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

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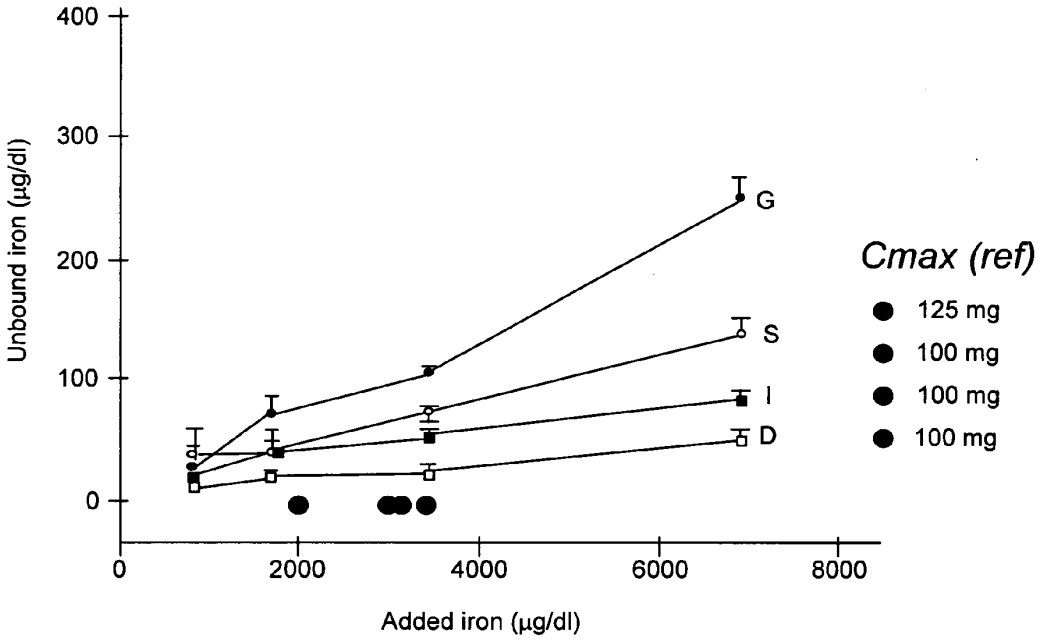
(57) **ABSTRACT**

The invention is directed to methods of treating Restless Leg Syndrome by administering iron complexes with specificed iron release rates or specified iron core size.

FIGURE 1



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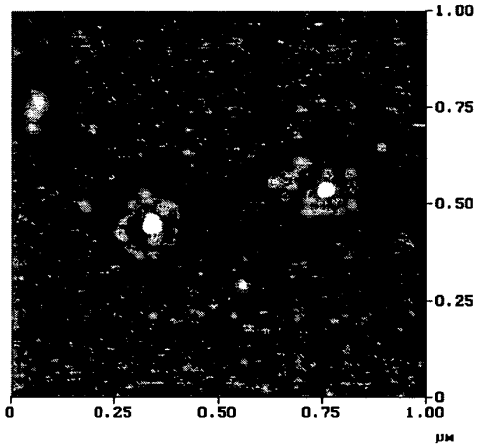

