

A REVIEW OF TOPICAL AGENTS FOR DERMATOPHYTOSIS

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Introduction

Quite a number of antifungal agents have been released into the market within the recent decade for the topical treatment of superficial skin fungal infections, including tinea pedis (athlete's foot), tinea cruris, tinea corporis caused by various dermatophytes such as *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum* and *Microsporum canis*; tinea versicolor (pityriasis versicolor) caused by *Candida Albicans*. Tables I A & B present a summary of the old and new preparations, from which some similarities and differences among them can be anticipated.

Clinical Studies

Well-controlled clinical studies on the effectiveness of the older agents like undecylenic acid-zinc undecylenate are very scanty.

Nystatin, the antifungal agent which has been available for many years has firmly established its effectiveness and safety in the treatment of cutaneous candidiasis through long-term experience with it.

Newer agents that are released recently, namely, tolnaftate, haloprogin, miconazole and clotrimazole have undergone quite extensive studies, some uncontrolled, some involved comparisons with the older agents and some involved comparisons with the respective vehicles. However, response rates reported from these clinical trials vary over a wide range and difficulty was encountered in evaluating and comparing the studies to make a definite indication as to the relative efficacy of the newer agents. Several reasons can be attributed to this problem, and they are listed as follows: (B)

1. The vehicle used for the topical medication. Better results seem to be reported from polyethylene glycol or propylene glycol solution than emulsion cream bases.

2. The criteria for evaluating final response. In some studies, response rates are judged by the degree of clinical improvement irrespective of mycological

studies, whereas in other studies, cures are based on complete clinical clearing and conversion of mycological examination to negative.

3. Environment. Some clinical trials are done in patients in hospital where their treatment was well monitored; whereas some trials are done in out-patient basis where compliance might be a problem. One study was done on prisoners who were in constant adverse environment of heat and humidity during their treatment.(9)

4. Sites of infection. Different skin sites respond differently. Tinea pedis has a lower response rate than both tinea cruris and corporis.

Tolnaftate was the first synthetic antifungal agent available. Cure rates with tolnaftate reported from various trials range from 72% to 93%. (8, 10-17) It is relatively less irritating and more effective than the older preparations like undecylenic acid-zinc undecylenate, Whitfield's ointment, etc. in the treatment of infections caused by various dermatophytes. (5, 8, 18)

Cure rates with haloprogin range from 68% to 92%. (8, 19-22) A large scale, well-controlled double-blind study was done by Hermann (19), and a good response was reported in patients with tinea pedis and those with tinea corporis. He also reported that haloprogin is effective in tinea versicolor and cutaneous candidiasis although the trial is uncontrolled.(19) Carter (21) conducted a comparative double-blind study of haloprogin and tolnaftate in 84 tinea pedis patients. There was no difference in cure rates and maintenance of cure as measured by clinical inspection, although mycological examinations showed a significantly higher cure rate and lower relapse rate with haloprogin than with tolnaftate.

Cure rates with miconazole range from 75% to 100%. (8, 28-30) In spite of a number of uncontrolled clinical trials, the studies done by Mandy and Garret (24) and Brugmans et al (23) were well-controlled and both indicated that clinical improvement and eradication of dermatophytes occurred significantly

more often in patients treated with miconazole than the vehicle alone. There is also evidence indicating that miconazole is active against *Melassezia furfur* and *Candida albicans*. (25, 28, 29)

Clotrimazole is the most widely studied agent among the new ones. Cure rates reported from various trials range from 59% to 70% (8, 9, 31-36), such a low figure is due to the fact that in most of their studies, negative mycological tests were required to be classified as cure. P. Hall-Smith (37) and O. Male (38) reported no significant difference between clotrimazole or tolnaftate 1% cream in tinea infections. Several clinical studies have shown that clotrimazole is more effective than the vehicle alone and is as effective as nystatin in the treatment of cutaneous candidiasis. (31, 33-36) For tinea versicolor, clotrimazole is at least as effective as Whitfield's ointment. (31, 32)

Discussion

Absorbine Junior[R] imparts a sensation of cooling as it evaporates. This might help to relieve itching or irritation that is associated with tinea pedis. The antifungal activity of thymol might have an effect in treating mild fungal infection of the feet.(2)

Sodium hyposulfite 20% solution is applied once or twice daily in the treatment of tinea versicolor. However, it requires continuous treatment for weeks or even months in order to prevent relapse of infections.(2, 39)

Salicylic acid and sulfur ointment may be helpful in promoting peeling of the scales in the squamous type of fungal infections. However, complete eradication of the causative organism(s) might not be achieved by this preparation alone since both agents have little or no antifungal activity.

