ARTYKUŁ PRZEGLĄDOWY REVIEW ARTICLE
DOI: 10.24292/01.OT.262324

Efficient antiseptic prophylaxis in the era of antibiotic resistance

Joanna Adamiec-Mroczek, Marta Misiuk-Hojło

Clinic of Ophthalmology, University Clinical Hospital in Wroclaw
Head: prof. Marta Misiuk-Hojło, MD, PhD

HIGHLIGHTS

In order to prevent infectious complications in procedures that do not standardly require perioperative antibiotic prophylaxis, such as intravitreal injections, the use of preparations with antiseptic action may be considered.

ABSTRACT

An excessive use of antibiotic preparations in daily practice frequently without clear medical indications has led to the development of dangerous strains of bacteria resistant to the available pharmaceutical drug. Today, antibiotics are used not only to treat infections, but also as preoperative infection prevention. Intravitreal injection is one of the most commonly performed ophthalmological procedures where, until recently, perioperative antibiotics prevention was recommended. Currently, antibiotics in this procedure are not advised at all. Nowadays, for anti-infective prophylaxis we use iodopovidone and preparations that combine antiseptic and soothing effects.

Key words: antibiotic resistance, prophylaxis, intraocular inflammation

INTRODUCTION

As one of the breakthroughs of the 20th century for humanity, antibiotic therapy has made it possible to successfully treat numerous diseases that were previously incurable. However, an excessive use of antibiotics in daily practice frequently without clear medical indications has led to the development of dangerous strains of bacteria resistant to the available pharmaceutical drugs. Yet another century of medicine unexpectedly collides with increasing antibiotic resistance. Also in ophthalmology, infections caused by drug-resistant bacterial strains are increasingly observed to be difficult to treat [1].

EPIDEMIOLOGY OF EYE INFECTIONS

When analysing the causes of eye infections from the epidemiological point of view, the most common pathogens include *Staphylococcus aureus, Staphylococcus epidermidis* and *Pseudomonas aeruginosa*. *Staphylococcus epidermidis* is the bacterium most commonly causing postoperative intraocular inflammation (endophthalmitis) [2]. On the other hand, *Pseudomonas aeruginosa* remains a major cause of corneal ulcers, particularly in contact lens wearers [3]. *Acanthamoeba* is a less common pathogen in this group of patients. In addition to bacterial lesions, inflammation of the eyeball resulting from fungal infections is also observed. According to a number of epidemiological analyses, *Candida* remains one of the key pathogens responsible for corneal ulcers and endogenous intraocular inflammation (endophthalmitis) [4, 5].

PREVENTION AND TREATMENT

Today, antibiotic preparations are used not only to treat infections, but also as perioperative infection prevention. This approach makes it possible to prevent severe inflammatory complications, and significantly improves postoperative prognosis. In the said cases, preparations offering a spectrum of activity against the most common pathogens are recommended. Unfortunately, the last 30 years in ophthalmology have been a time of second and III generation fluoroquinolone preparations (ciprofloxacin, ofloxacin, levofloxacin) overuse. Application of this group of drugs to treat the common benign ophthalmological conditions (e.g. conjunctivitis, corneal erosion, viral infections) has led to the development of increasing antibiotic resistance [6, 7].

Intravitreal injection is one of the most commonly performed ophthalmological procedures where, until recently, perioperative antibiotic prevention was recommended. The aim of this procedure was to reduce the risk of endophthalmitis. It is in this group of patients that antibiotic-resistant strains become most easily isolated due to the high frequency of procedures performed. Quite frequently, monthly injections administered along with perioperative and prophylactic topical antibiotic therapy (i.e. a few days before or after the injection) has significantly contributed to the observed changes in the degree of susceptibility of pathogens to the fluoroquinolones in use [8, 9]. Hence the need to restrict the use of antibiotic preparations to rigorous medical indications while simultaneously implementing antiseptics into daily practice. The perioperative intravitreal injections procedure may be an example of the said therapeutic evolution. Currently, antibiotics are not recommended at all [10, 11]. These standards are the result of numerous studies showing that topical antibiotic therapy has no impact on the incidence of endophthalmitis. Also, the estimated risk of endophthalmitis following an intravitreal injection is relatively low, ranging from 0.019% to 0.07% according to various publications, depending on whether the procedure was performed in the operating room, operating theatre, or using a sterile air supply [12]. Nevertheless, any treatment entails the risk of inflammation.

Nowadays, iodopovidone is the most commonly used substance with a strong antiseptic effect, and it is applied in varying concentrations depending on the type of tissue to be disinfected (skin, conjunctiva). However, the proven high disinfecting efficacy of iodopovidone is associated with a strong irritant effect, often resulting in damage to corneal and conjunctival epithelial cells. In addition to iodopovidone, chlorhexidine is used, especially in patients allergic to iodine. Also hexamidine diisethionate has found its way into medical applications.

