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Can Topical Magistral Antibiotics Drops be Applied When Resistant Agents Grow in Eye and Ear Infections?

Göz ve Kulak Enfeksiyonlarında Dirençli Etken Ürediğinde, Topikal Majistral Antibiyotikli Damla Uygulanabilir mi?

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Question: *Can topical magistral antibiotic drops be applied when resistant agents grow in eye and ear infections?* **Öykü Şen, MD.**

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Introduction and general information: Some eye (such as keratitis, conjunctivitis, dacryocystitis) and ear infections (such as chronic suppurative otitis, tympanostomy tube otorrhea, external auditory canal infections) infections may be treated with topical antibiotic drops (and/or topical pomade). Commercial antibiotic drops (tobramycin, gentamicin, netilmicin) are usually at a concentration of 0.3% (3 mg/mL). These concentrations may be insufficient to limit the infection in some infections such as resistant keratitis (1). Likewise, the agents grown in some localized superficial eye and local suppurative ear infections may be resistant to readily available commercial drops. Such cases may be encountered in eye and ear infections in newborn infants and children, sometimes in superficial skin infections or in infected closed cavity irrigation and supportive therapies. Sometimes multi-resistant pathogens may respond inadequately to systemic therapy. The most common pathogens include gram-positive cocci (including MRSA), gram-negative cocci, gram-negative bacteria (such as *pseudomonas*, *klebsiella*), non-tuberculous mycobacteria, fungal agents and sometimes amoeba. In this case, topical treatment appropriate to the pathogen and antimicrobial susceptibility (e.g. vancomycin, linezolid, colistin, imipenem-cilastatin, amphotericin B, voriconazole, trimethoprim/sulfamethoxazole) may be required. Or topical treatment with a higher concentration (e.g. 14 mg/mL for gentamicin, 1.4% concentration) than the standard commercially available antibiotic drops (e.g. gentamicin 3 mg/mL, 0.3% concentration) may be required.

Magistral eye drops prepared at higher concentrations than routinely recommended and commercially available ready-to-use eye drops are called fortified eye drops (1,2). Even if these types of prepared drops are not routine, they may be a alternative treatment in some patient groups. They may have disadvantages such as their relatively high cost, risk of contamination, shorter shelf life because they do not contain preservatives, and the need for cold storage (such as +4°C) (1). In addition, prolonged or frequent use may delay healing or have toxic effects on corneal epithelial

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cells (3,4). However, in some cases, magistral fortified eye drops are considered as the standard treatment for severe bacterial keratitis (4,5). Some considerations should be taken into account when preparing major eye and ear drops. The content of the selected magistral drops should be planned according to the target pathogen and antibiotic sensitivity. They should be prepared by the pharmacist or physician under sterile conditions, the date of preparation should be indicated and stored at +4°C. It should be shaken before use to ensure homogeneity (1,2,6). Magistral drops can be prepared using liquid or lyophilized forms of commercially available parenteral antibiotic/antifungal drugs. Sterile artificial tears (such as vancomycin, cefazolin ceftriaxone, ceftazidime, amikacin in eye drops), or sterile water for injection (such as colistin, imipenem-cilastatin, amphotericin B, voriconazole), or saline (such as vancomycin) can be used as the carrier liquid. In some cases, commercial antibiotics ready for direct parenteral use (such as linezolid 2 mg/mL, trimethoprim/sulfamethoxazole 16/80 mg/mL, amikacin 40 mg/mL) can be given directly into a dropper bottle. In addition, commercially available antibiotics containing gentamicin or tobramycin at a concentration of 0.3% can be fortified in the existing bottle, adding the parenteral antibiotic form by targeting a higher antibiotic concentration (fortified; for example, 1.4% concentration) (1,2,7,8). It has been reported that the risk of contamination in preservative-free topical magistral eye drops is very low for up to four weeks when stored at +4°C (6). It was found that some fortified eye drops prepared with artificial tears (vancomycin 50 mg/mL, cefazolin 100 mg/mL, ceftriaxone 133 mg/mL) had no decrease in efficacy for 20

