US 20040180849A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2004/0180849 A1**

Helenek et al. (43) **Pub. Date: Sep. 16, 2004**

(54) **METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON FOR THE TREATMENT OF RESTLESS LEG SYNDROME**

(76) Inventors: **Mary Jane Helenek**, Brookville, NY (US); **Ralf A. Lange**, Amagansett, NY (US); **Fred B. Oldham**, West Chester, PA (US); **Marc L. Tokars**, Douglassville, PA (US)

Correspondence Address:
SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. BOX 061080
WACKER DRIVE STATION, SEARS TOWER
CHICAGO, IL 60606-1080 (US)

(21) Appl. No.: **10/389,228**

(22) Filed: **Mar. 14, 2003**

Publication Classification

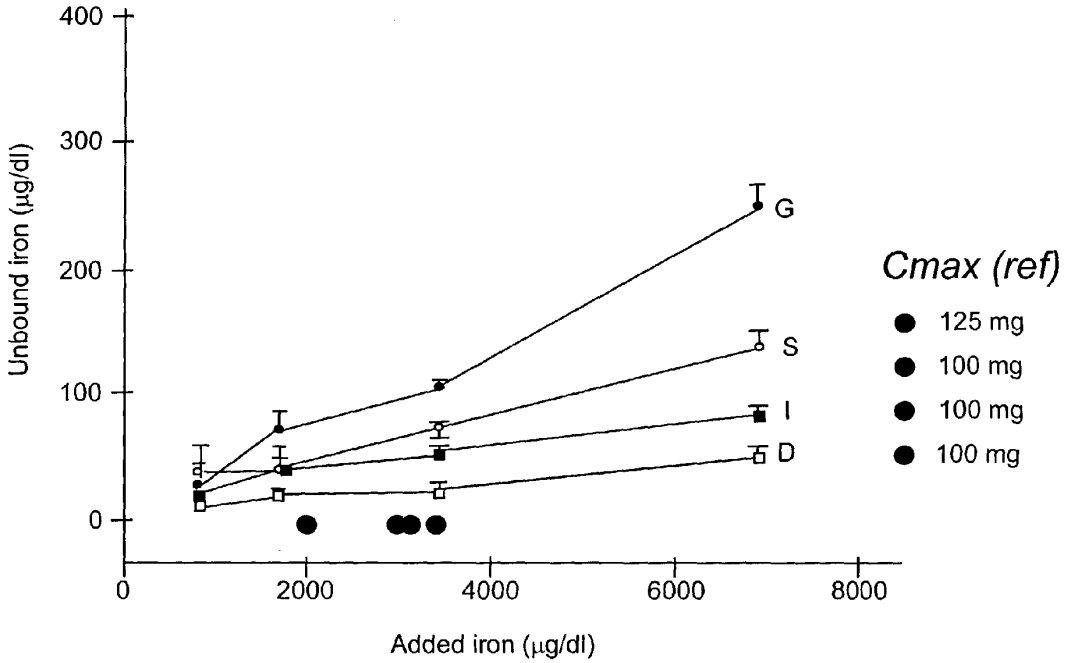
(51) **Int. Cl.**[7] **A61K 31/7012**; A61K 31/555

(52) **U.S. Cl.** **514/53**; 514/184

(57) **ABSTRACT**

A method of treating Restless Leg Syndrome, includes administering to a subject an iron complex having an iron release rate greater than IDI. The iron release rate is determined at a concentration of at least 2,000 μg/dl.