For anti-infective prophylaxis, some authors indicate the beneficial effect of using preparations that combine antiseptic and soothing effects, such a product containing 0.05% hexamidine isethionate, 0.0001% polyhexanide hydrochloride, disodium edetate, 5% dexpanthenol, polyvinyl alcohol, methylsulfonylmethane, dibasic sodium phosphate, monobasic potassium phosphate, purified water (Keratosept).

When assessing the efficacy of above mentioned combined product, the published results of both *in vitro* and *in vivo* studies should be thoroughly analysed. The antiseptic effect of the preparation is due to the presence of hexamidine diisethionate, polyhexanide hydrochloride and disodium edetate in its formulation. Hexamidine diisethionate – a substance that has been used in medicine for more than half a century – shows the strongest effect among the substances listed above. This water-soluble cationic agent demonstrates proven efficacy against bacteria, protozoa, as well as fungi, including yeasts. The mechanism of action of this substance is not fully understood. As it has been proved, due to its positive molecular charge hexamidine diisethionate exhibits the ability to bind the negatively

charged bacterial cell wall, leading to the eradication of these organisms by means of disruption of oxygen uptake, and disruption of amino acid flux.

Hexamidine diisethionate has been shown to be highly effective in removing microorganisms such as *Pseudomonas aeruginosa, Proteus, Escherichia coli, Staphylococcus aureus, Tsukamurella paurometabolum* [13, 14]. What is important, hexamidine diisethionate is efficient against a lot of drug-resistant strains of Gram-positive bacteria [20]. In an *in vitro* study, Grare et al. demonstrated hexamidine diisethionate efficacy against 39 drug-resistant strains of Gram-positive bacteria (15 forms of *S. aureus*, 12 coagulase-negative *Staphylococci*, 14 *Enterococcus spp.*) and 30 drug-resistant strains of Gram-negative bacteria (20 *Enterobacteriaceae*, 10 non-fermenting bacilli) [15].

The high efficacy of hexamidine diisethionate specified above has been used in the combined preparation. The antiseptic effect of the preparation was confirmed in *in vitro* studies, and the results were published in the renowned journal, "Cornea" [16]. During the research program, the effectiveness of combined preparation in the eradication of *Staphylococcus aureus* (including methicillin-resistant strains), drug-resistant forms of *Staphylococcus epidermidis*, *Pseudomonas aeruginosa* and *Candida species* (*Candida albicans, Candida parapsilosis, Candida tropicalis, Candida glabrata, and Candida krusei*) was assessed. As demonstrated just 1 min after administration of combined preparation, no growth of *Staphylococcus aureus, Staphylococcus epidermidis* and the 5 types of *Candida* strains tested was shown on the experimental plates. The above results from the published studies are particularly relevant in the context of the treatment of fungal corneal ulceration caused specifically by *Candida* strains. Conflicting scientific reports indicate that iodopovidone, which is the most commonly used perioperative disinfectant, has limited ability to eradicate certain *Candida* species [17]. Given the high efficacy of hexamidine diisethionate in removing the most common forms of *Candida*, it may be optimal to administer hexamidine diisethionate drops following a prior application of the standard 0.6% iodopovidone.

In the case of *Pseudomonas aeruginosa*, eradication of the pathogen was achieved after 24 h of exposure to the preparation (tab. 1).

Similar results were obtained *in vitro* by the Mencucci et al. [18]. Also for this research programme, high efficacy in the eradication of *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Streptococcus pneumoniae, Streptococcus pyogenes* and *Streptococcus mitis* was confirmed. Similarly to the Grare et al. observations, combined preparation did not show any antiseptic effect on *Pseudomonas aeruginosa* (incubation time up to 6 h). An interesting part of the established study was to evaluate the effect of medicinal product containing hexamidine diisothionate, polyhexanide hydrochloride, disodium edetate and dexpanthenol on cultured human corneal and conjunctival epithelial cells. Cell preparations were incubated with the formulation components at two different dilutions: 1:1 and 1:10. Incubation times were 5, 10 or 15 min. Damage in human corneal and conjunctival epithelial cells was assessed by way of quantitative measurement of the soluble LDH (lactate dehydrogenase) enzyme released into the extracellular fluid as a result of the destruction of the cellular structures analysed. As shown, the cytotoxic effect of the components of analysed combined preparation at a dilution of 1:1 was only observed after 15 min of continuous exposure. At a concentration of 1:10, no features of corneal or conjunctival cell damage were observed. The next stage of the study was to analyse the degree of re-epithelialisation of damaged epithelial cells following the incubation of preparations in 5% D-panthenol solution and 1.25% polyvinyl alcohol. The authors indicate full repair of the layer of cell structures in question after 24 h of expo-

TABLE 1

Effectiveness of medicinal product containing hexamidine diisothionate, polyhexanide hydrochloride, disodium edetate and dexpanthenol in eradicating pathogens causing the most common infectious conditions of the ocular surface (modified after [17]).

