Iron is an essential mineral that is critical to many physiological processes including oxygen transport, DNA synthesis, and energy production. It is also a critical component for erythropoiesis, particularly in the development of proerythroblasts to mature RBC and hemoglobin synthesis. Therefore, overt iron deficiency or functional inability to transport iron will result in anemia.

In health, iron uptake and storage are tightly regulated. When iron stores are inadequate, ferrous iron is transported into duodenal enterocytes via divalent metal transporter 1 and exported into the bloodstream by ferroportin, the only known iron membrane exporter protein. It circulates bound primarily to transferrin and is either immediately used by tissues or stored as ferritin, which most accurately reflects total body iron status. When iron stores are adequate, the protein hepcidin binds to ferroportin, resulting in internalization of the complex, which prevents iron transfer from enterocytes into the blood stream, as well as export from other storage cells. Hepcidin production is also increased by inflammatory mediators, such as interleukin-6. Therefore, in inflammatory disease states, there is limited ability to access intracellular iron stores or absorb iron from the gastrointestinal (GI) tract, resulting in the development of a functional iron deficiency (FID).

FID was historically considered relatively refractory to oral iron supplementation due to this hepcidin-induced blockade. Oral iron supplementation is also poorly tolerated due to GI side effects. Due to reduced GI side effects, ability to bypass the hepcidin blockade, and improved response in human patients

Intravenous iron sucrose is safe but does not prevent development of anemia or iron deficiency in healthy cats undergoing serial venipuncture

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OBJECTIVE
To evaluate IV iron sucrose safety and impact on hematologic and iron indices in healthy cats.

ANIMALS
5 healthy research cats.

PROCEDURES
Cats were administered iron sucrose (0.5 mg/kg, IV) over 30 minutes. Monitoring for acute reactions (temperature, heart rate, respiratory rate, and blood pressure) was performed every 5 minutes during injection and every 15 minutes for an additional hour. Baseline, 24-hour, and 1-, 2-, and 3-week postinjection measurements of CBC with reticulocyte indices, iron panel (ferritin, total iron-binding capacity, and iron), calculated transferrin saturation (TSAT), and serum amyloid A (SAA) concentration were performed.

RESULTS
No cat experienced an acute drug reaction. SAA concentration was increased at 24 hours versus baseline. TSAT and ferritin decreased over time, with 3 cats developing concurrent functional iron deficiency (FID) and anemia. Hct (Spearman correlation $r_s = 0.805$), hemoglobin ($r_s = 0.770$), and reticulocyte hemoglobin content ($r_s = 0.581$) correlated with TSAT.

CLINICAL RELEVANCE
IV iron sucrose was well tolerated in healthy cats but was associated with transient increase in the systemic inflammatory marker SAA. Efficacy evaluation of dose based on iron deficit is needed in sick cats. Despite cumulative blood draw volume below recommended limits, anemia and FID were observed, which has important implications for experimental designs and serial hematologic monitoring. Further evaluation of inflammatory response to IV iron sucrose administration is warranted.
with both absolute and FID, parenteral iron supplemen-
tation is recommended. IM-administered iron is absorbed slowly, requiring 1 to 3 weeks for 90% lymphatic uptake. IM carries similar side-effect risks to IV-administered iron and is less effective in reaching target hemoglobin levels in some human disease processes; therefore, IV supplementation is recommended. High-molecular-weight iron dextran solutions administered IV resulted in serious adverse drug events. However, recent human studies have demonstrated the safety of lower-molecular-weight non-dextran-containing solutions, such as iron sucrose.

FID and anemia have been described in cats with chronic kidney disease and GI disease, and anemia increases all-cause morbidity in sick cats, warranting the need for effective supplementation methods. To the authors’ knowledge, there are no available data on administration of IV iron sucrose in cats. Therefore, the primary objective of this study was to evaluate the safety of IV iron sucrose in healthy cats through serial assessment of clinical parameters and systemic inflammatory markers. A secondary objective was to evaluate the impact of IV iron supplementation on CBC and reticulocyte parameters, as well as serum iron indices.

Materials and Methods

Study protocol

Five castrated male purpose-bred cats (median age, 1.33 years; range, 1.25 to 2.33 years), determined to be healthy by screening physical examination, CBC, and serum biochemistry panel, were enrolled prospectively. Cats were acclimated to their environment for 7 days prior to study initiation (T0). On T0, venipuncture was performed using a 22-gauge butterfly catheter from the medial or lateral saphenous vein for baseline serum amyloid A (SAA) measurement, serum iron panel (iron and ferritin concentrations and total iron-binding capacity [TIBC]), and CBC.

