Epidemiologic studies have shown that the prevalence of dermatophytoses is 20%–25% worldwide (1). Combined topical treatment is an effective shortcut for improving the efficacy of drugs against pathogenic fungal infection, but currently the common treatment strategy is to use two or more antifungal agents of different structures, or corticosteroids and antifungal agents together (2-4). The addition of a safe agent that enhances the efficacy of antifungal agents would represent a breakthrough. Previously, we demonstrated that the bisbenzylisoquinoline compound, tetrandrine (TET), which is extracted from the natural medicinal plant, fourstamen stephania root, could significantly increase the susceptibility of fungi toazole drugs in vitro and in experimental animals and volunteers. The mechanism is related to the inhibition of the system, which is responsible for drug efflux in fungi (5-13). In this study, we examined the clinical efficacy and safety of the combined topical use of TET and ketoconazole (KCZ) cream in volunteers with dermatophytoses.

METHODS

Volunteers with dermatophytoses (tinea corporis and/or tinea cruris, tinea pedis and/or tinea manuum) who sought medical treatment at the Department...
of Dermatology in our hospital from October 2006 to January 2008 were included in this study. The diagnostic criteria have been previously described\(^\text{14,15}\).

To be included, patients must have fulfilled the following criteria: positive microscopic findings and fungal culture results of skin lesion smears; no use of any topical antifungal agents or corticosteroids within 2 weeks before the study or oral antifungal agents within the previous month. The patients signed an informed consent, and their participation in the study and follow-up was voluntary. We excluded the patients with severe combined local bacterial infection or other skin diseases that might interfere with the treatment, patients with diabetes mellitus or severe heart, liver, or kidney disease, patients who could not cooperate with the treatment, or patients who were allergic to TET or KCZ.

The randomized, double blind clinical trial included a total of 120 patients with dermatophytoses. Six patients were lost during the study, 13 terminated the treatment early, and 97 completed the study. The patients with tinea corporis and/or tinea cruris and the patients with tinea pedis and/or tinea manuum were randomly assigned to 3 groups by means of a random number table and received combined therapy with 2% TET cream and 2% KCZ cream (KCZ + TET group), with 2% KCZ cream only (KCZ group), or with 2% TET cream only (TET group) separately. There were no significant differences in age, sex, course of disease, pretreatment clinical symptoms, or physical sign scores among the groups (\(P>0.05\), Table 1).

**Mycologic Examination**

The results of pretreatment microscopic examination and fungal culture were positive in all the patients. The KANE/FISHER dermatophyte identification method\(^\text{16}\) was used in combination with microscopic morphologic analysis. The isolated pathogens in the KCZ + TET group, KCZ group, and TET group were Trichophyton rubrum (30, 21, and 19 strains in the 3 groups, respectively), Trichophyton mentagrophytes (4, 4, and 3 strains in the 3 groups, respectively), Epidermophyton floccosum (4, 4, and 2 strains in the 3 groups, respectively), and Microsporum canis (4, 4, and 2 strains in the 3 groups, respectively). The \(\chi^2\) test (Fisher’s exact test) revealed no significant differences among the 3 groups (\(P>0.05\)).

**Determination of Minimum Inhibitory Concentrations**

The experimental strains were clinical isolates of dermatophytes. The methods described in the CLSI M38-A program\(^\text{17}\) were used to determine minimum inhibitory concentrations (MICs), and the final concentrations of KCZ and TET were 16–0.03 \(\mu\)g/mL and 40 \(\mu\)g/mL, respectively, according to our previous report\(^\text{11}\).

**Treatment Methods**

TET (batch No. Cac0205; purity 99.6%; China Aroma Chemical Co., Ltd., Hangzhou) and KCZ (Nanjing Second Pharmaceutical Factory, China; purity \(\geq 99\%\)) were dissolved in dimethyl sulfoxide simultaneously, post-condensation cream matrix was added, and the sample was mixed continuously until it became coagulated. The cream containing KCZ, or TET, or both was applied on the affected skin twice per day, once in the morning and once in the evening, at the indicated dose. The duration of treatment was 2 weeks for tinea corporis and/or tinea cruris, and 4 weeks for tinea pedis and/or tinea manuum. Symptoms, physical signs, and laboratory parameters were observed weekly during treatment and at 2 weeks and 4 weeks after drug withdrawal; the efficacy and safety were also evaluated.

\[\begin{array}{cccc}
\text{Table 1. General Characteristics of the Three Groups of Patients with Dermatophytes before Treatment} \\
\hline
\text{Group} & \text{Case} & \text{Male} & \text{Female} & \text{Age (Year, } \overline{x} \pm s) & \text{Course (Day, } \overline{x} \pm s) & \text{Overall scores (} \overline{x} \pm s) \\
\hline
\text{tinea corporis and/or tinea cruris} & & & & & & \\
\text{KCZ+TET group} & 16 & 12 & 4 & 29.81 \pm 8.40 & 14.69 \pm 14.10 & 6.63 \pm 2.06 \\
\text{KCZ group} & 15 & 12 & 3 & 26.67 \pm 8.89 & 14.87 \pm 14.99 & 6.40 \pm 2.13 \\
\text{TET group} & 12 & 9 & 3 & 28.28 \pm 9.43 & 14.41 \pm 20.24 & 6.25 \pm 2.05 \\
\text{tinea pedis and/or tinea manuum} & & & & & & \\
\text{KCZ+TET group} & 24 & 18 & 6 & 34.96 \pm 12.65 & 34.46 \pm 19.80 & 5.33 \pm 1.37 \\
\text{KCZ group} & 20 & 16 & 4 & 33.05 \pm 11.59 & 33.90 \pm 13.41 & 5.35 \pm 1.60 \\
\text{TET group} & 10 & 7 & 3 & 34.20 \pm 12.80 & 34.30 \pm 16.18 & 5.80 \pm 1.87 \\
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