Fig. 1



METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON FOR THE TREATMENT OF RESTLESS LEG SYNDROME

BACKGROUND

[0001] Restless Legs Syndrome

[0002] Victims seriously afflicted with Restless Leg Syndrome (RLS; also known as Ekbom's syndrome), are virtually unable to remain seated or even to stand still. Activities that require maintaining motor rest and limited cognitive stimulation, such as transportation (car, plane, train, etc.) or attending longer meetings, lectures, movies or other performances, become difficult if not impossible. Tortured by these sensations which become more severe at night, RLS patients find sleep to be virtually impossible, adding to the diminishing quality of their lives. The urge to move, which increases over periods of rest, can be completely dissipated by movement, such as walking. However, once movement ceases, symptoms return with increased intensity. If an RLS patient is forced to lie still, symptoms will continue to build like a loaded spring and, eventually, the legs will involuntary move, relieving symptoms immediately. Rhythmic or semi-rhythmic movements of the legs are observed if the patient attempts to remain laying down (Pollmacher and Schulz 1993). These movements are referred to as dyskinesias-while-awake (DWA) (Hening et al. 1986) or more commonly, periodic limb movements while awake (PLMW).

[0003] Clinically, RLS is indicated when four diagnostic criteria are met: (1) a sensation of an urge to move the limbs (usually the legs); (2) motor restlessness to reduce sensations; (3) when at rest, symptoms return or worsen; and (4) marked circadian variation in occurrence or severity of RLS symptoms; that is, symptoms worsen in the evening and at night (Allen and Earley 2001a). First recognized by Willis in 1685, RLS has been misunderstood and confused with periodic limb movements in sleep (PLMS; which may be a part of RLS, but does not define RLS), periodic limb movement disorder (PLMD; a sleep disorder) and nocturnal (or sleep) myoclonus (Allen and Earley 2001a).

[0004] Iron and Dopamine Concentrations are Intertwined Factors in RLS

[0005] Lack of iron and reduced dopamine synthesis in the brain are important factors in RLS (Ekbom 1960, Nordlander 1953). Dopamine is a neural transmitter synthesized in the brain that is essential for proper central nervous system (CNS) function. In the synthesis of dopamine, iron is a cofactor for the enzyme tyrosine hydroxylase, which is the rate-limiting step in dopamine metabolism (Cooper et al. 1991). Iron in the dopaminergic system appears to be an important component in RLS pathophysiology (Chesson A L et al. 1999, Ekbom 1960, Hening et al. 1999, Montplaisir et al. 1991).

[0006] Because iron is a co-factor for tyrosine hydroxylase in dopamine synthesis, dopamine is reduced. When chelators (substances that bind metals such as iron, and make them physiologically unavailable) are administered to rats having excessive brain iron, they were effective in reducing dopamine and dopamine turnover (Ward et al. 1995). Studies in iron-deficient animals have also demonstrated decreases in dopamine receptors (Ben-Shachar et al. 1985, Ward et al. 1995), dopamine transporter function and receptor density with an elevation in extracellular dopamine (Erikson et al. 2000, Nelson et al. 1997). These observations in rats are also observed in RLS patients. For example, a decrease in dopamine receptors has been observed in basal ganglia (Staedt et al. 1995, Turjanski et al. 1999). RLS patients have 65% less cerebral spinalfluid (CFS) ferritin (an important iron storage protein) and three-fold more CSF transferrin (iron transport protein in blood and body fluids), despite normal serum levels of ferritin and transferrin in both RLS and controls (Earley et al. 2000). Iron concentrations vary throughout the brain; RLS patients have less iron in the substantia nigra and in the putamen parts of the brain, both sites of dopamine synthesis (Allen et al 2001). In general, decreased ferritin levels are indicative of RLS severity (O'Keeffe et al. 1994, Sun et al. 1998). These observations indicate that the ability of the brain to transport or store iron is abnormal in idiopathic RLS (RLS having no apparent cause)

TABLE 1

Side effects of current treatments for Restless Legs Syndrome (RLS)[1]

