

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
24 August 2006 (24.08.2006)

PCT

(10) International Publication Number
WO 2006/088790 A2

(51) International Patent Classification:
A61K 33/08 (2006.01) *A61P 31/10* (2006.01)

(74) Agent: SPADT, Jonathan, H.; RatnerPrestia, P.O. Box 980, Valley Forge, Pennsylvania 19482 (US).

(21) International Application Number:
PCT/US2006/005024

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(22) International Filing Date:
13 February 2006 (13.02.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/652,664 14 February 2005 (14.02.2005) US

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): CDG RESEARCH CORPORATION [US/US]; 140 Webster Street, Bethlehem, Pennsylvania 18015 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): ROSENBLATT, Aaron, A. [US/US]; 21 West 86th Street, #1502, New York, New York 10024-3616 (US). MCWHORTER, Thomas, E. [US/US]; 2977 Fairfield Drive, Allentown, Pennsylvania 18103 (US). ROSENBLATT, David, H. [US/US]; 3316 Old Forest Road, Baltimore, Maryland 21208 (US).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE OF CHLORINE DIOXIDE FOR THE TREATMENT OF ONYCHOMYCOSIS (NAIL FUNGUS)

(57) Abstract: A method for treating nail fungus by soaking the infected nail(s) in a dilute solution of chlorine dioxide in water.



WO 2006/088790 A2

USE OF CHLORINE DIOXIDE FOR THE TREATMENT OF ONYCHOMYCOSIS (NAIL FUNGUS)

BACKGROUND OF THE INVENTION

Onychomycosis is an infection of the finger or toe nails which is very difficult to cure. Onychomycosis is caused by a fungus, though the term is sometimes used to describe any infection (e.g., bacterial) of the nail. Often a person will have had athlete's foot for a long time prior to the development of onychomycosis. Sometimes trauma or damage to a nail predisposes to the development of onychomycosis.

Onychomycosis accounts for up to 50% of diseases of the nail. The distribution of different pathogens is not uniform; it depends on various factors such as climate, geography and migration. However, two dermatophytes, *Trichophyton rubrum* and *Trichophyton mentagrophytes*, reportedly account for more than 90% of cases of onychomycosis.

Fungal infections of the nails are common. The fungus grows in the nail bed, where the nail meets the skin. Generally, in a relatively healthy person, fungus grows slowly and does not spread to internal organs. The main concern is the nail discoloration (usually yellow) and change in nail texture and growth. Nails can become crumbly, break easily, and grow irregularly. But because other nail conditions can mimic fungal infection, most doctors will confirm the diagnosis by sending a nail clipping for laboratory evaluation, especially if treatment is being considered. However, such laboratory analyses often yield false negative results.

Fungal infections are not commonly contagious or easily spread between people. The fungus grows in people whose bodies "allow" the fungus to become established without mounting an immune response to suppress the fungus.

Because the fungus grows slowly, and is "protected" by the nail, it is hard to eliminate. Generally, once fungus gets into the nails, it is very difficult to treat.

The systemic antifungal medications that are used to eliminate nail fungus are strong, must be taken by mouth, and must be taken conscientiously for months in order to be effective. Each drug has potential side effects on other body organs (especially the liver, skin, and bone marrow). To monitor for side effects, periodic blood testing is advised, usually monthly, during the time the medication is taken.

- 2 -

For example, onychomycosis of the finger nails can be treated by taking pills called griseofulvin. The pills must be taken for six months to one year and have side effects. These include headaches, nausea, and liver damage. A course of treatment costs approximately \$350 and reportedly has a 50-70% chance of curing the condition.

Terbinafine, a newer medication than griseofulvin, is available for the treatment of toe and finger nail fungal infections. Terbinafine is taken once a day for 6 to 12 weeks. This medication reportedly has fewer side effects than griseofulvin. A 12 week course of treatment costs approximately \$500 and reportedly has a 50-70% chance of curing the condition.

Physicians usually recommend treating fungal nail infections only when such infections cause secondary problems, like pain, recurring ingrown toenails, or secondary bacterial infections of the nails or skin. If the nail infection causes no symptoms, then doctors often will discourage treatment because of the potential side effects, the need to monitor the blood throughout therapy, and the high recurrence rate. Patients with liver or heart disease generally cannot take antifungal medications.

Removal of the infected nail generally will not get rid of onychomycosis. When the new nail grows in, it almost always becomes reinfected. Among other things, reinfection of the nail can be due to pathogens which reside on other parts of the patient's foot.

Many chemical compounds exhibit antifungal (fungistatic or fungicidal) properties, and can be incorporated into creams, lotions, gels, solutions and the like. However, prior to the present invention, antifungal compounds applied topically (i.e., directly to the nail) cannot penetrate the nail bed to kill the fungus at its source, so they are not usually effective.

BRIEF DESCRIPTION OF THE INVENTION

It has been discovered that an effective way to treat fungal nail infection comes from applying chlorine dioxide topically, so that it penetrates the nailplate and inactivates pathogens residing in the nailbed—for example, by dissolving chlorine dioxide gas in water, permitting the patient to soak the infected fungal infected nail in the solution for a period of time and for a series of successive treatments to improve the aesthetic appearance of the nail, destroy the fungal infection and to promote healthy nail growth.

