ISSN: 2583-8288
Popular Article
Published on: 24.**08.2024**

Iron Deficiency Anemia in Animals - Pathophysiology and Management

Dr. J. Shashank[1]*, Dr. M. Fibi Rani[2]

[1]Subject Matter Specialist (Veterinary Medicine), Krishi Vigyan Kendra, P.V. Narsimha Rao Telangana Veterinary University, Mamnoor, Warangal.

[2]PhD Scholar, Division of Parasitology, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly.

DOI:10.5281/Vettoday.13620008

Abstract

Iron is required by almost all living species and plays an important role in a variety of metabolic processes. The primary function of haemoglobin is to transport oxygen. Iron deficiency anaemia in dogs and cats is typically caused by persistent blood loss and can be detected unintentionally since animals may have evolved to the anaemia. Severe iron shortage is distinguished by a microcytic, hypochromic, possibly severe anaemia with varying regeneration responses.

Introduction

Iron deficiency anaemia in dogs and cats is usually caused by persistent external blood loss and does not develop until iron stores in the tissues have been depleted. Treatment consists of addressing the underlying syndrome that causes blood loss and replenishing iron reserves.

Iron metabolism and homeostasis

Iron in the form of heme is essential for several metabolic activities, including oxygen transport in haemoglobin. Iron is also a component of several enzymes, including cytochromes, which are required for energy production and drug metabolism. Through the donation or acceptance of an electron, iron exists in either a reduced ferrous (Fe^{2+}) or an oxidative ferric (Fe^{3+}) state. The majority of functional iron is contained in hemoglobin, with smaller quantities found in myoglobin and cytochromes (Crichton, 2009). The liver, which is the site of the production of iron transport proteins, contains the largest non-functional iron stores either as ferritin or hemosiderin. Ferritin is both diffuse and soluble and is the primary iron storage protein. Hemosiderin is similar in structure, but has more iron relative to protein and is insoluble. Iron is also stored in reticuloendothelial cells of the bone marrow and spleen, but is not commonly stored in the bone marrow of cats (Harvey *et al.*, 2008). Dietary iron is absorbed mainly in the duodenum. Only ferrous iron is absorbed, and it is transported across the apical membrane of the enterocyte by divalent metal transporter 1. It is then transferred across the enterocyte to the basolateral membrane by an unknown mechanism. Iron is exported across the basolateral membrane of enterocytes by ferroportin, then bound to transferrin in the plasma and transported for use in target organs and/or storage (Knovich et al., 2009). Body stores of iron are tightly regulated to provide adequate iron for cellular needs without developing toxicity from excess. Because the body lacks a mechanism to excrete excessive iron, homeostasis is tightly controlled by limiting enteric iron uptake through impaired efflux from enterocytes. Iron efflux is regulated by hepcidin, a recently discovered hormone produced by hepatocytes. When iron stores are adequate or high, hepcidin is released and binds to intestinal ferroportin causing internalization and destruction of ferroportin. The

reduction in ferroportin causes absorbed dietary iron to remain in the enterocyte, where it is lost by enterocyte shedding. Conversely, when iron stores are low, hepcidin production and secretion are suppressed, increasing iron efflux from enterocytes into the blood (Figure 1) (Crichton, 2009).Tight homeostasis of iron is critical, as excessive iron accumulation in hepatocytes can cause pathologic damage, termed hemochromatosis. Subsequently, increased fibrosis and cirrhosis can occur. In contrast, iron deficiency leads to the depletion of body iron stores, and ultimately, iron deficiency anemia and other metabolic dysfunctions. The duodenum's ability to absorb dietary iron is very limited but can be upregulated. However, the upregulation in iron absorption secondary to chronic blood loss and resulting iron deficiency may be insufficient to restore adequate iron homeostasis, even after blood loss has been arrested (Weiss, 2010).

Causes of iron deficiency anemia

Iron deficiency results when either dietary intake does not meet the body's requirement or

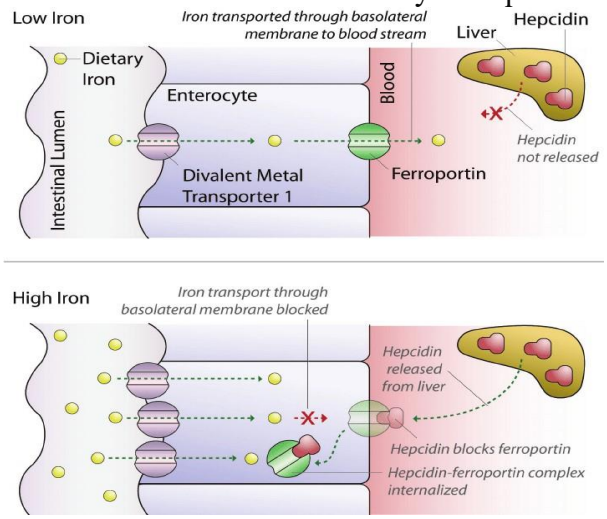

Figure 1: Mechanism of intestinal iron absorption at low and high serum iron levels