Medication	Disease[2]	Side effects	% affected[3]
levodopa/carbidopa	Parkinson	dyskinesia (inability to control movements), nausea, hallucinations	4–17
Pergolide w/ levodopa/carbidopa	Parkinson	dyskinesia, nausea, hallucinations, rhinitis (mucous membrane inflammation), constipation, pain	7–62
Pramipexole	Parkinson	somnolence, insomnia, nausea, constipation, hallucinations	9–28
Narcotic analgesics	Pain control	respiratory depression, nausea, somnolence, pruritus (severe itching), constipation, urinary retention	none reported
Clonazepam	Epilepsy	somnolence, depression, in-coordination	6–37
Triazolam	Insomnia	drowsiness, dizziness, memory impairment	1–14
Gabapentin	Epilepsy	fatigue, dizziness, somnolence, ataxia (unable to coordinate muscular movement)	11–19
Carbamazepine	Epilepsy	fetal malformation, rash, hyponatremia (blood sodium deficiency), hepatotoxicity, blood disorders, ataxia, gastro-intestinal problems, sexual dysfunction, toxicity	1–33
Clonidine	Hypertension	reduced blood pressure, dermatitis, systemic side effects (dry mouth, somnolence, dizziness, headache)	8–89

TABLE 1-continued

Side effects of current treatments for Restless Legs Syndrome (RLS)[1]

Medication	Disease[2]	Side effects	% affected[3]
intravenous iron dextran	iron deficiencies (Fishbane et al. 1996) and random sampling (Hamstra et al. 1980)	anaphylaxis, possibility resulting in death	0.3–1.7 (Fishbane et al. 1996, Hamstra et al. 1980)

[1]Table derived from (Chesson AL et al. 1999), except for intravenous iron dextran.
[2]Studies were performed on patients suffering from the indicated disease, not RLS, with the indicated drug.
[3]As reported in the studies referenced within (Chesson AL et al. 1999). See Chesson et al. 1999 for more information. The percent (&) range is derived from the reported percentages for each side effect; thus in the first example, 12–17% suffered from dyskinesia, 6% from nausea and 4% from hallucinations; the reported range is 4–17%.

[0007] Treating RLS

[0008] Current treatments for RLS are varied and plagued with undesirable side effects (see Table 1). Therapies have included the administration of dopamine agonists (substances that promote the production of dopamine), other dopaminergic agents, benzodiazepines, opiates and anti-convulsants. In cases where RLS results from a secondary condition, such as pregnancy, end-stage renal disease, erythropoietin (EPO) treatment and iron deficiency, removing the condition, such as giving birth or treating with traditional iron supplementation, can reduce or eliminate symptoms in at least some cases (Allen and Earley 2001a). However, RLS resulting from non-secondary conditions "idiopathic" RLS), presents a greater treatment challenge.

[0009] Dopaminergic agents such as levodopa generally provide effective initial treatment, but with continued use, tolerance and symptom augmentation occur in about 80% of RLS patients (Allen and Earley 1996); this complication is also common for dopamine agonists (Earley and Allen 1996, Silber et al 1997). The other alternatives, benzodiazepines, opiates and anti-convulsants are not as uniformly effective as the dopamine agents (Chesson AL et al. 1999, Hening et al. 1999). Despite changes in ther treatment regimes, 15-20% of patients find that all medications are inadequate because of adverse effects and limited treatment benefit (Earley and Allen 1996).

[0010] Because of the link between iron and dopamine synthesis, iron administration would appear to be a simple and safe treatment to increase body iron stores. An obvious choice is oral administration of iron since such administration is simple and inexpensive. In fact, RLS patients with iron deficiency respond dramatically to oral iron supplements (Ekbom 1960, O'Keeffe et al. 1994). However, in RLS patients with normal serum ferritin levels, the benefits of oral iron therapy decrease inversely to baseline serum ferritin levels: the higher the ferritin at the time of initiating therapy, the less pronounced the benefits (O'Keeffe et al. 1994). This approach to raise body stores of iron is ineffective because the intestinal epithelium controls iron absorption, responding not to dopamine synthesis cues, but to serum iron levels (Conrad et al. 1999). Therefore, oral doses of iron are ineffective, and not tolerated. To increase body stores of iron when serum ferritin levels are normal, methods that bypass intestinal epithelial regulation would need to be used. For example, in the anemia of chronic disease, iron absorption and transport is dramatically impaired and serium ferritin levels being elevated does not accurately reflect stored iron levels in the body. Also in the anemia of chronic disease the only effective way to deliver adequate iron for erythropoiesis to a deprived system is by intervenus administration.

