ARTYKUŁ PRZEGLĄDOWY REVIEW ARTICLE
DOI: 10.24292/01.OT.290923

Will antiseptics become the standard in ophthalmology in the future?

Dorota Szumny[1,2]

[1] Department of Pharmacology, Wroclaw Medical University
Head: Prof. Adam Szeląg, MD, PhD

[2] Department of Ophthalmology, Mikulicz-Radecki University Clinical Hospital in Wrocław
Head: Prof. Marta Misiuk-Hojło, MD, PhD

HIGHLIGHTS

Thanks to efficiency, low number of side effects and low price antiseptics have has a strong and unthreatened position in medicine, including ophthalmology, for many years.

ABSTRACT

Antiseptics are a group of substances widely used in ophthalmology for many years. They are well established, especially in the prevention of perioperative infections. For decontamination in ophthalmology, a 5% povidone-iodine solution is used as a standard for the conjunctival sac. It is considered the most effective preoperative antisepsis. In patients with an allergy to iodine, a solution of 0.05% chlorhexidine is recommended. There are also attempts to use other antiseptics and antibiotics for perioperative prophylaxis. Recently, there has also been interest in potential use antiseptics for the treatment of conjunctivitis.

Key words: antiseptics, povidone-iodine, chlorhexidine, antibiotics

INTRODUCTION

Antiseptics are substances that have been known and used in medicine for a long time. Antiseptics, from Greek: anti, sepsis, means a disinfecting procedure aimed at destroying microorganisms on the skin, mucous membranes, and wounds. Unlike disinfection, it does not refer to the decontamination of surfaces or objects [1, 2].

In Poland, antiseptics are defined by the Office of Registration of Medicinal Products, Medical Devices, and Biocidal Products as agents that destroy microorganisms applied topically to the skin or mucous membranes [3].

Antiseptics, since the beginning of their introduction into medicine, have been the standard for use in the operating room setting, including in ophthalmology. This does not preclude attempts to expand the indications for their use in the treatment of certain conditions or to replace them with other substances that destroy microorganisms, such as antibiotics.

HISTORY OF ANTISEPTICS

The term *antiseptica* was used in a scientific and practical context for the first time by surgeon John Pringle in 1750 for treatments and substances that prevent wounds from rotting. Pringle developed the army's sanitary regulations, and called for soldiers to follow hygienic rules [4].

The history of antisepsis begins in the mid-19th century. The first promoter of antisepsis was Hungarian obstetrician Ignaz Semmelweis, who in 1847 introduced hand sanitising with a chlorine solution in maternity clinics. In a short time, this succeeded in halving the mortality rate among women in labor [1].

More famous than Semmelweis, the doctor who popularized the use of antiseptics, dubbed the "father of antiseptics," was British surgeon Joseph Lister. He recommended the use of carbolic acid (i.e. phenol) during surgical procedures (1867). This is estimated to have reduced the mortality rate of hernia surgery from 78% to 10% [1].

In Poland, antiseptic was introduced by Jan Mikulicz-Radecki, who used iodoform from 1880. This antiseptic was in use until the middle of the 20th century and, despite its high effectiveness, was withdrawn due to its toxicity and potential to cause allergies [1].

It is worth noting that the period of the mid-19th century, when the use of disinfectants began, was a time when antibiotics were not yet known, which were discovered only in 1928 by Alexander Fleming, so the use of antiseptics greatly contributed to reducing mortality and perioperative complications [5].

THE PERFECT DISINFECTANT

An most desired disinfectant should have a broad antimicrobial spectrum, exhibit rapid action even in the presence of organic matter and be non-toxic to the patient. Commonly used antiseptics that act on Gram-negative and Gram-positive bacteria are: compounds with a biguanide system (chlorhexidine, picloxidine, polyhexanide), halides (chlorine compounds such as sodium hypochlorite, iodo-derivatives of polypyrrolidone, e.g. povidone-iodine), alcohols (ethanol), chlorophenol compounds (triclosan) and others (hydrogen peroxide, propamidine, octenidine hydrochloride, or silver compounds).

These agents are selected according to the type of surface to be disinfected, such as skin, mucous membranes, surgical field, and determine the appropriate concentration that will destroy microorganisms and at the same time not damage their own tissues.

