

Current use of Antifungal Eye Drops and How to Improve Therapeutic Aspects in Keratomycosis

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Abstract

Background: Fungal keratitis is a disease that has a low prevalence and poor outcome because of its minimal therapeutic spectrum.

Objective: The purpose of the current study is to provide an overview of the use of antifungal topical eye drops in a third level hospital and to highlight possible improvements that can optimize their therapeutic use.

Methods: Fungal keratitis cases treated in the Ophthalmology Department of a Tertiary hospital were reviewed in a four-year retrospective study.

Results: For four years, 24 patients received an antifungal eye drop treatment for fungal keratitis: 20% were treated with topical fluconazole and 80% were treated with topical voriconazole (79% in monotherapy and 21% in conjunction with topical natamycin). In most cases, fungal growth was been detected and susceptibility was rarely reported, facilitating the realization of directed treatment towards the most frequently isolated fungi (*Fusarium*, *Candida*, *Paecilomyces*).

Conclusion: In a disease with low prevalence and complicated management, we have detected improvement in the three involved departments: ophthalmology, pharmacy and microbiology.

Keywords: Fungal keratitis; Eye antifungals; Voriconazole; Natamycin; Fluconazole; Therapeutic optimization; Pharmaceutical recommendations

Introduction

Fungal keratitis (FK) is a corneal infection that can lead to pain, loss of vision, light sensitivity and tearing. Despite representing only 5% of all infective keratitis cases in developed countries, if left untreated, it can cause blindness [1].

Filamentous fungi, such as *Fusarium* spp. and *Aspergillus* spp. are the most common etiologic agents in hot, humid, tropical or semi-tropical climates and they are the most common infections in agricultural workers [2]. Although there are cases of infections unrelated to these fungi, such as infections resulting from *Paecilomyces* spp. filamentous infections are usually preceded by an ocular injury with vegetables [3]. Furthermore, among yeast, *Candida albicans* is the most common fungus, especially in the coldest climates. It usually affects patients with a pre-existing corneal disease or who have received long-term corticoid therapy [4].

All FK cases must be confirmed microbiologically to detect the causative agent and choose the best treatment [5]. Usually, FK appears as a white-greyish lesion with indistinct margins and finger-like projections in the adjacent stroma. The production of necrotizing areas with inflammatory infiltrate is typical of this pathology. Once microorganisms penetrate in the anterior chamber and reach the crystalline lens, they are extremely difficult to remove [6]. Usually, treatment for these microorganisms is very complex, requiring the use of antifungal drugs for a prolonged period of time and frequent debridations to facilitate the activity of the antifungal drug [7]. FK has a worse visual prognosis than bacterial keratitis, most likely because of the lack of effective treatments. Thus, it often requires a corneal graft because the cornea is damaged [8].

Currently, there is a significant lack of commercialized ophthalmic drugs because they are not profitable or have low stability. Thus, a significant number of patients are in distress, and ophthalmologists are forced to seek alternative options, such as antifungal eye drops, which are produced in pharmacy departments [9].

Polyene is the first choice for KF treatment because topical natamycin (Natacyn 5%) is the best option against filamentous fungi and amphotericin B (eye drops Amphotericin B 0.15%) is the best

option against yeast [10]. The emergence of new azole antifungal drugs, such as voriconazole (Vfend®), may replace the classical treatment because they are less toxic than amphotericin [11] and have better penetration [12].

Objective

The purpose of the current study is to provide an overview of the use of antifungal topical eye drops in a third level hospital and to highlight possible improvements that can optimize therapies.

Methods

We present a retrospective study of all fungal keratitis treated by the Department of Ophthalmology of Santiago de Compostela during a period between January 2010 and December 2014. We used a formulation database (Pharmabase®) and a pharmacotherapeutic management program, SILICON[®], to analyse the antifungal eye drops produced in the pharmacy.

We collected the following parameters using the electronic national history system (Applicative IANUS): age, sex, history of ocular pathology, diagnostic confirmation of fungal keratitis, microbiological examinations, type of eye drop used, duration of treatment with the topical antifungal prescribed and resolution of medical-pharmacological treatment. The work was conducted in compliance with the Institutional Review Board Human Subjects Research Committee requirements and was conducted in accordance with the Helsinki Declaration.

