Benefit of Polyhexamethylene Biguanide in *Fusarium* Keratitis

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Key Words

Fungus · *Fusarium* · Hyphomycete · Keratitis · Polyhexamethylene biguanide

Abstract

Purpose: To report a series of 3 patients with soft contact lens-related *Fusarium* keratitis. Two of them were treated with the antiamebic polyhexamethylene biguanide 0.02% (PHMB) in combination with antifungal drugs, and 1 patient was treated with PHMB as sole antifungal regimen. **Methods:** Chart review of 3 patients treated with PHMB in *Fusarium* keratitis. Two of them were refractory to the commonly used therapy. The antifungal power of PHMB and propamidine isethionate was tested against the patients' isolates as well as against the clinical isolates from another 9 patients with ocular mould infections. **Results:** An excellent outcome could be achieved in 2 patients with *Fusarium solani* keratitis refractory to common antifungal treatment by the additional use of PHMB 0.02%. In another patient PHMB alone was sufficient to resolve *Fusarium proliferatum* infection. The drug was well tolerated. In all patients repeated abrasion was done for better penetration of the drugs. PHMB revealed a marked in vitro antifungal activity for the three *Fusarium* isolates as well as for another 9 isolates of ocular infections from other patients including also the genera *Scedosporium*, *Aspergillus* and *Rhizopus* giving minimal inhibitory concen-

trations ranging from 1.56 to 3.12 µg/ml. **Conclusions:** *Fusarium* keratitis is a severe ocular infection. We report on the use of PHMB in 3 patients given additionally or as sole antifungal drug. We emphasize the benefit of PHMB 0.02% in *Fusarium* keratitis which might be considered as a therapeutic option especially in cases refractory to common antifungal therapy and possibly in keratitis due to other fungi.

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Infections of the eye due to moulds are on the increase [1]. Among these, *Fusarium* predominates causing severe keratitis often not responding to commonly used therapy. The benefit of the antiamebic polyhexamethylene biguanide (PHMB) in experimental *Fusarium* keratitis was first published in 1997 by Fiscella et al. [2]. In vitro activity is well documented [3, 4], but its use in ocular fusariosis has not been described so far. We report on 3 patients with *Fusarium* keratitis treated with PHMB. It was used in combination with other antifungal drugs in 2 patients showing keratitis refractory to standard therapy and in 1 patient as primary antimycotic therapy. The rationale for using PHMB is supported by the in vitro antifungal activity of this drug, which was examined against the patients' isolates as well as further hyphomycetes from eye infections of other patients.

Table 1. Patient and clinical data

Case No.	Age/gender	Fungal organism	Methods to isolate the organism	Contact lens brand/type	Contact lens solution	Onset of symptoms before treatment	Clinical features	Treatment (beginning, end)	Improvement	Outcome and visual acuity (final)
1	38/M	<i>Fusarium solani</i>	corneal scraping	SCL, monthly wear	Complete®, AMO, Germany	2 weeks	hypopyon (day 10), HM	CA; TV (day 1, 10 weeks), TN (day 1, 4 months), TP (day 1, day 10), TL (day 1, day 10), PHMB (day 10, 8 weeks), VS (day 10, 1 week), PS (day 18, 7 weeks), TD (day 10, 4 months)	after 3 weeks	cured 20/20
2	29/F	<i>Fusarium solani</i>	culture of contact lens and solution	SCL, FreshLook Dimensions®, Cibavision, Germany	Acumed®, Acucell, Germany	<1 day (treated 10 days before presentation by home physician)	hypopyon (day 10), B.-B.-1-sign, B.-B.-2-sign, HM	CA; TM (day 1, day 10), TPBN (day 1, day 10), TF (day 1, day 10), TC (day 1, day 16), TVa (day 10), TCe (day 10), PHBM (day 10, day 51), TP (day 10, day 51), TV (day 10, day 51), VS (day 10, 2 weeks), TN (day 17, day 51), TA (day 17, day 44), TD (day 17, 3 months)	day 16	cured 20/30
3	50/M	<i>Fusarium proliferatum</i>	corneal scraping, HRT II-RCM	SCL, monthly wear	unknown	<1 day	stromal infiltration and severe pain (day 1), B.-B.-2-sign	CA; PHMB (day 1, 3 months), TP (day 1, 3 months), TL (day 1, 3 weeks), TS (day 1, 1 week), TD (day 90, 3 months)	day 5	cured 20/20

