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Use of Oral Terbinafine in Children

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Although it is currently approved by the Food and Drug Administration (FDA) only for adults, terbinafine may be a useful alternative to standard therapies in the management of refractory superficial fungal infections in children. Since the initial reports in 1992, over two dozen papers, including several clinical trials, have been published which support the efficacy of terbinafine in the pediatric population.¹ This issue of *Pediatric Pharmacotherapy* will review the pharmacology of terbinafine and present the results of several studies describing its use in children.

Mechanism of Action and Antifungal Spectrum

Terbinafine is a synthetic allylamine derivative. It is believed to act through inhibition of squalene epoxidase, leading to a reduction in the biosynthesis of ergosterol in fungal cell membranes.¹⁻³ Terbinafine is currently indicated for the treatment of onychomycosis of the toenail or fingernail (tinea unguium). It has been shown in both *in vivo* and *in vitro* testing to have activity against the organisms commonly associated with this disease, *Trichophyton mentagrophytes* and *T. rubrum*. In clinical studies, terbinafine has been found to be effective against other causes of tinea capitis, tinea corporis, and tinea pedis, including *T. tonsurans*, *T. schoenleini*, *T. verrucosum*, *T. violaceum*, *Microsporum canis*, *M. audouinii*, and *M. gypseum*.¹⁻³

Clinical Experience in Children

In 1995, Nejjam and colleagues published the results of a pilot study of terbinafine in children with tinea capitis in the *British Journal of Dermatology*.⁴ Thirteen children (5 to 11 years of age) were enrolled in this open-label study for 6 to 8 weeks. All were treated with a dose of 125 mg given once daily. Of the 12 evaluable patients, 10 were infected with *T. violaceum*, one with *M. canis*, and one with *T. schoenleini*. At the end of 3 weeks, seven patients had negative mycological tests and one patient was considered to have a complete cure (no clinical signs or symptoms of infection). At 6 weeks,

another five patients had negative tests and 10 were considered to have a complete cure. By the end 8 weeks, the final patient had achieved a negative mycological test and clinical cure. At follow-up 2 weeks later, none of the patients showed signs of recurrence.

An overview of this paper plus five other clinical studies conducted by the manufacturer was published later that year.⁵ A total of 264 children were enrolled in these studies, with 152 children able to be evaluated for efficacy and 196 for tolerability. Patients weighing less than 20 kg were treated with 62.5 mg terbinafine given once daily, while children 20 to 40 kg were treated with a dose of 125 mg. Clinical cure was demonstrated in 93% of the children. The duration of treatment varied by diagnosis, with the author recommending a 4 week course for tinea capitis, 2 weeks for tinea corporis and tinea pedis, 6 weeks for fingernail onychomycosis, and 12 weeks for toenail onychomycosis.

Since that time, a number of other clinical studies and case reports have been published with terbinafine in children. In 1998, Filho and colleagues published a prospective, open-label, multicenter study of terbinafine in 132 children (1-14 years of age) with tinea capitis.⁶ Patients were treated with 125 or 250 mg/day for a period of either 1, 2, or 4 weeks. Follow-up evaluation done at 12 weeks showed resolution of infection (negative microscopy and culture results) in 48.6% of patients treated for 1 week, 60.5% of those treated for 2 weeks, and 69.7% of those treated for 4 weeks. Clinical cure (resolution of symptoms) was present in 54.3%, 60.5%, and 84.8% of patients in the three respective groups.

In 2002, Friedlander, writing for the Tinea Capitis Study Group, published the results of a randomized, double-blind, parallel-group, duration-finding study of terbinafine in tinea capitis.⁷ A total of 176 children were treated with an oral dose of 3 to 6 mg/kg/day for 1, 2, or 4 weeks. At the end of the study, negative cultures and minimal symptoms were achieved in

59% of the children treated for 1 week, 69% of those treated for 2 weeks, and 65% of those treated for 4 weeks. The authors concluded that a 2 week treatment period was optimal for most children with *T. tonsurans* tinea capitis.