Results

During the period of study, 24 cases of fungal keratitis required treatment with topical antifungal drops. The average patient age was 62 years old (SD=15); 58.3% were women (n=14), and 45.83% of total cases (n=11) presented with a history of ophthalmic disease (corneal

transplantation, herpetic keratitis repeat, bacterial infectious keratitis with a prolonged treatment of antibiotics, dry eye and necrotizing scleritis).

We analysed the microbiological results of all of the patients who had fungi. These microbiological cultures resulted in corneal scraping in 75% of cases and in a conjunctival exudate in 25% of cases. In 45.83% of cases, it was not possible to isolate and identify the causative agent. However, we identified the microorganism agent in 54.17% of cases: *Candida* spp. (25%), *Fusarium* spp. (12.5%), *Paecilomyces* spp. (12.5%) and *Aspergillus fumigatus* (4.16%). Concomitant treatment was similar in all patients. They received an oral antifungal drug, topical moxifloxacin, and, in some cases, intracameral voriconazole.

Regarding the topical pharmacotherapy approach, voriconazole is the most widespread treatment because it was used in up to 80% (n=19) of cases. In 79% of cases, a monotherapy of voriconazole (n=15) was used for an average of 55 days (SD=30). Among them, 21% (n=4) were initially treated with voriconazole eye drops in monotherapy; ten days later, natamycin eye drops were added, and finally, the treatment ended with the use of only this molecule, completing a full cure period of 40 days (SD=15). The second-most preferred therapeutic eye drop was fluconazole, which was prescribed for 20% (n=5) of the patients, with a treatment period of a mean of 40 days (SD=25).

In 80% of patients treated with topical fluconazole, the agent was identified (guided by antibiotic susceptibility twice). However, treatment with voriconazole was only started with an identified causal agent in 47% of cases. Therefore, most of the cases were treated based on an empirical treatment.

Table 1 describes the cases treated with previous therapies and their microbiological results. In 90% of cases, the pharmacological treatment failed, resulting in a loss of vision because of corneal opacity, which was residually triggered by the infection and/or the treatment itself or because of the occurrence of perforations that led to eye enucleation.

	Fungus identified	Fluconazole	Voriconazole	Caspofungin	Amphotericin
Treatment with fluconazole eye drops (n=5)	<i>Candida albicans</i> (n=1)	0.094	-	-	0.047
	<i>Candida tropicales</i> (n=1)	0.19		0.016	
	<i>Paecilomyces</i> sp. (n=1)	-	-	-	-
	<i>Fusarium</i> sp. (n=1)	-	-	-	-
	No identified (n=1)				
Treatment with voriconazole eye drops (n=15)	<i>Candida albicans</i> (n=1)	"Sensible"	-	"Sensible"	-
	<i>Candida parapsipolis</i> (n=1)	"Sensible"	-	"Sensible"	-
	<i>Aspergillus fumigatus</i> (n=1)	-	-	-	-
	<i>Paecilomyces</i> spp. (n=1)	-	-	-	-
	<i>Fusarium</i> sp. (n=2)	-	-	-	-
	No identified (n=9)				
Treatment with voriconazole eye drops and natamycin (n=4)	<i>Candida albicans</i> (n=2) ^{1*} 2*	(1.1) ^{1*} (0.251) ^{2*}	(0.008) ^{2*}	(0.094) ^{1*} (0.064) ^{2*}	-
	<i>Paecilomyces</i> sp. (n=1)	-	-	-	-

No identified (n=1)				
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Table 1: Patients treated with fluconazole, voriconazole and/or natamycin etiologic agents and the sensitivity of the antifungal drugs tested.

Discussion

In the current study, we confirmed the low prevalence of FK, a disease that affects a very small number of patients (24 cases in four years) in an area that covers 470000 inhabitants. According to the definition of a rare disease (a disease that affects 1 in 2000 people), FK could be included in this group [13]. For the pharmaceutical industry, these diseases are not economically profitable for drug development; thus, the Hospital Pharmacy Services produces them [14]. We should consider that although FK is a rare disease in our country, it is quite common in some underdeveloped countries, such as India [5]. We need to realize that research, development and innovation in these countries is very limited, and so it is quite difficult to formulate an efficient treatment for this purpose. Diseases that have a low prevalence, such as FK, suffer from a significant lack of clinical and scientific interest. There is no real research or public health policy on solutions related to this field [15]. Currently, there is no commercial ophthalmic topical antifungal treatment available, except those produced in pharmaco-technical laboratories in hospitals [16,17].