For iron administration, a 20-gauge IV catheter was placed into a cephalic or lateral saphenous vein. Baseline vital parameters (rectal temperature, heart rate, respiratory rate, and indirect blood pressure) were obtained. Cats were administered a 0.5-mg/kg dose of iron sucrose (Venofer; American Regent Inc) IV over 30 minutes. Iron sucrose was diluted to 3 mL total volume in sterile saline (0.9% NaCl) solution, resulting in a final concentration of 0.8 to 0.9 mg/mL administered to all cats. The above listed vital parameters were recorded every 5 minutes during administration and then every 15 minutes for 1 hour following administration. Serum amyloid A measurement, iron panel, and CBC were repeated at 24 hours (T1) and 1 (T2), 2 (T3), and 3 weeks (T4) postinjection. This study was approved by the Institutional Animal Care and Use Committee at Kansas State University (protocol 4441).

Sample collection, storage, and analysis

A maximum volume of 8 mL whole blood was collected from each cat per time point. The maximum blood draw volume was < 5% of circulating blood volume per week based on a circulating blood volume calculation of 55 mL/kg. Blood was immediately divided between EDTA (CBC) and serum (SAA and iron panel) tubes. Blood for serum was allowed to clot at room temperature (20 °C) and then centrifuged (3,500 rpm) for 15 minutes and separated immediately. Serum for SAA was stored at −80°C and analyzed in bulk at study completion using a commercially available immunoturbidimetric assay (University of Miami Miller School of Medicine Acute Phase Protein Laboratory). Serum for iron parameters was stored at 4 °C and analyzed within 1 wk through the Kansas State University Veterinary Diagnostic Laboratory. A commercially validated feline-specific ELISA (Comparative Hematology Laboratory, Kansas State Veterinary Diagnostic Laboratory) was used to measure ferritin. Transferrin and TIBC were measured using spectrophotometry (Cobas c501 chemistry analyzer; Roche Diagnostics). Transferrin saturation (TSAT) was calculated as iron concentration/TIBC X 100. The CBC with reticulocyte indices were performed immediately through the Kansas State Veterinary Diagnostic Laboratory (ADVIA 2120 Hematology System; Siemens Medical Solutions Inc).

Statistical analysis

Data were assessed for normality using the Shapiro-Wilk test. Due to small sample size and several variables failing normality assumptions, non-parametric tests were used. Data are reported as median (range). The Friedman test was used to compare median vital parameters, hematologic indices, iron indices, and SAA concentration over time, followed by Dunn correction for multiple comparisons, with P < 0.05 considered significant. The Spearman correlation (r) was used to compare iron indices, SAA concentration, and CBC parameters. Strength of correlation was defined as previously described (0 to 0.99 = negligible; 0.1 to 0.39 = weak; 0.4 to 0.69 = moderate; 0.7 to 0.89 = strong; and 0.9 to 1.0 = very strong). Bonferroni corrected P values for multiple comparisons were used.

For statistical analysis, cats were considered anemic if their Hct was below the lower limit of the laboratory reference interval (< 35%). Absolute iron deficiency was defined as a serum ferritin concentration below the lower limit of the reference interval ( < 82 ng/mL) and TSAT < 20%. FID was defined as a serum ferritin concentration > 100 ng/mL and TSAT < 20%. Cats with serum ferritin concentrations between 82 and 100 ng/mL and TSAT < 20% were considered to have a combination of absolute and functional iron deficiency. Statistical analysis was performed using commercial software (GraphPad Prism 9.1.2; GraphPad Software).

Results

Clinical tolerance

All 5 cats that were enrolled safely completed the study. No cat experienced significant changes in vital parameters (blood pressure [P = 0.82], heart rate, respiratory rate, and indirect blood pressure [Doppler]) were obtained. Cats were administered a 20-gauge IV catheter from the medial or lateral saphenous vein for baseline serum amyloid A (SAA) measurement, serum iron panel (iron and ferritin concentrations and total iron-binding capacity [TIBC]), and CBC. For iron administration, a 20-gauge IV catheter was placed into a cephalic or lateral saphenous vein. Baseline vital parameters (rectal temperature, heart rate, respiratory rate, and indirect blood pressure [Doppler]) were obtained. Cats were administered a 0.5-mg/kg dose of iron sucrose (Venofer; American Regent Inc) IV over 30 minutes. Iron sucrose was diluted to 3 mL total volume in sterile saline (0.9% NaCl) solution, resulting in a final concentration of 0.8 to 0.9 mg/mL administered to all cats. The above listed vital parameters were recorded every 5 minutes during administration and then every 15 minutes for 1 hour following administration. Serum amyloid A measurement, iron panel, and CBC were repeated at 24 hours (T1) and 1 (T2), 2 (T3), and 3 weeks (T4) postinjection. This study was approved by the Institutional Animal Care and Use Committee at Kansas State University (protocol 4441).
rate \( [P = 0.28] \), and respiratory rate \( [P > 0.99] \); Supplementary Table S1). Median SAA concentration was increased at 24 hours postinjection (3.90 mg/L; range, 1.30 to 27.70 mg/L), compared with that at baseline (1.20 mg/L; range, 0.60 to 8.40 mg/L; \( P = 0.03 \)), but was not associated with adverse clinical findings (Figure 1).