SCL = Soft contact lens; HM = hand movements; CA = corneal abrasion; PS = posaconazole systemically; TA = topical amphotericin B; TC = topical cyclopentolate; TCe = topical ceftazidime; TD = topical dexamethasone; TF = topical fluconazole; TM = topical moxifloxacin; TN = topical natamycin; TP = topical propamidine isethionate; TPBN = topical polymyxin/bacitracin/neomycin (sulphate); TS = topical scopolamine; TV = topical voriconazole; TVa = topical vancomycin; VS = voriconazole systemically.

Case Series

In 2007 and 2010, 3 patients with contact lens-related *Fusarium* keratitis were diagnosed and treated successfully. Clinical and demographic data are presented in table 1.

Patient 1

A 38-year-old male patient suffered from conjunctivitis for 2 weeks. He wore soft contact lenses and was admitted to the hospital with severe pain and diffuse eccentric superficial keratitis with satellites and positive fluorescein staining (fig. 1). The microbiological examination of corneal scrapings revealed *Fusarium solani* confirmed by molecular methods. Treatment was started with voriconazole 1% (Vfend®, Pfizer, Germany) in addition to natamycin solution (Natacyn®, Alcon, USA), both given hourly and completed with propamidine isethionate 0.1% (Brolene®, Aventis Pharma, UK) and levofloxacin (Oftequix®, Santen Oy, Tampere, Finland), which were administered 5 times a day. Ten days later an additional central corneal infiltrate with a hypopyon was observed. At that time visual acuity had declined to hand motion. Therapy was intensified with oral voriconazole 2 × 200 mg/day and topically by a 2% voriconazole solution and natamycin solution every half an hour. Propamidine isethionate was replaced by PHMB 0.02% (Lavanid®, Serag-Wiessner, Germany) and applied every hour with a 10-min interval between drops; dexamethasone drops 1% (Dexagel®, Mann-Pharma, Germany) were given twice daily and corneal abrasion was repeated every

second day to facilitate drug penetration into the corneal stroma. Due to insufficient response after 1 week systemic therapy was changed to oral posaconazole (400 mg twice daily). Maintaining the local treatment, *Fusarium* keratitis slowly improved and the hypopyon disappeared. Three weeks later polyhexanide, voriconazole and posaconazole were discontinued. Under the umbrella of natamycin, dexamethasone drops were administered 5 times daily over a period of 2 months and then tapered off. One year later, the corneal situation continued to be stable and the best corrected visual acuity had improved to 1.0 (50/50; fig. 2).

Patient 2

A 29-year-old female wearing soft contact lenses presented with a paracentral corneal infiltrate of the left eye (fig. 3) and a visual acuity of 0.3. She had been treated by her home physician topically with acyclovir and moxifloxacin for 10 days. Therapy was started with topical moxifloxacin (Vigamox®, Alcon Pharma, Germany), polymyxin/bacitracin/neomycin (Polyspectran®, Alcon Pharma) every half an hour, fluconazole eye drops (Diflucan®, Pfizer) every hour and cyclopentolate eye drops (Alcon Pharma) 3 times per day for 16 days. After 10 days the slit-lamp findings deteriorated and visual acuity was reduced to hand motion; vancomycin plus ceftazidime were injected intracamerally. The cultural detection of *F. solani* resulted in changing the regimen to topical voriconazole 1% every hour, systemic voriconazole (Vfend, Pfizer) 400 mg daily, additionally PHMB and propamidine isethionate both applied every hour with 10 min between

Fig. 1. Paracentral infiltrate of varying intensity.

Fig. 2. Patient 1: corneal scar without inflammation. Visual acuity 20/20.

Fig. 3. Patient 2: landscaped corneal infiltrate with intact epithelium and satellites.

