Oral bleeding associated with pancreatic enzyme supplementation in three dogs with exocrine pancreatic insufficiency

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- Administration of powdered pancreatic enzyme supplements in dogs with exocrine pancreatic insufficiency may cause oral bleeding.
- Oral bleeding associated with administration of pancreatic enzyme supplements appears to be dose dependent, and a reduction in dose of the supplement will result in resolution of the oral bleeding without a recurrence of signs of exocrine pancreatic insufficiency in most dogs.

An 8-year-old castrated male German Shepherd Dog, 4-year-old spayed female Welsh Corgi, and 3-year-old spayed female Welsh Corgi developed bleeding from the oral cavity at the time of feeding or shortly after intake of food mixed with a pancreatic enzyme supplement. In all 3 dogs, a diagnosis of **exocrine pancreatic insufficiency (EPI)** had been made on the basis of results of an assay of serum trypsin-like immunoreactivity, and treatment with a powdered pancreatic enzyme supplement[a,b] had resulted in an improvement in clinical signs. The dogs were participants in a feeding trial to investigate the effect of medium-chain triglycerides on the well-being of dogs with exocrine pancreatic insufficiency. Before enrollment in the feeding trial, a full medical workup had been performed on each of the dogs. This workup included a physical examination, CBC, serum biochemical analysis, urinalysis, fecal analysis for intestinal parasites including *Giardia* spp, serum triglyceride concentration, serum lipase activity, serum cholesterol concentration, serum canine trypsin-like immunoreactivity, serum canine pancreatic lipase immunoreactivity, and serum cobalamin and folate concentrations. In all 3 dogs, results of the workup were consistent with a diagnosis of exocrine pancreatic insufficiency. None of the dogs had any evidence of concurrent diseases or of any other abnormalities other than severely low serum canine trypsin-like and serum canine pancreatic lipase immunoreactivities and abnormal serum cobalamin and folate concentrations. Owners of the dogs did not report the oral bleeding to their veterinarians at the time of reexamination 3 months after enrollment in the feeding trial; therefore, all descriptions of the oral bleeding were based on reports of the owners. The oral bleeding was apparently mild in all 3 dogs, and none of the owners reported melena or signs of anemia. However, repeated PCVs and Hcts were not evaluated.

The 8-year-old German Shepherd Dog weighed 31.8 kg (70 lb) and was being fed canned food before being enrolled in the feeding trial. After the dog was enrolled in the feeding trial, its diet was changed to dry food to which 4 teaspoons of a powdered pancreatic enzyme supplement[a] (2.5 [approx 20 mL] teaspoons/20 kg of body weight) were added. According to the owner, the dog started to bleed from its mouth 10 weeks after being enrolled in the feeding trial. Blood-stained saliva dripped from the dog's mouth shortly after it ate, and water in the dog's water dish had a red discoloration. The owner also reported that the dog's mouth appeared tender, and the dog appeared reluctant to eat.

The amount of pancreatic enzyme supplement added to the dog's food was reduced to 2 teaspoons (1.3 teaspoons/20 kg), and the owner was instructed to moisten the food with water before offering it to the dog. The owner reported that after these changes were implemented, the bleeding stopped.

After 4 months, the dog's feeding regimen was again changed to determine whether decreasing the dose of the pancreatic enzyme supplement or moistening the food had been responsible for the disappearance of oral bleeding. The owner was instructed to add 4 teaspoons of the supplement to the food but to continue to moisten the food with water before offering it to the dog. The owner reported that after 2 days, the dog started to eat more slowly, and its mouth appeared to be painful. After 16 days, the dog again started to bleed from the oral cavity. Bleeding stopped immediately after the amount of pancreatic enzyme supplement was again reduced. The dog returned to its previous eating pattern after 2 days and did not have any further problems or clinical signs of exocrine pancreatic insufficiency, such as voluminous stools, diarrhea, ravenous appetite, flatulence, or borborygmus, with the reduced dose of the pancreatic enzyme supplement.

The 4-year-old Welsh Corgi weighed 11.4 kg (25 lb) and was fed 1.5 teaspoons (2.6 teaspoons/20 kg) of pancreatic enzyme supplement before enrollment in the feeding trial. After enrollment in the trial, the dog received 2 teaspoons (3.5 teaspoons/20 kg) of pancreatic enzyme supplement, and its food was moistened with water. During the feeding trial, the owners noticed a brown mustache around the white fur on the dog's snout after the dog would eat. The owners also

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reported that the cleft in the middle of the dog's tongue appeared noticeably redder than the rest of the tongue. After the dose of pancreatic enzyme supplement was decreased to 1.5 teaspoons (2.6 teaspoons/20 kg), these signs disappeared. After bleeding was reported, a coagulation panel consisting of measurement of prothrombin time, activated partial thromboplastin time, fibrinogen split products concentration, and concentration of proteins induced by lack of vitamin K absence was performed, and all results were within reference ranges. The dog did not have any clinical signs suggestive of EPI after the dose of pancreatic enzyme supplement was reduced.

The 3-year-old female spayed Welsh Corgi weighed 8.0 kg (17.6 lb) and, according to the owner, would bleed from the oral cavity once or twice a month when fed 2 teaspoons (5.0 teaspoons/20 kg) of pancreatic enzyme supplement with 1 to 1.25 cups of moistened dry food before and during the feeding trial.

