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Onychomycosis in Children: Treatment with Bifonazole-Urea

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Abstract: We assessed the safety and efficacy of a two-phase topical treatment with bifonazole-urea ointment in children with onychomycosis. Twenty-five children younger than 16 years old with proved onychomycosis were included in the study. Bifonazole-urea ointment was administered under occlusion until the nontraumatic removal of the nail was achieved. Bifonazole cream was then applied for 4 weeks and a follow-up visit 4 weeks after cessation of medication was scheduled. During the study, periodic clinical and mycologic evaluations were carried out. Of the 25 patients included, 17 were cured (68%), 6 improved, and 2 failed treatment. The main etiologic agent isolated was *Trichophyton rubrum* (92%). Two patients had minor side effects, both during the occlusive phase, one each with mild pain and a probable dermatitis from the adhesive strips. Treatment was not discontinued in both of these cases. We concluded that a two-phase treatment with bifonazole-urea is effective and safe, and represents a new therapeutic choice for onychomycosis in children.

Onychomycoses are chronic, recurrent infections of the nails caused by dermatophytes, yeasts, and opportunistic fungi. They are usually observed in adults as a consequence of chronic tinea pedis (1,2). Onychomycoses in children are not very common, most occur in adolescents reaching puberty. Although onychomycosis has been reported in children, it is attributable to, among other factors, the constant use of plastic shoes. Ungual candidiasis, unlike tinea unguium, is more common in fingernails, normally affects only one nail, and is seen after trauma or associated with diabetes (1,3–5). In general, there are no exact statistics on this problem in children, even though most authors agree that this disease is increasing.

Treatment of onychomycosis in general is a problem and is even more difficult in children. Systemic treatment, such as griseofulvin, is effective only in tinea unguium (dermatophytes) and ketoconazole is usually recommended in candidosis. Systemic nail treatment is lengthy (10–12 months) and may cause side effects; for example, griseofulvin may cause headaches and gastric irritation, and ketoconazole may cause liver damage. Therefore the use of systemic treatment in children should be carefully evaluated (6–8).

Topical therapy in nails has been used for many years without much success. Products such as iodine solution (2%), tolnaftate, miconazole, econazole, and tioconazole have had low cure rates due to their low penetration into the keratinized structures of the nail. Keratolytic products (urea, salicylic acid, glutaraldehyde) have also been used for many years with variability in results and side effects (9–12).

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The purpose of our study was to assess the safety and efficacy in children of the combination of a two-phase treatment, the first, occlusive with bifonazole-urea ointment for the chemical avulsion of the nail, and the second, an application of an imidazolic antimycotic agent (bifonazole). This therapy has been previously used in adults with good results (12–15). Its use in children with onychomycosis is a new treatment alternative.

MATERIALS AND METHODS

A clinical, open, nonrandomized study was carried out with 25 children with onychomycosis who were classified according to Zaias' clinical criteria (16). Permission for participation in the study was obtained from the parents or guardians of each of the patients. Boys and girls younger than 16 years old with onychomycosis proven both clinically and mycologically through direct examination with potassium hydroxide (KOH) and positive cultures in Sabouraud dextrose agar and Mycosel (Sabouraud + antibiotics) (17) were included in the study. Patients who had received systemic antimycotic treatment within the last 3 months or topical treatment 1 month before, and patients with onychomycosis with paronychia were excluded from the study. Patients who, during the study, had severe adverse events, were not cooperative, or who voluntarily decided to withdraw from the study were eliminated.

The study was divided into several treatment phases (TPs) (Fig. 1). During the first phase, patients applied bifonazole cream (1%) and urea (40%) ointment with occlusion (with adhesive, impermeable strips) to each of the affected nails. The drug was renewed every 24 hours after the elimination of cellular debris with a plastic spatula. This treatment phase lasted 15 days or less if a total removal of the affected area of the nail occurred earlier. In the second treatment phase, bifonazole cream (1%) was applied daily for 4 weeks. Clinical and mycologic evaluations were carried out at the beginning of treatment, after the occlusive phase, at the end of treatment, and 1 and 4 months after cessation of therapy. Patients with tinea pedis were treated with bifonazole cream during the 4 weeks and evaluated by clinical and mycologic means.