That same year, Heikkila and Stubb published a retrospective study of 47 children (mean age 9.4 years) with onychomycosis.⁸ Fourteen of the patients were given terbinafine at an average dose of 4 mg/kg/day for a period of 2 to 5 months. The remaining children were treated with standard doses of itraconazole, griseofulvin, or topical antifungal therapy. Sixty-nine percent of the terbinafine patients experienced a clinical cure, compared to 80% of the itraconazole group and 25% of the griseofulvin group. None of the children treated with topical therapy had complete resolution of symptoms. Mycological cure (by microscopy or culture) occurred in 77% of the terbinafine group, 84% of the itraconazole group, 25% of the griseofulvin group, and 20% of the topical therapy group.

It has been suggested by several authors that higher doses of terbinafine or longer treatment periods may be required for eradication of tinea capitis caused by *Microsporum* species.^{1,9-11} In a study of 14 children (1-15 years of age) given standard doses of terbinafine for *M. canis* tinea capitis, Koumantaki and colleagues found that none of the patients had a response by the fourth week of treatment.⁹ The authors doubled the dose for an additional 4 to 8 week period in six patients and continued the original dose in another six. The remaining two patients dropped out of the study. On subsequent follow-up, four of the patients had a complete cure. Three of those patients had been given the double dose, and the remaining patient had been receiving the standard adult dose throughout the study. The authors recommended terbinafine doses of 125 mg/day in children weighing 10-25 kg and 250 mg/day in children greater than 25 kg who have documented *M. canis* tinea capitis.

Two clinical trials have been conducted in children to further examine terbinafine dosing in the treatment of *Microsporum* infections.^{10,11} In 2002, a randomized, parallel-group, duration-finding study was conducted to compare terbinafine to griseofulvin in 134 children (mean age 7.7 years) with tinea capitis.¹⁰ Patients were randomized to one of four terbinafine treatment groups (6, 8, 10, or 12 weeks of treatment with daily doses of 62.5 mg in patients < 20 kg, 125 mg in patients 20-40 kg, and 250 mg in patients > 40kg) or high-dose griseofulvin (20 mg/kg/day) for 12 weeks. Patients were evaluated at 4 weeks and at the end of treatment.

Clinical cure was demonstrated in 76% of the patients given 6 weeks of terbinafine, 80% of those treated for 8 weeks, 74% of those treated for 10 weeks, 70% of those treated for 12 weeks, and 96% of those given griseofulvin. Mycologic cure rates ranged from 48 to 58% in the terbinafine groups, compared to 76% in the griseofulvin group. When analyzing their data, the authors found that while treatment duration made little difference, the patients who received a dose greater than 4.5 mg/kg/day demonstrated a better response, suggesting that dose may be more critical than duration.

These results were similar to those found in a dose-ranging study published in 2004.¹¹ The authors studied 100 children with *M. canis* tinea capitis. Patients were treated for 8 weeks with either 3.3 to 6 mg/kg/day (group A), 6 to 7 mg/kg/day (group B), or 7 to 12.5 mg/kg/day (group C). At the end of treatment, mycologic cure was achieved in 2.7% of group A patients, 91.3% of group B patients, and 97.1% of patients in group C. While further studies are needed to confirm these results, this information may be useful to clinicians seeing children who have failed to respond to standard doses.