Many antiseptics are not suitable for use in ophthalmology due to their toxicity to the corneal epithelium. Disinfectants containing alcohol cannot be used on the surface of the eye.

SURFACE AREA OF THE VISUAL ORGAN

The surface of the organ of vision and the eye's appendages are constantly in contact with various undesirable external factors that can potentially pose a threat. With a large part of them, the tissues of the eye and its surroundings can cope perfectly well, thanks to the body's defence and repair mechanisms and the preservation of tissue continuity.

The surface of the eye of healthy individuals is colonized by aerobic and anaerobic bacteria, which form the normal bacterial flora of the conjunctiva. The conjunctiva has multiple defense mechanisms that work in synergy to prevent and limit infection. The normal conjunctival flora includes aerobic and anaerobic bacteria that maintain surface homeostasis and immunoregulation. The most common bacterium cultured from the ocular surface is *Staphylococcus epidermidis*, but *Corynebacterium, Propionibacterium,* and *Klebsiella* species are also present. The conjunctival flora in children contains fewer bacterial species and tends to have more *Streptococcus species* [6].

The most commonly isolated bacterial species in postoperative endophthalmitis are Gram-positive bacteria (*Staphylococcus epidermidis* 33–77%, *Streptococcus viridans, Staphylococcus aureus* 10 –21%). Genetic studies have shown that in endophthalmitis caused by *Staphylococcus epidermidis*, the pathogen originates from the patient's own ocular flora and enters the eye by direct inoculation during surgery.

Fungal colonization of the ocular surface is less common, with an incidence of up to 8%. Most fungal inflammation of the interior of the eyeball after cataract extraction is caused by filamentous fungi (*Aspergillus species*).

ANTISEPTICS IN OPHTHALMIC SURGERY

The use of antiseptics has been an important part of perioperative prophylaxis since their introduction. In ophthalmology, postoperative intraocular inflammation, endophthalmitis, remains a serious complication of intraocular procedures. Preoperative prophylaxis reduces the morbidity associated with this disease and is the standard of care before ophthalmic procedures.

Since periocular skin and eyelashes are a possible source of endophthalmitis formation, a careful preoperative clinical evaluation of the patient is necessary, as it is the primary preventive measure. Anterior segment inflammation should be treated before performing intraocular surgery. A thorough ophthalmologic examination can reveal signs of periorbital skin disease, staphylococcal or seborrheic conjunctivitis, conjunctival congestion, chalazion, a history of long-term corticosteroids and other local infections. When performing surgical draping, an important action is to completely cover the eyelashes to minimize contamination of the wound with eyelid flora.

Complete sterilization of the ocular surface prior to intraocular surgery should not be expected, as no antiseptic regimen has been found that consistently decontaminates the ocular surface throughout the perioperative period.

There are several pharmacological methods to reduce the incidence of preoperative infections. The most commonly used antiseptic in ophthalmology is povidone-iodine (PVI). A 5% solution of PVI for the conjunctival sac is used as standard. PVI is considered the most effective method of preoperative antisepsis. Its use is rarely associated with complications, such as postoperative eye pain, persistent corneal epithelial defects and the accompanying risk of keratitis. True allergy to iodine is rare, in most cases due to direct toxicity, especially with repeated procedures. Inadequate preoperative antisepsis in patients with self-declared iodine allergy has led to a high incidence of endophthalmitis [7, 8]. In the ophthalmic setting, PVI is used in various concentrations (0.01–10%) and durations (30 s–3 min) [9].

An aqueous solution of 0.05% chlorhexidine is recommended for patients with iodine allergy. In a 2021 publication, the authors evaluated various antiseptics that could potentially be used instead of PVI. They found no evidence in the available publications to suggest that switching from PVI to other antiseptics was beneficial. In cases of poor tolerance of PVI, it is recommended to use a lower concentration (if considered toxic) or to use chlorhexidine 0.05% or 0.1% (if allergy is suspected). The optimal concentration and dosage regimen for chlorhexidine has not yet been determined. The researchers believe that disinfecting solutions other than PVI or chlorhexidine will require further study to demonstrate their potential usefulness in eye surgery [10].

