Ototoxicity of Topical Therapy

A systematic Review

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Abbreviations

ABR	**:**	Auditory brain stem evoked response
AUG	**:**	Augmentin
BERA	**:**	Brainstem evoked response audiometry
CAP	**:**	Compound action potential
CIP	**:**	Ciprofloxacin
CSOM	**:**	Chronic suppurative otitis media
C.T	**:**	Connective tissue
DNA	**:**	Deoxyribonucleic acid
DPOAEs	**:**	Distortion product oto-acoustic emissions
FGD	**:**	Framycetin, gramicidin, dexamethasone
GM	**:**	Gentamicin
GM-S	**:**	Gentamicin steroid combination
HL	**:**	Hearing loss
Hz	**:**	Hertz
IHCs	**:**	Inner hair cells
kHz	**:**	Kilo-Hertz
LD	**:**	Laser Doppler
mg	**:**	Milligram

ml	**:**	Milliliter
mm	**:**	Millimeter
MMC	**:**	mitomycin C
OFLX	**:**	Ofloxacin
OHCs	**:**	Outer hair cells
PETS	**:**	Pressure equalizing tubes
PTA	**:**	Pure tone average
RCTs	**:**	Randomized controlled trials
RW	**:**	Round window
RWM	**:**	Round window membrane
SEM	**:**	Scanning electron microscopy
SNHL	**:**	Sensorineural hearing loss
TM	**:**	Tympanic membrane
TTs	**:**	Tympanostomy tubes
ug	**:**	Microgram
ul	**:**	Microlitre
um	**:**	Micrometer
VS	**:**	Versus

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Introduction

Otic drops commonly are used to treat chronic otitis media when there is a tympanic membrane perforation. Drops also are used for otorrhea when a ventilation tube is in place and for prophylaxis after placement of ventilation tubes. The controversy regarding the use of potentially ototoxic topical agents for treatment and prophylaxis of middle ear disease remains far from resolved for clinicians who manage otologic problems **(Pickett et al, 1997).**

When ototoxicity of antibiotics, solvents, and antiseptics is considered, most, if not all, ototopical medications are potentially harmful if applied to the round window niche. Whereas cochleotoxicity of otic drops can be identified in animal studies, toxicity in humans has been shown infrequently **(Rohn et al, 1993)**.

The actual potential for ototoxicity of these ototopical preparations has been a subject of considerable debate. Since the introduction of non-ototoxic fluoroquinolone ear drops in 1997–1998, recent literature regarding the possible issues of unrecognized ototoxicity from ototopical preparations, and increasing litigation from alleged inappropriate use of ototopical drops has garnered significant attention among

practitioners on the subject of ototoxicity from ototopical preparations. Several years ago, a survey of otolaryngologists in the United States found that few were concerned about ototoxicity from topical medications in patients with tympanic membrane (TM) perforations **(Lundy and Graham, 1993).**

Whether ototopical solutions actually can pass through TM perforations or pressure equalizing tubes (PETS) and whether certain ototopical (especially aminoglycoside containing) antibiotics might cause a sensorineural hearing loss has been questioned by some clinicians **(Linder et al, 1995).**

The passage of otic solutions through PETs into the middle ear has been demonstrated using an artificial model of the ear, in this model, massage of the tragus created pressures that exceeded those needed for passage of otic solutions through even small tympanostomy tubes **(TTs) (Saunders and Robinson, 1999).**

In patients with active chronic suppurative otitis media (CSOM), instillation of a solution of gentamicin into the external auditory canal was associated with detectable plasma levels of gentamicin, which indicated systemic absorption **(Lancaster et al, 1999).**

Several reports in the literature described symptoms of ototoxicity after administration of ototopical agents in patients with TM perforations or TTs in place, which also indicated passage of the drops into the middle ear space **(Marais and Rutka, 1998)**.

