Keywords: Efinaconazole, onychomycosis, fungal infection, nail infection

ABSTRACT

Efinaconazole is a class of triazole which is used for the healing of Onychomycosis. It has a property of suppressing the fungal lanosterol 14α-demethylase in Ergosterol biosynthesis pathway which has action on candida species and non-dermatophyte molds. Topical route has difficulty in penetration of nail plate which reflected in least efficacy of formulations than oral route because of larger (greater) drug interaction of oral route, topical route is of preferred route in many subjects. Lowest keratin affinities of Efinaconazole have higher delivery through nail plate. The properties of its low surface tension provide effective wetting property. Concentration of 10% topical solutions shown best efficacy in treatment of Onychomycosis patients in phase 3 clinical trials.
INTRODUCTION

Fungal contagion of the nail unit caused by dermatophyte, yeasts, and non-dermatophyte molds is known as Onychomycosis. It is a most customary disease with a prevalence of 10–12% in the US1. Both physical and psychological problems are seen with these disease. It is suffering from this infection have clinical manifestation of pain, trouble in wearing shoes, secondary contagion and difficulties performing everyday functions due to nail dystrophy and unacceptable cosmetic visualance [Appearance]2,3.

The cure objective is to destroy the fungus and produce a normal nail. The best treatment for onychomycosis is anti-fungal drugs where 4 classes of anti-fungal are approved for effective treatment i.e. azoles, allylamines, hydroxypyridinones, morpholines4 most b frequently and ridiculously used class of drugs is the azoles, which antagonise lanosterol 14α –demethylase [step in the ergosterol biosynthesis pathway] 5. Previously most extensively used in treating onychomycosis are oral Itraconazole and oral fluconazole due to increase the drug-drug interaction and various systematic side effects of oral agents and poor efficacy and time consuming treatment with topical drug course have begun. it is because of decreased side effect and better efficacy6.

Efinaconazole an FDA approved drug which is used for topical use are generally used for onchomycosis7, in recent days previously it was called as IDP-108 and KP-103. Efinaconazole has potent efficacy against dermatophyte compare to Itraconazole and also have higher activity against candida species8.

MECHANISM OF ACTION

Fungal cell membranes are calm of ergosterol which is used for balancing membrane fluidity which is essential for fungal cell viability where inhibition of ergosterol affect integrity of cell membrane and antagonise growth of fungal cell9, 10. Efinaconazole which states in inhibition of ergosterol synthesis in both the species of Candida albicans and Trichophyton mentagrophytes11.

CHEMICAL NAME AND FORMULATION

It is an azoleamine derivative whose chemical name is 1-piperidineethanol-ethanol12.C18H22F2N4O is its molecular formula and 348.39 are its molecular weight13. It is
formulation of 10% solution which weighs of 100 mg of drug per gram of a clear, colourless and yellow solution. Excipients used for the formulation are alcohol, anhydrous citric acid, butylated hydroxytoluene, C12-15 alkyl lactate, cyclomethicone, di-isopropyl adipate, disodium EDTA, and purified water. Because of its low surface tension aids in easy penetration and spreading and is frugally soluble in water. Since there have been studies of the drug in pregnant women, where it is categorised as pregnancy C. As subcutaneous use of Efinaconazole found in milk of breastfeeding women. Hence warning “should be used during pregnancy only if possible benefit justifies the potential risk to the fetus”.

Table No. 1. Hyphal morphology changes with Efinaconazole

<table>
<thead>
<tr>
<th>Efinaconazole concentration: 0.001-0.01 μg/mL</th>
<th>Efinaconazole concentration: 0.1-10 μg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortening of interseptal distance</td>
<td>Distance Nonuniform widths and flattening of hyphae</td>
</tr>
<tr>
<td>Globular swelling</td>
<td>Separation of plasma membrane from the cell wall</td>
</tr>
<tr>
<td>Thickening of the cell</td>
<td>Accumulation of electron-dense granules between the cell wall and the plasma membrane</td>
</tr>
<tr>
<td></td>
<td>Discontinuity of the plasma membrane Degeneration of organelles</td>
</tr>
</tbody>
</table>

NOTE: Data from Tatsumi et al. 1

IN-VITRO AND IN-VIVO STUDIES:

IN-VITRO STUDY:

According to in-vitro studies conducted by researchers for treatment of Onychomycosis. Its efficacy is higher against C. Albicans, Cryptococcus neoformans, aspergillus fungi 12. Where Efinaconazole compounds with other anti-fungal agents, other antifungal agent get deactivated, when it get bound to keratin, but the keratin has low de-activating level when compared to other anti-fungal. Even when the Efinaconazole tested against T-Mentagrophyte in Guinea pig model of tenia corporus it showed the best effective level, hence it get criterion to 4-methylenepiperidone which has excellent penetration power via transepidermal and transfollicular route. It has also excellent in-vitro activity. Trichophyton...
rubrum and Trichophyton mentagrophytes. The same efficacy level was seen in many other organisms like Trichophyton ajelloi, Trichophyton violaceum, Microsporum gypseum, Epidermophyton floccosum, Microsporum canis, and Epidermophyton floccosum.

