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Short Communication

Athlete's foot disease: A comparative study on marketed products

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Abstract

An infection of the foot with fungi, such as the Athlete's foot, is frequently observed globally, both in men and women. In the present review, different marketed products used in treating Athlete's foot disease were critically analysed and compared. The marketed products include Oral medications and Topical medications like creams, gels, dusting powders, and sprays to meet the needs of Athlete's foot disease patients. Oral products are prescribed only when topical treatments are unsuccessful and the infection becomes systemic or deep-rooted. They may cause mild side effects like nausea, dizziness, and digestive problems to serious side effects like liver damage. In comparison to oral medications, topical fungal therapy is usually preferred due to no systemic side effects, ability to bypass first-pass metabolism, and minimum toxicity. Gels are preferred over creams for being effective and easily washable. With powders, moisture retention may delay the healing process leading to secondary infections with bacteria. Sprays can release the drug easily in hard-to-reach corners of the body. However, propellants used in them are inflammable, and the products are expensive. Oral products are best for treating chronic infections despite their side effects, and topicals are suitable for mild infections, with sprays being the most convenient formulation. Several studies have indicated that topical nanocarriers with antifungal agents display superior therapeutic efficacy and minimal toxicity due to their ability to overcome challenges associated with conventional drug delivery systems like poor retention and low bioavailability. There is a good scope for developing topical nanocarrier-based antifungal formulations to treat Athlete's foot disease with minimum side effects effectively.

Keywords: Athlete's foot disease, Orals, Topicals, Creams, Gels, Powders, Sprays.

Introduction:

The common name of "Tinea pedis" is the Athlete's foot, as the infection is often seen among athletes. Athletes' foot is a contagious fungal skin infection of the foot. It primarily affects the space between the toes and sole. The main signs and symptoms of an Athlete's foot are rashes between the toes with itching, scaling, flaking, and blister formation. The rashes often extend to the sides and soles of the feet. Sometimes this disease can also spread from toenails to other body parts. It may spread to the other foot or even to the hands if the person continuously scratches the infected area. The person with an Athlete's foot experiences intense itching immediately after removing his/her shoes and socks.¹ Around 15% to 25% of people are likely to suffer from Athlete's foot disease. This infection can spread from the foot to other parts of the body and other people as well.² Although it is not a life-threatening disease, most of the time, the person infected may not pay attention to his/her regular work due to uneasiness or discomfort in the infected area. This review article mainly emphasizes the Athlete's foot disease, its etiology, signs and symptoms, risk factors and management using marketed antifungal formulations.

Etiology:

An athlete's foot is caused by a dermatophyte infection. These dermatophytes are nothing but a group of keratinophilic fungi which attack and infect the keratinized tissues of feet, causing dermatophytosis.³ Tinea pedis, also known as foot ringworm, is an infection of the feet that affects interdigital gaps between

toes, soles, and nails. Another name for this infection is athlete's foot.^{4,5} Dermatophytes primarily cause this infection. Trichophyton rubrum, a type of dermatophyte, is mainly responsible for causing tinea pedis in about 70% of the cases. The other causative organisms include Trichophyton interdigitale, Epidermophyton floccosum, and Trichosporium violaceum.⁶ Trichophyton rubrum was once endemic to many parts of Africa, Asia, and Australia, but today the organism can be found in Europe and America.^{6,7}

Signs and symptoms:

Athlete's foot disease is a superficial fungal skin infection, which can be initially noticed between toes and may gradually spread to soles. It is mainly characterized by redness, itching, burning sensation, flaking, scaling or blister formation, and skin fissuring. When associated with bacterial infection, a foul odor may also develop. Athlete's foot is mainly manifested in three ways: the skin between toe gaps may appear soaked (white) and damp; the soles or the plantar aspects of the feet might appear dry and flaking; the skin all over the foot may turn red (toe redness), and vesicular eruptions might occur.^{2,8}

Evaluation:

Generally, physical examination is adequate to recognize tinea pedis. Diagnosis of tinea pedis can also be verified using microscopy and cultures of skin scrapings. Confirmation of fungus is done after examining the skin scrapings of the infected site under a microscope. Using the edge of a microscopic glass slide, the dry scales of the heel and sides of

the foot are gathered and examined. For testing blisters, entire roof-mounted intact or scrapings made from the underside of the roof are taken. Before testing under the microscope, a few drops from a 10%-20% sodium hydroxide solution are taken on the glass slide and then covered with a coverslip. The addition of 20%-40% of Dimethyl sulfoxide (DMSO) solution can further hasten the defoliation of keratin, avoiding the need for heating. The staining method may be achieved by diluting 100 mg of chlorazol black dye with 10 mL of DMSO and adding 5% KOH solution. Toluidine blue, 0.1%, can also be used for thin specimens. Under a microscope, 10 x10 magnification makes it possible to see the hyphae and spores of fungi.^{9,10,11}

Risk factors:

Hot, humid environments, tight shoes worn for long periods lead to excessive sweating, and damp socks and shoes will eventually lead to prolonged contact with water, which can contribute to the spread of infection. Transmission occurs through clothing, dirty towels, bed sheets, mats, socks, shoes, and floors.¹² It is easily transmitted in communal and public areas such as swimming pools or locker rooms by people walking barefoot¹. A high prevalence of the infection is found in people taking antibiotics, steroid drugs, birth control pills, and drugs that suppress the immune system and those who are obese, with a weakened immune system, and have diabetes mellitus. Complications of athlete's foot include Osteomyelitis, Lymphangitis, Cellulitis, and Pyoderma.⁴

Preventive measures:

It is essential to refrain from sharing shoes, sheets, towels, and other personal belongings. One has to dry feet thoroughly, particularly between toes, after coming in contact with water. Wear cotton socks and wash them regularly. Do not wear tight shoes. Protecting foot from accidents by wearing footwear in public places is essential. Products containing bleach should be used to clean showers and bathroom floors. If one already has an athlete's foot, he/she should wash socks and towels at 60° C or more and dry their shoes thoroughly. Alternatively, using two pairs of shoes and dusting talcum powder between toes before wearing socks and shoes is recommended. Wash socks, towels, and bed sheets in hot water to prevent recurrence of infection. Soak feet in baking soda solution for 15 minutes. Turmeric powder may be applied if the skin is dry and the feeling of burning is more intense.^{4,8}

Management of Athlete's Foot:

Oral medications: An athlete's foot is almost always treated topically. Tablets are only recommended in cases where the topical treatment was not successful. It is necessary to treat systemically only if the infection is recurrent or blister-covered or involves the dorsum of the foot, the heel, or the sole.¹³ At a dosage of 250mg/day, oral Terbinafine produces a rapid and long-lasting remission in adults. In 200 mg/day regimens for 30 days, Itraconazole, an azole from the triazole family, inhibits the demethylation step in the formation of ergosterol on the fungal cell membrane. For more extended treatment duration, Fluconazole is given in a 150 mg/week dosage regimen. With a dosage range of 500 to 1000 mg/day, Griseofulvin can also be used. For children, Itraconazole is given in a dosage of 5 mg/kg/day, or Griseofulvin, which has a dosage range of 10 to 20 mg/kg/day, may be used.^{4,14} The advantages of oral medications include high patient acceptability, ease of accurate dosing, and good physical and chemical stability. At the same time, the disadvantages include difficulty in administration while swallowing in the case of children and unconscious patients.

Side effects: Tablets for fungal infections cause more side effects compared to topical medications. Itraconazole may

cause dizziness, headaches, digestive problems (stomach and bowel), and rashes. With Fluconazole, gastrointestinal side effects are uncommon but possible. In the studies, terbinafine caused temporary taste and smell loss and gastrointestinal problems. However, these side effects did not last long. Taking these two medications together could lead to potential interaction with other medications, so it is essential to inform the doctor if the patient is taking any other medications. Due to the small risk of severe liver damage, these medications are only given if absolutely necessary to people with liver problems.^{15,16} Fluconazole and Itraconazole both cause a much lower rate of hepatotoxicity than Ketoconazole.⁴

Topical medications: Infections caused by fungi are treated most frequently with topical therapy because they are self-administered, more patient compliant, and have no adverse systemic effects. Most of the drugs used as a topical treatment for Athlete's foot are well tolerated. They can cause slight reddening of the skin or a mild burning sensation, but other side effects are rare.²

There are several products available to treat fungal infections that contain a drug that stops the fungus' growth or kills it. These products include creams, gels, dusting powders, and sprays. Several commonly used products in treating fungal infections contain allylamines or azoles.¹⁷ Among the allylamines are tolnaftate, amorolfine, terbinafine, and naftifine. Among the azoles are Miconazole, Econazole, Ketoconazole, Bifonazole, Clotrimazole, Tioconazole, Sulconazole, Isoconazole, Fluconazole, and Oxiconazole.⁷ Tinea pedis patients with the hyperkeratotic variant may require additional treatment with salicylic acid or urea-containing topical keratolytic creams¹⁵.

Compared to Clotrimazole, the topical application of Terbinafine and Amorolfine has been shown to produce faster results.⁴ Repeated KOH scrapings and cultures need to be negative throughout the treatment. The length of therapy will depend on the response to the treatment. With newer antifungal agents, shorter courses are possible.^{13,18,19}

In studies on the effectiveness of allylamine products, it was found that 17 people out of 100 who did not have athlete's foot had gotten rid of it after six weeks, but 73 out of 100 had. About 56 of 100 people received allylamine treatment and were cured of the fungal infection. Terbinafine works even if it is used for just one week. Azole medicines are similarly effective.¹⁴