Fig. 4. Patient 2: ropy hypopyon (so-called B.-B.-1 sign) in the form of a cone (arrowheads).

drops for 7 days. A hypopyon developed in the form of a cone typical of fungal infection (as well as a pyramid-convex shaped due to its ropy consistency – the so-called B.-B.-1 sign) [5] (fig. 4). The epithelium on the whole infiltrate was intact except for a very small central part (B.-B.-2 sign) [6] in contrast to a typical bacterial ulcer which is largely denuded. Local antibiotics were discontinued and due to the known low susceptibility of *F. solani* the topical 1% voriconazole solution was replaced by a 2% solution and therapy was escalated by local treatment with natamycin every hour, PHMB and propamidine isethionate every second hour for 34 days. Additionally 0.1 ml of amphotericin B 0.5% was injected into the anterior chamber 9 times every second to third day and for better corneal penetration of the drugs corneal abrasion was performed every 3–4 days, after the epithelium had healed.

After 17 days additional dexamethasone drops 0.1% were applied. Under this complex and intensive therapy, the slit-lamp findings improved and visual acuity was 0.63 after nearly 3 months.

Patient 3

A 50-year-old male using soft contact lenses presented with severe pain of his left eye. By slit-lamp examination a broad corneal stromal infiltration with a small central epithelial defect was

Fig. 5. Patient 3: broad corneal infiltration with only small epithelial defect (so-called B.-B.-2-sign).

seen (B.-B.-2-sign) [6] (fig. 5). Because of extreme pain *Acanthamoeba* keratitis was suspected. After corneal abrasion with a hockey-knife, therapy was started with PHMB (Lavanid) and propamidine isethionate (Brolene) alternately every 15 min from 8 a.m. to 10 p.m. Additionally, levofloxacin (Oftequin, Santen Oy) and scopolamine eye drops (Boro-Scopol®, Dr. Winzer Pharma GmbH, Berlin, Germany) were administered 5 times and 3 times, respectively, per day. Corneal swab of the left eye revealed no *Acanthamoeba* but growth of *Serratia marcescens* and *Fusarium proliferatum*, the latter identified by micromorphology and confirmed by PCR and sequencing. No fungi could be cultured from the contact lens fluid but coagulase-negative *Staphylococcus*, *Staphylococcus aureus* and *S. marcescens* were obtained. Using the Rostock Cornea Module-HRT II (confocal laser scanning microscope, HRT II-RCM) no *Acanthamoeba* could be demonstrated but filamentous structures consistent with *Fusarium* spp. were recognized (fig. 6).

After 11 days pain declined and the therapy could be reduced to hourly polyhexanide and propamidine for a period of 3 months. Thereafter dexamethasone was given 2 times daily for 2 months and then tapered off. The patient remained without any symptoms and visual acuity was fully restored.

Discussion

Fungi increasingly contribute to ocular infections and *Fusarium* species are the most frequent corneal fungal pathogens [1]. These moulds are ubiquitous in the environment. Generally, fusariosis is difficult to treat, especially in systemic mycoses. Several predisposing factors for keratomycosis have been identified including foreign bodies, contact lenses, ocular surgery and extensive use of cor-

Fig. 6. Patient 3: filamentous structures (arrows) consistent with *Fusarium* species.

ticosteroids and antibiotics [5–7]. New diagnostic options like the HRT II-RCM can be successfully used to diagnose fungal keratitis and to detect causal pathogens [8, 9]. To date, a standard therapeutic strategy has not yet been established. In cases of *Fusarium* keratitis there are few therapeutic options including solutions of natamycin, amphotericin B and voriconazole [10] for topical treatment and systemic therapy with new drugs such as voriconazole or posaconazole. Generally, individual pharmacokinetics as well as strain-specific differences in susceptibility to antifungal drugs have to be considered. The topical drug of choice in cases of *Fusarium* keratitis is natamycin (also known as pimaricin) 5% [11–15], but delayed diagnosis may lead to insufficient response [16]. The penetration of natamycin through the corneal epithelium is poor [17, 18] due to its high molecular weight of 665.75 Da. Therefore, corneal abrasion is necessary. In order to achieve a higher concentration of voriconazole in the corneal stroma (and anterior chamber) we administered the twofold concentration (table 2). This concentration was well tolerated by our patients. Because of imminent endophthalmitis in case 1 we replaced systemic voriconazole therapy by posaconazole which had been described to be successful in 3 cases of pan-resistant *Fusarium* keratitis [17].

