Original Research Article

Natamycin treatment outcome in keratomycosis patients

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Abstract

In this study, 50 fungal isolates from 50 patients with fungal keratitis were tested *in vitro* for their susceptibility to natamycin and the mean minimum inhibitory concentrations of natamycin (MICn) were correlated with clinical outcome. The mean MICn for various groups of fungi from patients with either early (<10 days) or late (≥10 days) presentation was correlated with the outcome. *Aspergillus flavus* showed resistance to natamycin with a high mean MICn (21 µg/ml). While the clinical response in all patients with early *A. flavus* keratitis was good it was poor in late cases. *Fusarium*species, *Acremonium* species were sensitive with low mean MICn (*Fusarium*: 7-9 µg/ml, *Acremonium*: 5-8 µg/ml. We conclude that despite susceptibility of most fungal species causing keratitis to natamycin, the treatment outcome is poor in advanced fungal keratitis.

Key Words: Keratomycosis, minimum inhibitory concentration, natamycin, susceptibility, treatment outcome.

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INTRODUCTION

Keratomycosis is the leading cause of ocular ulceration worldwide and fungi are the most common etiological agent causing corneal infections[1-3]. Polyenes, triazoles, and echinocandins are the antifungal drugs commonly used for treatment of fungal keratitis[1-3]. Among these antifungal drugs, natamycin is the mainly used for the treatment of corneal ulcer worldwide. Although there are antifugal drugs, but treatment outcome is poor in fungal keratitis as compared to bacterial infections[1-3]. In the non-ophthalmic literature a fairly wide range of antifungal susceptibility test results are available for prediction of clinical outcome in fungal infections[4]. In contrast, such information is lacking in keratomycosis. Only a limited number of antifungal susceptibility testing of ocular isolates has been reported and except for one none have correlated with response to treatment in the patients[5,6]. Therefore in the present study fungal isolates from keratitis patients were tested *in vitro* for their susceptibility to natamycin eye drop and the mean minimum inhibitory concentrations (MIC) were correlated with the clinical outcome with topical 5% natamycin eye drops.

MATERIALS AND METHODS

In this prospective, interventional study corneal scrapings from 50 patients with microbial keratitis were processed and interpreted as per standard protocol[3]. Consent was obtained from all patients. Taking appropriate laboratory precautions all significant fungal growth were tested for their susceptibility to natamycin eye drop (Sun pharmaceutical Ind. Ltd, Mumbai, India) by the previously described microbroth dilution method[7]. All patients received intensive treatment with one hourly 5% natamycin eye drops in the affected eye for the first three days with subsequent modification as per response. 20 patients were given oral ketoconazole (200 mg twice

daily) and 5 patients received oral fluconazole (150 mg twice daily). Clinical outcome at one month was considered for analysis. An ulcer was defined either completely healed or resolving (reduction in infiltrate size) or worsened (increase in infiltrate size, keratoplasty). Since the treatment outcome is known to be affected by severity of disease the mean MIC of natamycin for different groups of fungi for patients presenting within 10 days (early onset) or after 10 days (late onset) of symptoms were correlated with the clinical outcome[8].

RESULTS

Fungal species wise comparison of mean MIC of natamycin with treatment outcome was made among the patients with early and late onset disease [Table 1]. *A. flavus* (n = 14) showed the highest mean MIC (early-15 µg/ml, late-21 µg/ml) suggesting lowest susceptibility to natamycin. Excluding the patients lost to follow up 2 out of 5 patients had poor clinical response in the late group (*A. flavus*) while 1 had worsened in the early group (*A. flavus*). *A. fumigatus*, in contrast, showed high susceptibility to natamycin *in vitro* with mean MIC of 2 µg/ml. MIC of natamycin was relatively low for *Fusarium* species with mean MIC between 7- 14 µg/ml. Among the dematiaceous fungi, *Curvularia* species were isolated in 3 patients and natamycin showed low MIC against these isolates (mean MIC in early - 1.4 µg/ml, late - 4 µg/ml).

Table 1: Treatment outcome of patients with early (<10 days) and late (>10 days) onset of fungal keratitis caused by various groups of fungi and their correlation with MIC of natamycin.

Fugal isolates	Treatment outcome	Total No. (%)	Mean MIC (µg/ml)	Healed	Resolving	Worsened	No follow up
Aspergillus fumigatus	Early	18	2	4	3	1	1
	Late	4	4	1	1	0	0
Aspergillus flavus	Early	18	15	4	3	1	1
	Late	10	21	2	1	2	0
Aspergillus terreus	Late	4	17	1	1	0	0
Aspergillus niger	Early	2	2	1	0	0	0
Curvularia spp	Early	4	1.4	1	0	1	0
	Late	2	4	0	1	0	0
Fusarium spp	Early	18	7	3	4	1	1
	Late	6	9	1	1	0	1
Acremonium spp	Early	8	5	2	1	0	1
	Late	4	8	1	0	1	0

DISCUSSION

A notable publication by Prajna *et al*, has convincingly shown that eye drop preparations are an alternative to pharmaceutical grade natamycin (not available to most laboratories) for testing antifungal susceptibility[7]. This study applied the same technique to evaluate the MIC of natamycin against various isolates of fungi from corneal scrapings of patients with mycotic keratitis. Owing to a small sample size in various groups of fungi, the mean MIC was considered for comparison rather than MIC_{90} or MIC_{50}[9]. Susceptibility breakpoints for natamycin have not been described so far in CLSI guidelines, however, MIC of 16 µg/ml or less is considered to indicate susceptibility of a fungal isolate[7]. This study reassuringly found low MIC of natamycin (≤16 µg/ml) in all fungal isolates tested except *A. flavus*. *A. flavus* associated with keratitis is a particularly virulent fungus and is known to be associated with poor outcome in keratomycosis[8]. Apart from the toxins, its perilous status is compounded by its resistance to natamycin. It is not known whether this resistance is inherent to this species[10]. All isolates of *Fusarium* species were sensitive to natamycin but that did not translate to good clinical outcome in patients with *Fusarium* keratitis irrespective of early or late presentation. This probably points to the well known fact of poor penetration of natamycin especially in presence of advanced fungal keratitis affecting deeper layers of the cornea. Most encouraging results were obtained with respect to dematiaceous fungi [Table 1]. This study shows that a low MIC of natamycin (susceptible fungi) was not always associated with good treatment outcome with natamycin in fungal keratitis. As is well known, a large number of factors affect success or failure of medical therapy of fungal keratitis, severity of infection being one of them[8,11,12]. Our treatment protocol for fungal keratitis includes systemic antifungals for patients with the ulcer more than 6 mm in diameter or extending beyond anterior half of the stroma or when there is hypopyon. Systemic antifungal therapy given in some of the patients in this study may be a confounding factor which was not analyzed and is one of the limitations of this study. Using logistic regression Shapiro *et al*., showed that a two fold increase in MIC results in 47% reduction in the odds of healing[6]. However, results of the present study suggest

that such a conclusion may be too simplistic and a considerably large study addressing multiple factors would be necessary to determine the effect of various parameters on the treatment outcome of fungal keratitis. Despite the limitation of small sample size in each group of fungi and statistically non significant results, we believe that our results are clinically significant. The susceptibility of *A. flavus* to natamycin is particularly poor and patients with this infection may require aggressive treatment, closer follow up and early surgical intervention. *In vitro* susceptibility of most other species of fungi, such as *Fusarium* spp., *A. fumigatus*, *Acremonium* spp., *Curvularia* spp. etc., to natamycin may account for good clinical response when the intervention occurs early in the disease.

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