When the dose of pancreatic enzyme supplement was reduced to 1 teaspoon (2.5 teaspoons/20 kg), the dog would develop loose stools after approximately 3 to 4 days, but signs of oral bleeding would cease. To ensure better stool quality, the dose would be increased to 2 teaspoons (5.0 teaspoons/20 kg body weight) after the oral bleeding had stopped. After this increase in the dose of pancreatic enzyme supplement, oral bleeding recurred. Results of a coagulation panel, consisting of measurement of prothrombin time, activated partial thromboplastin time, fibrinogen split products concentration, and concentration of proteins induced by lack of vitamin K, performed at this time were within reference ranges.

Pancreatic enzyme supplements contain digestive enzymes that are needed for digestion of nutrients.[1] In healthy individuals, most digestive enzymes are synthesized and secreted by the exocrine portion of the pancreas.[2] In response to eating, pancreatic juice containing digestive enzymes and zymogens is secreted into the duodenum.[2] In addition, pepsinogen, the zymogen of another proteolytic enzyme, and gastric lipase are secreted by the gastric glands.[2,3] Lingual lipase is secreted in rats and mice,[4] but not in any other species, and salivary amylase is the only digestive enzyme in the oral cavity in most species.[2] Thus, in healthy animals, digestive enzymes do not come into contact with the oral mucosa, as is the case when enzymes are being supplemented in the form of pancreatic enzyme powder for treatment of EPI.

In pharmaceutical manufacturing plants where these supplements are produced, employees have developed allergies to pancreatic enzyme supplements, resulting in epidermal bleeding and pustules and loss of hair.[c] There is also anecdotal evidence that long-term use of pancreatic enzyme powder in human beings can lead to loss of teeth because of digestion of the dental attachment apparatus.[c] In human beings, pancreatic enzyme supplements are often administered as enteric-coated capsules to avoid direct contact between the digestive enzymes and the proximal intestinal tract. However, it has been recognized that pancreatic enzyme powder is more efficacious than enteric-coated products in treating EPI in human beings and dogs.[5,d]

The 3 dogs described in the present report suggest that in dogs, the oral mucosa may be sufficiently sensitive to pancreatic enzyme supplements to result in oral bleeding even when these supplements are administered at therapeutic doses. Other causes of bleeding, including vitamin K-responsive coagulopathy, were ruled out. Therefore, the oral bleeding observed in these 3 dogs was likely a result of local effects of the pancreatic enzyme supplement.

The feeding protocol also appeared to play a role in the pathogenesis of oral bleeding in these dogs, and it is known that direct contact of dry enzyme powder with mucosa can cause ulceration.[e] Therefore, it is recommended that dry food be moistened when feeding pancreatic enzyme supplements to dogs. However, dogs described in the present report had oral bleeding even when the food and pancreatic powder mixture were moistened with water.

The potentially harmful effects of the pancreatic enzyme supplement appeared to be dose dependent in the dogs described in the present report. The dose of pancreatic enzyme supplement necessary to control clinical signs of EPI in dogs varies widely.[6] Most dogs are initially treated with 2 teaspoons of pancreatic enzyme supplement/20 kg of body weight.[6,7] Although some dogs may require higher doses, in most dogs, the dose can be substantially decreased after remission of clinical signs.[6] The amount of supplement needed probably depends on factors such as efficiency of preduodenal digestion, gastric acidity, and residual exocrine function of the pancreas. Results in dogs described in the present report, particularly the 3-year-old Welsh Corgi, illustrate that some dogs may need more than the recommended dose of pancreatic enzyme supplement to maintain formed feces.

Importantly, findings described in the present report do not suggest that tablets or enteric-coated pancreatic enzyme products should be used instead of powdered pancreatic enzyme supplement in dogs with EPI. The oral bleeding described in these dogs occurs rarely and was easily treated by reducing the dose of pancreatic enzyme supplement that was administered. Powdered pancreatic enzyme supplements remain the most efficacious treatment for EPI in dogs, whereas enteric-coated enzyme formulations are less effective in dogs, probably because of failure of the pancreatic enzymes to sufficiently mix with the chyme as a result of differences in gastric emptying between enteric-coated products and food.[5] We recommend individually adjusting the amount of pancreatic enzyme powder administered to each dog, starting with a dose of 2 teaspoons/20 kg of body weight with each meal. If clinical signs of EPI resolve at this dose, the dose should be reduced to the minimally effective dose. In children with cystic fibrosis, which is a major cause of EPI in humans, administration of pancreatic enzyme supplements at a high dose has been associated with thickening of the colonic wall, fibrosing colonopathy, strictures of the ascending colon, and hyperuricosuremia.[8-11] Therefore, we recommend adjusting the treatment with pancreatic enzyme supplement to the

minimally effective dose to prevent oral bleeding and other potentially adverse effects.

[a]Pancrezyme, Daniels Pharmaceuticals Co, St Petersburg, Fla.
[b]Viokase, Fort Dodge Animal Health, Fort Dodge, Iowa.
[c]Peschke G, Solvay Deutschland, Hannover, Germany: Personal communication, 1999.
[d]Somogyi L, Toskes PP. Conventional pancreatic enzymes are more efficient than enteric-coated enzymes in delivering trypsin to the duodenum of chronic pancreatitis patients (abstr). *Gastroenterology* 1998;114:A500.
[e]Furman B, King Pharmaceuticals, Bristol, Tenn: Personal communication, 1999.

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