The Use of Topical Treatment and Middle–Inner Ear Interaction

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Introduction

The use of otologic drops as topical treatment for external otitis, for some forms of otitis media, in otologic surgery and for mastoid cavities is well established. Potential ototoxicity involves the concept that under specific circumstances, some of the components of these preparations (ototoxic components) can reach the inner ear and cause sensory damage.

Until 1995 [1], there were at least nine reports totaling 165 documented patients who developed sensorineural hearing loss owing to the use of ear drops for otitis media. In a survey composed of 2235 otolaryngologists, 3.4% reported having seen cochlear damage owing to otologic drops [2, 3]. If each of these otolaryngologists would have seen at least one case, this would represent 76 additional cases. Moreover, if 3.4% of otolaryngologists worldwide (ear drops are used universally) would see, at the very least, one case (a very conservative estimate), ototoxicity to otologic drops would constitute a significant problem. To our knowledge, no new reviews documenting groups of publications describing patients who developed sensorineural hearing loss owing to the use of ear drops have been available. However, isolated case reports keep appearing in the literature. Moreover, in our daily otologic practice, we occasionally receive patients who are referred because they developed sensorineural hearing loss after using ear drops with ototoxic components. In brief, ototoxicity due to components of ear drops is a reality to be addressed and with awareness it can be significantly diminished. Therefore, to avoid this complication while benefiting from the use of these preparations, it is important to review the potential routes of passage of these components to the inner ear, the pathogenesis of these events, and the experimental and clinical evidence available. With this information in hand, safer means of using drops can be developed.

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Potential Routes from Middle to Inner Ear

Potential routes include round and oval windows, bony fistulae, micro-fissures, and blood and/or lymph vessels. Bony fistulae, micro-fissures, and the oval window do not seem to play a significant role, and lymphatics which are abundant in the round window membrane seem to participate in a peripheral rather than in a central direction. This is because the inner ear is of neurectodermal origin; therefore, it should not have lymphatics [3]. Blood vessels are an important route to consider because of the abundant vascular connections between the middle and inner ear in the round window [3–5].

The predominant pathway—and the most evaluated—seems to be the round window membrane. This membrane is the only soft tissue barrier between the middle and the inner ear. It is located inferiorly in the medial wall of the middle ear and lies in a niche, being therefore susceptible to exposure to fluids in the middle ear cavity.

Ultrastructural studies of the round window membrane of humans, monkeys, felines, and rodents have disclosed three basic layers: an outer epithelium, a middle core of connective tissue, and an inner ear epithelium. Despite being formed by three layers, experimental evidence has suggested that it behaves like a semipermeable membrane. Such evidence suggests that the layers of the round window participate in resorption and secretion of substances to and from the inner ear. Different substances, including antibiotics and tracers, when placed in the middle ear, traverse the membrane. Permeability is selective. Factors affecting permeability include size, concentration, electrical charge, thickness of the membrane, and facilitating agents [6, 7].

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Available evidence of ototoxicity and/or passage of the components of commonly used ear drops that can be detected directly or indirectly in the inner ear after placing them in experimental animals in the round window niche are described in Table 31.1. Those detected when placed in the middle ear of humans are described in Table 31.2.

Table 31.1 Components of commonly used ear drops that can be detected directly or indirectly in the inner ear after placing them in experimental animals in the round window niche

Antibiotics
Chloramphenicol
Gentamicin
Neomycin
Polymyxin B
Antiseptics
Acetic acid
Ethanol
Local anesthetics
Lidocaine
Solvents
Propylene glycol
Corticosteroids (beneficial)
Hydrocortisone
Betamethasone

Table 31.2 Components of commonly used ear drops that can be detected directly or indirectly in the inner ear after placing them in the middle ear of humans

Antibiotics
Chloramphenicol
Gentamicin
Neomycin
Polymyxin B
Local anesthetics
Lidocaine
Corticosteroids (beneficial)
Dexamethasone

Inner Ear Effects of Ear Drop Components

Chloramphenicol, neomycin, polymyxin B, and gentamicin have been shown to cause hair cell damage [3, 8, 9]. Propylen gycol is ototoxic and in addition causes inflammatory reactions in the middle ear mucosa[10]. On the other hand, ciprofloxacin [11], dexamethasone, and methyl prednisolone [12, 13] traverse the round window membrane and are safe to use.