Fig. 2A

Venofer

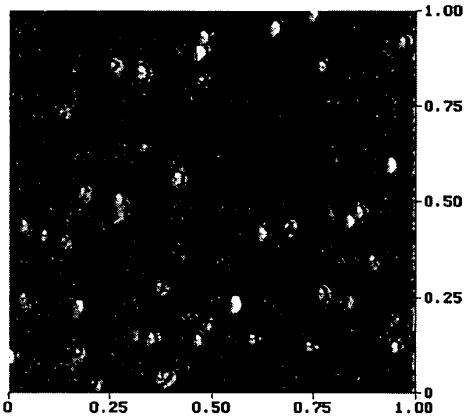

Fig. 2B

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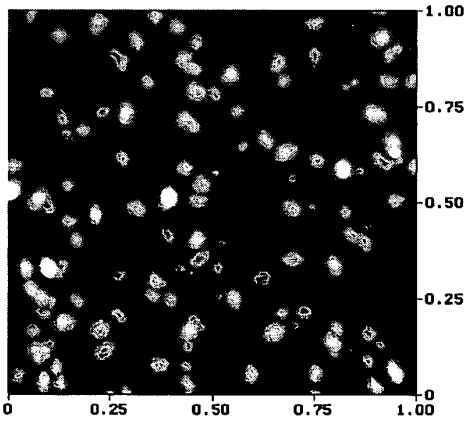

Fig. 2C

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

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This is a continuation-in-part of co-pending U.S. patent application Ser. No. 10/389,228, filed Mar. 14, 2003. The above reference is incorporated herein by reference in its entirety.

BACKGROUND

[0002] Restless Legs Syndrome

[0003] 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).

[0004] 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).

[0005] Iron and Dopamine Concentrations are Intertwined Factors in RLS.

[0006] 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).

[0007] Because iron is a co-factor for tyrosine hydroxylase in dopamine synthesis, dopamine is reduced. When chelators (substances that make iron 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 density, and 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 spinal fluid (CFS) ferritin (an important iron storage protein) and three-fold more CSF transferrin (iron transport blood protein), despite normal serum levels of ferritin and transferrin in both RLS and controls (Earley et al. 2000). Iron concentrations vary throughout the brain, the site of dopamine synthesis; RLS patients have less iron in the substantia nigra and in the putamen parts of the brain (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

TABLE 1-continued

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

Medication	Disease[2]	Side effects	% affected[3]
Clonidine	Hypertension	reduced blood pressure, dermatitis, systemic side effects (dry mouth, somnolence, dizziness, headache)	8–89
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%.

[0008] Treating RLS

[0009] 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 prod 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.

[0010] 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 A L et al. 1999, Hening et al. 1999). Despite changes in their treatment regimes, 15-20% of patients find that all medications are inadequate because of adverse effects and limited treatment benefit (Earley and Allen 1996).

[0011] 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 serum 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 gut controls iron absorption, responding not to dopamine synthesis cues, but to serum iron levels (Conrad et al. 1999). To increase body stores of iron when serum ferritin levels are normal, unacceptably high oral doses for months would need to be administered, or methods that bypass gut regulation would need to be used.

[0012] 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 dextrose 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 Laboratories, Inc.; Shirley, N.Y.) and those outlined in (Andreasen and Christensen 2001); 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% of those suffering anaphylaxis die.

SUMMARY OF THE INVENTION

[0013] Among the various aspects of the present invention is the provision of a method of treating Restless Leg Syndrome (RLS). Briefly, therefore, the present invention is directed to treating RLS with an iron carbohydrate complex of particular iron release rate and/or iron core size. Thus, the methods described herein provide for the safe and efficacious delivery of iron to subjects in need thereof as well as allowing thorough tissue distribution, faster labile iron release, and increased in vitro donation of iron to transferrin.

[0014] The present teachings include methods for treating Restless Leg Syndrome that involve the administration of an iron complex to a patient suffering from RLS. The iron complex can be selected from an iron carbohydrate, an iron aminoglycan, or an iron polymer. The iron release rate of the iron complex used in this aspect of the invention is at least 115 μg/dl at a concentration of at least 2,000 μg/dl.

[0015] In accordance with a further aspect, RLS is treated by administering an iron complex of particular iron core size to a patient suffering from RLS. The iron complex can be selected from an iron carbohydrate, an iron aminoglycan, or an iron polymer. The iron core size of the iron complex used in this aspect is no greater than 9 nm.

[0016] Yet another aspect provides kits, comprising an iron complex having an iron core size no greater than 9 nm (in solution or lyophilized), a syringe, and a syringe needle. The kit may also include instructions for use.

[0017] Other objects and features will be in part apparent and in part pointed out hereinafter.

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