Pharmacokinetics

Terbinafine is well absorbed after oral administration. Bioavailability is only 40%, as the result of significant first pass metabolism. Peak plasma concentrations occur approximately 2 hours after an oral dose in adults. Food does not significantly affect absorption. Terbinafine is more than 99% bound to plasma proteins. It is extensively metabolized, primarily through cytochrome P450 enzymes CYP1A2, CYP3A4, and CYP2C9. It exhibits triphasic elimination. The effective, or β -phase, half-life in adults is approximately 36 hours. The terminal γ -phase half-life is 200 to 400 hours, resulting from the slow elimination of the drug from tissues, primarily skin and adipose. Clearance of terbinafine is reduced by approximately 50% in patients with renal or hepatic impairment.¹⁻³

Two studies have been conducted to evaluate the pharmacokinetics of terbinafine in children.^{4,12} As part of their pilot study, Nejjam and colleagues evaluated the pharmacokinetics of terbinafine in 12 children (5 to 11 years of age) and compared them to results obtained from 16 healthy adult volunteers.⁴ Both groups were given a single oral dose of 125 mg. Maximum concentration, time to achieve maximum concentration, and volume of distribution were not significantly different between the two groups. Area under the concentration-time curve (AUC) was significantly greater for the pediatric

patients (2,967±965 h-ng/mL compared to 2,135±1,131 h-ng/mL in adults; $p < 0.05$). The effective elimination half-life was significantly shorter in the children (14.7±4.3 hours) compared to adults (26.7±11.7 hours; $p < 0.001$).

In 2005, Abdel-Rahman and colleagues studied the pharmacokinetics of terbinafine in 22 children between 4 and 8 years of age with tinea capitis.¹² The patients were treated according to weight (125 mg terbinafine for children less than 25 kg and 187.5 mg for children weighing 25 to 35 kg; approximately 6 mg/kg). Serum sampling was done after the first dose and at the midpoint of treatment. When corrected for dose, maximum serum concentrations were significantly lower in children than in adults (200±104 ng/mL compared to 454±185 ng/mL per mg/kg dose; $p < 0.01$). A slight, but statistically significant, reduction in clearance was seen with increasing age. The authors concluded that children may require a significantly higher weight-based dose to achieve serum concentrations similar to those obtained with standard dosing in adults.

Drug Interactions

There are several potential drug interactions with terbinafine, resulting from its inhibition of CYP2D6 activity. The effect of this inhibition may be a prolongation of the half-life of drugs eliminated through the CYP2D6 pathway, including dextromethorphan, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), type B monoamine oxidase inhibitors, and beta-adrenergic blocking agents. Although the clinical significance of these reactions has not been studied, patients receiving these drugs who are treated with terbinafine should be monitored and the dose of the affected drug reduced as needed.¹⁻³

Terbinafine decreases the clearance of IV caffeine by 19% and increases the clearance of cyclosporine by 15%. Cimetidine, an CYP P450 enzyme inducer, decreases the clearance of terbinafine by 33%, while rifampin, a CYP P450 enzyme inhibitor, increases the clearance of terbinafine by 100%. There have been case reports of changes in prothrombin time, both increases and decreases, when terbinafine is used concomitantly with warfarin. A definite interaction between these two drugs has not been established.¹⁻³

Adverse Effects

In clinical trials of adults, the most commonly reported adverse effects with oral terbinafine include diarrhea (in 5.6% of patients), rash (5.6%), dyspepsia (4.3%), serum transaminase

abnormalities (3.3%), pruritus (2.8%), taste disturbances (2.8%), nausea (2.6%), abdominal pain (2.4%), urticaria (1.1%), and visual disturbances (1.1%). Less frequently reported adverse effects included malaise, fatigue, arthralgia, myalgia, vomiting, and hair loss. Most of these reactions were mild and did not require discontinuation of therapy.^{2,3}

Similar results have been found in the pediatric studies.^{1,5,6} Gupta and colleagues summarized the adverse effect data from 989 children enrolled in 20 terbinafine studies.¹ A total of 106 children (10.7%) experienced an adverse effect, however only eight children discontinued treatment. The most common adverse effects were gastrointestinal complaints (in 2.8% of patients), followed by hepatic enzyme abnormalities (1.8%), hematologic parameter abnormalities (1.3%), rash and urticaria (1.2%), other laboratory abnormalities (1%), nervous system events, including headaches, somnolence hyperesthesia, and vertigo (0.9%), and body ache or fever (0.3%). Most of the events were transient and considered mild by investigators.

