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(54) **METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON**

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A61K 31/715 (2006.01)
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(58) **Field of Classification Search** 514/53, 514/54; 556/146
See application file for complete search history.

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(57) **ABSTRACT**

The present invention generally relates to treatment of iron-related conditions with iron carbohydrate complexes. One aspect of the invention is a method of treatment of iron-related conditions with a single unit dosage of at least about 0.6 grams of elemental iron via an iron carbohydrate complex. The method generally employs iron carbohydrate complexes with nearly neutral pH, physiological osmolarity, and stable and non-immunogenic carbohydrate components so as to rapidly administer high single unit doses of iron intravenously to patients in need thereof.

57 Claims, 2 Drawing Sheets

FIGURE 1

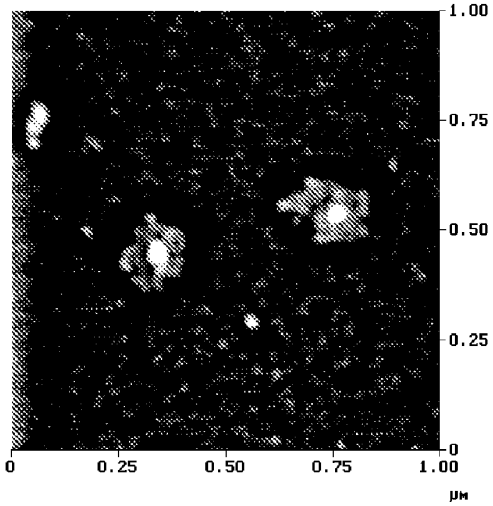


FIG. 1A

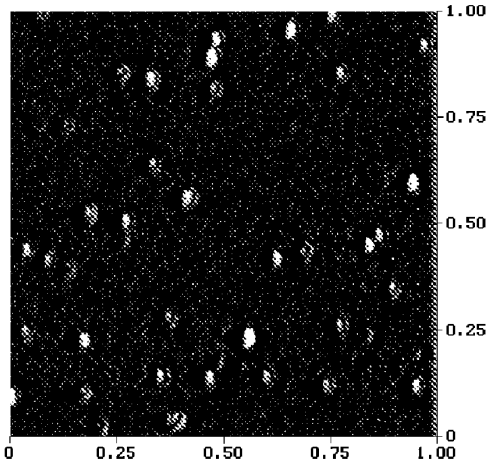


FIG. 1B

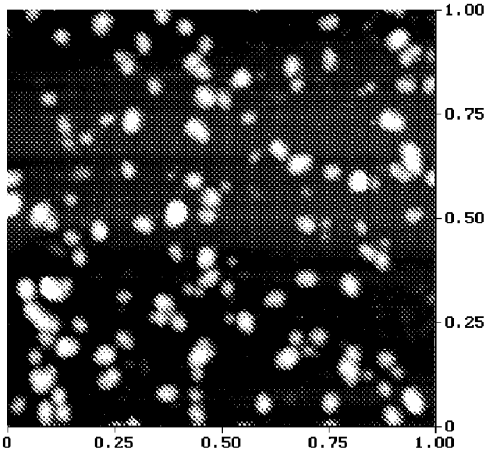
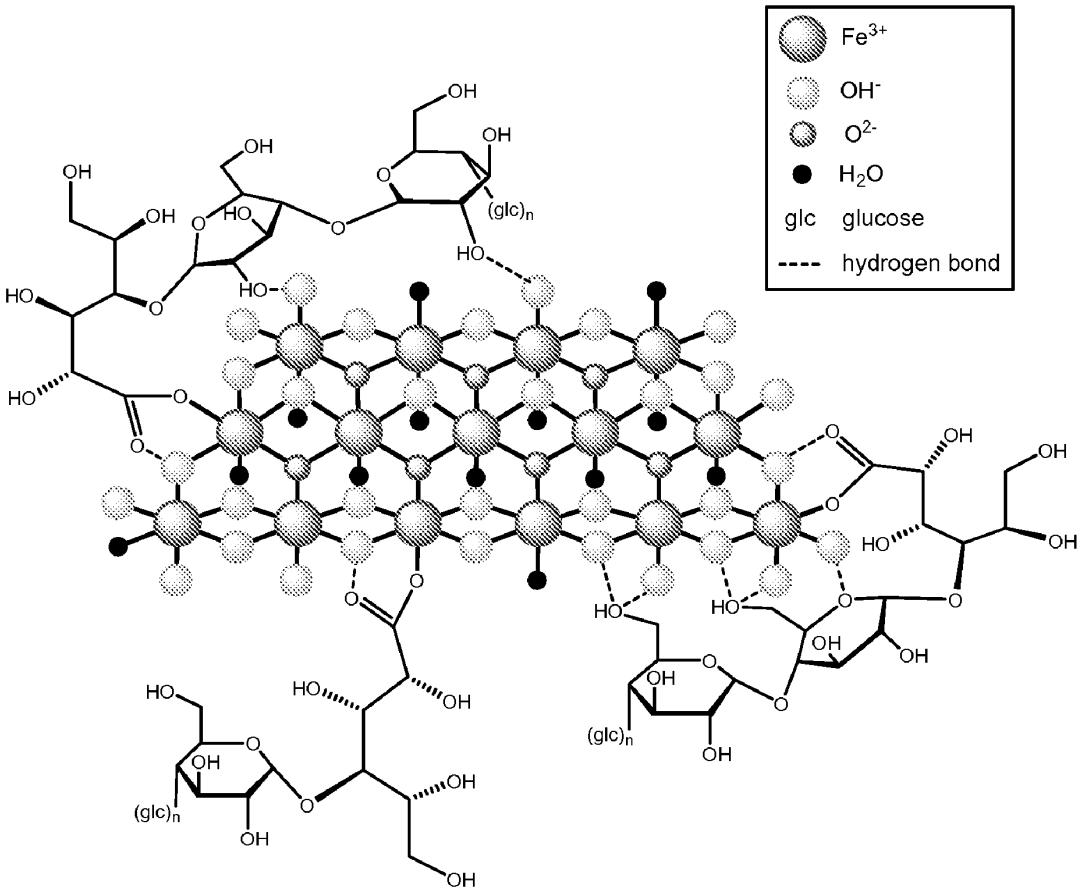