Incompetent use of antiseptics also carries certain risks. Higher concentrations of antiseptics show toxicity to the corneal epithelium. Edema of the corneal epithelium and stroma, bullous keratopathy, corneal discoloration, and irritation of the eyeball after improperly administered disinfectants have been described. In clinical practice, PVI solutions have been widely used for several decades with adequate tolerance and safety. At low concentrations, PVI is tolerated by most patients, even without anesthesia. In addition, PVI is highly effective in reducing the bacterial load in a very short time. True allergies to antiseptics are extremely rare. The clinical feature of ophthalmic exposure to an antiseptic as an allergen is the immediate (not delayed) onset of symptoms and localized (not systemic) reactions. The incidence of anaphylaxis to chlorhexidine is low, given that general surgery patients are commonly exposed to it, as chlorhexidine is the skin antiseptic of choice in general surgery [11].

Among the antiseptic substances in ophthalmology, propamidine is used in addition to PVI and chlorhexidine [12]. The use of propamidine as a disinfectant is mainly associated with *Entamoeba histolytica* infection. However, in in vitro tests, chlorhexidine eye drops were found to be less cytotoxic than propamidine [13].

Most debatable is the use of antibiotics as a prophylactic before surgery. There are papers that describe both the advantages and disadvantages of this option. PVI can be supplemented with topical antibiotics, although no studies have shown their actual effectiveness in reducing the risk of endophthalmitis when administered before surgery [11]. Endophtalmitis prophylaxis also includes intraoperative intraventricular administration of cefuroxime. A multicenter randomised controlled trial of the European Society of Cataract and Refractive Surgeons (ESCRS) in 2007 involving 16,211 patients that examined prophylactic measures for endophthalmitis after cataract surgery (cefuroxime intraoperatively versus fluoroquinolones perioperatively) found that cefuroxime significantly reduced the risk of developing endophthalmitis after cataract surgery [14].

The use of antibiotics can have a general detrimental effect on the homeostasis and ocular surface, as well as increase methicillin resistant *Staphylococcus aureus* (MRSA) bacterial resistance to fluoroquinolones. The use of antibiotic prophylaxis should not replace thorough preparation of the operating room and sterile techniques because, unless strict antisepsis is maintained, the risk of endophthalmitis will always be high, regardless of the type of prophylaxis used. While preoperative antisepsis with PVI or chlorhexidine is mandatory to reduce the bacterial load on the conjunctiva, the value of preoperative topical antibiotic therapy is uncertain [11].

ANTISEPTICS IN THE TREATMENT OF ANTERIOR OCULAR SURFACE INFECTIONS

Recently, there has also been interest in ophthalmology in the use of disinfectants for common inflammatory conditions of the ocular surface treated on an outpatient basis. To reduce the frequency of topical antibiotic use and the rate at which bacterial antibiotic resistance develops, comparative studies of the efficacy of disinfectants and antibiotics are being conducted.

An example is the use of an experimental model of bacterial conjunctivitis in vivo, in which PVI, bibrocatol, ethacridine and bacitracin + polymyxin B + neomycin were administered. The differences between the effects of the substances were not significant. It was observed that antiseptics are superior to antibiotics in achieving regression of congestion and elimination of germs [15].

An in vitro study in human corneal and conjunctival cells tested a disinfectant solution: hexamidine, which could be used to treat conjunctival infections. In the tests carried out, it showed antibacterial activity against *Staphylococcus aureus*, MRSA, *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Streptococcus mitis* [16].

PVI in a 1.25% solution was compared with neomycin, polymyxin B and gramicidin in the treatment of infectious conjunctivitis in a Philippine study of 459 young patients aged from 7 months to 21 years. It was observed that the younger the patient, the faster the conjunctivitis resolved. No statistically significant differences were observed between the different ophthalmic solutions for the four groups of test substances. This suggests that PVI is as effective as neomycin, polymyxin B and gramicidin in treating bacterial conjunctivitis [17].

It should be noted that in the treatment of common conjunctival and corneal infections, the use of eye drops containing disinfectants is not often used. Few published works on this subject have been published. In such situations, targeted drugs tailored to the etiology of the existing inflammatory process are most often chosen: antibacterial, antiviral, antifungal drugs [12].