and is higher in puppies and kittens due to their rapid growth. Inadequate intake is rare except in nursing animals due to the low concentration of iron in milk. Inadequate dietary iron intake does not occur in dogs and cats fed commercial pet foods, but can rarely occur with home-cooked and vegetarian diets without appropriate iron supplementation (Michel, 2006). High iron content is found in meat products (such as liver, heart, and muscle), but also in brewer's yeast, wheat germ, egg yolks, oysters, some dried beans, and some fruits. Green vegetables, cereals, fish, and fowl have an intermediate amount of iron. Foods low in iron includes milk, milk products, and most non-green vegetables.

During acute blood loss, body iron stores are generally sufficient for accelerated erythropoiesis and subsequent iron uptake is adequate for restoring iron homeostasis. Iron deficiency anemia only develops over weeks to months of chronic or recurrent blood loss in both juvenile and adult animals. Causes of chronic external blood loss include ectoparasitism, endoparasitism, hematuria, epistaxis, hemorrhagic skin pathology, coagulopathy, thrombocytopenia, thrombocytopathia, and gastrointestinal hemorrhage. Gastrointestinal hemorrhage can result from primary gastrointestinal disease (benign or malignant neoplasm, ulceration, arteriovenous fistula), ulcerogenic drugs (most commonly non-steroidal anti-inflammatory agents and corticosteroids), or secondary to systemic diseases such as renal and hepatic diseases, bleeding disorders, and hypoadrenocorticism (White and Reine, 2009). Nursing animals are particularly prone to developing iron deficiency anemia due to lower body iron stores, larger requirements, and decreased intake from a milk-based diet. Surgical resection of the entire duodenum will result in iron malabsorption. Iron deficiency anemia can be induced iatrogenically through excessive phlebotomies of blood donor animals, as a regular blood donation of 450 mL removes approximately 200 mg of iron from the body. Finally, iron deficiency anemia can also be induced by repeated phlebotomies for diagnostic and monitoring purposes in smaller animals; the phlebotomy volume should not exceed 1% of the animal's body weight per week (Abrams-Ogg, 2010).

Pathogenesis of iron deficiency anemia

Iron deficiency anemia may be classified into 3 stages: storage iron deficiency, iron deficient erythropoiesis, and iron deficiency anemia. Initially, during blood loss, iron body stores are preferentially utilized for accelerated erythropoiesis. After depletion of body iron stores, erythropoiesis and production of other iron-containing proteins (such as myoglobin) become limited, leading to an overt iron deficiency anemia. Anemia is exacerbated as

iron-deficient erythrocytes have a shortened survival due to their fragility, which accelerates reticuloendothelial cell sequestration and destruction. The observed erythrocyte morphologic changes with the underlying iron deficiency reflect the severely hampered hemoglobin synthesis and are characterized by hypochromasia and microcytosis (Figure 2 &3). Furthermore, the hemoglobin-deficient erythroid precursors are thought to undergo additional mitoses while attempting to achieve ideal cytoplasmic hemoglobin levels, thereby exaggerating the microcytosis (Stockholm and Scott, 2002).

While normocytic normochromic erythrocytes contain approximately 1/3 hemoglobin, red blood cell indices of animals with iron deficiency anemia demonstrate progressive decreases in mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and mean corpuscular volume. Early iron deficiency states may not be suspected as the anemia may be initially normocytic and normochromic. However, evaluation of the erythrogram and reticulocyte count, along with novel parameters such as reticulocyte hemoglobin content, may provide an earlier indication of iron deficiency anemia once these assays are available in canine and feline commercial laboratories. Initially, reticulocytosis is present due to increased production and release of reticulocytes secondary to anemia. However, as iron stores are depleted and iron deficiency becomes more severe, the absolute reticulocyte count becomes inadequate for the degree of anemia. Furthermore, due to the lack of heme and reduced hemoglobin synthesis, the red blood cells become more fragile which can result in mild hemolysis, worsening the anemia.

Disease states with functional iron deficiency can occur when iron is not available for heme synthesis despite normal to increased body stores of iron. One example is anemia of inflammatory disease, which can be mistaken for iron deficiency anemia based on the hemogram. In this condition, serum iron levels are decreased secondary to iron sequestration in the liver, spleen, and bone marrow , which results in a functional iron deficiency, defective heme synthesis, and the formation of some microcytic and possibly hypochromic erythrocytes despite adequate body iron stores. Animals with chronic renal disease develop anemia, which is most commonly normocytic, normochromic, and non-regenerative. This anemia is mostly due to decreased renal erythropoietin synthesis, but chronic low-grade gastrointestinal hemorrhage with loss of iron and anemia of inflammatory disease can also contribute. Following treatment with recombinant human erythropoietin, the iron reserves can become limited and thus impair erythropoietin-induced erythropoiesis (Polzin, 2010).

