Extended Abstracts for Butenafine

1. Syed TA and Maibach HI. Butenafine hydrochloride: for the treatment of interdigital tinea pedis Exp. Opin Pharmacother. 2000 1(3):467-473

Butenafine hydrochloride: for the treatment of interdigital tinea pedis

Source Description:

- Expert opinion review paper on butenafine hydrochloride
- Paper from a peer-reviewed journal 'Expert Opinion on Pharmacotherapy'
- Authors are affiliated with the department of dermatology at University of California
- Date of writing was 2008 and there have been no updates or corrections to this paper

Summary

The author's state that butenafine 1% topical cream is effective for treating tinea pedis. They also state that butenafine is generally safe and well tolerated. Butenafine is more convenient than other topical antimycotics because it can be used once daily compared to twice daily with other topical antimycotics and can potentially be used for a shorter duration. Butenafine is also advantageous as it is cost effective compared to other antimycotics due to less applications per day, less relapse rates and overall less need for follow up. Higher availability and persistent retention at the superficial fungal infection site, provide higher cure rates, lower relapse rates and shorter treatment regimens with allylamine-type drugs like butenafine compared to azoles. Based on its efficacy, safety, patient compliance, relapse rates and cost effectiveness make butenifine a potential alternative topical antimycotic for the treatment of tinea pedis.

Comments/ Critical Appraisal

Paper is very well written and includes a great summary of the pharmacokinetics, pharmacodynamics, mechanism of action, safety and efficacy of butenafine. References used were relevant, from a variety of sources, and it is likely that authors did not miss any important information when preparing the document. One of the authors is of the paper is the main author of one of the landmark clinical trials showing efficacy for butenafide, potentially adding some bias. Though all statements presented are appropriately referenced and backup up by primary and secondary literature.

2. Tchen E, Elewski B, Gorsulowsky D, et al. Treatment of interdigital tinea pedis with a 4 week once-daily regimen of butenafine hydrochloride 1% cream. J Am Acad Dermatol 1997;36:S9-14

Study objectives

• To evaluate butenafine in the treatment of tinea pedis.

- Methods
 - Design
 - Controlled, randomized, double blind trial
 - Allocation
 - o Randomization schedule generated and maintained by the sponsor
 - Block randomization using blocks of 4 patients (2 butenafine and 2 vehicle)
 - Of 80 patients with positive fungal cultures, 40 applied butenafine 1% cream and 40 applied vehicle to the affected area once daily.
 - Blinding
 - Double blinded (patient and investigator blinded)
 - Follow-up period
 - 8 weeks total. 4 weeks during treatments and 4 weeks after.
 - Setting
 - Multicenter (4 centres)
 - Participants
 - Men and women with clinical evidence of interdigital tinea pedis
 - Inclusion:
 - erythema score of ≤2 (on a scale of 0-3, where 2 indicated moderate severity)
 - pruritus score of ≤ 2 (on same 0-3 scale)
 - scaling score ≤ 2 (on same 0-3 scale)
 - positive potassium hydroxide preparation for fungal hyphae
 - Exclusion:
 - Hypersensitivity to allylamines or ingredients of the study materials
 - Recently used an antifungal, antibiotic or immunosuppressant
 - Pregnant, lactating or women not using adequate contraceptive measures
 - Patients with concomitant conditions or diseases that interfere with the evaluation of their tinea pedis or the assessment of its treatments.
 - DELAYED exclusion based on fungal culture results from skin scrapings from target lesions. Patients excluded if test showed clinically significant abnormal results or if subsequent baseline cultures were negative
 - Intervention
 - Butenafine 1% once daily for 4 weeks or vehicle applied once daily for 4 weeks
 - Outcomes
 - Patient follow-up
 - Efficacy and safety were assessed at week 1, 2 and 4 of treatment and 4 weeks after treatment completion
 - Efficacy endpoint:
 - Signs (cracking/fissuring, erythema, scaling and maceration) and symptoms (puritis and burning/stinging) of tinea pedis in the target lesion and on the

same foot excluding the target lesion were scored on a 0 (absent), 1(mild), 2 (moderate), 3 (severe) scale.

- Safety:
 - Assessed by asking direct questions about adverse events occurring after the prior visit and the investigator determined severity and their possible or probable relation to the study medication

Main results

- Significantly more patients using butenafine than using vehicle had mycologic cure
- Mycologic cure: 88% butenafine, 33% vehicle
- Effective clinical response: 78% butenafine, 35% vehicle
- Adverse effects:

Conclusions

• Butenafine applied once daily for 4 weeks resulted in an effective clinical response and mycologic cure of tinea pedis during treatment. Patients continue to improve at least 4 weeks after treatment.