FIG. 1C

FIGURE 2



METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority from U.S. Provisional Application Ser. No. 60/757,119 filed on Jan. 6, 2006, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention generally relates to treatment of iron-related conditions with iron carbohydrate complexes.

BACKGROUND

Parenteral iron therapy is known to be effective in a variety of diseases and conditions including, but not limited to, severe iron deficiency, iron deficiency anemia, problems of intestinal iron absorption, intestinal iron intolerance, cases where regular intake of an oral iron preparation is not guaranteed, iron deficiency where there is no response to oral therapy (e.g., dialysis patients), and situations where iron stores are scarcely or not at all formed but would be important for further therapy (e.g., in combination with erythropoietin). Geisser et al., Arzneimittelforschung (1992) 42(12), 1439-1452. There exist various commercially available parenteral iron formulations. But many currently available parenteral iron drugs, while purportedly effective at repleting iron stores, have health risks and dosage limitations associated with their use.

Currently available parenteral iron formulations approved for use in the U.S. include iron dextran (e.g., InFed, Dexferrum), sodium ferric gluconate complex in sucrose (Ferrlecit), and iron sucrose (Venofer). Although serious and life-threatening reactions occur most frequently with iron dextran, they are also known to occur with other parenteral iron products. In addition, non-life threatening reactions such as arthralgia, back pain, hypotension, fever, myalgia, pruritus, vertigo, and vomiting also occur. These reactions, while not life-threatening, often preclude further dosing and therefore iron repletion.

Iron dextran, the first parenteral iron product available in the United States (US), has been associated with an incidence of anaphylactoid-type reactions (i.e., dyspnea, wheezing, chest pain, hypotension, urticaria, angioedema). See generally Fishbane, Am J Kidney Dis (2003) 41 (5Suppl), 18-26; Landry et al. (2005) Am J Nephrol 25, 400-410, 407. This high incidence of anaphylactoid reactions is believed to be caused by the formation of antibodies to the dextran moiety. Other parenteral iron products (e.g., iron sucrose and iron gluconate) do not contain the dextran moiety, and the incidence of anaphylaxis with these products is markedly lower. Fishbane, Am J Kidney Dis (2003) 41(5Suppl), 18-26; Geisser et al., Arzneimittelforschung (1992) 42(12), 1439-52. However, the physical characteristics of, for example, iron gluconate and iron sucrose lead to dosage and administration rate limitations. Negative characteristics include high pH, high osmolarity, low dosage limits (e.g., maximum 500 mg iron once per week, not exceeding 7 mg iron/kg body weight), and the long duration of administration (e.g., 100 mg iron over at least 5 minutes as an injection; 500 mg iron over at least 3.5 hours as a drip infusion). Furthermore, injectable high molecular mass substances produce more allergic reactions than the corresponding low molecular mass substances. Geisser et al. (1992) *Arzneimittelforschung* 42: 1439-1452.