**Changes in hematologic indices over time**

Values for Hct \( (P < 0.01) \), hemoglobin (Hgb; \( P < 0.01 \)), mean cell volume \( (P < 0.01) \), and percentage of hypochromic reticulocytes \( (P = 0.03) \) decreased during the study period (Figure 2). Over the course of the study, 3 of 5 cats became anemic. In contrast, there was no difference in reticulocyte hemoglobin content (CHR) between baseline and any other study time point \( (P = 0.098) \).

**Changes in iron parameters over time**

Serum ferritin concentrations decreased over time, with lower concentrations at T3 compared with baseline (Figure 3). Values for TSAT insignificantly increased from T0, followed by a decrease over time, with a significant \( (P < 0.01) \) difference between T1 and T2. There was no difference in serum iron concentration or TIBC between baseline and any other time point.

Based on the defined ferritin cutoffs for iron deficiency, FID was observed in 4 cats at T2, 2 cats at T3, and 3 cats at T4. No cat developed an absolute iron deficiency based on serum ferritin concentration.

**Correlation of hematologic indices and iron parameters**

Values for Hct and Hgb were positively correlated with serum iron concentration and TSAT, and CHR was positively correlated with serum iron concentration (Table 1). Although not statistically significant, CHR was generally positively correlated with TSAT and TIBC. Conversely, the percentage of hypochromic reticulocytes was negatively correlated with TIBC. No correlations were observed between serum ferritin concentration and any hematologic parameter. Individual values for hematologic parameters and iron indices for each cat were summarized (Supplementary Table S2).

**Discussion**

IV iron sucrose administration at a dose of 0.5 mg/kg, administered over 30 minutes following dilution to 0.8 to 0.9 mg/mL, was clinically well tolerated in a small group of healthy cats. Few hematologic changes related to iron sucrose administration were noted. Rather, anemia and a pattern toward iron deficiency developed over 3 weeks. Correlation analysis between hematologic parameters and iron indices reinforced the nonspecificity of routine CBC parameters for iron deficiency.25,29–31
A metaanalysis revealed a lower relative risk of infusion reactions (compared with a placebo) following iron administration of lower-molecular-weight compounds (eg, iron sucrose; RR, 1.75; 95% CI, 0.69 to 4.43) versus iron dextran (RR, 3.10; 95% CI, 0.86 to 11.22).\(^{33}\) Iron sucrose also appears to be well tolerated in humans that have previously experienced AEs following administration of iron dextran.\(^{34}\) While uncommon, infusion reactions (eg, flushing, pruritus, or urticaria), neurologic complications (eg, paresthesia, weakness, or back pain), and hypotension have been reported. It should be noted that the risk of some reactions (eg, neurologic AEs) was not increased over placebo following metaanalysis, regardless of iron compound.\(^{35}\) The risk of minor infusion reactions decreases as the stability of carbohydrate complex binding to the iron core increases.

Because iron sucrose is considered moderately stable, monitoring for these reactions is still warranted,\(^{35}\) but none were observed in the cats of the present study. More serious AEs (eg, dyspnea or hypotension) are related to both the stability of the iron complex, as well as the speed of infusion. Respiratory rate was an unreliable parameter in this group of cats due to temperament, so subtle changes in tachypnea could have been overlooked. However, because the respiratory rate generally decreased following injection, and respiratory effort remained normal, a respiratory-related AE was considered unlikely. Other AEs that are reported in humans, such as paresthesia or myalgia, may be difficult to detect in feline patients. Progression of AEs has been noted over 24 hours following IV iron sucrose administration in humans.\(^{36}\) Although vital parameters were recorded for only 1 hour following administration, cats were directly monitored for several hours after infusion and then at the 24-hour time point, with no onset of adverse clinical signs in the intermediate period.