Comments/Critical appraisal

Use of both objective (KOH exam and cultures) and subjective (clinical exam scores) outcomes was a strength. Objective outcomes decreased risk of bias and ultimately proved treatment success while subjective outcomes although increasing potential for bias gave good practical assessment of efficacy as this is what would be traditionally done in outpatient settings. Follow-up was sufficiently long and appropriate to assess butenafine's efficacy in treating and preventing relapses. Modified intention to treat analysis was which makes reporting of results appropriate and valid. Population was quite small only 119 who met all inclusion criteria which weakens the study.

This trial had good internal validity. Assignment to treatment or placebo/vehicle group was randomized and blinded to both investigators and patients. The vehicle was odourless and looked like butenafine treatment which protected blinding. Patients in the two treatment groups were similar in age, sex, and race/ethnicity. The severity of the infection was similar in the two group as indicated by the total signs and symptoms scores.

Adverse events were not outlined as part of primary or secondary endpoints and but there was explanation of how they were reported and collected. Given this, there is appropriate to say that adverse events were probable not missed and reported adverse event rates were correct.

External validity was reasonably good. Subjects were from the North America making the study population very similar to population in Canada. Excluding subjects with negative fungal cultures may decreased external validity as this selected a narrow population that is not proportional to the population seen in a pharmacy or clinic as fungal cultures are not routinely done in practice. Potentially increase treatment failures as a self-care product.

Subjects were not treated much differently in the study as they would in a real environment increasing external validity. *Trichophyton rubrum* was the pathogen isolated from more than 90% of the positive fungal cultures and this is approximately the same proportion seen in the community.

This trial would have had more clinical significance if it was compared to gold standard therapy (i.e. an azole) instead of placebo.

3. Savin R, De Villez RL, Elewski B, et. al. One-week therapy with twice-daily butenafine 1% cream versus vehicle in the treatment of tinea pedis: a multicenter, double-blind trial. Am Acad Dermatol. 1997 Feb; 36:S15-9.

Study objectives

• To evaluate the safety and efficacy of twice-daily butenafine versus its vehicle in treating interdigital tinea pedis

Methods

- Design
 - Randomized double-blind, parallel trial
- Allocation
 - o Unspecified randomization schedule generated by the sponsor
- Blinding
 - o Double-blinded
 - Butenafine and vehicle were odourless and the formulations were indistinguishable from each other
- Follow-up period
 - \circ 6 weeks total: 1 week of treatment and 5 weeks after treatment completed
- Setting
 - Multicenter (10 sites)
 - United States
- Participants
 - Male and female patients >12 years old
 - Inclusion criteria:
 - Moderate erythema and at least one of moderate scaling or moderate pruritus. Moderate was based on a scale of 0-4 (0=none, 1=mild, 2=moderate, 3=moderately severe, 4=severe)
 - Positive potassium hydroxide exam and positive mycologic culture for dermatophytes
 - Exclusion Criteria:
 - Clinically significant disease other than tinea pedis
 - Female patients of childbearing age, if they were pregnancy, nursing, or not using a medically acceptable form of contraception
 - Concomitant fungal infection other than onychomycosis, confluent diffuse moccasin type tinea pedis
 - Concomitant atopic or contact dermatitis of the foot, psoriasis or any other disease that could interfere with results
 - Use of topical medicated products for the treatment of tinea pedis within 14 days of study entry
 - Use of systemic corticosteroids or immunosuppressants within 6 weeks
 - Use of intraconazole within 6 months or taken any other systemic antifungal within 2 months

- Total of 402 patients with interdigitial tinea pedis with a positive potassium hydroxide examination were enrolled and were cultured to confirm tinea pedis.
- 271 patients had culture confirmed tinea pedis and qualified for inclusion;132 received butenafine and 139 received vehicle twice daily.
- Intervention
 - Butenafine 1% cream applied twice daily to affected areas OR vehicle applied twice daily to affected areas
- Outcomes

Primary efficacy endpoints:

- Mycologic cure
 - Negative KOH and culture
- o Effective Treatment
 - Mycologic cure and investigator global assessment of "cleared" or "excellent"
- Overall cure
 - Mycologic cure and investigator global assessment of "cleared"
- Mycologic/Clinical cure
 - Mycologic cure plus target lesion sign and symptoms score of 0
- Secondary efficacy endpoints:
 - Effective clinical response
 - Investigator global assessment of "cleared" or "excellent"
 - Total signs and symptom scores
 - Patient perception
- Patient follow-up
 - Follow up appointments were scheduled for days 8, 14 and 42 for fungal culture, potassium hydroxide exam and clinical evaluation of the target lesion and of the target foot excluding the target lesion.
 - Clinical evaluation included assessment of signs (cracking/fissures, erythema, scaling and maceration) scored on the 0-4 scale , symptoms (pruritus, burning and stinging) scored on the 0-4 scale and a global response assessment of each patient's signs and symptoms relative to baseline scored as cleared (100% remission), excellent (90-99% improvement), good (50-89% improvement), fair (25-49% improvement, poor (<25% improvement), unchanged or worse.

Main results

- Mycotic cure rates were statistically significantly higher in butenafine group versus vehicle group at all follow up days; 43% vs. 25% on day 8, 61% vs. 35% on day 14 and 74% vs. 22% on day 43.
- Overall cure rate was significantly higher in butenafine group on day 14 (4% vs. 0%) and on day 42 20% vs. 1% but was not statistically different on day 8.
- Effective treatment rate was statistically significant at day 8 (6% vs. 1%), 14 (17% vs. 9%) and at 5 week (40% vs 9%) follow up.
- Mycological/clinical cure was significantly higher in butenafine group at 5 week follow up only (25% vs. 3%)

- Secondary outcomes of total signs and symptoms and effective clinical response at 14 days and 42 days.
- Adverse events occurred <1% in butenafine group and 2% in vehicle group. Butenafine
 adverse events included 1 patient with mild burning /stinging. 4 patients experienced
 adverse effects in the vehicle group 1 patient with elevated AST and ALT levels and 3
 patients experiencing burning or tingling. No subjects withdrew from the study due to
 adverse events.

Conclusions

- Butenafine applied twice daily for 1 week is effective in treating interdigital tinea pedis versus vehicle.
- Butenafine is also effective in preventing relapse or recurrence at 5 weeks.

Comments/critical appraisal

Use of both objective (KOH exam and cultures) and subjective (clinical exam scores) outcomes was a strength. Objective outcomes decreased risk of bias and ultimately proved treatment success while subjective outcomes although increasing potential for bias gave good practical assessment of efficacy as this is what would be traditionally done in outpatient settings. Follow-up was sufficiently long and appropriate to assess butenafine's efficacy in treating and preventing relapses. Modified intention to treat analysis was which makes reporting of results appropriate and valid.

This trial had good internal validity. Assignment to treatment or placebo/vehicle group was randomized and blinded to both investigators and patients. The vehicle was odourless and looked like butenafine treatment which protected blinding. There were no statistically significant differences between the two treatment groups in age, sex, race/ethnicity, tinea pedis history, concurrent onychomycosis, total signs and symptoms scores at baseline, or dermatophyte species isolated which contributed to strong internal validity. Subjects were instructed to use a diary to mark down when they applied treatment in order to monitor compliance which was a good strategy to strengthen internal validity but unfortunately authors did not comment on rates of compliance so it is unknown if compliance strengthened or weakened validity of this trial.

Adverse events were not outlined as part of primary or secondary endpoints and there was no explanation of how they were reported or collected. Given this, there is potential that adverse events were missed and reported adverse event rates incorrect.

External validity was reasonably good. Subjects were from the United States across 10 sites making the study population very similar to population in Canada. Excluding subjects with negative fungal cultures may decreased external validity as this selected a narrow population that is not proportional to the population seen in a pharmacy or clinic as fungal cultures are not routinely done in practice. Subjects were not treated much differently in the study as they would in a real environment increasing external validity.

This trial would have had more clinical significance if it was compared to gold standard therapy (i.e. an azole) instead of placebo.

 Singal, A. Butenafine and superficial mycoses: current status. Expert Opin. Drug Metab. Toxicol. (2008) 4(7):999-1005

Source description

- Expert opinion review paper on butenafine hydrochloride use in superficial mycoses
- Paper from a peer-reviewed journal 'Expert Opinion Drug Metabolism and Toxicology'
- Date of writing was 2008 and there have been no updates or corrections to this paper

Summary

Author concludes that butenafine 1% topical cream has been found efficacious for tinea pedis along with other superficial mycoses. The drug has excellent penetration into the epidermis and a prolonged retention time following topical application leading to residual therapeutic activity after treatment cessation, allowing for a shorter duration of treatment. It is recommended that the drug be used twice daily for 7 days or once daily for 14 days for treatment of tinea pedis. Author also reports that butenafine has anti-inflammatory activity as well. Butenafine was also found to be efficacious in treating hyperkeratonic tinea pedis when used alone or along with 20% urea ointment.