Table 1. Ingredients of some medicinal drops (1,2,7-10)*

Active substance	Concentration**	Reconstitution liquid
Tobramycin	1.4% (14 mg/mL)	• Sterile tears • Can be added to a 0.3% commercial bottle
Gentamicin	1.4% (14 mg/mL)	• Sterile tears • Can be added to a 0.3% commercial bottle
Amikacin	4% (40 mg/mL)	• Sterile tears, • Sterile water for injection*** • Parenteral form available (can be reconstituted with sterile water for injection)
Cefazolin	5-10% (50-100 mg/mL)	• Sterile tears • Sterile water for injection
Ceftazidime	5% (50 mg/mL)	• Sterile water for injection
Ceftriaxone	5-10% (50-100 mg/mL)	• Sterile tears • Sterile water for injection
Imipenem cilastatin	1% (10 mg/mL)	• Sterile water for injection
Vancomycin	2.5-5% (25-50 mg/mL)	• Sterile tears • Sterile water for injection
Linezolid	0.2% (2 mg/mL)	• Direct parenteral linezolid solution can be used
Colistin	0.19% (1.9 mg/mL) As colistimethate sodium; 1 million units= 75 mg	• Sterile water for injection
TMP/SMX	1.6/8% (16/80 mg/mL)	• Direct parenteral TMP/SMX solution can be used
Clindamycin	5% (50 mg/mL)	• Can be prepared using parenteral solution
Amphotericin-B	0.15% (eye)-0.25% (ear) (1.5-2.5 mg/mL)	• Sterile tears • Sterile water for injection
Voriconazole	1% (10 mg/mL)	• Sterile water for injection

*: The short product information (SmPC) of the medicinal products licensed in Türkiye was also used in the preparation of the table.
**: By paying attention to the dilution ratios at the appropriate concentration, it will be appropriate to prepare in a total of 10 ml dropper bottle, preferably dark colored and/or low light transmittance, and store at +4°C. The bottle should be shaken before each use.
***: Sterile water for injection or sterile distilled water.

days when stored at room temperature or +4°C. However, drops containing amikacin (20 mg/mL) showed a decrease in efficacy after >15 days at room temperature or +4°C. The authors concluded that in terms of antimicrobial efficacy, topical magistral fortified eye drops can be used at room temperature or +4°C for 7-14 days without any decrease in efficacy (7).

Fortified eye drops can be given as often as needed (such as 2-12 times a day) according to the advice of the monitoring physician. In some cases, they may be instilled every two hours. If necessary, they may be given in hourly alternations (e.g. vancomycin every hour and tobramycin every other hour). After clinical response, the frequency of administration can be gradually reduced according to the physician's recommendation. After complete clinical improvement is achieved, it is discontinued, especially to avoid increasing the risk of corneal toxic effects and delaying epithelial healing (4,5,9). In drops containing aminoglycosides, dose intervals may be given less frequently due to post-antibiotic effect and pharmacodynamic/pharmacokinetic properties. For example, 1-2 drops in the eye can be given 2-6 times a day, more frequently if necessary. In the ear, 2-3 drops 3-4 times a day, more frequently if necessary (4,9-11).

In chronic suppurative otitis or purulent discharges associated with tympanostomy tube, vancomycin-containing magistral drops (25 mg/mL) can be administered after ear hygiene as three drops administered after ear hygiene as three times a day for up to two weeks (9,10). In fungal otitis externa, amphotericin B containing magistral drops (0.25%, 2.5 mg/mL) were given as 1-2 drops three times a day for seven days (10). According to the susceptibility of the growing agent and the type of the microorganism, it will be useful to choose magistral drops by considering the pharmacodynamic/pharmacokinetic properties. In addition, cleaning the secretions (in the eye or ear) before drop treatment for homogeneous distribution will increase the effectiveness of the treatment. Combined magistral drops may be given according to the causative agent and the nature of the infection, but they should be given separately without mixing them together. For example, mixtures of vancomycin and beta-lactam antibiotic solutions (e.g. ceftazidime) are not physically stable and may cause precipitation. Therefore, they should not be given simultaneously, and a reasonable time should be allowed between them (8).

The concentrations and liquid contents of the magistral eye/ear drops that can be prepared are given in the table (1,2,7-10).

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