[0011] Intravenous administration of iron circumvents the problems and ineffectiveness of orally-administered iron for those RLS patients with normal serum ferritin levels. In fact, intravenous administration of iron dextran solutions, such as INFeD® (Watson Pharma, Inc.; Corona, Calif. (having an average apparent molecular weight of 165,000 g/mole with a range of approximately±10%), and Dexferrum® (American Regent Inc., Shirley, N.Y.) (referred to collectively as "IDI") successfully treats RLS. However, the dosage is high—1000 mg/administration; or about two- to ten-fold more than the usual dose when used to treat other conditions. While IDI offers hope to some RLS patients, it also suffers from significant disadvantages: not only is the dosage high, but also dextran causes anaphylaxis in about 1.7% of the population (Fishbane et al. 1996), a life threatening condition; just less than 50% or those suffering anaphylaxis die.

SUMMARY

[0012] In a first aspect, the present invention is a method of treating Restless Leg Syndrome, comprising administering to a subject an iron complex having an iron release rate greater than IDI. The iron release rate is determined at a concentration of at least 2,000 μg/dl.

[0013] In a second aspect, the present invention is a method of treating Restless Leg Syndrome, comprising administering to a subject an iron complex having an iron release rate of at least 115 μg/dl at a concentration of 3438 μg/dl by the alumina column test.

[0014] In a third aspect, the present invention is a method of treating Restless Leg Syndrome, including administering IDI, the improvement comprising replacing IDI with an iron complex having a greater release rate than IDI.

[0015] In a fourth aspect, the present invention is a kit, comprising an iron complex composition having a release rate greater than IDI, a syringe, and a needle for the syringe. The iron release rate is determined at a concentration of at least 2,000 μg/dl.

DESCRIPTION OF THE FIGURES

[0016] **FIG. 1** shows the change in serum transferrin-bound iron (Δ iron) of the intravenous injection preparations

for ferric gluconate (also known as sodium ferric gluconate complex in sucrose or Ferrlecitg; Watson Pharma, Inc.; Corona, Calif.), iron sucrose (Venofer® (iron sucrose injection USP); American Regent Inc.; Shirley, N.Y.), iron dextran (INFeD®; Watson Pharma, Inc.), and another iron dextran (Dexferrum®; American Regent Inc.) as related to the amount of added iron. x-axis, added elemental iron (μg/dl); y-axis, Δ iron (μg/dl).

DETAILED DESCRIPTION

[0017] The present invention makes use of the discovery that an iron complex, having a higher release rate of iron than IDI, has the same effect for the treatment of RLS as IDI, at a lower dosage. These iron complexes avoid the risks of anaphylaxis associated with IDI when administered intravenously due to antibodies against the dextran moiety not being present in other iron complexes and, because of the higher release rate, therapadic dosage can be lowered.

[0018] An example of such an iron complex is Venofer® (iron sucrose injection USP), an iron sucrose complex that has an incidence of anaphylactoid reactions of 0.0046% (that is, 1 out of 20,000 people; IDI has a rate of anaphylaxis of 1.7%, or almost 2 out of 100 people). However, any iron complex that has a release rate greater than that of IDI is an effective RLS therapeutic.

[0019] Iron Compositions for the Treatment of RLS

[0020] Iron complexes are compounds which contain iron in (II) or (III) oxidation state, complexed with an organic compound. These include iron polymer complexes, iron carbohydrate complexes, and iron aminoglycosan complexes. These complexes are commercially available, or have well known syntheses (see, for example, (Andreasen and Christensen 2001, Andreasen and Christensen 2001, Geisser et al. 1992, Groman and Josephson 1990, Groman et al. 1989)).

[0021] Examples of iron carbohydrate complexes include iron simple saccharide complexes, iron oligosaccharide complexes, and iron polysaccharide complexes, such as: iron sucrose, iron polyisomaltose (iron dextran), iron polymaltose (iron dextrin), iron gluconate, iron sorbital, iron hydrogenated dextran, which may be further complexed with other compounds, such as sorbital, citric acid and gluconic acid (for example iron dextrin-sorbitol-citric acid complex and iron sucrose-gluconic acid complex), and mixtures thereof.