Therefore, in a first aspect the present invention is a method treating nail fungus comprising the steps of: preparing a solution of chlorine dioxide in water, and

- 3 -

soaking the infected nail or nails in the chlorine dioxide solution for a period of at least 45 minutes, once a day for a minimum of three days.

In another aspect of the present invention the method incorporates soaking the affected nail(s) along with the entire foot, in order to destroy pathogens thereon and help prevent reinfection of the nail by pathogens residing elsewhere on the foot.

In another aspect of the present invention the method incorporates protecting the solution of chlorine dioxide and water from ambient light during the treatment to prevent premature destruction of the chlorine dioxide by photolysis.

In another aspect the present invention comprises using a solution of chlorine dioxide in water containing a minimum of 80 parts per million chlorine dioxide as the treating agent.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is a method for treating fungal infection, especially *Trichophyton rubrum* and *Trichophyton mentagrophyte*, using chlorine dioxide.

In surprising results, the chlorine dioxide molecule appears to be able to penetrate the nail plate to kill fungus in the nailbed.

In additional surprising results, the chlorine dioxide molecule appears to be able to improve quickly the aesthetics of the infected nail by bleaching the yellowed nail back to a healthier color.

Chlorine dioxide is a relatively small, volatile and highly energetic molecule. Chlorine dioxide is almost never used commercially as a gas at high concentrations because of its instability; rather, it is generated at the point of use.

Chlorine dioxide gas has an intense greenish yellow color with a distinctive odor similar to that of chlorine. Chlorine dioxide is highly soluble in water but, unlike chlorine, chlorine dioxide does not react with water. It exists in aqueous solution as a dissolved gas.

Chlorine dioxide functions as a highly selective oxidant owing to unique, one-electron transfer mechanisms, wherein it attacks electron-rich centers in organic molecules and, in the process, is reduced to chlorite ion.

Chlorine dioxide is an extremely effective disinfectant, which rapidly inactivates bacteria, viruses, encysted parasites, molds and fungi. Because chlorine dioxide oxidizes but does not chlorinate, chlorinated organic by-products (e.g., THM,

- 4 -

HAA, dioxins, furans) typically are not produced. Neither does chlorine dioxide produce appreciable amounts of aldehydes, ketones, ketoacids or other problematic compounds associated with oxidation of organic matter by other, less selective means.

Chlorine dioxide gas, dissolved in neutral-pH solution at ambient temperature, in a concentration of approximately 80-100 parts-per-million, was administered to several patients suffering from toenail fungus. The chlorine dioxide solution was administered as a "foot soak", under low-light conditions. Treatments were for up to 1 hour/day for up to 7 days. In each case significant improvement in nail appearance was visible early in the protocol or treatment process. New nails reportedly grew in normally within several months, with little to no evidence of the original infection.

The chlorine dioxide can be administered as a gas, or dissolved in a aqueous solution, oil, cream, gel, lotion or incorporated into a polymeric matrix or nail lacquer.

Several experiments were conducted to prove the efficacy of chlorine dioxide solutions in treating nail fungus. The following summary outlines three case studies which show that the dilute solution of chlorine dioxide in water may have beneficial effect in treating a nail fungus. This finding is especially significant for those subjects testing the solution that have or may have a compromised immune system.

Subject 1 was a 50 year old woman with a recent history of breast cancer and attendant chemotherapy etc. (Her immune system is thus likely compromised). She was experiencing toe nail fungus. She was given Aseptrol™ brand packets. Aseptrol packets contain a ClO₂ releasing powder comprising a dry acid and sodium chlorite, which creates a near-neutral pH chlorine dioxide solution when mixed with water. Aseptrol packets are manufactured by Engelhard Corporation. The resulting solution was pH neutral and ~80-100 mg/liter (ppm). The Subject's "protocol" was as follows:

- mix 1 pack with ~1 quart tepid water (in low light)
- put into pan (preferably plastic) to soak toes
- protect from light (using a towel or black plastic bag)
- soak for ~1hr
- after treatment, rinse foot thoroughly with water
- discard used solution

She repeated the protocol for 7 days in a row. She reported no irritation of the skin, color of toenail improved early on during course of treatment, signs of

- 5 -

infection disappeared, and her nail grew in normally. Results were still good (new nail normal) after 3 months.

Subject 2 was a 77 year old man with a recent history of prostate cancer and Parkinson's, experiencing toe nail fungus. He was give Aseptrol brand packets and instructions. The resulting solution was pH neutral and -80-100 mg/liter (ppm). His "protocol" was as follows:

- mix 1 pack with ~1 quart tepid water (in low light)
- put into pan/preferably plastic to soak toes
- protect from light (using a towel or black plastic bag)
- soak for ~1hr
- after treatment, rinse foot thoroughly with water
- discard used solution

He repeated the protocol for 5 days over the course of a week, skipping two days during the week. He reported no irritation of the skin, color of toenail improved early on during course of treatment, signs of infection disappeared, and the nail appears to be growing in normally. Results were still good after 1.5 months.

