

Human Nail Penetration Of AN2690, A New Antifungal Agent In Development For The Topical Treatment Of Onychomycosis

S.J. Baker¹, V. Sanders¹, J.J. Plattner¹, K. Beutner,¹ D. Perry,¹ X. Hui², R.C. Wester², S. Barbadillo², A.K. Cashmore² and H.I. Maibach²

1. Anacor Pharmaceuticals, Inc., 1060 East Meadow Circle, Palo Alto, CA 94303, USA.

2. Surge Building, Room 110, 90 Medical Center Way, Dept. of Dermatology, University of California, San Francisco, CA 94143, USA

ABSTRACT

AN2690 is a member of a new class of antifungal agent in clinical trials to treat onychomycosis topically. This poster reports the following results:

- AN2690 has excellent ability to penetrate full thickness human nails
- Almost equal concentrations were found throughout the nail plate
- After 14 days dosing, 16% of the applied dose had penetrated through the nail plate
- Turchub studies using full thickness nails confirmed concentrations below the nail plate were above it's MIC against dermatophytes.
- Promising 3 month clinical trial data further supports effective penetration

INTRODUCTION

Onychomycosis, a common fungal infection of toe and fingernails, remains difficult to treat.¹ It is widely believed that the reason for this high rate of treatment failures is due to the lack of penetration and dissemination of the active antifungal agent into and throughout the infected nail plate and nail bed.² We are developing a novel boron-containing small molecule AN2690, (Figure 1) as a topical treatment for onychomycosis. It has broad spectrum antifungal activity (Table 1). In order to treat the disease, AN2690 must penetrate through the nail plate to the nail bed in concentrations above it's minimum inhibitory concentration (MIC) against the causative fungi. In this poster, we report the results of our nail penetration studies of AN2690 and early clinical data.

FIGURE 1. Structure of AN2690 (5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole)

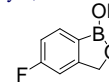


TABLE 1. MIC (µg/mL) values of AN2690 compared to ciclopirox

	<i>T. rubrum</i>	<i>T. mentagrophytes</i>	<i>E. floccosum</i>	<i>M. audouinii</i>	<i>M. furfur</i>	<i>C. albicans</i>	<i>F. solani</i>	<i>A. fumigatus</i>
AN2690	1-8	2-8	= 0.5	2	1	1	= 0.5	0.25
Ciclopirox	1	0.5	= 0.5	1	= 0.5	0.5	4	nt

RESULTS and DISCUSSION

We assessed the ability of AN2690 to penetrate into and through human cadaver fingernails and compared it to ciclopirox. The nails were mounted on a wetted cotton ball reservoir in a one-chamber diffusion cell³ (Figure 2). A dose of 10 µL of radioactive AN2690 (10% w/v in ethanol/propylene glycol 4:1), or ciclopirox (8% w/w in commercial lacquer) was applied to the top of the nails over a surface area of 0.75 cm² daily for 14 days. The supporting cotton balls were replaced every three days. At study end, the top and bottom halves of the micro-dissected nails, remaining nail plate, cotton balls and surface washings were analyzed by scintillation counting for AN2690 or ciclopirox. The results of this study are given in Table 2. Figure 3 shows that AN2690 was nearly equally distributed throughout the nail plate and Figure 4 shows the amount of AN2690 penetrating through the nail into the cotton ball increased over time, presumably as the nail plate became more saturated with drug. The day 15 cotton ball samples showed that in the final three days of the study, nearly one-third of the applied dose penetrated through the nail plate and into the cotton ball.

FIGURE 2. Diagram of quantitative nail penetration cell design including layers analyzed for drug

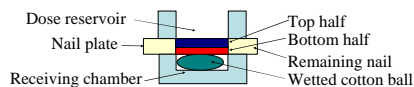


FIGURE 3. Amounts of AN2690 and ciclopirox found within the nail plate

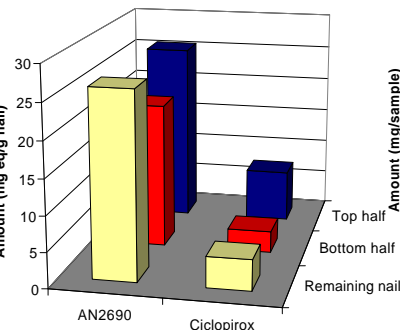


FIGURE 4. Amounts of AN2690 and ciclopirox found under the nail plate

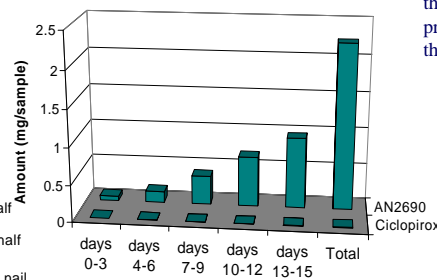


FIGURE 5. Turchub cells designed so that formulations pass through human nails prior to contact with the test organism.⁴