CONCLUSIONS

Antiseptics are a group of substances widely used in ophthalmology for many years. They are well established, especially in the prevention of perioperative infections. Like any drug, they can act on tissues, damaging them. They also cannot fight all microbial infections. However, their efficacy, low number of side effects and their low price make this group, despite the passage of years, of great importance in medicine and ophthalmology all the time. It is the standard now and, according to available knowledge, will continue to be so in the future.

CORRESPONDENCE
Dorota Szumny, MD, PhD
Department of Pharmacology, Wroclaw Medical University
50-345 Wrocław, ul. Mikulicza-Radeckiego 2
e-mail: dorota.szumny@umw.edu.pl

ORCID
Dorota Szumny – ID – http://orcid.org/0000-0002-7814-3517

References

1. Wikipedia. Antyseptyka. Online: https://pl.wikipedia.org/wiki/Antyseptyka.
2. Parikh SR, Parikh RS. Chemical disinfectants in ophthalmic practice. Indian J Ophthalmol. 2021; 69(3): 510-6.
3. Biuletyn Informacji Publicznej. Wykaz produktów biobójczych. Online: https://bip.urpl.gov.pl/pl/biuletyny-i-wykazy/produkty-biob%C3%B3jcze.
4. Różański H. Środki antyseptyczne i odkażające stosowane w medycynie. Środki antyseptyczne stosowane w leczeniu i w profilaktyce chorób skórnych oraz błon śluzowych. Środki antyseptyczne dawne i współczesne. Dzieje antyseptyki. Przegląd literatury i badania własne. Online: https://pwsz.ch/wp-content/uploads/2020/03/antisepticum.pdf.
5. Alharbi SA, Wainwright M, Alahmadi TA et al. What if Fleming had not discovered penicillin? Saudi J Biol Sci. 2014; 21(4): 289-93.
6. Azari AA, Barney NP. Conjunctivitis: a systematic review of diagnosis and treatment. JAMA. 2013; 310(16): 1721-9.

7. Grzybowski A, Kanclerz P, Myers WG. The use of povidone-iodine in ophthalmology. Curr Opin Ophthalmol. 2018; 29(1): 19-32.
8. Grzybowski A, Turczynowska M. More Antisepsis, Less Antibiotics Whenever Possible. Asia Pac J Ophthalmol (Phila). 2018; 7(2): 72-5.
9. Liu JY, Chu HS, Wei YH et al. Review, analysis, and education of antiseptic related ocular injury in the surgical settings. Ocul Surf. 2021; 22: 60-71.
10. Kanclerz P, Myers WG. Potential substitutes for povidone-iodine in ocular surgery. Eye. 2021; 35(10): 2657-9.
11. Zaharia AC, Dumitrescu OM, Rogoz RE et al. Preoperative antisepsis in ophthalmic surgery (a review). Rom J Ophthalmol. 2021; 65(2): 120-4.
12. Smit D. Anti-infective ophthalmic preparations in general practice. S Afr Fam Pract. 2012; 54(4): 302-7.
13. Fernández-Ferreiro A, Santiago-Varela M, Gil-Martínez M et al. In Vitro Evaluation of the Ophthalmic Toxicity Profile of Chlorhexidine and Propamidine Isethionate Eye Drops. J Ocul Pharmacol Ther. 2017; 33(3): 202-9.
14. Barry P, Seal DV, Gettinby G et al. ESCRS study of prophylaxis of postoperative endophthalmitis after cataract surgery: Preliminary report of principal results from a European multicenter study. J Cataract Refract Surg. 2006; 32(3): 407-10.
15. Behrens-Baumann W, Begall T. Antiseptics versus antibiotics in the treatment of the experimental conjunctivitis caused by Staphylococcus aureus. Ger J Ophthalmol. 1993; 2(6): 409-11.
16. 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.
17. Abelson MB. Get to Know Your Antiseptic Options. Review of Ophthalmology. 2008; 16 December. Online: https://www.reviewofophthalmology.com/article/get-to-know-your-antiseptic-options.

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.