Selenium sulfide 2.5% suspension has been used in

the treatment of tinea versicolor.(2) It only requires one to two applications in the initial treatment, but recurrence of infection is common after six months.(40)

Whitfield's ointment has been used in the treatment of various superficial fungal infections of the skin.(2) Because of its thick consistency, patient acceptability appears to be low in spite of its effectiveness. It is inappropriate in acute inflammatory condition.(43)

Undecylenic acid-zinc undecylenate combination may be helpful in mild cases, especially when hygienic measures are done concurrently.(18)

When the causative organism is identified to be of the *Candida* species, nystatin still remains to be the drug of choice because of long-term experience with it.

The other four agents, namely tolnaftate, haloprogin, miconazole and clotrimazole, all appear to be effective in the treatment of superficial fungal infections caused by various dermatophytes. All are relatively non-toxic and non-irritating to the skin. All require once or twice daily applications for two to four weeks (may be up to eight weeks in tinea pedis). Up to date, no well-controlled study comparing all these newer agents in patients with similar infections, environment and criteria for evaluating response has been published or carried out. (8, 42, 42) Therefore, it is not possible to conclude definitely which agent is more effective than the others although some clinicians do prefer miconazole or clotrimazole over haloprogin and tolnaftate.(18) One main advantage which is offered by haloprogin, miconazole and clotrimazole but not tolnaftate is that all three of them possess a wide spectrum, i.e. they are equally effective in *Candida* as well as dermatophyte infections. Therefore, in mixed mycotic infections or when the causative organism is unknown, these three agents are particularly preferred to nystatin or tolnaftate alone.

TABLE IA
COMPARISON OF DIFFERENT TOPICAL ANTIFUNGAL PREPARATIONS
 (Table Compiled from References 1 - 7)

PREPARATION OR AGENT	CHEMISTRY OR COMPOSITION	PROPERTIES	USE	AVAILABILITY	COST TO PHARMACY***
Absorbine Junior (R)	Each gm of liquid contains Menthol 12.5mg Iodine 0.2mg Potassium iodide 2.67mg Thymol 2.5 mg Chloroxylenol 5 mg Oil of sassafras 12mg	Iodine and chloroxylenol are antiseptics; thymol is a fungicidal agent.	Use in the treatment of tinea pedis.	Liquid Non-prescription item	\$ 1.78/120ml
Sodium hyposulfite (sodium thiosulfate)	Sodium hyposulfite 20%	NOT ESTABLISHED	Used in the treatment of ringworms and tinea versicolor.	Aqueous solution Non-prescription item*	\$ 3.00/120ml
Salicylic acid & sulfur ointment	Salicylic acid 3% Sulfur 3%	Both are keratolytic agents, i.e. they promote peeling of skin.	Has been used in various tinea infections.	Ointment Non-prescription items.*	\$ 3.25/60gm
Selenium sulfide Selsun (R)	Selenium sulfide 2.5%	Cytostatic agent i.e. it reduces the rate of epidermal cell turnover.	Has been used in the treatment of tinea versicolor.	Suspension Non-prescription item.	\$ 2.33/120ml
Whitfield's Ointment	Benzoic acid 5%** Salicylic acid 3.5%	Benzoic acid is antibacterial and antifungal; Salicylic acid has little or no antifungal activity but it possesses keratolytic property.	Used for the treatment of various types of skin fungal infections.	Ointment Non-prescription item.*	\$ 1.27/60gm

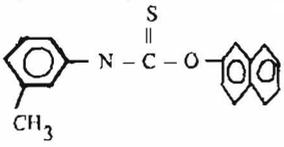
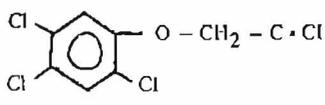
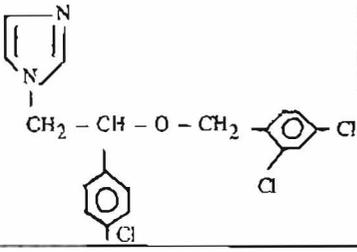
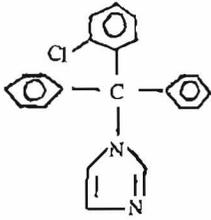
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***Approximate cost only. May vary depending on quantity bought or manufactured.

