Probable Vitamin K-Deficient Bleeding in Two Cats With Malabsorption Syndrome Secondary to Lymphocytic-Plasmacytic Enteritis

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Two cats with intestinal malabsorption developed a hemorrhagic diathesis. Although unsubstantiated, the probable cause of bleeding was a chronic malabsorption of fat and the fat-soluble vitamin K. When treated with vitamin K1 per os, one cat's clotting times were only partially corrected. Since vitamin K1 is actively absorbed in the proximal small intestine, the incomplete response of this case to orally administered vitamin K1 was predictable. The infrequent occurrence of bleeding in animals with malabsorption is, in part, attributable to the ileal and colonic absorption of bacterially derived vitamin K2. For this reason, nonspecific use of antibiotics in these animals is contraindicated. Since long-chain, polyunsaturated fats impair vitamin K absorption, dietary fat given to animals with malabsorption should be restricted to medium- and short-chain, saturated fats. Vitamin K should be administered subcutaneously to these animals if prolonged clotting times or active bleeding is present, and routinely prior to surgery. Oral supplementation with vitamin K3, which is absorbed in the colon and less lipid soluble than vitamin K1, should be given to animals with malabsorption that are maintained as outpatients. Adequate dosage levels of vitamin K3, however, are yet to be established for the cat, and dose-dependent hemolytic anemia is a probable toxic manifestation. (Journal of Veterinary Internal Medicine 1987; 1:97-101)

VITAMIN K is a generic term for lipid-soluble compounds required in the hepatic synthesis of specific proteins (i.e., factors II, VII, IX, and X, and proteins C and S) involved in the clotting process.1 Vitamin K exists in three major forms. Phylloquinone (K1), present in green leafy vegetables, is the primary source of vitamin K for mammals.2 Menaquinone (K2) is produced by intestinal bacteria (especially Escherichia coli and Bacteroides spp.), and menadione (K3) is a chemically related synthetic compound.3

The mechanism and site of absorption of the different forms of vitamin K are variable. Vitamin K1 uptake is a saturable, energy-dependent process requiring micellar solubilization and occurs only in the proximal small intestine.2 Vitamins K2 and K3 are passively absorbed in the ileum and colon.4-6 Vitamins K1 and K2 are primarily transported in the intestinal lymphatics,5,6,7 whereas the less fat-soluble vitamin K3 is absorbed into the portal blood.8

All three forms of vitamin K function in the hepatic production of coagulation proteins.9 Vitamin K carboxylates glutamic acid residues on preformed vitamin K-dependent proteins.1 The carboxyglutamate residues bind calcium, which is essential for adherence of these proteins to phospholipid-rich surfaces. Lack of vitamin K inhibits glutamate carboxylation, resulting in non-functional precursor proteins with fewer than the normal number of carboxyl groups. These under carboxylated proteins are referred to by the acronym PIVKA (proteins induced by vitamin K absence/antagonists).10 Disorders of fat absorption in man frequently result in reduced vitamin K levels.2,11 In bile salt deficiency, the micelles necessary for transport of fat are absent. This results in vitamin K deficiency, but bleeding is uncommon.12 In exocrine pancreatic insufficiency, deficiency of lipase prevents the breakdown of triglycerides into monoglycerides and fatty acids. Without these lipids, there are poor solubilization and absorption of vitamin
K. Lipolysis, however, is usually not totally absent; therefore, bleeding is rare in affected patients. With intestinal malabsorption, defects in absorption and transport of lipids lead to vitamin K deficiency. Bleeding is an uncommon, but well-documented, sequela of this disorder.\textsuperscript{14,15} The purpose of this report is to describe the clinical history, laboratory data, and pathologic features of two cats with chronic lymphocytic-plasmacytic enteritis and a probable vitamin K-deficient hemorrhagic diathesis.

