°C).

Excursions permitted between 59°F and 86°F (15°C and 30°C). Brief exposure to temperature up to 104°F (40°C) may be tolerated provided the mean kinetic temperature does not exceed 77°F (25°C); however such exposure should be minimized.

Made in the UK.

Manufactured by:
Norbrook Laboratories Limited
Newry, BT35 6PU, Co. Down, Northern Ireland

Loxicom® is a registered trademark
of Norbrook Laboratories Limited



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RED LIGHT, GREEN LIGHT ► CONTINUED FROM PAGE 72

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