Ferumoxytol is a newer parenteral iron formulation but limited information is available as to its efficacy and administration. See e.g., Landry et al. (2005) Am J Nephrol 25, 400-410, 408; and Spinowitz et al. (2005) Kidney Intl 68, 1801-1807; U.S. Pat. No. 6,599,498.

Various pharmacokinetic studies suggest that doses of iron complexes higher than 200 mg of iron are generally unsuitable and that the conventional therapy model prescribes repeated applications of lower doses over several days. See Geisser et al., (1992) *Arzneimittelforschung* 42: 1439-1452. For example, to achieve iron repletion under current therapy models, a total dose of 1 g typically requires 5 to 10 sessions over an extended period of time. These delivery modes incur significant expense for supplies such as tubing and infusate, costly nursing time, multiple administrations, and patient inconvenience.

SUMMARY OF THE INVENTION

Among the various aspects of the present invention is the provision of a method of treatment of iron-associated diseases, disorders, or conditions with iron formulations. Briefly, therefore, the present invention is directed to use of iron carbohydrate complexes that can be administered parenterally at relatively high single unit dosages, thereby providing a safe and efficient means for delivery of a total dose of iron in fewer sessions over the course of therapeutic treatment.

The present teachings include methods of treating a disease, disorder, or condition characterized by iron deficiency or dysfunctional iron metabolism through the administration of at least 0.6 grams of elemental iron via a single unit dosage of an iron carbohydrate complex to a subject that is in need of such therapy.

In various embodiments, the method treats anemia. In some embodiments, the anemia is an iron deficiency anemia, such as that associated with chronic blood loss; acute blood loss; pregnancy; childbirth; childhood development; psychomotor and cognitive development in children; breath holding spells; heavy uterine bleeding; menstruation; chronic recurrent hemoptysis; idiopathic pulmonary siderosis; chronic internal bleeding; gastrointestinal bleeding; parasitic infections; chronic kidney disease; dialysis; surgery or acute trauma; and chronic ingestion of alcohol, chronic ingestion of salicylates, chronic ingestion of steroids; chronic ingestion of non-steroidial anti-inflammatory agents, or chronic ingestion of erythropoiesis stimulating agents. In some aspects, the anemia is anemia of chronic disease, such as rheumatoid arthritis; cancer; Hodgkins leukemia; non-Hodgkins leukemia; cancer chemotherapy; inflammatory bowel disease; ulcerative colitis thyroiditis; hepatitis; systemic lupus erythematosus; polymyalgia rheumatica; scleroderma; mixed connective tissue disease; Sojgren's syndrome; congestive heart failure/cardiomyopathy; or idiopathic geriatric anemia. In some embodiments, the anemia is due to impaired iron absorption or poor nutrition, such as anemia associated with Crohn's Disease; gastric surgery; ingestion of drug products that inhibit iron absorption; and chronic use of calcium. In various embodiments, the method treats restless leg syndrome; blood donation; Parkinson's disease; hair loss; or attention deficit disorder.

In various embodiments, the single dosage unit of elemental iron is between at least about 0.6 grams and 2.5 grams. In some embodiments, the single dosage unit of elemental iron

is at least about 0.7 grams; at least about 0.8 grams; at least about 0.9 grams; at least about 1.0 grams; at least about 1.1 grams; at least about 1.2 grams; at least about 1.3 grams; at least about 1.4 grams; at least about 1.5 grams; at least about 1.6 grams; at least about 1.7 grams; at least about 1.8 grams; at least about 1.9 grams; at least about 2.0 grams; at least about 2.1 grams; at least about 2.2 grams; at least about 2.3 grams; at least about 2.4 grams; or at least about 2.5 grams.

In various embodiments, the single dosage unit of elemental iron is administered in about 15 minutes or less. In some embodiments, the single dosage unit of elemental iron is administered in about 10 minutes or less, about 5 minutes or less, or about 2 minutes or less.

In various embodiments, the subject does not experience a significant adverse reaction to the single dosage unit administration.

In various embodiments, the iron carbohydrate complex has a pH between about 5.0 to about 7.0; physiological osmolarity; an iron core size no greater than about 9 nm; a mean diameter particle size no greater than about 35 nm; a blood half-life of between about 10 hours to about 20 hours; a substantially non-immunogenic carbohydrate component; and substantially no cross reactivity with anti-dextran antibodies.

In various embodiments, the iron carbohydrate complex contains about 24% to about 32% elemental iron; contains about 25% to about 50% carbohydrate; has a molecular weight of about 90,000 daltons to about 800,000 daltons, or some combination thereof.