**Case 1**

A 9-year-old, neutered female, 2-kg, domestic shorthair cat was presented to the referral veterinarian for progressive weakness of 2 days' duration. The cat was in lateral recumbency and hypothermic (36.5°C), and had pale mucous membranes and a 9% PCV. Dramatic improvement followed intravenous fluid therapy (200 ml lactated Ringer's solution). Three days after the initial examination, the cat was referred to the University of Tennessee Veterinary Teaching Hospital for evaluation of its anemia. Historically, the cat was always small and had recently lost weight despite a good appetite. It was kept strictly indoors with two other cats, which were healthy. On examination, the cat was thin but alert and active. The rectal temperature was 38.3°C, and the heart rate was 160 beats/minute. Mucous membranes were pale with a capillary refill time of 2 seconds.

Abnormal results on a hemogram included a normocytic, normochromic anemia (PCV, 21%). Platelet number was judged to be adequate from a blood smear. Urinalysis and serum chemistry values were unremarkable except for hyperglobulinemia (total protein, 7.7 g/dl; globulin, 5.2 g/dl). Results of indirect immunofluorescent antibody tests for coronavirus antibody and feline leukemia virus were negative. A small amount of free fluid in the abdomen was suspected on the basis of radiographically indistinct serosal margins.

A saline lavage was used to recover abdominal fluid following multiple unsuccessful needle aspirates. During the abdominal lavage, excessive and unrelenting bleeding occurred from the skin and subcutaneous tissue at the puncture site. A pressure bandage and transfusion of freshly obtained blood was required to stop the hemorrhaging. Clotting times on venous blood obtained prior to the transfusion were prolonged (OSPT, >60 sec, control, 9.5 sec; APTT, 44 sec, control, 13.9 sec). Treatment with vitamin K\textsubscript{1} (5 mg, PO, bid) and hetacillin (50 mg, PO, tid) was initiated. The owner denied any possible exposure of the cat to poisons, specifically dicoumarols or indandiones.

The following day the cat had a large, malodorous bowel movement, which was pasty and slate-grey in appearance. Fecal analysis was negative for parasites and starch, but positive for trypsin, muscle fibers, and split fat. After D-xylose was administered orally produced peak serum values of 27 mg/dl at 2 hours. Abdominal radiographs were unremarkable. At exploratory laparotomy, the abdominal viscera appeared grossly normal, but histologic findings in biopsy specimens from the small intestine were consistent with a diagnosis of lymphocytic-plasmacytic enteritis.

The cat was discharged on prednisone (2.5 mg, PO, qod) and with the recommendation that unconventional foods (e.g., lamb and turkey) be fed. Occasionally antibiotic therapy was used (hetacillin 50 mg, PO, tid). The cat was closely monitored over a 13-month period during which it maintained its body weight despite intermittent episodes of voluminous, gray-colored stools. One day the owner left the cat for a period of 2 hours only to find it dead upon return. Hematochezia was observed 2 days prior to the cat's death, but no other abnormalities were noted. The cat was never permitted outdoors, and the owner denied any possible exposure of the cat to poisons, specifically dicoumarols or indandiones.

Gross pathologic findings included extensive subcutaneous hemorrhages on both sides of the thorax and the ventral abdo-
men. Histologically, there was severe villous atrophy and diffuse infiltration of small lymphocytes between glands in the lamina propria of the duodenum, jejunum, and ileum (Fig. 1). The submucosa of the duodenum and ileum had a moderate infiltration of cells, whereas the submucosa of the jejunum was thickened by a marked cellular infiltrate, which extended between the muscularis layers and into the serosa (Fig. 2). There was lymphoid hyperplasia of Peyer's patches. Scattered crypts were lined by flattened cuboidal epithelium and contained neutrophils and necrotic epithelial cells. Beneath the luminal epithelium there were many macrophages containing lipofuscin pigment. The colon was unremarkable. Mesenteric lymph nodes were characterized by paracortical and medullary hyperplasia and the presence of many hemosiderin-laden macrophages in the medullary sinusoids. Histologic changes in the liver were diffuse. In many areas, the entire acinar units were composed of swollen hepatocytes containing lipofuscin pigment in the cytoplasm. Variable numbers of neutrophils, lymphocytes, and macrophages were present. Vacuolated hepatocytes appeared to have hydropic degeneration. Few lymphocytes were present in the portal areas, and the hepatic sinusoids contained numerous hemosiderin-laden macrophages.