Consistent with what is reported in humans, a transient increase in the inflammatory marker SAA, considered a reliable marker of systemic inflammation in cats,\(^{37}\) was observed 24 hours after iron sucrose administration. Systemic inflammation secondary to IV iron administration is related to generation of reactive oxygen species.\(^{35}\) Due to the redox capacity of iron and inclusion in many enzymatic biochemical redox reactions, unbound iron (ie, not bound to transferrin or ferritin) leads to the generation of hydroxyl radicals. Increased markers of systemic inflammation (eg, interleukin-6, hepcidin, or C-reactive protein) have been noted in multiple in vivo and in vitro studies following administration of various IV iron formulations.\(^{35}\) Many in vitro models utilized much higher doses than are used clinically, which have the potential to overwhelm transferrin-binding capacity, and limit the extrapolation of risk to clinical patients.\(^{35}\) Importantly, while generation of reactive oxygen species and other inflammatory markers have been noted in human patients, these appear transient.\(^{38-42}\) Similarly, in the present study, the increased SAA concentrations were transient and no different at 1, 2, or 3 weeks postinjection of iron sucrose, compared with those at baseline. Additionally, the increased SAA concentrations were not associated with adverse clinical signs (eg, fever).

No significant changes in iron parameters (iron, ferritin, TIBC, or TSAT) were attributed to iron sucrose administration. This finding can be explained, in part, by the study design, as this was not designed as a pharmacokinetic study but rather designed with the objective to determine changes in

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**Figure 3**—Box-and-whisker plots of serum iron indices in the cats of Figure 1. A—Ferritin. B—Transferrin saturation (TSAT). C—Iron. D—Total iron-binding capacity (TIBC). The comparison indicated by the ends of the bracket is considered significant (*P < 0.05).

**Table 1**—Spearman correlation (\(r_s\)) between hematologic parameters and serum iron indices in 5 healthy cats administered iron sucrose (0.5 mg/kg, IV) with serial blood draws over 3 weeks.

| Variable | \(r_s\) | 95% CI | \(P\) value |
|----------|--------|--------|-------------|
| Hct and iron | 0.66 | 0.34 to 0.84 | < 0.001 |
| Hct and TSAT | 0.81 | 0.59 to 0.91 | < 0.001 |
| Hgb and iron | 0.71 | 0.43 to 0.87 | < 0.001 |
| Hgb and TSAT | 0.77 | 0.53 to 0.90 | < 0.001 |
| Chr and iron | 0.63 | 0.30 to 0.82 | < 0.001 |
| Chr and TSAT | 0.58 | 0.23 to 0.80 | 0.002 |
| Chr and TIBC | 0.58 | 0.23 to 0.80 | 0.002 |
| Percentage of hypochromic reticulocytes and TIBC | -0.64 | -0.83 to -0.31 | < 0.001 |

\(\text{CHr} = \text{Reticulocyte hemoglobin. Hgb = Hemoglobin. TIBC = Total iron-binding capacity. TSAT = Transferrin saturation.}\)
hematologic parameters and ferritin concentrations. Iron sucrose is rapidly cleared from the blood, with changes in transient parameters, such as serum iron concentration, TIBC, and TSAT, returning to baseline in < 24 hours. In humans, approximately 70% to 75% of iron sucrose undergoes renal elimination 4 to 24 hours following injection, respectively, with a half-life of 5 to 6 hours. Based on pharmacokinetic calculations, it would be expected that < 0.1 as a fraction of the administered dose would remain in circulation at 24 hours postinjection. Therefore, changes in serum iron, TIBC, or TSAT at any measured time point were not expected. More frequent, short-term sampling would be needed to evaluate pharmacokinetics of IV iron sucrose in cats. Importantly, while there was an insignificant increase in TSAT, neither TSAT nor TIBC (no change) at 24 hours postadministration suggested risk of iron overload at this dose, even in healthy cats without iron deficiency.

