Increasing Patient Adherence in Antifungal Infection Treatment
Once-Daily Dosing of Sertaconazole

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ABSTRACT
Adherence to treatment is an important issue in all areas of clinical medicine, including dermatology. Consequences of poor compliance include reduced treatment benefits, biased assessments of treatment efficacy, increased healthcare costs, and in some cases even death. To date, even the most effective interventions in patients’ habits have not led to large improvements in either adherence or treatment outcome. New objective electronic measures permit unbiased reporting of actual adherence to therapy regimens and have revealed that nonadherence is more pervasive than had been suspected, usually occurring when patients omit or delay a dose. In dermatology, adherence to therapy for dermatomycosis is known to decrease with the duration of treatment and the number of applications required each day, particularly once symptoms have disappeared. Simpler dosing regimens are sought for the treatment of cutaneous fungal infections. Sertaconazole, an imidazole antifungal, has pharmacokinetics that are considered favorable for once-daily antymycotic therapy. It is hypothesized that its prolonged dermal retention may translate into the need for less frequent application for successful treatment in clinical practice. (J Clin Aesthetic Dermatol. 2009;2(2):38–42.)

Adherence to treatment is an important issue in all areas of clinical medicine, including dermatology, and one that has received much attention in the recent literature. Generally, in clinical medicine, rates of patient adherence are highly variable, depending on such factors as whether the conditions being treated are acute or chronic, with adherence higher in acute conditions. In fact, even clinical trials report average adherence rates of only 43 to 78 percent among patients receiving treatment for chronic conditions. Adherence can vary anywhere from 0 to more than 100 percent (patients who take more medication than prescribed); one study of topical therapy for psoriasis reported an overall adherence rate of just less than 60 percent. Possible consequences of nonadherence in clinical practice include death, reduced treatment benefits, biased assessments of treatment efficacy, and increased healthcare costs; 33 to 69 percent of medication-related hospital admissions in the United States are the result of poor adherence.

Multiple possible causes for patient nonadherence have been postulated. They include the following: problems with the therapy, such as side effects; poor instructions given to the patient by the prescriber; poor physician-patient relationship; poor memory on the part of patients; and patients’ inability to pay for medications.

With short-term treatment, adherence can usually be enhanced with fairly simple interventions, such as patient education and followup by telephone or e-mail, but interventions capable of increasing adherence in patients with chronic health problems tend to be complex, involving combinations of patient education, reminders, family therapy, psychological therapy, crisis intervention, and close followup. As one report has noted, even the most effective interventions in patients’ habits do not lead to large improvements in adherence or...
treatment outcome. With the advent of new techniques, the dimensions of the problem have been revealed to be more significant than previously thought. We now know that questionnaires, pill counting, and weighing medications tend to overestimate patients' actual adherence because new objective electronic measures, such as electronic cap monitors, permit unbiased reporting of actual adherence to therapy regimens and have demonstrated that nonadherence is more pervasive than had been suspected. As a result, patterns of adherence are now being studied with such electronic medication-monitoring devices, which have revealed that most deviations from prescribed regimens occur when patients omit or delay a dose.

One central finding of studies examining compliance is that adherence is inversely proportional to the frequency of dosing. Figure 1 illustrates an example based on pooled results from 76 studies in which electronic-monitoring devices were used to measure patients’ compliance with prescribed medications.

ADHERENCE IN DERMATOLOGY

Several studies have examined the concept of adherence in dermatology; one author noted poor adherence to be “a fundamental principle of dermatology.” Because many dermatologic therapies are topical, measuring adherence has posed a particular challenge. Patients typically over-report their own adherence in patient logs, and it is obviously more difficult to measure how much of a topical therapy has been used than it is to count pills. In one pilot study that used electronic-monitoring system caps on topical creams, gels, and ointments without patients’ knowledge, researchers found that it became easier to detect missed doses with such monitoring than with patient self-reporting. The same researchers undertook a study in 30 patients with psoriasis, following them for eight weeks using three methods of monitoring adherence (electronic-monitoring caps, patient logs, and medication weighing). The authors found that electronic monitoring detected consistently higher rates of nonadherence than did the other methods ($P<.05$). Patients’ adherence declined from 84.6 to 51 percent over the eight weeks ($P<.0001$), with higher rates of adherence found among women and older patients and lower rates of adherence noted on weekends.