Discussion

Spontaneous bleeding is an infrequent but well-documented complication of intestinal malabsorption in man. Clinically, human beings present with subcutaneous hematomas at pressure points, hemarthrosis, hematemesis, melena, epistaxis, and hematuria. On rare occasions, bleeding can be the primary symptom. The acquired hemorrhagic diathesis is characterized as a hypoprothrombinemic disorder secondary to malabsorption of the fat-soluble vitamin K. As with other causes of vitamin K deficiency or antagonism, the laboratory parameters of hemostasis include early and marked prolongation of the OSPT, and mild to moderate prolongation of the APTT. Typically, the thrombin clot time, fibrinogen concentration, and platelet number are normal; however, the fibrinogen concentration and platelet number can be transiently reduced during extensive hemorrhaging. Vitamin K deficiency resulting from bile salt deficiency or intestinal malabsorption is confirmed by the shortening of clotting times following the parenteral administration of vitamins K$_1$ or K$_3$. Anticoagulant antagonism of vitamin K will respond only to vitamin K$_1$. In human beings, measurement of PIVKA is the most sensitive assay of vitamin K deficiency. Normally, plasma does not contain PIVKA, but with liver disease or vitamin K deficiency due to malabsorption, or anticoagulants, these undercarboxylated vitamin K-dependent proteins are detected.

The sudden onset of bleeding in two cats with chronic intestinal malabsorption was consistent with observations in human patients. In case 1, an acute intra-abdominal bleeding episode would account for the sudden onset of weakness, rapid response to intravenous fluids, spontaneous rise of the PCV (i.e., 9–21% in 72 hours) and radiographic evidence of peritoneal effusion. The results of coagulation tests (OSPT, >60 sec; APTT, 44 sec; platelets, adequate) were suggestive of vitamin K deficiency. The incomplete response to oral vitamin K$_1$ therapy can be attributed to the continued malabsorption of fat. Since vitamin K$_1$ undergoes active transport in the proximal small intestine and has a high lipid solubility, the intestinal inflammation would disrupt the cellular uptake of vitamin K$_1$, and it would be retained in the unabsorbed fats. In case 2, laboratory verification of hypoprothrombinemia is lacking, but the spontaneous and extensive subcutaneous hemorrhaging in a cat with chronic malabsorption that was kept strictly indoors and had no exposure to anticoagulant rodenticides is consistent with vitamin K deficiency. Similar
cases of spontaneous, lethal hemorrhaging have been reported in human beings with intestinal malabsorption.\textsuperscript{14,15}

The pathogenesis of vitamin K–dependent bleeding associated with intestinal malabsorption is more complex than the simple malassimilation of dietary vitamin K. In human patients with malabsorption, acquired liver damage, antibiotic therapy, and dietary fat composition can accentuate the vitamin K deficiency.\textsuperscript{1,2} Hepatic lesions occur commonly in human beings with intestinal malabsorption.\textsuperscript{22} These degenerative and inflammatory lesions result from the chronic malnutrition and/or an extension of the intestinal disease. As observed in case 2, cats with lymphocytic-plasmacytic enteritis can have increased serum ALT activity and portal mononuclear cell infiltrates.\textsuperscript{23,24} Since the liver produces most coagulation proteins, the hepatic disease secondary to intestinal malabsorption may promote a bleeding diathesis.

Bacterially derived vitamin K\textsubscript{2} represents a major source of vitamin K. Rats on vitamin K\textsubscript{1}–deficient diets rarely develop bleeding tendencies, but germ-free rats on the same diet develop fatal hemorrhages within 2–4 weeks.\textsuperscript{25} Vitamin K–responsive bleeding is common among anorectic human patients treated with antibiotics.\textsuperscript{26,27} In many disorders causing malabsorption, duodenal and jejunal lesions predominate, with the colon being minimally affected. Hence, the absorption of bacterially derived vitamin K\textsubscript{2} in the ileum and colon may account for the infrequent appearance of hypoprothrombinemic bleeding in human beings and animals with malabsorption. Under these circumstances, the use of antibiotics could precipitate bleeding by turning a hypovitaminosis into an avitaminosis. The intermittent use of antibiotics in case 2 may have contributed to the onset of bleeding.