Based on human research, it was expected that peak iron sucrose utilization (ie, changes in ferritin) would be noted 2 to 3 weeks following injection and effects on erythropoiesis noted in 3 to 4 weeks. In contrast, both serum ferritin concentration and TSAT decreased, and anemia developed in the majority of these cats over the course of the study. Given the absence of other causes for anemia development, it was most likely iatrogenic due to repeated blood draw, which has important implications for both healthy and sick cats. Although the Institutional Animal Care and Use Committee protocol set the limit for sequential blood draw volume at 5% of circulating volume per week (approx 15 mL per cat), a substantially lower volume (less than or equal to 8 mL) was drawn within that timeframe. The iron deficiency that developed was characterized as functional, based solely on the defined serum ferritin concentrations and a TSAT for FID and absolute deficiency, respectively. Iatrogenic iron deficiency has been reported in humans secondary to repeated phlebotomy, with repeated venipuncture leading to a negative total body iron balance. Over time, as body stores are depleted, the ferritin concentration subsequently decreases and is the most likely cause for the decreasing ferritin and TSAT in this population. While the serum ferritin concentration in the cats of the present study did not decrease below the set threshold (< 82 ng/mL) to be categorized as an absolute deficiency, this might have occurred were repeated venipuncture continued. As SAA concentrations returned to baseline after the 24-hour time point and time to maximum SAA concentration in cats following an inflammatory stimulus is 24 to 48 hours, the effects of serial venipuncture were considered the most likely cause of anemia and FID rather than inflammation secondary to iron sucrose. A control group undergoing only venipuncture would be needed, although iatrogenic anemia has been previously described in cats following repeated blood draws. It should be noted that the study subjects referenced above consisted of sick, hospitalized cats, and comparisons of iron status or inflammatory markers were not performed. Concurrent measurement of additional inflammatory markers (eg, hepcidin) could also further clarify the impact of iron sucrose administration. This consideration is clinically relevant, as an inflammatory response secondary to iron sucrose could negate its beneficial effects.

Consistent with previous literature in dogs and cats, none of the conventional hematologic parameters (eg, mean cell volume) correlated with serum iron parameters. While the percentage of hypochromic reticulocytes has been cited as a more sensitive marker of iron-deficiency anemia in dogs, that variable was not correlated with any conventional CBC parameters (eg, Hct or Hgb), serum iron concentration, or TSAT in this study. This could have been due to low sample size or differences in reticulocyte parameter changes among species, as this value was not different in a previous study between cats with low versus normal serum iron concentrations. In contrast to several previous veterinary studies, CHr did not correlate with any iron parameters in this group of cats. Notably, no conventional CBC parameters or reticulocyte parameters (eg, CHr) correlated with serum ferritin concentration. This highlights the previously demonstrated insensitivity of hematologic parameters to predict total body iron status and underscores the importance of measuring serum ferritin in patients where iron deficiency is a concern. This is particularly important in cats where other methods to distinguish FID from absolute iron deficiency are either not available (eg, hepcidin) or not applicable to this species (eg, bone marrow iron stores).

The present study had several limitations. While IV iron sucrose appeared to be well tolerated in this group of cats, this group was small in number, limiting the ability to screen for rare AEs, which may be observed across a larger population. Furthermore, hypotensive reactions are related to speed of administration and suspected due to exceeding the rate of anaphylotoxin clearance, so safety cannot be extrapolated to shorter infusion times. Secondly, administration of iron sucrose to healthy cats and the dose chosen could have a limited effect on iron indices and hematologic parameters. As there was no iron deficit in this population, the dose was extrapolated from the effective maintenance dose in human pediatric patients. It is possible that a higher percent of cat dose or dose calculation based on iron deficit in sick cats (total iron deficit = weight [kg] X (target Hb – actual Hb) [g/L] X 2.4 + iron stores [mg]) would have a greater effect. Additionally, human studies suggest that healthy patients have a blunted response to iron supplementation compared with iron-deficient patients.

Assessment of iron sucrose efficacy was confounded by development of anemia and iron deficiency, warranting consideration of sampling protocols in future studies. While the cutoff for anemia was based on laboratory reference range and higher than the definition of anemia in other feline studies, the decreased Hct over the duration of the study remains clinically relevant, even though the magnitude of anemia was not clinically significant.
This study also did not compare IV iron administration to traditional iron supplementation methods in cats (eg, iron dextran). However, our goal was first to evaluate the safety of IV iron, and comparison among iron forms would be an objective for a different study. While IM administration is most common in cats, to the authors’ knowledge, efficacy in sick cats has not been evaluated. Lastly, although sample size likely limited evaluation of correlations between iron parameters and hematologic indices, most findings were consistent with previous literature.

This study provided preliminary evidence that IV iron sucrose is safe in healthy cats at a dose of 0.5 mg/kg when diluted to 0.9 mg/mL and administered over 30 minutes. Future studies screening for AEs in larger groups and evaluating doses based on iron deficit in cats with iron deficiency are warranted. While not the intent of this study, results showed that sequential blood draws below currently accepted limits have the potential to cause iron deficiency and anemia in cats. This finding should be considered both in future research study designs and in hospitalized cats that undergo serial hematologic monitoring over short periods of time.