Pathogen	Exposure time							
	1 min	5 min	10 min	15 min	20 min	25 min	30 min	24 h
S. aureus ATCC 43300	no growth	no growth	no growth	no growth	no growth	no growth	no growth	no growth
S. aureus	no growth	no growth	no growth	no growth	no growth	no growth	no growth	no growth
S. epidermidis	no growth	no growth	no growth	no growth	no growth	no growth	no growth	no growth
P. aeruginosa ATCC 27853	growth	growth	growth	growth	growth	growth	growth	no growth
P. aeruginosa	growth	growth	growth	growth	growth	growth	growth	no growth
Candida albicans	no growth	no growth	no growth	no growth	no growth	no growth	no growth	no growth
Candida parapsilosis	no growth	no growth	no growth	no growth	no growth	no growth	no growth	no growth
Candida tropicalis	no growth	no growth	no growth	no growth	no growth	no growth	no growth	no growth
Candida glabrata	no growth	no growth	no growth	no growth	no growth	no growth	no growth	no growth
Candida crusei	no growth	no growth	no growth	no growth	no growth	no growth	no growth	no growth

sure to the analysed combined preparation components. In comparison, the lack of application of these substances extended the spontaneous repair time of the corneal epithelial cell layer twice.

The results of the *in vitro* observations presented above unequivocally demonstrate the high antiseptic efficacy of hexamidine diisethionate. In an era of overuse of antibiotic preparations, the application of effective disinfectants with such a high safety profile seems to be the optimal solution. This applies especially to the most frequent ophthalmological procedures, which include intravitreal injections. Intraocular inflammation (endophthalmitis) remains the most serious complication of the procedure, the occurrence of which requires hospitalisation, intensive topical and general antibiotic therapy and, very often, vitrectomy. The prognosis for visual acuity enhancement is poor. Pathogens most commonly causing endophthalmitis include *Staphylococcus spp., Streptococcus spp., Corynebacterium spp., Propionibacterium, Haemophilus* and *Neisseria*. Current standards for intravitreal injections do not recommend the use of antibiotic drops as prophylaxis for intraocular inflammation. Indeed, the available data even indicated a higher risk of endophthalmitis in these patients due to the achieved sterilisation of the natural bacterial flora of the conjunctival sac, which favoured the growth of the bacterial strains most frequently causing intraocular inflammation [19]. The full antiseptic effect is to be achieved by the application of a povidone-iodine or chlorhexidine preparation to the conjunctival sac prior to injection of the drug into the vitreous chamber [20]. Until recently, topical antibiotic drop therapy, recommended to be used for several days, has become contraindicated. There are, however, no alternatives to reduce the risk of developing intraocular inflammation in the contemporary standards.

In 2023, a paper was published evaluating the *in vivo* effect of using drops containing 0.05% hexamidine diisethionate or 0.6% iodopovidone for 3 days following intravitreal injections [21]. As part of the research program, a swab was taken on the day of the injection and after 3 days of topical use of disinfectant drops. Not only the antiseptic effectiveness of the preparations used but also their tolerance in patients was assessed. The disinfecting effect of both preparations was shown to be similar, with a particular focus on the bacterium most frequently causing intraocular inflammation, i.e. *Staphylococcus epidermidis*. It is worth noting, however, that hexamidine diisethionate is much better tolerated compared to 0.6% iodopovidone eye drops.

CONCLUSION

In conclusion, it should be noted that there is a necessity for the use of effective drops with disinfectant action in intraocular procedures, particularly including intravitreal injections. 5% iodopovidone/0,05% chlorhexidine remains an obligatory preparation administered during the intravitreal injection procedure. The preparation containing hexamidine diisethionate, polyhexanide hydrochloride, disodium edetate and dexpanthenol has a high antiseptic efficacy and a high safety profile. In the era of combating antibiotic resistance, this drug is a good alternative to antibiotic drops in the period after injection. Although intraocular inflammation following the intravitreal therapy remains a rare complication, it often has a dramatic course ending in permanent vision loss. The use of 0.05% hexamidine diisethionate after intravitreal injection offers a chance to reduce the risk of such complications while fully maintaining the patient's comfort.