The absorption of natural forms of vitamin K is affected by the amount and type of dietary fat. Severe dietary fat restriction in animals with malabsorption can aggrivate vitamin K deficiency because the uptake of vitamin K is dependent on fat absorption. Intestinal absorption of vitamin K is reduced by progressively longer-chain fatty acids and greater degrees of unsaturation.\textsuperscript{28,29} Therefore, dietary fat requirements of animals with malabsorption should be met by short- or medium-chain, saturated fatty acids.

Vitamin K treatment should be given to all animals with malabsorption, especially when abnormal clotting is detected or prior to surgery. Abnormal clotting may be present as a laboratory finding (i.e., prolonged OSPT) or as clinical bleeding. Routine clotting tests (OSPT and APTT) are insensitive indicators of vitamin K deficiency, and prolonged values occur only after vitamin K–dependent coagulation factors decrease to approximately 35% of normal activity. Therefore, a prolonged OSPT in an animal with malabsorption would warrant immediate parenteral vitamin K\textsubscript{1} or K\textsubscript{3} administration. Since intramuscular injections in a hypoprothrombinemic animal can produce hematomas and intravenous administration of vitamin K\textsubscript{1} has been associated with anaphylaxis, subcutaneous injection of vitamin K preparations in normovolemic animals is the preferred parenteral route of administration. Because of the time required (4–8 hours) to increase clotting factor activity following vitamin K supplementation, animals with clinical bleeding should receive fresh plasma or blood transfusions prior to vitamin therapy.

Surgical biopsy of the intestines is frequently used to make a specific diagnosis in animals with malabsorption. Since clotting parameters are a poor determinant of vitamin K levels, animals with intestinal malabsorption should routinely receive parenteral vitamin K prophylactically 8–12 hours before surgery. The time interval is critical because of the delay in carboxylation of vitamin K–dependent proteins and the relatively short half-lives of these proteins (e.g., factor VII, 6 hours) and vitamin K, especially vitamin K\textsubscript{3}.

Animals with malabsorption in a home environment should receive daily oral supplementation with vitamin K. Because of its colonic absorption and lower lipid solubility, vitamin K\textsubscript{3} is the most effective oral form of vitamin K in these animals. Vitamin K\textsubscript{3} is associated with a dose-dependent Heinz body hemolytic anemia and methemoglobinemia in human beings\textsuperscript{30} and dogs.\textsuperscript{31} Reactions involving vitamin K\textsubscript{3} and the metabolic intermediate, semiquinone, deplete RBC-glutathione and inhibit in vitro activity of hepatic glucuronyl transferase.\textsuperscript{31,32} Cats are very sensitive to oxidant drugs and have low levels of hepatic glucuronyl transferase\textsuperscript{33}; therefore, hemolytic anemia and, possibly, hepatotoxicity are anticipated with inappropriately high doses of vitamin K\textsubscript{3} in this species. A safe but effective dose of vitamin K\textsubscript{3} has not been established for the cat. Although massive doses of vitamin K\textsubscript{1} have been administered to infants without resultant hemolysis,\textsuperscript{30} it should not be given indiscriminately to cats because hemolytic anemia was produced in a dog that received an excessively large dose.\textsuperscript{31}

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Erratum

In the article "Effect of Thyrotropin Storage on Thyroid-Stimulating Hormone Response Testing in Normal Dogs" by D. S. Bruyette, R. W. Nelson, and G. D. Bottoms, which appeared in the April-June 1987 issue, an error occurred on page 92 in the first sentence of the second paragraph of the "Results" section. The sentence should read, "In seven of the eight dogs, there was no significant difference (P > 0.05) between the post-TSH T3 concentrations or the post-TSH T4 concentrations for the duration of the study (Figs. 1, 2)."