A number of small studies have looked at the effect of nonadherence on treatment outcomes. A small (N=24), controlled study in patients with psoriasis found that nonadherence, measured by electronic monitors, may have played a significant role in altering clinical trial data, tilting results toward a finding of ineffectiveness. The authors concluded that interventions to improve adherence might improve treatment outcomes.

Another small (N=29), observational study also involving patients with psoriasis used electronic monitors to assess adherence and found that adherence rates were significantly higher around the time of scheduled office visits, a phenomenon known as “white-coat compliance” ($P<.05$). The authors of this study recommended relatively aggressive followup, including scheduled follow-up visits soon after starting any new therapy, along with follow-up phone calls and e-mails.

A large survey undertaken in Germany in 1982 studied nonadherence in 230 patients with dermatomycosis treated with topical antifungal therapy. The survey revealed that nonadherence was widespread, with the following findings: 48 percent of patients did not follow the daily dosage schedule; 44 percent reduced the number of daily applications; four percent increased the number of daily applications, and one-quarter of patients stopped treatment as soon as symptoms disappeared (particularly older patients, who did not view fungal infections as very important).

STRATEGIES TO IMPROVE ADHERENCE IN DERMATOLOGY

As a general rule, most strategies intended to improve adherence involve such practical actions as more and better communication with patients on the part of healthcare personnel, more and better patient education, and easier dosing schedules. Isolated measures to improve adherence are not considered particularly effective, but clear oral communication during the physician-patient encounter is generally viewed as essential. Some authors have noted that clinicians must consider patients’ lifestyles before choosing medications. Others have noted the importance of designing therapeutic regimens with realistic expectations of patients’ behavior in mind, aiming at single-dose treatment per day and reduced length of therapy whenever possible; these have been called “forgiving” regimens, ones that provide good coverage even with dosage omission.
ADHERENCE AND ONCE-DAILY DOSING IN THE TREATMENT OF FUNGAL INFECTIONS

As a general rule, simpler, shorter treatment regimens optimize adherence.\textsuperscript{11} However, even though once-daily dosing is recommended as a way to promote patient adherence, many imidazole antifungals are still currently approved for twice-daily dosing, including clotrimazole, miconazole, and sertaconazole. In the treatment of mycotic infections, it is known that a variety of factors determine the optimal treatment with any given antifungal, including skin type, size, location, characteristics of the lesion, and each patient’s particular needs.\textsuperscript{12} However, since therapeutic success is strongly correlated with patient adherence,\textsuperscript{11} an additional consideration must be the prescriber’s estimate of how likely the patient is to adhere to the treatment plan. Unfortunately, patient compliance with therapy for dermatomycosis is known to decrease with the duration of treatment and the number of applications required each day, particularly once symptoms have disappeared.\textsuperscript{11}

Some attempts have been made to explore the efficacy of once-daily antifungal regimens.

PHARMACOKINETICS AND ONCE-DAILY DOSING OF SERTACONAZOLE

Pharmacokinetic profile. The key to the successful treatment of mycotic infections is rapid action of the antifungal agent at the site of infection, which requires the drug to reach therapeutically effective concentrations without appreciable systemic absorption.\textsuperscript{10} Sertaconazole nitrate is synthesized with a lipophilic benzothiophene ether, which is believed to enhance its ability to penetrate the stratum corneum. Systemic absorption of sertaconazole after skin application is negligible, with no detectable presence in serum or urine. Moreover, therapeutic concentrations persist in the skin after application, with one study demonstrating that the percentage of cutaneous absorption 24 hours postapplication was 72 percent of the dose applied.\textsuperscript{14} Because of its rapid appearance in the stratum corneum after administration, sertaconazole’s pharmacokinetics are considered favorable for once-daily antimycotic therapy,\textsuperscript{15} and it is possible that its prolonged dermal retention might translate into the need for less frequent applications in clinical practice.\textsuperscript{11,16}