Table 2. Preparation of voriconazole eye drops 2%

a Dissolve 1 ampoule of voriconazole 200 mg (Vfend™, Pfizer) in 9.5 ml of water for injection under laminar flow conditions
b Shake carefully and let rest for 5 min to clear
c Filter the solution through a 0.2-µm filter into sterile eye drop bottle
d Store at 2–8°C no longer than 7 days

As the patients responded well to the treatment regimen, we would like to recommend this combination of topical antifungals with the antiamebic drug polyhexanide in ocular fusariosis. It should be noted that since keratomycosis typically reveals intact corneal epithelium to a large extent over deep mycotic stromal infiltrates (so-called B.-B.-2 sign) [6], repeated corneal abrasion is mandatory. Despite iatrogenic erosion, low dose corticosteroids are helpful in our experience to prevent over-reactive immune response which has been experimentally proven [20]. Which component has been the mainstay in eliminating the fungus remains unclear; possibly the interaction of various drugs together with topical (and systemic in cases 1 and 2) administration may have contributed to this outcome.

The benefit of PHMB in experimental *Fusarium* keratitis was first published in 1997 and several reports exist on its in vitro activity against fungi [2–4]. Recently PHMB was reported to be successful in the treatment of a mixed infection due to *Acanthamoeba* and *Fusarium* [21]. PHMB has also shown antifungal effects in an experimental *Aspergillus* keratitis in a mouse model [22], but its clinical use and the benefit for treatment of refractory *Fusarium* keratitis has not yet been described. High in vitro activity of PHMB in contrast to poor antifungal activity of propamidine isethionate could be demonstrated not only for the isolates of our 3 patients but also for another 9 hyphomycetes from eye infections of other patients comprising highly resistant species (table 3). In all isolates the minimal inhibitory concentrations of PHMB often proved to be also fungicidal (data not shown separately). PHMB 0.001% is the active ingredient in the contact lens fluid used by patient 1, but the PHMB concentration for treatment is 200-fold higher.

Out of clinical necessity, the main shortcoming of our report is that in cases 1 and 2 conventional antimycotic therapy in combination with PHMB and propamidine was used. In case 3, *Acanthamoeba* keratitis was suspect-

Table 3. In vitro antifungal activity of PHMB and propamidine isethionate

Strains	PHMB	Propamidine isethionate
RKI 01-0765 <i>Fusarium solani</i>	1.56	>1,024
RKI 05-0480 <i>Fusarium solani</i>	1.56	256
RKI 07-0009 <i>Fusarium solani</i> ^a	1.56	256
RKI 07-0529 <i>Fusarium solani</i>	1.56	256
RKI 09-0011 <i>Fusarium solani</i> ^b	1.56	256
RKI 98-0496 <i>Fusarium oxysporum</i>	1.56	32
RKI 98-0499 <i>Fusarium oxysporum</i>	1.56	256
RKI 10-0323 <i>Fusarium proliferatum</i> ^c	1.56	32
RKI 98-0557 <i>Fusarium lichenicola</i> ^d	1.56	>256
RKI 96-0871 <i>Scedosporium apiospermum</i>	1.56	>1,024
RKI 01-0085 <i>Aspergillus fumigatus</i>	3.12	>1,024
RKI 02-0465 <i>Rhizopus microsporus</i>	3.12	512

Minimal inhibitory concentrations (µg/ml) according to CLSI M38-A2 guidelines [19].

^a Clinical isolate of case 1. ^b Clinical isolate of case 2. ^c Clinical isolate of case 3. ^d Previously *Cylindrocarpon lichenicola*.

ed due to extreme pain of the patient. Based on good experiences in the first 2 cases and in vitro results, antiamebic treatment using PHMB and propamidine was performed; successful results were achieved with reduction of pathogens after the microbiological detachment of *Fusarium* spp. In our cases, no toxic effects were observed at the corneal epithelium and other eye structures.

However, in all cases the corneal epithelium should be removed by corneal abrasion to allow better penetration of PHMB because this agent has a high molecular weight of about 5,000 Da, which is known to poorly penetrate an intact corneal barrier.

In any case, emphasis should be placed on the antifungal activity of PHMB as this drug has not yet been described for the treatment of refractory *Fusarium* keratitis. Further studies have to confirm the beneficial use of PHMB before its general recommendation for topical application in *Fusarium* keratitis.

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