Round Window Membrane

Potential pathways between the middle ear and inner ear include the hematogenic or lymphatic, the oval window or round window (RW) and bony fistulas. Overwhelming evidence from human temporal bone studies and experimental studies in animals suggests that, apart from the round window membrane (RWM), there are no major routes of entry into the inner ear. The RWM is the only true soft tissue barrier between the middle and inner ears. **(Schachern, 1992)**

The generally accepted theory concerning the function of the RWM is that it releases the mechanical energy supplied by the ossicular chain to the labyrinthine fluids. In addition, the RWM layers participate in the absorption and secretion of substances to and from the inner ear, so that the whole membrane may play a part in a middle and inner ear ‘‘defense system’’ **(Goycoolea, 2001).**

The RW niche forms a wall on which various substances, including middle ear effusions, may collect. It may enhance the diffusion of middle ear effusions by entrapping the effusion adjacent to its surface. The RWM separates the niche from the scala tympani and is in direct contact with perilymph. In

humans, however, mucosal membranous veils often cover the RWM **(Alzamil, and Linthicum, 2000).**

The presence of these mucosal membranes adjacent to the surface of the RWM may inhibit diffusion by adding an extra barrier, thus protecting the RWM. It has been demonstrated that the RWM and mucosal membranous veils are ultra-structurally similar **(Carpenter et al., 1989).**

The RWM of the human ear shows differences from, and similarities to, the corresponding membrane in other species **(Alzamil, and Linthicum 2000, Schachern et al., 1982).**

The structure of the RWM

The human round window membrane lies in a triangular recess within the round window niche. It is slightly convex toward scala tympani and thicker at the margins than in the center. It separates scala tympani from the middle ear space **(Nomura, 1984).**

The membrane consists of 3 layers: an outer epithelium facing the middle ear, a core of connective tissue, and an inner epithelium bounding the inner ear **(Belluci et al., 1972; Carpenter et al., 1989; Irurato and Recchia, 1968; Miriszlai et al., 1983; Revesz et al., 1983; Schachern et al., 1984).**

The outer layer faces the middle ear and is continuous with the promontory. It consists of low cuboidal squamous epithelium and is characterized by tight junctions with sparse microvilli. Mitochondria, rough endoplasmic reticulum, and Golgi bodies can be seen in small numbers. The outer membrane rests on a basement membrane **Goycoolea et al., 1997; Schachern, 1982 and Kawabata and Paparella, 1971).**

The middle layer consists of continuous layer of fibrocytes with scant cytoplasm. There are large extracellular spaces filled with collagen. The collagen fibers run in multiple directions. Varying amounts of elastin fibers can be identified. Both myelinated and unmyelinated nerve fibers can be seen within the middle layer of the round window membrane and appear to arise from the tympanic plexus. Both lymph vessels and blood vessels are found in the middle layer of the round window membrane (**Goycoolea et al., 1997; Schachern, 1982andGoycoolea, 1995).**

The inner layer faces scala tympani. It consists of squamous epithelium with long lateral extensions that gives this layer the appearance that cells are overlapping. There are large extracellular spaces and loose junctions. These junctions appear to allow direct contact between the extracellular spaces of the

inner layer and perilymph (**Goycoolea et al., 1997; Schachern, 1982 and Goycoolea, 2001).**

Although its thickness varies among species, the morphological structure of the RWM (and probably therefore its permeability) is much the same. In humans, the average thickness of 70 μm does not change with advancing age **(Schachern et al, 1982 and Sahni et al, 1987).**

The outer and inner epithelium is thicker in infants and the connective tissue core is uniformly cellular, with fibroblasts containing large nuclei, irregularly arranged collagen fibers, very few elastic fibers and an abundance of ground substance. With time, the connective tissue core acquires an orderly array of fibers, and thick and thin elastic fibers are present. In the elderly, the connective tissue has a looser arrangement, there is an increase in ground substance and the elastic fibers become thicker; the fibroblast nuclei lose their flat, elongated configuration, becoming larger, rounder and less uniform, with extensions **(Cureoglu et al, 2005).**

FALSE ROUND WINDOW MEMBRANES

The "false" membrane is a mucosal veil across the triangular fossa. The distance between the medial wall of the false membrane and the round window membrane proper