CORRESPONDENCE
Joanna Adamiec-Mroczek, MD, PhD
Clinic of Ophthalmology,
University Clinical Hospital in Wroclaw
50-556 Wrocław, ul. Borowska 213
e-mail: joanna.adamiec-mroczek@umw.edu.pl

ORCID
Joanna Adamiec-Mroczek – ID – http://orcid.org/0000-0002-6804-358
Marta Misiuk-Hojło – ID – http://orcid.org/0000-0002-4020-3203

References

1. Asbell PA, DeCory HH. Antibiotic resistance among bacterial conjunctival pathogens collected in the Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) surveillance study. PloS One. 2018; 13(10): e0205814. https://doi.org/10.1371/journal.pone.0205814.
2. Ciulla TA, Starr MB, Masket S. Bacterial endophthalmitis prophylaxis for cataract surgery: an evidence-based update. Ophthalmology. 2002; 109: 13-24.
3. Pinna A, Usai D, Sechi LA et al. Detection of virulence factors in Pseudomonas aeruginosa strains isolated from contact lens-associated corneal ulcers. Cornea. 2008; 27: 320-6.
4. Sengupta J, Khetan A, Saha S et al. Candida keratitis: emerging problem in India. Cornea. 2012; 31: 371-5.
5. Kreslov MS, Castellarin AA, Zarbin MA. Endophthalmitis. Surv Ophthalmol. 1998; 43: 193-224.
6. American Academy of Ophthalmology. Bacterial keratitis preferred practice patterns. https://www.aao.org/preferredpractice-pattern/bacterial-keratitis-ppp-2018.
7. Leaming DV. American Society of Cataract and Refractive Surgery: practice styles and preferences of ASCRS members: 2000 survey. J Cataract Refract Surg. 2001; 27: 948-955.
8. Kim SJ, Toma HS. Antimicrobial resistance and ophthalmic antibiotics: 1-year results of a longitudinal controlled study of patients undergoing intravitreal injections. Arch Ophthalmol. 2011; 129: 1180-8.
9. Yin VT, Weisbrod DJ, Eng KT et al. Antibiotic resistance of ocular surface flora with repeated use of a topical antibiotic after intravitreal injection. JAMA Ophthalmol. 2013; 131: 456-61.
10. Phan ADT. Intravitreal Injection Procedure. https://www.aao.org/education/basic-skills/intravitreal-injection-procedure.
11. Uhr JH, Xu D, Rahimy E et al. Current Practice Preferences and Safety Protocols for Intravitreal Injection of Anti-Vascular Endothelial Growth Factor Agents. Ophthalmol Retina. 2019; 3(8): 649-55. https://doi.org/10.1016/j.oret.2019.03.013.
12. 2018 Update on Intravitreal Injections: Euretina Expert Consensus Recommendations.
13. van Ketel WG. Allergic contact eczema by Hexomedine®. Contact Dermatitis. 1975; 1(5): 332.
14. Granel F, Lozniewski A, Barbaud A et al. Cutaneous infection caused by Tsukamurella paurometabolum. Clin Inf Dis. 1996; 23(4): 839-40.
15. Grare M, Dibama HM, Lafosse S et al. Cationic compounds with activity against multidrug-resistant bacteria: interest of a new compound compared with two older antiseptics, hexamidine and chlorhexidine. Clin Microbiol Inf. 2010; 16(5): 432-8.
16. Pinna A, Donadu MG, Usai D et al. In Vitro Antimicrobial Activity of a New Ophthalmic Solution Containing Hexamidine Diisethionate 0.05% (Keratosept). Cornea. 2020; 39(11): 1415-8. https://doi.org/10.1097/ICO.0000000000002375.
17. Pinna A, Donadu MG, Usai D et al. In vitro antimicrobial activity of a new ophthalmic solution containing povidone-iodine 0.6% (IODIM). Acta Ophthalmol. 2020; 98: e178-80.
18. Mencucci R, Favuzza E, Bottino P et al. A new ophthalmic formulation containing antiseptics and dexpanthenol: In vitro antimicrobial activity and effects on corneal and conjunctival epithelial cells. Exp Eye Res. 2020; 201: 108269. https://doi.org/10.1016/j.exer.2020.108269.
19. Hunyor AP, Merani R, Darbar A et al. Topical antibiotics and intravitreal injections. Acta Ophthalmol. 2018; 96: 435-41.
20. Grzybowski A, Told R, Sacu S et al.; Euretina Board. 2018 Update on Intravitreal Injections: Euretina Expert Consensus Recommendations. Ophthalmologica. 2018; 239(4): 181-93. https://doi.org/10.1159/000486145.
21. Avogaro F, Florido A, Calandri A et al. Intravitreal injections primary prevention: a case-control study. Eur Rev Med Pharmacol Sci. 2023; 27(8): 3664-9. https://doi.org/10.26355/eurrev_202304_32153.

Authors' contributions:
Joanna Adamiec-Mroczek: preparation of publications; Marta Misiuk-Hojło: content-related support.

Conflict of interest:
None.

Financial support:
None.

Ethics:
The content presented in the article complies with the principles of the Helsinki Declaration, EU directives and harmonized requirements for biomedical journals.