- i. **Creams:** Creams' cooling, moisturizing, and emollient properties are attributed to their oil-in-water emulsion structure. Emulsifying agents can enhance cream stability.²⁰ Majority of antifungal drugs available are formulated as creams like Tolnaftate, Clotrimazole, Miconazole, Ketoconazole, Sulconazole, Oxiconazole, Econazole, Butenafine, Naftifine, Terbinafine.²¹ Using cream can leave the foot with a greasy, wet feel that is uncomfortable to the user and messy on clothing and shoes. As they are less hydrophobic than other semi-solid dosage forms, the risk of contamination is also high.
- ii. **Gels:** Gels are clear, colourless, semisolid, colloidal dispersions that liquefy when contacted with warm skin or when rubbed upon friction. Moreover, on drying from a non-occlusive film. Unlike creams, gels are nongreasy, washable with water, aesthetically pleasing for treating hairy areas, and are particularly useful for treating eczema.²¹ Hydrophilic polymers like Carbopol 940, Hydroxy Propyl Methyl Cellulose (HPMC), and sodium alginate are used in topical gel formulations as hydrophilic polymers. These polymers are used between 1-5 %, depending on the molecular fraction of the polymer.²² The treatment time for topical gels containing azoles and

allylamines is 2 – 4 weeks long.⁵ Tolnaftate (Tinactin), Miconazole (Micatin), and Naftifine (Naftin) are widely used in gel formulations. Advantages of gels include prolonged contact time between the drug and the wound, improved local bioavailability, a diminution in dose concentration, and improved patient compliance and comfort. Depending on the solubility of the drug in the vehicle, the thermodynamic activity of the drug may be higher, leading to greater partitioning of the antifungal into the skin and increased bioavailability.²³

iii. Dusting powders: Powders can be either hydrophobic or hydrophilic based on the base used. For example, talc-based powders are considered hydrophobic, and starch-based powders are hydrophilic. When applied to flexures, they minimize friction between toes or opposing surfaces. These are mainly used prophylactically to prevent tinea pedis.²⁴ Under azoles, Clotrimazole, Miconazole, and Ketoconazole are commonly given as dusting powders in treating athlete's foot. Under allylamines, Terbinafine is widely used as a dusting powder. Studies show that prophylactic application of tolnaftate powder at swimming pools reduces the incidence of toe cleft tinea pedis resulting from *T. interdigitale*.¹² According to recent studies, clotrimazole powder effectively treated and possibly prevented cutaneous fungal infections in combination with clotrimazole cream.²⁵ However, powders should be avoided by those with moist lesions, as they tend to cake and can abrade the skin.²⁰ Maintaining and retaining the powder on the application site can be challenging.

iv. Sprays: Apart from topical creams and gels, various sprays are available in the market to treat athlete's foot disease. These spray formulations are quick, convenient, and have no-touch applications. They relieve itching, burning, scaling, and cracking of the athlete's foot. They treat athletes' feet efficiently in hard-to-reach places and provide instant cooling and soothing, leaving no powder residue. Tolnaftate, Clotrimazole, Miconazole, and Terbinafine are commonly used antifungal agents as sprays.²⁶ Spray formulations do not require any manual/direct contact with the medicament, thereby avoiding contamination of the product. The drug release on the affected area occurs in a controlled and uniform manner. However, topical sprays are costly preparations, and some of the propellants used in them could be toxic. Sometimes cooling effect caused by the highly volatile propellants may cause discomfort to injured skin. As the contents of the spray are under high pressure, the sprays are inflammable and should not be used while smoking or near heat or flame. They should be kept away from children below two years. Deliberate misuse by intentional inhaling of contents could be harmful and fatal.

Discussion:

The athlete's foot is an infectious fungal infection of the foot and is likely to occur at least once in a person's lifetime. There are different formulations available to treat the disease. Among these formulations, topical medications are well tolerated. Between the topical formulations, clear transparent gels have gained more patients acceptance. Unlike powders, they do not absorb moisture and are lighter than creams; therefore, can be easily absorbed into the skin. Sprays have an added advantage over gels as they are no-touch applications and have a faster drying rate of the product on the application site due to the use of volatile solvent in the formulation. Despite these added advantages, marketed spray products are limited due to their high manufacturing cost. Today, there are a multitude of antifungals available for treating fungal infections, however, researchers are pursuing new ways to

optimize these drugs due to inadequate penetration, limited aqueous solubility and low bioavailability. Consequently, during the last two decades, the development of drug-delivery systems based on nanoparticles to enhance antifungal functions has gained prominence.^{27,28}

Conclusion:

Preventive measures help to prevent the recurrence of the Athlete's foot infection to a great extent. Treatment with topical products is good enough to clear the infection in most cases. However, in severe cases, it is mandatory to use a combination of topical products and oral antifungals for the efficacy of the treatment. The excipients used in dusting powders attract moisture which may favour the growth of other germs. Whereas in cases where a gel or cream is applied to the patient's foot, the patient should pay proper attention when stepping on wet and smooth surfaces to prevent slipping. Among the various products studied, very few antifungal drugs in the form of sprays are available, making it clear that there is a need to develop more marketed antifungal sprays to treat Athlete's foot disease more conveniently and effectively. Sprays reach the infection site directly, and touching the product with a finger can be avoided. Though expensive, the product reaches easily in hard-to-reach places, leaves no powder residue at the application site, and treats the infection effectively.

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