Subject 3 was a 55 year old woman in good health, experiencing toe nail fungus. She was given a bottle of chlorine dioxide solution at a concentration of about 2000 ppm and neutral pH. The solution was made by bubbling high-purity chlorine dioxide gas through water. Her "protocol" was as follows:

- Protect the bottle from light at all times by wrapping in aluminum foil
- Store in a cool dark place. Do not allow the temperature of the bottle to exceed 50 degrees F during storage, prior to use.
- dilute the solution 20:1 (in low light) to produce a solution of about 100 ppm
- put into pan to soak toes
- perform the treatment in a low-light environment
- soak for ~1hr
- after treatment, rinse foot thoroughly with water
- discard used solution
- repeat the treatment for 7 consecutive days

She soaked the infected nail(s) for 3 days for approximately 45 minutes each day. After 2 months she reported that signs of the infection have disappeared and the nails are growing in normally.

- 6 -

The foregoing results reported by people treating a fungal nail infection with chlorine dioxide solutions demonstrates the efficacy of the treatment.

As stated above the patient can soak the infected nail in a dilute solution of chlorine dioxide, which can be made by any of several means, including bubbling
5 chlorine dioxide into a water bath at a rate sufficient to produce wanted concentration of chlorine dioxide in water.

The human toenail consists of Keratin, fibrous insoluble protein that is the main structural element in hair, nails, feathers, hooves, and some components of animal horns. The ability of chlorine dioxide to penetrate keratin and kill pathogens
10 protected thereby would also make it capable of curing animal diseases that occur within or below keratinous structures. An example of such a disease is the hoof rot that is a common affliction in hoofed animals.

It is also within the scope of the present invention to incorporate chlorine dioxide into topical medications that can be placed on the infected nail or other
15 keratinous structure so that the chlorine dioxide penetrates the keratin and kills pathogens otherwise protected by the keratin.

Although the invention is illustrated and described herein with reference to specific embodiments, the invention is not intended to be limited to the details shown. Rather, various modifications may be made in the details within the scope and
20 range of equivalents of the claims without departing from the invention.

- 7 -

What is Claimed:

1 1. A method of diseases caused by pathogens affecting keratin and
2 the tissues surrounding keratinous structures comprising the steps of contacting the
3 surface of the keratinous tissue with an effective amount of chlorine dioxide for a time
4 sufficient to permit penetration of chlorine dioxide molecules through the keratin and to
5 kill pathogens residing in keratin and the surrounding tissues.

1 2. A method of treating nail fungus comprising the steps of
2 contacting the nail with an effective amount of chlorine dioxide for time sufficient to
3 permit penetration of chlorine dioxide molecules through the nailplate and to kill
4 pathogens residing in the nailbed.

1 3. A method of treating nail fungus in accordance with Claim 2,
2 wherein the concentration of chlorine dioxide which penetrates into the nail is sufficient
3 to improve the color of the nail, by making it appear less "yellow".

1 4. A method of treating nail fungus in accordance with Claim 2
2 comprising the steps of preparing a solution of chlorine dioxide in water; and soaking
3 infected nail or nails in said solution for a period of at least forty five minutes each day
4 for a minimum of three days.

1 5. A method of treating nail fungus in accordance with Claim 2,
2 wherein the chlorine dioxide is dissolved in water.

1 6. A method of treating nail fungus in accordance with Claim 2,
2 wherein the chlorine dioxide is dissolved in a gel.

1 7. A method of treating nail fungus in accordance with Claim 2,
2 wherein the chlorine dioxide is dissolved in a polymeric matrix.

1 8. A method of treating nail fungus in accordance with Claim 2,
2 wherein the chlorine dioxide is dissolved in a lotion.

1 9. A method of treating nail fungus in accordance with Claim 2,
2 wherein the chlorine dioxide is dissolved in a hydrocarbon.

1 10. A method of treating nail fungus in accordance with Claim 2,
2 wherein a chlorine dioxide solution is absorbed onto a porous substrate and said
3 substrate is applied to an infected nail.

1 11. A method of treating nail fungus in accordance with Claim 2,
2 wherein the chlorine dioxide is in the gas phase.

- 8 -

1 12. A method according to claim 4 including the step of protecting
2 said solution from ambient light during said soaking step.

1 13. A method according to claim 4 including soaking the entire foot.

1 14. A method according to claim 4 including the step of preparing said
2 solution with a minimum concentration of 80 ppm chlorine dioxide.

1 15. A kit for treatment of nail fungus comprising:

2 a substantially opaque container adapted to hold an infected foot or feet
3 of a user, said container also adapted to hold a quantity chlorine dioxide solution
4 sufficient to cover the toes of said user;

5 one of a dry chlorine-dioxide forming formulation, or a chlorine dioxide
6 concentrate which, when mixed with a quantity of water, will yield a chlorine dioxide
7 solution; or, alternatively, a container of chlorine dioxide solution that is of the desired
8 concentration, without further dilution.