**IN-VIVO STUDY**

Topical Efinaconazole has its 80% mycological cure when experimented against Guinea Pig with cutaneous candidiasis. The study was conducted in comparison to other anti-fungal drugs (neticonazole, and lanoconazole); comparison drugs were ineffective in minimizing the counts fungi in affected area. When Efinaconazole was led for 10 days of topical application in infected Guinea Pig resulted in dose dependent therapeutic effect with 1.0% of maximum drug concentration and resulted in negative culture test in feet of infected animals. Comparison of drugs for anti-dermetophyte relatively both neticonazole and Efinaconazole shows same effective level and low efficacy when compound with l lanoconazole relapse of infection in the feet of infected animals after 30 days of treatment was seen only in 8/20 treated feet.

In tinea Corporis model 3/10 animals treated got relapsed of infection treated with Efinaconazole for 9 days. Its binding capacity to keratin has much lower than comparative drug about 60.3% against neticonazole and 58.6% against lanoconazole. It gets released from keratin when washed with saline.

**PHARMACOKINETIC PARAMETER**

Efinaconazole is absorbed slowly and it lacks elimination phase, it is metabolised through both oxidation and reduction of phase I reaction yielding an H3 metabolite. The average half-life of drug and its metabolite is 29.9 hrs and 82.4 hrs. The drug and metabolite have longer elimination half-lives. The drug and the metabolite have low concentration in blood. Efinaconazole is a compelling inhibitor of several cytochrome P450 enzymes its calculated Cmax/K1 is 0.007 and that of metabolite is 0.0005 both of which are well below the threshold of clinical drug-drug interaction protein binding affinity is 95.8%-96.5% binding mainly to albumin, α1-acid glycoprotein, and γ-globulin.
Table No. 2. Inclusion and exclusion criteria for Efinaconazole Phase II clinical trial

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLSO affecting at least one great toenail</td>
<td>Dermatophytoma (fungal abscess)</td>
</tr>
<tr>
<td>Clinical involvement Age 18–65 years 20%–50% of the target toenail</td>
<td>Matrix ( lunula) History of immunosuppression and/or clinical signs revealing of possible immunosuppression</td>
</tr>
<tr>
<td>Target toenail with uninfected length (from the proximal nail fold) ≥ 3 mm</td>
<td>Known human immunodeficiency virus infection</td>
</tr>
<tr>
<td>Target toenail with thickness ≤ 3 mm</td>
<td>Uncontrolled diabetes mellitus</td>
</tr>
<tr>
<td>Evidence of toenail growth</td>
<td>Existence of toenail infection other than dermatophytes and Candida</td>
</tr>
<tr>
<td>Positive potassium hydroxide microscopy</td>
<td>Severe mucocutaneous-type tinea pedis at the screening or baseline visit</td>
</tr>
<tr>
<td>Culture of a dermatophyte or mixed dermatophyte/Candida ≤ 42 days before baseline visit</td>
<td>Any disease/condition that might have caused toenail abnormalities</td>
</tr>
<tr>
<td>Females of childbearing possible had to be using effective birth control</td>
<td>Previous target toenail surgery</td>
</tr>
</tbody>
</table>

Notes: Data from Tschen ET al.21

DESIGN AND RESULTS FROM CLINICAL TRIALS:

Randomised, parallel group and double blind control study was lead in Mexico in 135 patients with mild-to-moderate distal lateral subungual onychomycosis (DLSO). Inclusion criteria and exclusion criteria are shown in Table 2.

Randomised of patients was done into a groups

1st group – (n=36) – semi occlusion 10% of Efinaconazole

2nd group – (n=39) – 10% Efinaconazole4 concentration

3rd group – (n=32) – 5% Efinaconazole

4th group– (n=22) – vehicle
And best effective concentration for treatment was tested and resulted in 10% Efinaconazole concentration\textsuperscript{21}.

For detection of short-term and long term safety data obtained from lab animals. When applied dermally to mice (3 weeks), rat (3 months) erythema, hyper keratitis, mild microscopic inflammation seen.