Permeability of the Round Window Membrane in Otitis Media

The question that comes up is what happens to the permeability of otologic drop components in middle ears with otitis media. The round window membrane in otitis media undergoes the same histopathologic changes that the mucoperiosteum of the middle ear does (it is part of it). These changes suggest that in early stages (the first 3–5 days of active inflammation), there may be an increase in permeability but that, as the inflammatory process develops (1 week of inflammation and thereafter), the membrane becomes thicker and develops protective mechanisms in terms of decreased permeability. As the active inflammatory process decreases (and the membrane regains its normality), so does the thickness and the protective mechanisms of the membrane decrease. Experimental evidence in cats, chinchillas, and guinea pigs using tracers and neomycin has confirmed this suggestion [6, 8].

There is an apparent discrepancy between experimental studies and clinical impressions in terms of ototoxicity of ear drops. As mentioned, animal studies have shown that during an established active inflammatory process (draining ears), round window membrane permeability drastically decreases

owing to an increase in the thickness of the membrane to defensive mechanisms in the membrane [14] and dilution effects by the middle effusion. In my opinion, this is what happens in clinical cases because the physician uses otologic drops once the inflammatory process is already established. Therefore, in light of the available experimental evidence, it comes as no surprise that in these cases, ototoxic drugs traverse the membrane less readily and are less likely to cause inner ear damage, leading to an "apparent discrepancy." However, once the active inflammatory process decreases or subsides, the defensive mechanisms decrease, and the membrane becomes more permeable. Moreover, if one reviews the documented cases of patients who have developed sensorineural hearing loss owing to the use of otologic drops for otitis media [1], these tend to coincide with this explanation. Most of the reported cases are related to prolonged use of drops and/or in patients who continued their use once the drainage had subsided. That is to say, ototoxicity occurred once the active inflammatory process had subsided, the defensive mechanisms had decreased, and the membrane had become more permeable.

Although the subject of discussion of this chapter is ototoxicity, there are two aspects to be mentioned as complications in the use of ear drops. The relatively high incidence of allergic reactions to the neomycin contained in ototopical drops, and the significant vertigo that develops when drops containing lidocaine enter the middle ear cavity.

Which Drops Are Safe to Use?

Based on the available evidence, our indications and rationale for the use of otologic drops are as follows:

In chronic otitis media (chronic draining ears), topical treatment is our main modality. In our Clinical Department, we consider it safe to use quinolones as a first line of treatment, based on their safety profile. It is also possible that shorter courses of other drops could be safe and reasonable, should quinolones be either unavailable or contraindicated (e.g., allergy) or that the bacteria are resistant to them, assuming that the round window membrane has an established inflammatory process, and its permeability is drastically reduced.

In recently draining ears, we consider it safe to use quinolones and, if needed, other types of otologic drops while drainage persists, assuming that the round window membrane has an inflammatory process and that patients are closely monitored, and as soon as the drainage decreases, if needed, we switch to quinolone drops (e.g., ciprofloxacin), assuming that the membrane becomes more permeable.

In ears without drainage (e.g., placement of ventilation tubes in patients with "cloudy" effusion), we use only quinolone drops.

Future Trends

In terms of future trends or alternatives, some of our experimental approaches include the following:

Developing slow-release biodegradable membranes that could release substances over time in the middle ear [15], because otologic drops achieve adequate local levels but only for very short periods of time. Another experimental approach that has been described is the use of a sustained-release ciprofloxacin hydrogel that could be used as a single administration [16].

Developing spheres of a size that would not traverse the round window membrane or be absorbed by the middle ear mucosa, to which ototoxic drugs could be attached (provided that they would stay attached and remain effective) [3].

Developing means of defining the stage of reactivity of the middle ear mucosa and of permeability of the round window to use ototoxic drugs safely. The stage of reactivity should eventually be determined by evaluating middle ear effusions, since they are a reflection of the stage of reactivity of the middle ear mucosa [17].

Better defining the "defense" mechanisms of the round window membrane (round window membrane defense system) [3].

Developing research protocols that would evaluate not only passage but also mechanisms, routes, and distribution in the inner ear. This would also allow the eventual development of therapeutic approaches.

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