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Effect of Oral Terbinafine Treatment on Cyclosporin Pharmacokinetics in Organ Transplant Recipients with Dermatophyte Nail Infection

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Eleven patients with either kidney, heart or lung transplants, immunosuppressed with cyclosporin A, and with culture-proven dermatophyte toe nail infection, were given 250 mg terbinafine orally daily for 12 weeks. No changes in cyclosporin A dosage were made.

A statistically significant decrease in mean specific cyclosporin A blood trough levels was found at 4, 8 and 12 weeks. No other statistically significant changes in the pharmacokinetic profile of cyclosporin A were seen.

Terbinafine possibly induces a cyclosporin A metabolic degradation, which, however, is of little clinical significance. Terbinafine treatment is a safe therapeutical option in cyclosporin A-treated patients with dermatophyte nail infection. Cyclosporin A levels should be controlled during treatment. ***Key words: onychomycosis; systemic treatment; immunosuppression; drug interaction.***

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Onychomycosis is common in organ transplant recipients immunosuppressed with cyclosporin A (CsA) (1). The antifungal drugs ketoconazole and itraconazole inhibit the metabolism of CsA by inhibiting cytochrome P450 enzymes and may lead to toxic blood levels of CsA (2–4). Terbinafine, an allylamine (5), binds only to a small fraction of the P450 enzyme (6) and has no significant effect on microsomal hepatocytic metabolism of CsA in vitro (7–9). It does not increase the blood levels of CsA in healthy volunteers (10). Investigations in organ transplanted patients immunosuppressed with CsA have not been performed. The aim of the present study was therefore to investigate whether oral terbinafine treatment of onychomycosis alters CsA metabolism in this patient category.

PATIENTS AND METHODS

Eleven stable organ transplanted patients immunosuppressed with CsA, with stable renal function, and with culture-proven dermatophyte toe nail infection, were included. Immunosuppressive therapy consisted of CsA, azathioprine and prednisolone. CsA was given b.i.d. as Sandimmun® capsules with mean doses 2.93 mg/kg/day (range 1.63–4.64 mg/kg/day). Patients with intercurrent disease were not included, and medication was not changed the last 3 months before the study.

After informed consent, 250 mg terbinafine was given orally each morning for 12 weeks. No changes in diet, concomitant medication, or CsA dosage were made during the trial. Before terbinafine treatment and after 4, 8 and 12 weeks the patients were examined clinically, and blood samples were taken for full blood count, liver function tests and measurements of plasma urea and creatinine.

CsA whole blood trough levels, i.e. specific CsA whole blood concentrations in the morning before administration of CsA, were taken before start of terbinafine treatment and after 4, 8 and 12 weeks by means of fluorescence polarization immunoassay (FPIA), using a monoclonal specific antibody CsA whole blood kit (Abbott Laboratories, Abbott Park, IL, USA). The therapeutic range for CsA with this assay is 75–175 µg/l in stable kidney recipients (11).

Eight-hour CsA pharmacokinetic profiles (i.e. specific CsA whole blood concentrations immediately before and at 0.5, 1, 2, 3, 4, 6, and 8 h after administration of CsA) were taken before start of terbinafine treatment and after 4 weeks. The maximum concentration (C_{max}), time of maximum concentration (T_{max}), the area under the concentration time curve from 0 to 8 h (AUC_{0-8}), and the elimination half-time ($T_{1/2}$) for CsA were calculated from the individual CsA whole blood concentrations. One patient was excluded from this analysis because of considerable delay in CsA absorption, rendering the calculation of $T_{1/2}$ and AUC_{0-8} incomprehensible.

To detect possible changes in CsA metabolism during terbinafine treatment, comparisons of the pharmacokinetic parameters before and during terbinafine treatment were performed by means of Wilcoxon's signed-rank test. A p-value of less than 0.05 was considered significant. All tests were performed two-tailed.

The effect on nail changes was recorded clinically only, by measuring the unaffected proximal part of most affected nail (index nail) (12) before treatment, at end of treatment and 1 year after treatment.

The study protocol was approved by the Regional Committee of Research Ethics, the Norwegian Drug Control Agency, and the Drug Committee at Rikshospitalet.

RESULTS

All patients completed the terbinafine treatment. The medication was well tolerated, and no patients reported serious side-effects or had signs of graft rejection. No significant abnormalities in the blood tests were recorded. CsA blood trough levels at 8 and 12 weeks were not recorded in 2 patients due to non-compliance.

A statistically significant decrease in mean CsA blood trough levels was found at 4 weeks. Thereafter, CsA blood trough levels were stable up to 12 weeks (Table I).

The 8-h pharmacokinetic profiles of CsA before and during terbinafine treatment, as means of CsA blood levels in 10 patients, were calculated. No statistically significant changes

Table I. *Cyclosporin blood trough levels (µg/l) in organ transplant recipients with dermatophyte nail infection before and during concomitant terbinafine treatment*

Values are means ±SE.