[0022] Examples of iron aminoglycosan complexes include iron chondroitin sulfate, iron dermatin sulfate, iron keratan sulfate, which may be further complexed with other compounds and mixtures thereof.

[0023] Examples of iron polymer complexes include iron hyaluronic acid complex, iron protein complexes, and mixtures thereof. Iron protein complexes include ferritin, transferritin, as well as ferritin or transferritin with amino acid substitutions, and mixtures thereof. Preferably, the iron complexes have a molecular mass of at least 30,000, more preferably of 30,000 to 100,000 as determined by HPLC/CPG (as described in Geisser et al 1992). Preferably, the iron complexes have a size of at most 0.1 micrometer, more preferably 0.035 to 0.1 micrometer, as determined by filtration.

[0024] The most preferred iron complex is iron sucrose (iron sucrose injection USP, Venofer®). This composition also avoids toxicity issues that are associated with smaller sugars, especially gluconates, which have high iron release rates. Iron sucrose compositions balance these toxicity issues with optimal iron release rates.

[0025] Determining Iron Complex Iron Release Rates

[0026] The methods of the invention take advantage of the discovery that iron complexes having higher release rates of iron than IDI can be effectively administered at lower doses. IDI has an iron release rate of 69.5-113.5 μg/dl. In the present invention, the iron complex must have a release rate of at least 115 μg/dl at a concentration of at least 2000 μg/dl; including 2000, 3000, 3500, 5000, and 10,000 μg/dl. Preferably, at least 120 μg/dl, more preferably, at least 140 μg/dl. Two tests can be implemented to determine iron release rates, that by Esposito et al. (2000) and by Jacobs et al. (1990).

[0027] "Chelator Test" (Esposito et al 2000)

[0028] The release rate of a candidate iron complex is the ability of the candidate complex to donate iron to apotransferrin or to an iron chelator, such as desferrioxamine. To detect such transfer, the probes fluorescein-transferrin (Fl-Tf) and fluoresceindesferrioxamine (F1-DFO) can be used, which undergo quenching upon binding to iron (Breuer and Cabantchik 2001). In short, the method involves mobilization of iron from serum with 10 mM oxalate and its transfer to the metallosensor fluoresceinated apotransferrin (F1-aTf). Gallium is present in the assay to prevent the binding of labile plasma iron to the unlabelled apotransferrin in the sample. Labile plasma iron values are derived from the magnitude of quenching of the fluorescence signal of fluoresceinated apotransferrin. Fluorescence may be measured using, for example, 96-well plates and a plate reader operating at 485/538 nm excitation/emission filter pair (gain=25).

[0029] "Alumina Column Test" (Jacobs et al. 1990)

[0030] In this test, samples (serum and candidate iron composition) are passed over an alumina column to absorb organic and drug-bound iron, the elutants are then collected and reconstituted to a pre-selected volume (e.g., 1.5 ml), and the final iron concentration determined using a chemistry analyzer, such as a Hitachi 717 chemistry analyzer. Ferrozine reagents are used, which included detergent, buffers of citric acid and thiourea, ascorbate, and ferrozine. This test is a non-proteinizing method in which detergent clarifies lipemic samples, buffers lower the pH to <2.0 to free iron as Fe^{3+} from transferrin, ascorbate reduces Fe3+ to Fe^{2+}, and ferrozine reacts with Fe^{2+} to form a colored complex measured spectophotometrically at 560 nm. From this result the value of a control (blank) sample is subtracted from the experimental sample readings, and the results are recorded as the Δ Tf-bound iron (μg/dl).

[0031] Pharmaceutical Compositions

[0032] In many cases, the iron complex may be delivered as a simple composition comprising the iron complex and the buffer in which it is dissolved. However, other products may be added, if desired, to maximize iron delivery, preservation, or to optimize a particular method of delivery.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.