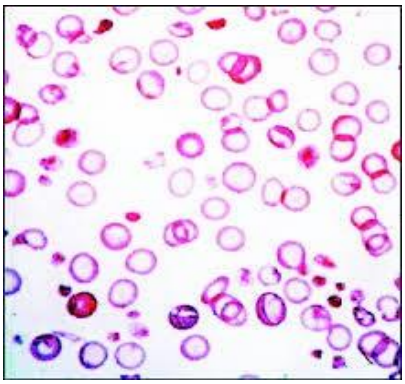

Figure 2: Blood smear of a dog with severe iron deficiency

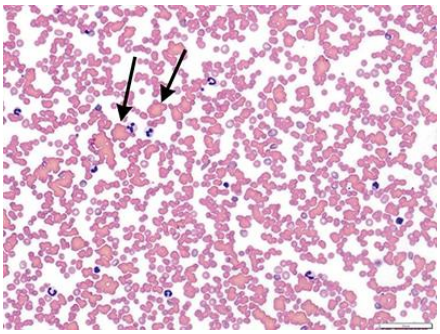

Figure 3: Grapelike clusters of agglutinated RBCs (arrows) can be seen in canine patients with immune-mediated hemolytic anemia (Wright-Giemsa stain; magnification, 200X).

Clinical findings

Clinical signs solely due to anemia do not occur until anemia is severe and can include lethargy, decreased exercise tolerance, weakness, weight loss, retarded growth, and generalized malaise. While these signs are typical for any anemia, the development of pica is unique to iron deficiency anemia. Clinical signs appear to arise from not only the anemia but also from a lack of other iron-containing proteins such as myoglobin,

cytochrome c, and metabolic enzymes. Evidence of blood loss, such as melena, hematuria, or bleeding from other sites may be noted by the owners or at the time of the examination. Physical examination results may be normal except pallor or may reflect the underlying disease process. The presence of fleas, other ectoparasites, or hemorrhagic dermal pathology may be seen. If the anemia is severe, bounding pulses, arrhythmia, and a systolic heart murmur may be noted. Melena or hematochezia may be noted on the examination of feces, on digital rectal examination, or the thermometer but may only be visible intermittently. Animals are usually normovolemic to even slightly hypervolemic. While animals can develop severe compensatory cardiomegaly to increase cardiac output, tachypnea and tachycardia are unusual with iron deficiency anemia.

Diagnostic approach to iron deficiency anemia

Diagnostic approach include complete blood (cell) count (CBC) with reticulocyte count, fecal occult blood test, serum iron parameters, coagulation parameters, biochemical profile (including albumin, globulins, and hepatic and renal parameters), urinalysis and abdominal imaging. Animals with chronic blood loss frequently have a marked reactive thrombocytosis which may exceed 1 x 10^6/µL; the mechanism causing the thrombocytosis is still undetermined. Furthermore, decreased neutrophil production due to iron deficiency may lead to neutropenia; the mechanism for this is also unknown.

Therapeutic approach to iron deficiency anemia

The general principles of treating animals with iron deficiency anemia include preventing further blood loss, correcting the anemia if severe, initiating iron supplementation, and addressing the underlying disease. A blood transfusion may be necessary before receiving results from diagnostic evaluation if the animal is severely anemic and demonstrating signs of hypoxemia

Volume to be transfused (mL) = Desired packed cell volume (PCV) increase x body weight (kg) x 2.

Blood transfusions bear inherent risks including acute hemolytic and hypersensitivity reactions, hemolysis, infectious disease transmission, and volume overload (Polzin, 2010). Iron supplementation is generally needed to restore iron homeostasis and should be based on the degree of anemia, underlying pathology, red blood cell count, serum iron panel, and erythrocyte morphology. Ferrous sulfate can be administered at a dose of 15 mg iron salt per kg body weight (5 mg elemental iron per kg) divided every 8 to 12 h . One of the more common side effects of oral iron supplementation is gastrointestinal irritation, which can be minimized by dividing the dose several times a day. Interaction with other drugs is recognized and should be avoided. For instance iron can bind tetracycline and other drugs thereby decreasing the efficacy of both; these and other drugs should be administered several hours apart if given concurrently. Moreover, the bioavailability of iron is decreased if administered concurrently with antacids, eggs, or milk.