The present study does not allow for conclusions about the most frequent etiologic agents nor the effectiveness of treatment groups because the low number of patients is not valid for the interpretation of these data. Multicentre studies are required for this prospective study to encompass more cases. However, this study highlights the problems encountered in the multidisciplinary management of this condition.

An important parameter needing improvement is the microbial aspect; only six antibiograms were performed in cases of fungal keratitis (those caused by *Candida*). Therefore, directed treatment against the causative agent was not possible. Moreover, the antifungal drugs that were tested, such as caspofungin, are not available in ophthalmic forms in most pharmacies departments [18]. In two cases, the antibiogram informed sensitivity to one agent without CMI results. This can be confusing because it is not possible to use the same breakpoints in ophthalmology, as defined by the committees, because the CMI should be interpreted by taking into account the pharmacokinetics and pharmacodynamics information [19]. For this, it is necessary, to first know where the antibiotic needs to penetrate (epithelium, stroma, anterior chamber or posterior chamber) and then to study the drug concentrations reached in each of these areas to overcome the CMI [20,21]. There are specific studies on corneal penetration and concentrations of different antifungal drugs [22], and there are also multiple microbiological studies on CMI in major ocular pathogens [23,24]. We believe that specific studies should be carried out to establish specific cut offs that consider these two factors together with a final assessment of the effectiveness of treatments [25,26].

Moreover, the pharmacy department also has several points of improvement. On the one hand, the optimization of ophthalmic master formulas is not as developed as it should be. The use of ophthalmic master formulas with little eye toxicological safety remains unknown, and eye drops are developed with concentrations of drugs that are only based on the clinical experience of ophthalmologists [27]. Although it has been observed that antifungal eye drops are well tolerated and have demonstrated relatively low eye irritation [28], they

are toxic for stromal cells (keratocytes) because they are harmful for corneal healing [29]. Commercial drugs used for the parenteral route, usually those commonly used in these preparations, are for dissolution or dilution in physiological buffers that are compatible with ocular use [30]. However, these are not designed or adapted to ocular use because some of the excipients that are incorporated or the active ingredients themselves can produce undesirable effects in the eye and should therefore promote research in pharmacy services for the development of new alternatives and optimization of existing ones.

Furthermore, the pharmacist who formulates the compound must actively participate in making pharmaco-therapeutic decisions with the ophthalmologist, encouraging the use of drugs with better risk benefits for the patient and with the least economic impact on society [31]. Recent studies showed the superiority of natamycin compared to voriconazole in the treatment of filamentous fungi. Moreover, voriconazole is significantly more expensive than natamycin. As a consequence, the use of natamycin should be encouraged. Furthermore, the combination of natamycin and voriconazole has shown a synergy in *in vitro* studies [32,33], although these studies are inconclusive and more research is needed [34]. Comparative data between natamycin eye drops and econazole (Aurozole®: Supplied in India) show similar results in efficiency. Thus, it could be a valid alternative because it is economical and easier to formulate for pharmacies by solubilizing econazole with cyclodextrins [35,36].

It should be noted that sometimes the lack of drugs at a national level is a bureaucratic problem. This is the case for topical natamycin (Natacyn 5%) in Spain, for example, where it is not approved. However, it is also important to note that amphotericin b (Fungizone®), a specialty ingredient that is commonly used in the formulation of eye drops, is no longer available on the market in numerous countries. Currently, a liposomal presentation is available (Ambisome®) that has occasionally been used in eye drop formulations, but the experience is poor [37]. In both drugs (Natacyn® and Fungizone®), it is necessary to establish a simple and effective procedure so that they can be available at any time in case of ophthalmologic emergencies, such as fungal keratitis.

The lack of experience resulting from the low numbers of cases requires an interdisciplinary collaboration between microbiology, pharmacy and ophthalmology services to optimize fungal keratitis therapy.

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