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The authors declare that there were no conflicts of interest.

References

1. Crichton RR. Iron Metabolism: from Molecular Mechanisms to Clinical Consequences, 3rd ed. John Wiley & Sons; 2009. doi: 10.1002/9780470010303.
2. Camaschella C, Pagani A, Nai A, Silvestri L. The mutual control of iron and erythropoiesis. J Lab Hematol. 2016;38(Suppl 1):S20–26. doi: 10.1111/jlh.12505.
3. Harvey JW. Iron metabolism and its disorders. In: Bruess ML, Harvey JW, Kaneko JJ, eds. Clinical Biochemistry of Domestic Animals. 6th ed. Academic Press; 2008: 259–285. doi: 10.1006/rhbe.2000.0009-X.
4. Knovich MA, Storey JA, Coffman LG, Torti SV, Torti FM. Ferritin for the clinician. Blood Rev. 2009;23(3):95–104. doi: 10.1016/j.bler.2008.08.001.
5. Nemeth E, Tuttle MS, Powelson J, et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. Science. 2004;306(5670):2090–2093. doi: 10.1126/science.1104742.
6. Weiss DJ. Iron and copper deficiencies and disorders of iron metabolism. In: Weiss D, Wardrop KJ, eds. Schalm’s Veterinary Hematology. 6th ed. Wiley-Blackwell; 2010: 167–171.
7. Goodnough LT. Iron deficiency syndromes and iron-restricted erythropoiesis (CME). Transfusion. 2012;52(7):1564–1592. doi: 10.1111/j.1537-2995.2011.03495.x.
8. Meléndez-Lazo A, Tvarijonaviciute A, Córón JJ, Planell-Las M, Pastor J. Evaluation of the relationship between selected reticulocyte parameters and inflammation determined by plasma C-reactive protein in dogs. J Comp Pathol. 2015;152(4):304–312. doi: 10.1016/j.jcpa.2015.01.008.
9. Schrage B, Rubsam N, Schulz A, Munzel T, Pfeiffer N, Wild PS. Iron deficiency is a common disorder in general population and independently predicts all-cause mortality: results from the Gutenberg Health Study. Clin Res Cardiol. 2020;109(11):1352–1357. doi: 10.1007/s00392-020-01631-y.
10. Cook JD, Skikne BS, Baynes RD. Iron deficiency: the global perspective. Adv Exp Med Biol. 1994;356:219–228. doi: 10.1007/978-1-4615-2554-7_24.
11. Hyder SM, Persson LA, Chowdhury AM, Ekström EC. Do side-effects reduce compliance to iron supplementation? A study of daily- and weekly-dose regimens in pregnancy. J Health Popul Nutr. 2002;20(2):175–179.
12. Makrides M, Crowther CA, Gibson RA, Gibson RS, Skeaff CM. Efficacy and tolerability of low-dose iron supplements during pregnancy: a randomized controlled trial. Am J Clin Nutr. 2003;78(1):145–153. doi: 10.1093/ajcn/78.1.145.
13. Maslovska I. Intravenous iron in a primary-care clinic. Am J Hematol. 2005;78(4):261–264. doi: 10.1002/ajh.20271.
14. Goddard AF, James MW, McIntyre AS, Scott BB. Guidelines for the management of iron deficiency anaemia. Gut. 2011;60(10):1309–1316. doi: 10.1136/gut.2010.228874.
15. Gordon M, Sinopoulou V, Iheozor-Ejiofor Z, et al. Interventions for treating iron deficiency anaemia in inflammatory bowel disease. Cochrane Database Syst Rev. 2021;1(1):CD013529. doi: 10.1002/14651858.CD013529.pub2.
16. Hedenus M, Karlsson T, Ludwig H, et al. Intravenous iron alone resolves anemia in patients with functional iron deficiency and lymphoid malignancies undergoing chemotherapy. Med Oncol. 2014;31(12):302. doi: 10.1007/s12032-014-0302-3.
17. Katsanos K, Cavalier E, Ferrante M, et al. Intravenous iron therapy restores functional iron deficiency induced by infliximab. J Crohn’s Colitis. 2007;12(9):97–105. doi: 10.1016/j.jcch.2007.08.005.
18. Beresford CR, Golberg L, Smith JP. Local effects and mechanism of absorption of iron preparations administered intramuscularly. Br J Pharmacol Chemother. 1957;12(1):107–114. doi: 10.1111/j.1476-5381.1957.tb01371.x.
19. Wali A, Musthaq A, Nilofer. Comparative study-efficacy, safety and compliance of intravenous iron sucrose and intramuscular iron sorbitol in iron deficiency anemia of pregnancy. J Pak Med Assoc. 2002;52(9):392–395.
20. Nissenson AR, Charytan C. Controversies in iron management. Kidney Int. 2003; 87:564–71. doi: 10.1046/j.1425-7556.2003.s21870.10.x.
21. Silverstein SB, Rodgers GM. Parenteral iron therapy options. Am J Hematol. 2004;76(1):74–78. doi: 10.1002/ajh.20056.
22. Auerbach M, Macdougall IC. Safety of intravenous iron formulations: facts and folklore. Blood Transfus. 2014;12(3):296–300. doi: 10.2450/2014.0094-14.
23. Goldstein SL, Morris D, Warday BA. Comparison of the safety and efficacy of 3 iron sucrose iron maintenance regimens in children, adolescents, and young adults with CKD: a randomized controlled trial. Am J Kidney Dis. 2013;61(4):588–597. doi: 10.1053/j.ajkd.2012.10.019.
24. Gest J, Langston C, Eatroff A. Iron status of cats with chronic kidney disease. J Vet Intern Med. 2015;29(6):1486–1493. doi: 10.1111/jvim.13630.
25. Hunt A, Jugan MC. Anemia, iron deficiency, and cobalamin deficiency in cats with chronic gastrointestinal disease. J Vet Intern Med. 2021;35(1):172–178. doi: 10.1111/jvim.15962.
26. von Roedern M, Buriko Y, Prittie J, Lamb K. Investigation of iron status and markers of inflammation in anaemic and non-anaemic hospitalised cats. J Small Anim Pract. 2017;58(6):323–329. doi: 10.1111/jsap.12658.
27. Schober BC, Schwarte LA. Correlation coefficients: appropriate use and interpretation. Anesth Analg. 2018;126(5):1763–1768. doi: 10.1213/ANE.0000000000002864.
28. Reinsch W, Staun M, Bhandari S, Muñoz M. State of the iron: how to diagnose and efficiently treat iron deficiency anemia in inflammatory bowel disease. J Crohn’s Colitis. 2013;7(6):429–440. doi: 10.1016/j.crohns.2012.07.031.