In various embodiments, the iron carbohydrate complex is an iron monosaccharide complex, an iron disaccharide complex, or an iron polysaccharide complex. In some embodiments, the iron carbohydrate complex is iron carboxymaltose complex, iron mannitol complex, iron polyisomaltose complex, iron polymaltose complex, iron gluconate complex, iron sorbitol complex, or an iron hydrogenated dextran complex. In some embodiments, the iron carbohydrate complex is an iron polyglucose sorbitol carboxymethyl ether complex. In some preferred embodiments, the iron carboxymaltose complex contains about 24% to about 32% elemental iron, about 25% to about 50% carbohydrate, and is about 100,000 daltons to about 350,000 daltons. In some preferred embodiments, the iron carboxymaltose complex is obtained from an aqueous solution of iron (III) salt and an aqueous solution of the oxidation product of one or more maltodextrins using an aqueous hypochlorite solution at a pH value within the alkaline range, wherein, when one maltodextrin is applied, its dextrose equivalent lies between 5 and 20, and when a mixture of several maltodextrins is applied, the dextrose equivalent lies between 5 and 20 and the dextrose equivalent of each individual maltodextrin contained in the mixture lies between 2 and 20. In some preferred embodiments, the iron carboxymaltose complex has a chemical formula of $[FeO_x(OH)_y(H_2O)_z]_n[\{(C_6H_{10}O_5)_m(C_6H_{12}O_7)\}_l]_k$, where n is about 103, m is about 8, l is about 11, and k is about 4; contains about 28% elemental iron; and has a molecular weight of about 150,000 Da. In some preferred embodiments, the iron carboxymaltose complex is polynuclear iron (III)-hydroxide 4(R)-(poly-(1→4)-O-α-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate.

In various embodiments, the iron carbohydrate complex comprises an iron core with a mean iron core size of no greater than about 9 nm. In some embodiments, the mean iron core size is at least about 1 nm but no greater than about 9 nm; at least about 3 nm but no greater than about 7 nm; or at least about 4 nm but not greater than about 5 nm.

In various embodiments, the mean size of a particle of the iron carbohydrate complex is no greater than about 35 nm. In some embodiments, the particle mean size is no greater than about 30 nm. In some embodiments, the particle mean size is no greater than about 25 nm. In some embodiments, the particle mean size is no greater than about 20 nm; no greater than about 15 nm; no greater than about 10 nm; or at least about 6 nm but no greater than about 7 nm.

In various embodiments, the iron carbohydrate complex is administered parenterally, for example intravenously or intramuscularly. In some embodiments, the iron carbohydrate complex is intravenously infused. In certain embodiments, the single unit dose of iron carbohydrate complex is intravenously infused at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent, for example, about 250 ml of diluent or about 215 ml of diluent. In some embodiments, the iron carbohydrate complex is intravenously injected as a bolus. In certain embodiments, the iron carbohydrate complex is intravenously injected as a bolus at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent, for example, about 250 ml of diluent or about 215 ml of diluent. In some embodiments, the iron carbohydrate complex is intramuscularly infused at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent, for example, about 250 ml of diluent or about 215 ml of diluent. In some embodiments, the iron carbohydrate complex is intramuscularly infused at a concentration of about 500 mg elemental iron in less than about 10 ml diluent.

In various embodiments, the method also includes a second administration of the iron carbohydrate complex upon recurrence of at least one symptom of the treated disease, disorder, or condition.

In various embodiments, the method also includes a second administration of the iron carbohydrate complex after 1 day to 12 months after the first administration.

In a preferred embodiment, the method of treating a disease, disorder, or condition characterized by iron deficiency or dysfunctional iron metabolism comprises intravenously administering to a subject in need thereof an iron carboxymaltose complex in a single dosage unit of at least about 1000 mg of elemental iron in about 200 ml to about 300 ml of diluent in about 5 minutes or less; wherein the iron carboxymaltose complex comprises an iron core with a mean iron core size of at least about 1 nm but no greater than about 9 nm; mean size of a particle of the iron carboxymaltose complex is no greater than about 35 nm; and the iron carboxymaltose complex is administered intravenously infused or intravenously injected at a concentration of about 1000 mg elemental iron in about 200 ml to about 300 ml of diluent. In some these embodiments, the iron carboxymaltose complex is polynuclear iron (III)-hydroxide 4(R)-(poly-(1→4)-O-α-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate. In some these embodiments, the iron carboxymaltose complex is obtained from an aqueous solution of iron (III) salt and an aqueous solution of the oxidation product of one or more maltodextrins using an aqueous hypochlorite solution at a pH value within the alkaline range, wherein, when one maltodextrin is applied, its dextrose equivalent lies between about 5 and about 20, and when a mixture of several maltodextrins is applied, the dextrose equivalent lies between about 5 and about 20 and the dextrose equivalent of each individual maltodextrin contained in the mixture lies between about 2 and about 20.

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