Parenteral forms of iron other than red blood cell products can be administered if oral supplementation causes side effects, is ineffective due to malabsorption, if the animal is vomiting, or if compliance is poor. A single dose of iron can also be administered parenterally before initiation of oral supplementation. Iron dextran is absorbed primarily by the lymphatic system following intramuscular administration, and approximately 70% of the iron is absorbed from the injection site within days. Iron dextran can be given at a dose of 10 mg elemental iron per kg body weight weekly to dogs, and at a dose of 50 mg per cat once every 3 to 4 wk (3, 30). A small dose should be administered first as hypersensitivity reactions can occur. Other side effects of intramuscular iron include irritation and pain at the injection site (Plumb, 2008).

Intravenous iron administration in dogs and cats is rarely performed but is more common in humans. Several intravenous iron preparations are available in humans, including iron gluconate, iron sucrose, iron dextran, and ferric carboxymaltose; iron sucrose is considered the safest of the preparations. In humans, an initial test dose is given; if no adverse effects are noted, the remainder of the dose is administered over several hours. Adverse reactions from rapid infusion can include hypotension, tachycardia, dyspnea, and phlebitis. Currently, there is no reported dose of intravenous iron for dogs and cats; however, a weight-proportional dose similar to that used in humans (approximately 10 mg elemental iron per kg body weight) approximately once every 3 wk will likely

be effective and safe based on anecdotal unpublished accounts (Munoz *et al*., 2009).

Several months of iron supplementation may be necessary for red blood cell parameters to return to normal, and therapy should be continued beyond normalization of red blood cell parameters as body iron stores take much longer to be replenished. While serum iron would be expected to be normal or even high when being actively supplemented with iron, red blood cell indices should be monitored closely to gauge response to therapy and resolution of functional iron deficiency. Body iron stores are rarely assessed post-treatment, but measurement of serum ferritin and other iron parameters is warranted after termination of iron supplementation to ensure normalization.

Conclusion

In conclusion, iron is a vital element for multiple metabolic functions, most notably oxygen transport by hemoglobin. Iron deficiency anemia typically develops following chronic blood loss after iron body stores have been exhausted. Iron deficiency anemia is characterized by microcytosis and hypochromasia with inadequate regeneration, and low serum iron, iron saturation, and ferritin. If iron deficiency is not resolved, animals will often progress to severe anemia, which is surprisingly well-tolerated unless the animal is stressed. Samples for diagnostic testing should be obtained before treatment. Iron deficiency anaemia treatment comprises preventing further blood loss, administering oral and parenteral iron supplements, and treating the underlying condition. Patients with iron deficiency anaemia can have a fair prognosis if the underlying condition is treated properly.

References

Crichton R. Iron Metabolism: From Molecular Mechanisms to Clinical Consequences. 3rd ed. West Sussex, UK: John Wiley and Sons, 2009; **17** (56):141–325.

Harvey JW. Iron metabolism and its disorders. In: Kaneko JJ, Harvey JW, Bruss ML, eds. Clinical Biochemistry of Domestic Animals. 6th ed. Burlington, Massachusetts: Elsevier, 2008:259–285.

Knovich MA, Storey JA, Coffman LG, et al. Ferritin for the clinician. Blood Rev 2009;**23**:95–104.

Weiss DJ. Iron and copper deficiencies and disorders of iron metabolism. In: Weiss DJ, Wardrop KJ, eds. Schalm's Veterinary Hematology. 6th ed. Ames: Blackwell Publishing, 2010:167–171

Michel KE. Unconventional diets for dogs and cats. Vet Clin North Am Sm Anim Practice 2006;**36**:1269–1281.

White C and Reine N. Feline nonregenerative anemia: Pathophysiology and etiologies. Compend Contin Educ Vet 2009;**31**:E1–E19.

Abrams-Ogg T. Nonregenerative anemia. In: Ettinger SJ, Feldman EC, eds. Textbook of Veterinary Internal Medicine. 7th ed. St. Louis, Missouri: Elsevier Saunders, 2010:788–797

Stockholm SL and Scott MA. Fundamentals of Veterinary Clinical Pathology. 2nd ed. Ames, Iowa: Blackwell Publishing, 2002:105–150

Polzin DJ. Chronic kidney disease. In: Ettinger SJ, Feldman EC, eds. Textbook of Veterinary Internal Medicine. 7th ed. St. Louis, Missouri: Elsevier Saunders, 2010:1990–2021

Plumb DC. Plumb's Veterinary Drug Handbook. 6th ed. Ames, Iowa: Blackwell Publ, 2008:329–331 and 424–425.

Munoz M, Gomez-Ramirez S, Barcia-Erce JA. Intravenous iron in inflammatory bowel disease. World J Gastroenterol 2009;**1**5:4666–4674.