TABLE 2. Amount of AN2690 and ciclopirox found within the nail plate and in supporting cotton balls

	AN2690	Ciclopirox	P-value (t-test)
Top half (mg eq/g nail)	25.6 ± 8.8	7.4 ± 3.5	0.0008
Bottom half (mg eq/g nail)	20.5 ± 4.7	3.1 ± 2.1	0.0001
Remaining nail (mg eq/g nail)	26.06 ± 12.41	4.38 ± 2.73	0.0022
Supporting cotton ball (mg eq/sample)			
days 0-3	0.0609 ± 0.0605	0.0011 ± 0.0020	0.004
days 4-6	0.1551 ± 0.1314	0.0013 ± 0.0027	0.002
days 7-9	0.3892 ± 0.3714	0.0018 ± 0.0030	0.002
days 10-12	0.6775 ± 0.6663	0.0014 ± 0.0019	0.002
days 13-15	0.9578 ± 0.6106	0.0033 ± 0.0041	0.002
Total	2.2405 ± 1.7325	0.0089 ± 0.0131	0.002
Mass balance (%)	88 ± 9%	89 ± 2%	0.06

We also tested AN2690 using turchub cells shown in Figure 5.⁴ In this study, the antifungal agent must first pass through full thickness human nail plates to show a zone-of-inhibition (ZOI). AN2690 (10% w/v in ethyl acetate, propylene glycol 1:1) was compared to ciclopirox (8% w/w in commercial lacquer) and amorolfine (5% w/w in commercial lacquer). Using 5-6 replicates, test articles were dosed daily for five days at a concentration of 40 µL/cm² nail plate. The results of this study are shown in Figures 6-9. The vehicle showed no ZOI nor did ciclopirox or amorolfine in their commercial lacquers. By contrast, AN2690 showed a significant ZOI (Figure 9), demonstrating its ability to penetrate full thickness nail plates and disseminate through a large area of the receiver cells at concentrations above its MIC to prevent the growth of the dermatophyte.

FIGURE 6. Turchub result of placebo: ethyl acetate, propylene glycol 1:1



FIGURE 7. Turchub result of ciclopirox, 8% w/w in commercial lacquer



FIGURE 8. Turchub result of amorolfine, 5% w/w in commercial lacquer

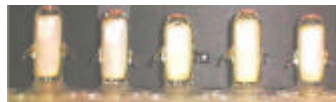


FIGURE 9. Turchub result of AN2690, 10% w/v in ethyl acetate, propylene glycol 1:1



PRELIMINARY CLINICAL DATA

An open-label two-arm clinical trial to treat onychomycosis is currently underway using 5% and 7.5% AN2690. In this trial the drug is applied topically to a designated great nail and all other affected nails once-daily for 180 days. Herein we present the preliminary interim 90 day efficacy data on the first 24 patients in the 5% group. Inclusion criteria for the targeted nail include area involvement of 20-60% and KOH positive mycology. Photos of the target toe are taken at baseline, 30, 90, 180, 240 and 360 days. Samples for mycology are taken at baseline, 30, 60, 90, 180, 240 and 360 days. For this interim analysis, efficacy is determined by new unaffected nail growth and by reduction in culture positive and KOH positive results. Preliminary results are shown in Table 3 and Figure 10. Halfway through this treatment period, average unaffected nail growth is 2.6 mm with 13/24 patients having >2.5 mm unaffected nail growth, 100% of mycology samples were culture negative and 70% were KOH negative. Photos show improvement in the appearance of the nail plate.

TABLE 3. Preliminary data from the first 90 days of treatment with 5% AN2690 in the first 24 patients

	Average unaffected nail growth, mm (range)	Culture positive	KOH positive
Baseline	0	50%	100%
30 days	1.8 mm (-0.8-6.1 mm)	4%	88%
60 days	N/A	0%	66%
90 days	2.6 mm (-1.7-6.6 mm)	not yet available	30%

FIGURE 10. Photos of the target toenail of two patients at baseline and day 90



CONCLUSIONS

AN2690, a novel boron-containing compound in clinical trials for the topical treatment of onychomycosis, exhibits excellent ability to penetrate full thickness human nail plates, which translates into good clinical efficacy.

- It achieves amounts under the nail plate over 200x that of ciclopirox in its commercial vehicle
- *Ex vivo* subungual activity is far superior to ciclopirox and amorolfine in their commercial vehicles
- Preliminary interim 90 day clinical data using 5% AN2690 show a good clinical response

References

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