Rare cases of hepatic failure, including cases leading to patient death or liver transplantation, have been linked to terbinafine use in adults. In many of the cases, the patient had underlying hepatic disease prior to treatment. Terbinafine is not recommended for use in patients with chronic or active liver disease. Pretreatment measurement of serum transaminases is recommended. Patients and their families should also be instructed to contact their health care provider for signs of persistent nausea, vomiting, anorexia, abdominal pain, jaundice, or a change in stool or urine color.^{2,3}

Hypersensitivity reactions to terbinafine, including angioedema and anaphylaxis, have also been reported. In addition, there have been reports of severe dermatologic reactions, including Stevens Johnson syndrome and toxic epidermal necrolysis, occurring after terbinafine use. Other potentially serious adverse reactions include a decrease in absolute lymphocyte count, neutropenia, and thrombocytopenia.^{2,3} Agranulocytosis was reported in a 15 year old patient who received terbinafine 250 mg once daily for 1 month. Cell counts returned to normal within a week after discontinuing therapy.¹³

Dosing Recommendations

In adults, the recommended dose of terbinafine is 250 mg given orally once daily for 6 weeks in patients with fingernail onychomycosis and 12 weeks in patients with toenail onychomycosis.^{2,3}

In pediatric studies, the standard dosing regimen has been a single daily dose of 62.5 mg for children 10 to 20 kg, 125 mg for children 20-40 kg, and 250 mg for children greater than 40 kg. Some investigators have suggested a weight-based dose of 4 to 5 mg/kg/day as an alternative.¹ Doses up to 12.5 mg/kg/day have been used in patients with refractory infections.¹¹ Treatment duration varies with indication, with most studies using 2 to 4 weeks of therapy in children with tinea capitis or tinea corporis and 6 to 12 weeks of therapy in children with onychomycosis.^{1,5}

Availability and Cost

Terbinafine (Lamisil®; Novartis) is available in 250 mg tablets. The average wholesale price is \$378.48 per 30 tablet bottle.¹⁴ For pediatric patients, an extemporaneous formulation is available to prepare a 25 mg/ml oral suspension. The suspension is stable at room temperature or refrigerated for up to 42 days.¹⁵

Summary

Based on the studies conducted to date, terbinafine appears to be a safe and effective therapy for superficial fungal infections in children. Compared to other agents, it has the advantage of once daily dosing and, for some patients, a shortened treatment duration. It is anticipated that terbinafine will become a useful tool in treating pediatric patients, particularly those who fail to respond to traditional therapy.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 6/23/06:

1. Glimepiride (Amaryl®), a sulfonylurea, was added to the Formulary.
2. Trypan blue (Vision blue®) was added for intraocular use to stain the anterior capsule for complicated cataract surgery.
3. Sodium hyaluronate 2.3% (Healon 5®), a viscoelastic, was added.
4. Tamsulosin (Flomax®) was added for the treatment of benign prostatic hypertrophy.
5. Intravenous ibandronate (Boniva®) was added for the treatment of osteoporosis in postmenopausal women, with restriction to Endocrinology.
6. Abatacept (Orencia®) was added for the treatment of symptoms in patients with refractory rheumatoid arthritis. It is restricted to Rheumatology.
7. Adalimumab (Humira®) was added for the treatment of children with arthritis or Crohn's disease or adults with Crohn's disease who fail or are intolerant of infliximab. It is restricted to Pediatric Rheumatology and Gastroenterology/Hepatology.
- 8 The restriction on rituximab (Rituxan®) was amended to include use by Rheumatology in patients who fail or have contraindications to anti-tumor necrosis factor agents.
9. Anidulafungin (Eraxis™) was added to the Formulary for use in adults. Caspofungin is now restricted to pediatric patients only.

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