NO- systemic toxicity is shown

Place metal effect in reproductive and development toxicity are seen but safer than other agents Efinaconazole in diabetes patients have been effective in minimal cure about 54%.

**OTHER SAFETY DATA:**

To know short and long term tolerance of Efinaconazole healthy volunteers are included in study for the evaluation of drug to produce ret and contact skin sensitization and its skin irritation for contact sensitization study, there were introduction, challenge and rechallenge phases for both the drug and vehicle 99.5% [206/207] of patients test with Efinaconazole and 99% [205/207] with vehicle, there is no evidence for contact sensitization, 3 of patients who have been for rechallenged. In 1 patient who receives the drug has not been found with contact sensitization with occlusive, semi occlusive or open application. In 2 patients who have been receiving vehicle upon rechallenge, it is likely to cause allergic reaction.37 patients have been went under 21-day cumulative irritation study who care receiving application of Efinaconazole 1%,5% and 10% solutions as well as positive control 0.2% sodium lauryl sulphate and the negative control deionized water. The calculated mean based on erythema scores were 1.12, 1.26 and 1.18 for the Efinaconazole solution respectively, 1.04 for the vehicle and 2.77 and 0.30 for the positive and negative controls\textsuperscript{22}.

From the above data, authors have concluded that Efinaconazole 10% solution have no effect contact sensitization and produce only minimal skin irritation.

Safety data are acquired from animal models Efinaconazole solution and vehicle both are delivered dermally to mice (13 weeks), rats (6 months)\textsuperscript{23}. 

\textit{Citation: HEMANTH A R et al. Ijppr.Human, 2019; Vol. 16 (2): 479-487.}
STUDIES IN PATIENTS WITH DIABETES:

Onychomycosis influence one-third of patients with diabetes and elevate the degree of foot disorders like non healing ulcers and secondary infections\textsuperscript{24}. From the Phase III trials, where analysis was conducted on 112 patients with diabetes aged 29-70 years. Among these 13\% of diabetic patients treated with Efinaconazole achieved complete primary cure in comparison with 3.7\% diabetic treated with vehicle (P<0.001) for secondary endpoint of mycological cure\textsuperscript{56}.56.5\% of diabetic patients have been achieved the result with active drug linked with 14.8\% of diabetic treated with vehicle(P=0.016)\textsuperscript{25}.

STUDIES ON COEXISTING TINEA PEDIS WITH ONYCHOMYCOSIS:

Tinea pedis is a risk factor of onychomycosis\textsuperscript{26}. Tinea pedis found in50\%of patients with onychomycosis\textsuperscript{27}. When application of Efinaconazole on patients with onychomycosis and coexisting tinea pedis in Phase III trials it is observed that 21.3\% (352/1,654) of onychomycosis study patients reported interdigital tinea pedis at baseline\textsuperscript{28}. 215 patients (61.1\%) with onychomycosis with coexisting tinea pedis are treated in along to being treated with Efinaconazole. Patients who are recently treated for tinea pedis, complete cure rates are observed with Efinaconazole were 29.4\% (P=0.03 v/s vehicle) and mycological cure rates 56.2\% (P\leq0.001).

STUDIES USING NAIL POLISH:

Study was conducted using the normal human cadaver thumbnails refined with two coats of three dissimilar brands and control. A group with uncoated nails with treatment one application. By above case control study’s authors concluded penetration of Efinaconazole has no relation with nail polish\textsuperscript{29,30}.

KERATIN AFFINITY AND TRANSUNGUAL PENETRATION IN-VITRO:

Dorsal layer of the nail is composed of only layer of cell of thick keratin which is main barrier for penetration of drug through nail plate\textsuperscript{31}. Keratin-bound drug i.e. other azoles results in accumulation on surface layers of nail\textsuperscript{32}.

Example ciclopirox was applied on nail for 14 days penetration into ventral side is 2-4 order magnitude less when compared to dorsal side\textsuperscript{33}. In comparison to azole Efinaconazole lower bonding capacity to keratin which can be early permeable and do not get accumulated on nail.
plate Efinaconazole free-drug concentration in keratin suspension was 14.3% ± 0.4% significantly greater in comparison of ciclopirox(0.7%±0.01)respectively P<0.00134.

**TRANSUNGUAL PENETRATION IN ONYCHOMYCOSIS PATIENTS:**

10% of topical Efinaconazole solution treated for oncho patients for 28 days with 2 weeks of follow-up after last drug application. Concentration of drug in toe nail [5.9 ± 5.1, 6.0±3.9 and 3.1±3.2 mg/g at week 2, 4 and 6 respectively] presence of disease or nail thickness is not influenced by concentration of Efinaconazole in nail35.

**REFERENCES**