The evaluation of treatment efficacy was made using the following criteria: therapeutic success—the patient was clinically and mycologically cured; improvement—the patient had important clinical changes and the KOH was positive or negative, but with negative cultures; and failure—no clinical or mycologic changes occurred, or there was exacerbation of the process, and positive mycologic tests. In order to evaluate drug safety, a record of all reported side effects was made, and those patients who had serious side effects were withdrawn from the study.

RESULTS

Twenty-five patients were included, 16 boys and 9 girls; the youngest being 1.8 years old and the oldest 15 years old (average 7.7 years). In 22 patients the onychomycosis affected toenails, and in 3 cases fingernails, with an average of 3 nails involved and 1.9 years of chronicity. Eighteen patients also had tinea pedis which was treated

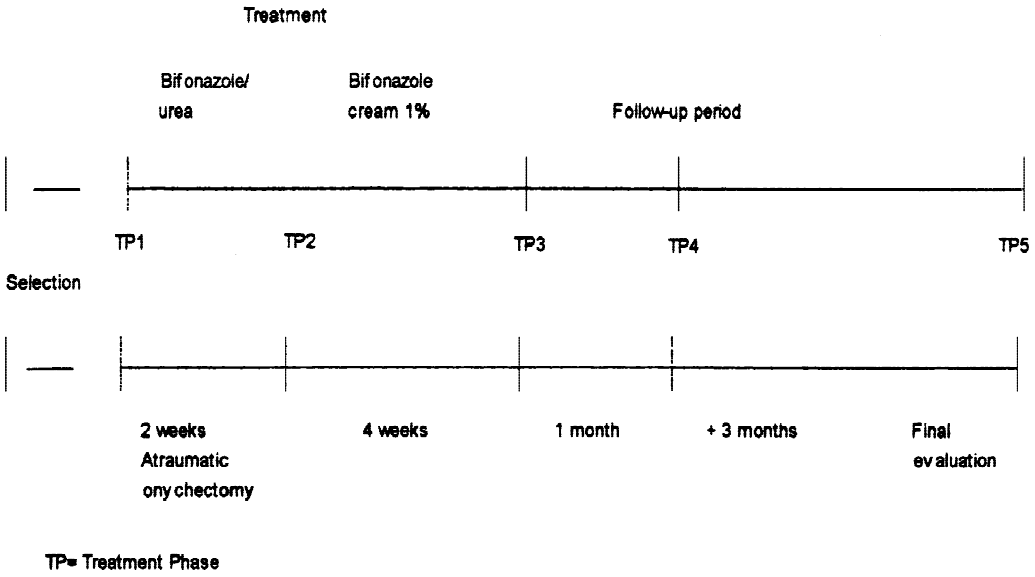

Figure 1. General scheme of the treatment.

TABLE 1. *Type of Onychomycosis and Etiology*

Type of Onychomycosis (*n*)	Etiology (*n*)
Distal-subungual (21)	*T. rubrum* (20)
	T. mentagrophytes (1)
Proximal-subungual (2)	*T. rubrum* (2)
Lateral subungual (1)	*T. rubrum* (1)
White-superficial (1)	*T. mentagrophytes* (1)

TABLE 2. *Results of the Study*

Evaluation	Number of patients (*n*)	Rates (%)
Failure	2/25	8
Improvement	6/25	24
Cured	17/25	68
Side effects	2/25	8

with bifonazole cream (1%) for 4 weeks. Of the 25 patients, 22 (88%) had tinea unguium, from which the following etiologic agents were isolated: *T. rubrum*, 23 instances, and *T. mentagrophytes*, 2 instances. The classification of the type of onychomycosis and its relation to the etiologic agent is shown in Table 1.