29. Fry MM, Kirk CA. Reticulocyte indices in a canine model of nutritional iron deficiency. Vet Clin Path. 2006;35(2):172–181.

30. Radakovich LB, Santageko KS, Oliver CS. Reticulocyte hemoglobin content does not differentiate true from functional iron deficiency in dogs. Vet Clin Path. 2015;44(4):511–518. doi: 10.1111/vcp.12294.

31. Schaefer DM, Stokol T. The utility of reticulocyte indices in distinguishing iron deficiency anemia from anemia of inflammatory disease, portosystemic shunting, and breed-associated microcytosis in dogs. Vet Clin Path. 2015;44(1):109–119. doi: 10.1111/vcp.12219.

32. Walters BA, Wyck DB. Benchmarking iron dextran sensitivity: reactions requiring resuscitative mediation in incident prevalent patients. Nephrol Dial Transplant. 2005;20(7):1438–1442. doi: 10.1093/ndt/gfh811.

33. Avni T, Bieber A, Grossman A, Green H, Leibovici L, Gafter-Ulofsky S. To induce oxidative and nitrosative stress. Br J Pharmacol. 2013;161(1):12–23. doi: 10.1016/j.bjp.2014.10.007.

34. Van Wyck DB, Cavallo G, Spinowitz BS, et al. Safety and efficacy of iron sucrose in patients sensitive to iron dextran. Am J Kidney Dis. 2000;36(1):88–97. doi: 10.1053/ajkd.2000.8276.

35. Koskenkorva-Frank TS, Weiss G, Koppenol WH, Burckhardt S. The complex interplay of iron metabolism, reactive oxygen species, and reactive nitrogen species: Insights into the potential of various iron therapies to induce oxidative and nitrosative stress. Free Radic Biol Med. 2013;65:1174–1194. doi: 10.1016/j.freeradbiomed.2013.09.001.

36. Louzada ML, Hsia CC, Al-Ani F, Ralley F, Xenocostas A, Martin J. Randomized double-blind safety comparison of intravenous iron dextran versus iron sucrose in an adult non-hemodialysis outpatient population: a feasibility study. BMC Hematol. 2016;16:1–8.