Clinical trials: Once-daily dosing. Several investigators have examined the efficacy and safety of sertaconazole used once daily in the treatment of cutaneous fungal infections. Noting that a once-daily regimen with sertaconazole may improve patient compliance, in addition to lowering costs of therapy, Susilo et al\textsuperscript{11} undertook a trial to evaluate the efficacy and safety of sertaconazole 2% cream administered once daily for three weeks in a double-blind, vehicle-controlled study in 400 adult patients with tinea of glabrous skin.\textsuperscript{11} Compared to vehicle, sertaconazole 2% used once a day for three weeks resulted in a higher cure rate (82% vs. 61%, respectively; \textit{P}=.014). Results obtained by mycologic culture also showed highly significant differences in favor of sertaconazole in both per-protocol patients and intent-to-treat patients—82 percent (\textit{P}=.014) and 83 percent (\textit{P}=0.0026), respectively.\textsuperscript{11} Using erythema and scaling as objective parameters by which to evaluate clinical cure, researchers found that the proportion of subjects with no or mild signs of both increased over time at higher rates with sertaconazole than with vehicle cream (Figure 2). No difference in safety findings was reported in the two treatment groups. The researchers concluded that the once-daily regimen was efficient and safe, emphasizing that once-a-day regimens may improve patient adherence.\textsuperscript{11}

In a small, open-label study in 16 children of both sexes, 2 to 16 years of age, with culture-confirmed cutaneous mycoses, researchers examined the efficacy of once-daily sertaconazole in a pediatric population.\textsuperscript{16}
Infections treated included tinea corporis (14), tinea pedis (1), and tinea cruris (1), caused by *Microsporum canis* in 50 percent and *Trichophyton rubrum* in 42 percent of cases. Lesions were treated once daily with sertaconazole 2% cream for two weeks, with clinical cure achieved in 31 percent of patients after one week, 75 percent after two weeks, and 100 percent after four weeks. No adverse events were reported throughout the study period. The researchers concluded that these results indicated good penetration and lengthy persistence of sertaconazole in the skin, thereby suggesting the clinical effectiveness of a once-daily regimen in the treatment of superficial mycoses. Figure 3 illustrates a summary of the resolution of symptoms over time.

A multicenter, randomized, parallel-group trial was performed in France in 191 patients with interdigital or moccasin-type tinea pedis, comparing sertaconazole cream 2% to bifonazole cream 1%, applied once daily for 21 days. Cure rates were significantly higher in patients who received sertaconazole. Clinical cure was achieved in 46.0 percent of patients receiving sertaconazole versus 18.9 percent of patients receiving bifonazole in 46.0 percent of patients receiving sertaconazole. Clinical cure was achieved in 46.0 percent of patients receiving sertaconazole versus 18.9 percent of patients receiving bifonazole (P<.01) after 21 days. Therapeutic cure was achieved in 40.0 percent of patients receiving sertaconazole versus 9.6 percent of patients receiving bifonazole (P<.001).

A three-week clinical trial carried out in Spain also compared sertaconazole cream 2% to bifonazole cream 1%, administered once daily for three weeks to 75 patients. This trial found both drugs equally effective when administered once daily. Complete clinical and mycologic cure was achieved in 90.6 percent (29/32) of sertaconazole patients, compared to 90 percent (27/39) of patients receiving bifonazole; the difference was not statistically significant.

**DISCUSSION**

The likelihood that a patient will adhere to a therapeutic regimen should be taken into account by prescribers whenever possible. Unfortunately, reports suggest that adherence may be the exception rather than the rule. One large review has noted that, in general, patients who are prescribed self-administered medications typically use less than half of the prescribed doses.

As former Surgeon General C. Everett Koop has pointed out, "Drugs don't work in patients who don't take them," so any modification of treatment regimens that encourages patients to be more adherent is desirable. Such modifications include simplifying regimens, customizing them to patients' particular lifestyles, asking patients about their medication-taking preferences, and engaging in frank discussion of the risks implicit in nonadherence, such as recurrence of disease or development of chronic conditions.

Simpler dosing, such as once per day, would be particularly valuable in the treatment of cutaneous fungal infections in which symptoms may disappear soon after treatment is initiated, which can deprive patients of the reminder to continue using their medication provided by their subjective discomfort, and thereby prevent effective therapy. When a once-daily application of a topical treatment has been shown to be clinically effective, as is the case with sertaconazole, physicians can be more confident about both cure and compliance. Conventional azole antifungals have been associated with high rates of disease recurrence caused in part by lack of adherence to therapy, which makes effective, once-daily dosing a valuable option for physicians treating topical fungal infections.

**REFERENCES**