	Before	4 weeks	8 weeks	12 weeks
All patients ($n=11$)	140±18	101±5 $p=0.001$	–	–
Pat.s with values at all four points ($n=9$)	126±19	97±13 $p=0.004$	92±13 $p=0.03$	101±15 $p=0.004$

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Table II. *Pharmacokinetic parameters of cyclosporin A (CsA) before and during concomitant terbinafine treatment*

Mean values ±SE calculated from the individual whole blood concentrations ($n=10$).

	CsA alone	CsA + terbinafine	
Predose level (μg/l/h)	141±20	102±13	$p=0.005$
C_{max} (μg/l)	619±101	494±77	ns[a]
T_{max} (hours)	2.40±0.34	2.55±0.28	ns
AUC_{0-8} (μg/l/h)	2340±352	1990±265	ns
$T_{1/2}$ (hours)	8.32±0.30	7.56±0.14	$p=0.059$

[a] not statistically significant.

in C_{max}, T_{max}, AUC_{0-8}, or $T_{1/2}$ were seen (Table II), although a slight decrease in $T_{1/2}$ was recorded ($p=0.059$).

Increased lengths of unaffected proximal part of index nails were seen in all but one patient at the end of terbinafine treatment and at the 1-year follow-up. Significant improvement was seen in only 6 of the 11 patients.

DISCUSSION

Our findings suggest that terbinafine possibly induces metabolic degradation of CsA, even though terbinafine is not a significant enzyme inducer in vitro (7). However, the maintenance of unchanged AUC_{0-8}, C_{max}, and T_{max} indicates that the possible enzyme induction by terbinafine is almost negligible and of little clinical significance. The apparent discrepancy between CsA blood trough levels and other pharmacokinetic parameters could reflect the different time period studied, as increased hepatic blood flow during sleep may be a prerequisite for detection of a possible enzyme induction caused by terbinafine. Long et al. (10) found in healthy volunteers a marginal reduction in CsA AUC and C_{max} and a slight increase in absorption half-life during concomitant administration of terbinafine, but the changes were not statistically significant.

The design and size of the study do not permit any certain conclusions regarding the efficacy of terbinafine on onychomycosis in organ transplant recipients.

We conclude that oral terbinafine is a safe therapeutical option for CsA-treated patients with dermatophyte nail infections. We recommend that CsA levels are controlled during treatment.

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REFERENCES

1. Abel EA. Cutaneous manifestions of immunosuppression in organ transplant recipients. J Am Acad Dermatol 1989; 21: 167–179.
2. Freeman DJ. Pharmacology and pharmacokinetics of cyclosporin. Clin Biochem 1991; 24: 9–14.
3. Yee GC, McGuire TR. Pharmacokinetic drug interaction with cyclosporin (Part I). Clin Pharmacokinet 1990; 19: 319–332.
4. Ferguson RM, Sutherland DER, Simmons RL, Najarian JS. Ketoconazole, cyclosporine metabolism and renal transplantation. Lancet 1982; ii: 882–883.
5. Goodfield MJD, Andrew L, Evans EGV. Short term treatment of dermatophyte onychomycosis with terbinafine. BMJ 1992; 304: 1151–1154.
6. Jensen JC. Clinical pharmacokinetics of terbinafine (Lamisil). Clin Exp Dermatol 1989; 14: 110–113.
7. Back DJ, Tji J. Comparative effects of the antimycotic drugs ketoconazole, fluconazole, itraconazole and terbinafine on the metabolism of cyclosporin by human liver microsomes. Br J Clin Pharmacol 1991; 32: 624–626.
8. Back DJ, Tjia JF, Abel SM. Azoles, allylamines and drug metabolism. Br J Dermatol 1992; 126(Suppl 39): 14–18.
9. Shah IA, Whiting PH, Omar G, Ormerod AD, Burke MD. The effects of retinoids and terbinafine on the human hepatic microsomal metabolism of cyclosporin. Br J Dermatol 1993; 129: 395–398.
10. Long CC, Hill SA, Thomas RC, Johnston A, Smith SG, Kendall F, et al. Effect of terbinafine on the cyclosporin pharmacokinetics in humans. J Invest Dermatol 1994; 102: 740–743.
11. Bergan S, Rugstad HE, Stokke O, Bentdal Ø, Frøysaker T, Bergan A. Cyclosporin A monitoring in patients with renal, cardiac, and liver transplants: a comparison between fluorescence polarization immunoassay and two different RIA methods. Scand J Clin Lab Invest 1993; 53: 471–477.
12. Zaias N, Drachman D. A method for the determination of drug effectiveness in onychomycosis. J Am Acad Dermatol 1983; 9: 912–919.