During the occlusive treatment phase with bifonazole-urea, the involved nails of all patients were removed. The least time necessary for removal was 5 days, the longest 15 days, with an average of 11.9 days and a standard deviation of 4.6 days. The two secondary effects observed in the study (8%) occurred during this phase, the first being pain when the nail was removed and the second being erythema, desquamation, pruritus, and a burning sensation attributable to the adhesive strips; neither of the affected children withdrew from the study and both continued with treatment phase two (bifonazole cream) without the addition of any concomitant treatment.

Figure 2 shows the course of the mycologic results (direct examinations and cultures) during the five phases studied. Final evaluation of treatment efficacy and secondary effects is shown in Table 2. Figure 3 shows a representative response to treatment in a child with *T. rubrum* onychomycosis. All patients who failed (2 of 25) or had improvement (6 of 25) with treatment had subungual-distal onychomycosis, and most (5 of 7) were children older than 10 years.

DISCUSSION

Onychomycoses are not very common in children, but are increasing both in normal children and in those having specific predisposing factors such as diabetes or immunosuppression (18,19). However, there are only a few reports on specific treatments, even systemic antimycotics, that may be used in children, that is, griseofulvin, ketoconazole, terbinafine, and fluconazole (8,20–23). These are not very efficacious for onychomycosis in children due to the prolonged treatment time and probable secondary effects. No specific topical antimycotic for onychomycosis in children is yet available. We consider that topical treatment should still be the first choice, especially with children younger than 3 years.

Our study included children of all ages, the average being 7.7 years old. Even a child 1.8 years old was included; this is important because the selection of treat-

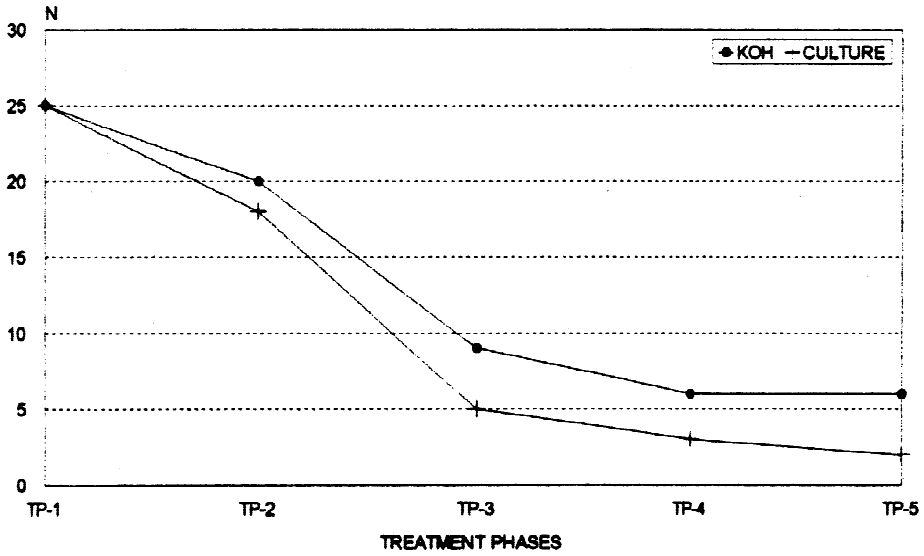

Figure 2. Course of the mycologic results (KOH and culture).