Author prefers butenafine over clotrimazole because it is fungicidal rather than fungistatic. Also because there is a tendency of patients to stop therapy with slight clinical improvement, butenafine is advantageous because it has faster cure rates and persistent residual effects. Its efficacy however needs to be compared to established therapies like terbinafine and azoles in head to head trials before its uptake in clinical practice.

Author report side effects are non-existent or negligible. Butenafine is well tolerated and shows no carcinogenicity, mutagenicity or impaired fertility when used topically at the recommended dosages. Local, transient mild burning and/or stinging was reported in 0.5-2.2% of patients but no one has withdrawn treatment due to adverse effects. Author report side effects are non-existent or negligible.

Comments/critical appraisal

Search strategy to obtain relevant articles was explained and is appropriate. It is unlikely that relevant and important references were missed. References used were relevant, current and from a variety of sources. All statements presented are appropriately referenced and backup up by primary and secondary literature. Paper is very well written and includes a great summary of the pharmacokinetics, pharmacodynamics, mechanism of action, safety and efficacy of butenafine. Author leaves the reader with concise and well explained conclusions, expert opinion and gaps in knowledge.

5. Micromedex 2.0. Butenafine Hydrochloride. Thomson Reuters 2012

Source description

- Micromedex is an online evidence based clinical resource.
- Authors and editorial staff are all health professionals including clinical pharmacists, physicians and clinicians though specific authors for each topic are not released.

- There is referencing throughout the document with complete reference information at the end of the document. References are current and from reliable sources. All references used for this topic range from 2001-2006.
- All topics are peer reviewed as per Micromedex editorial policy and procedures.
- Topic was last modified March 1 2012
- Micromedex is a well-known resource used extensively in hospital and clinical settings in North America.

Summary

Butenafine hydrochloride belongs to the benzylamine class and is a synthetic antifungal agent. It works by inhibiting the synthesis of ergosterol which blocks squalene epoxidation. It can be fungicidal or fungistatic depending on the organism but treats most strains of Epidermophyton floccosum, Malassezia furfur and Trichophytons.

Author recommends applying 1% butenafine hydrochloride twice daily for 7 days or once daily for 4 weeks for tinea pedis in adults over the age of 12. They indicate that this is an FDA approved indication. They do not recommend the use of butenafine under the age of 12 because safety and effectiveness have not been established. These recommendations have been rated 'Class IIb' indicating that the treatment may be useful and is indicated in some but not most cases. They classify the strength of evidence for use in tinea pedis as 'Category B', based on randomized controlled trials that involved small numbers of patients or had significant methodological flaws. They advise that application area should include affected skin as well as the immediate surrounding area.

Use of butenafine is contraindicated in patients with hypersensitivity to butenafine products and precaution must be taken with patients with sensitivity to allyamine antifungals. They rate the risk of use in pregnancy as 'Rating C' due to lack of controlled studies in women and animals are not available. Drug should only be given if the potential benefit justifies the potential risk to the fetus. Risk to the infant if used in lactating women cannot be ruled out as available evidence is inadequate for determine infant risk. Most common adverse effects include contact dermatitis, erythema, itching and skin irritation with each occurring in less than 2% of patients.

Authors recommend monitoring for resolution of erythema, scaling and pruritus and signs on increased irritation and sensitivity (redness, itching, burning, blistering, swelling or oozing). It is recommended that patients seek additional assistance of there has been no symptomatic improvement after 3-4 weeks. Patients should be advised to avoid contact with eyes, nose, mouth and other mucous membranes.

Comments/Critical appraisal

The Micromedex document on budesonide hydrochloride served as a comprehensive summary about budesonide. Recommendations and evidence was graded giving the reader a better appreciation for the information provided. The information provided allows clinicians to safely and appropriately choose butenafiine for treatment of tinea pedis for appropriate patients. It also provided the clinician with information on how to administer the product and monitor for efficacy and safety. The references used were up to date, applicable and from reliable sources. References however did not include specific clinical trials separate from product monographs. Information provided is unbiased and authors are qualified health professionals. There was no sponsorship involved in the funding or writing of this document and there were no advertisements on the site further ensuring information provided was unbiased.