37. Sasaki K, Ma Z, Khatlani TS, Okuda M, Inokuma H, Onishi T. Changes in concentrations of serum amyloid A protein, α1-acid glycoprotein, haptoglobin, and C-reactive protein in feline sera due to induced inflammation and surgery. Vet Immunol Immunopathol. 1999;68(1):91–98. doi: 10.1016/S0165-2427(99)00012-4.

38. Pai AB, Conner T, McGuade CR, Olp J, Hicks P. Non transferrin bound iron, cytokine activation and intracellular reactive oxygen species generation in hemodialysis patients receiving intravenous iron dextran or iron sucrose. Biometals. 2015;24(4):603–613. doi: 10.1007/s10534-011-9409-6.

39. Argawal R, Vasavada N, Sachs NG, Chase S. Oxidative stress and renal injury with intravenous iron in patients with chronic kidney disease. Kidney Int. 2004;65(6):2279–2289. doi: 10.1111/j.1523-1755.2004.00648.x.

40. Malindretos P, Sarafidis PA, Rudenco I, et al. Slow intravenous iron administration does not aggravate oxidative stress and inflammatory biomarkers during hemodialysis: a comparative study between iron sucrose and iron dextran. Am J Nephrol. 2007;27(6):572–579. doi: 10.1159/000107928.

41. Mitsopoulos E, Lysitska A, Pateinakis P, et al. Efficacy and safety of a low monthly dose of intravenous iron sucrose in peritoneal dialysis patients. Int Urol Nephrol. 2020;52(2):387–392. doi: 10.1007/s11255-019-02362-4.

42. Steffanson BV, Haraldsson B, Nilsson U. Acute oxidative stress following intravenous iron injection in patients on chronic hemodialysis: a comparison of iron-sucrose and iron-dextran. Nephron Clin Pract. 2011;118(3):249–256. doi: 10.1159/000321645.

43. Danielson BG, Salomonson T, Derendorf H, Geisser P. Pharmacokinetics of iron(III)-hydroxide sucrose complex after a single intravenous dose in healthy volunteers. Arzneimittelforschung. 1996;46(6):615–621.

44. Geisser P, Burckhardt S. The pharmacokinetics and pharmacodynamics of iron preparations. Pharmaceutics. 2011;3(1):12–33. doi: 10.3390/pharmaceutics3010012.

45. Mainous AG, Gill JM, Carek PJ. Elevated serum transferrin saturation and mortality. Ann Fam Med. 2004;2(2):133–138. doi: 10.1370/afm.25.

46. Beshara S, Lundqvist H, Sundin J, et al. Pharmacokinetics and red cell utilization of iron(III)-hydroxidesucrose complex in anemic patients: a study using positron emission tomography. Br J Haematol. 1999;104(2):296–302. doi: 10.1046/j.1365-2141.1999.01179.x.

47. Kalantar K, Streja E, Miller JE, Nissenson AR. Intravenous iron versus erythropoiesis-stimulating agents: friends or foes in treating chronic kidney disease anemia? Adv Chronic Kidney Dis. 2009;16(2):143–151. doi: 10.1053/j.ackd.2008.12.008.

48. Barton JC, Bottomley SS. Iron deficiency due to excessive therapeutic phlebotomy in hemochromatosis. Am J Hematol. 2000;65(3):223–226.

49. Kajikawa T, Furuta A, Onishi T, Tajima T, Sugii S. Changes in concentrations of serum amyloid A protein, α1-acid glycoprotein, haptoglobin, and C-reactive protein in feline sera due to induced inflammation and surgery. Vet Immunol Immunopathol. 1999;68(1):91–98. doi: 10.1016/S0165-2427(99)00012-4.

50. Balakrishanan A, Drobatz KJ, Reineke EL. Development of anemia, phlebotomy practices, and blood transfusion requirements in 45 critically ill cats (2009-2011). J Vet Emerg Crit Care. 2016;26(3):406–411. doi: 10.1111/vec.12363.

51. Szebeni J, Fishbane S, Hedenus M, et al. Hypersensitivity to intravenous iron: classification, terminology, mechanisms and management. Br J Pharmacol. 2015;172(21):5025–5036. doi: 10.1111/bph.13268.

52. Ganzi AM. Intravenous iron-dextran: therapeutic and experimental possibilities. Schweizerische Medizinische Wochenschrift. 1970;100(7):301–303.

53. Danielson BG. Structure, chemistry, and pharmacokinetics of intravenous iron agents. J Am Soc Nephrol. 2004;15(Suppl 2):S93–98. doi: 10.1097/01.ASN.0000143814.49713.C5.

Supplementary Materials

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