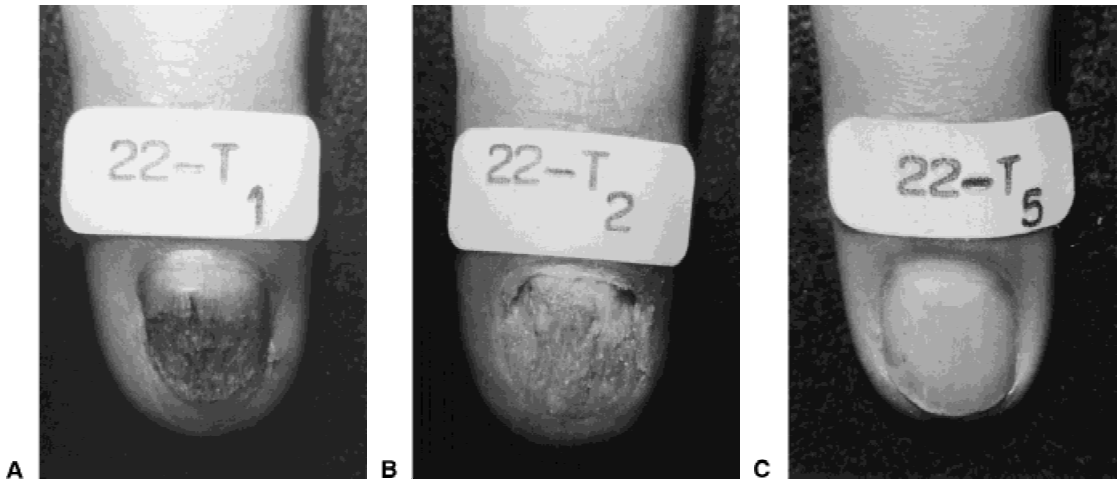

Figure 3. Subungual distal onychomycosis (due to *T. rubrum*) (A) before treatment, (B) after occlusive treatment, and (C) 3 months after treatment.

ment is more difficult in younger patients. Figure 1 shows that the complete treatment time from the occlusive phase until last medication was 8 weeks, which is less time compared to systemic antimycotics like griseofulvin and ketoconazole which require approximately 30–50 weeks. As far as etiology is concerned, only dermatophytes were isolated, predominantly *T. rubrum* (23 of 25; 92%); this is important since it represents the most difficult dermatophyte to treat. Table 1 shows the types of onychomycoses included, with a predominance of the subungual-distal type. The white-superficial type responded faster to treatment; and the two patients with the subungual-proximal type had a good response to therapy. This is important since this type of infection starts from the ungual matrix, which topical treatments hardly reach.

Figure 2 shows the course of mycologic results (direct examinations and cultures). A marked decrease may be observed, especially in the phase TP-3 corresponding to the termination of medication; in phase TP-5, indicating the last evaluation, only two positive cultures were obtained, although 6 of 25 had a positive KOH.

The occlusive phase, which ends with the detachment of the involved nail, lasted an average of 11.9 days, even with a response of less than 5 days in a child 1.8 years old; this is very important since in clinical trials (12,13) carried out in adults, the average time of involved nail detachment is about 22 days. Even in a study of ours (15), we observed that not only is the removal slower in adults, but adequate cleaning of the nail bed is not achieved, which we think directly influences the efficacy of the drug. We speculate that the faster nail removal in children is possibly because the children's nails may be formed of a softer keratin.

The study results are shown in Table 2. We believe that with the use of bifonazole-urea an average cure rate of nearly 70% is reached, which may be increased when the child is younger, since the improvements and failures obtained correspond to those of adolescents, who are considered to be more like adult patients since their disease is more chronic, their nails are more like adult nails, and there are more predisposing factors such as common use of plastic shoes.

Only two secondary effects occurred (Table 2). One child had pain when the nail detached, however, at the beginning of the second phase of treatment (Fig. 1) with bifonazole cream, the pain disappeared without the necessity of adding any analgesic. The second child's side effect was probably due to a dermatitis caused by contact with the rubber of the adhesive strips and no specific treatment was needed. Both phenomena have been previously reported in the literature (12,13,15).

CONCLUSIONS

Two-phase treatment with bifonazole-urea in children with onychomycosis is effective in nearly 70% of cases, even in younger children, and it is safe since no important secondary effects occur. This type of treatment represents an alternative for the treatment of onychomycosis in children, no matter what their age.

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