**Strength quoted from product from Drug Trading Company? B.P. formula contains Benzoic acid 6%, Salicylic acid 3%

TABLE IB
COMPARISON OF DIFFERENT TOPICAL ANTIFUNGAL AGENTS

(Table compiled from References 1 - 7)

AGENT	CHEMISTRY	MECHANISM OF ACTION	ANTI-MICROBIAL SPECTRUM	AVAILABILITY (For topical use only)	HOSPITAL PRICE
Undecylenic acid-zinc undecylenate (Desenex [R])	Combination of an organic fatty acid 2% and its salts 20%	Exact mode of action of the acid is not known. It is believed that zinc undecylenate liberates undecylenic acid when it comes in contact with moisture (eg. perspiration). In addition, zinc undecylenate has astringent properties due to the presence of zinc ion.	Weakly fungistatic to various strains of dermatophytes (Trichophyton, Microsporum, Epidermophyton) that cause tinea infections.	Powder Ointment Solution Non-prescription items.	\$ 1.27/45gm \$ 1.05/28.25gm \$ 0.75/60ml
Tolnaftate (Tinactin [R])	Synthetic naphthol derivative 	Exact mode of action unknown, believed to distort the hyphae and stunt mycelial growth in susceptible fungi.	Fungistatic or fungicidal to most strains of dermatophytes; little or no clinical effect on <i>Malassezia furfur</i> ; no effect on <i>Candida</i> species.	1% Powder 1% Cream 1% Solution	\$ 1.89/30gm \$ 1.83/15gm \$ 1.68/15ml
Nystatin (Mycostatin [R])	Antifungal antibiotic; produced by <i>Streptomyces noursei</i> . The drug is an amphoteric polyene macrolide.	Exerts its activity by binding to sterols in the fungal cell membrane which then ceases to be a functional selective barrier, resulting in loss of cellular constituents.	Fungistatic or fungicidal against <i>Candida Albicans</i> & other <i>Candida</i> species; no effect on dermatophytes or <i>Malassezia furfur</i> .	100,000 u/gm Ointment 100,000 u/gm Cream Non-prescription items (topical products only)	\$ 3.11/30gm \$ 2.80/30gm
Haloprogin (Halotex [R])	Synthetic halogenated phenyl ether derivative 	NOT KNOWN	Fungistatic or fungicidal to various strains of dermatophytes; also active against <i>Malassezia furfur</i> & <i>Candida Albicans</i> .	1% Cream 1% Solution Prescription-only items	\$ 3.43/30gm \$ 3.68/30ml
Miconazole (Micatin [R])	Synthetic imidazole derivative 	Exerts its antifungal & antibacterial activity by altering cell membrane permeability; exact site of action is not known.	Exhibit broad spectrum fungistatic activity against genus <i>Candida</i> & inhibits several other genera of fungi including yeast, dermatophytes & <i>Malassezia furfur</i> ; and a few strains of gram-positive bacteria such as <i>Staphylococcus aureus</i> .	2% Cream Prescription-only items	\$ 4.06/30gm
Clotrimazole (Canesten [R])	Synthetic imidazole derivative (that is structurally similar to miconazole). 	Exerts its antifungal activity by altering cell membrane permeability, apparently by binding with phospholipids in the fungal cell membrane.	Inhibits or kills many genera yeasts & dermatophytes; also active against <i>Malassezia furfur</i> , <i>Candida Albicans</i> and a few strains of <i>Staphylococcus aureus</i> & <i>Streptococcus pyogenes</i> . Higher concentration may inhibit growth of <i>Trichomonas vaginalis</i> .	1% Solution 1% Cream Prescription-only items	\$ 3.15/20ml \$ 3.15/20gm