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Review Article

Pharmacokinetic principles in the inner ear: Influence of drug properties on intratympanic applications

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ABSTRACT

Local drug delivery to the ear has gained wide clinical acceptance, with the choice of drug and application protocol in humans largely empirically-derived. Here, we review the pharmacokinetics underlying local therapy of the ear using the drugs commonly used in clinical practice as examples. Based on molecular properties and perilymph measurements interpreted through computer simulations we now better understand the principles underlying entry and distribution of these and other drugs in the ear. From our analysis, we have determined that dexamethasone-phosphate, a pro-drug widely-used clinically, has molecular and pharmacokinetic properties that make it ill-suited for use as a local therapy for hearing disorders. This polar form of dexamethasone, used as a more soluble agent in intravenous preparations, passes less readily through lipid membranes, such as those of the epithelia restricting entry at the round window membrane and stapes. Once within the inner ear, dexamethasone-phosphate is cleaved to the active form, dexamethasone, which is less polar, passes more readily through lipid membranes of the blood-perilymph barrier and is rapidly eliminated from perilymph without distributing to apical cochlear regions. Dexamethasone-phosphate therefore provides only a brief exposure of the basal regions of the cochlea to active drug. Other steroids, such as triamcinolone-acetonide, exhibit pharmacokinetic properties more appropriate to the ear and merit more detailed consideration.

Contents

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1. Introduction

It has been known for years that injecting a drug solution through the tympanic membrane into the middle ear allows the drug to reach and influence function of the inner ear (Ersner et al., 1951; Schuknecht, 1956). The field of local drug delivery to the ear took on greater relevance when in the mid-1990's local delivery of gentamicin became a widely-accepted clinical therapy for the treatment of Meniere's disease (Lange, 1989; Nedzelski et al., 1993; Toth and Parnes, 1995). Since that time, we have learned that the pharmacokinetics of the inner ear with locally-applied drugs is rather complex, involving the interaction of multiple elements. Some share similarities with other systems of the body, such as entry from the vasculature which has some similarities to that in the eye or the brain. Others, such as passage through the round window membrane, distribution through the different fluid and tissue compartments of the ear, and fluid exchange across the cochlear aqueduct, are unique to the ear. Here we review what we know so far about inner ear pharmacokinetics with a primary emphasis on drugs currently used in clinical practice.

The ear consists of a number of interconnected compartments that an applied drug can access.

1) *Middle ear.* The middle ear is normally gas-filled but becomes a fluid-filled space communicating with perilymph when drug solution is applied there. The middle ear is lined with epithelium that on the ventral surface, leading to the Eustachian tube, is of endodermal origin and is densely ciliated. In contrast, dorsal surfaces of the epithelium and regions in the vicinity of the round window membrane and stapes are of neural crest origins and are not ciliated (Thompson and Tucker, 2013). The epithelium is both highly vascularized and includes lymphatic drainage to the retroauricular and junctional lymph nodes (Lim and Hussl, 1975). Fluid and/or drug loss through the Eustachian tube, via the vasculature and via the lymphatics can all contribute to the decline of middle ear concentration with time after drug application, as can fluid or mucus secretion by the epithelium. An initial breakdown (metabolism) of drugs in the middle ear also likely occurs but only limited quantitative data are yet available. The primary function of the middle ear epithelium is to maintain the normal gas-filled state and removal of applied drug solutions by these multiple processes occurs as a result of that specialization.
2) *Inner Ear.* The inner ear comprises prominent fluid spaces containing endolymph or perilymph, but drugs entering the inner ear do not remain confined to just the fluid spaces. Most of the adjacent tissue spaces are not bounded by tissues with tight junctions so drugs rapidly equilibrate with the extracellular spaces of the spiral ligament, the organ of Corti, the spiral ganglion and of the auditory and vestibular nerves. Depending on permeability properties, drugs may enter the intracellular compartments of these tissues or become membrane-bound if lipophilic. Distribution between endolymph and perilymph depends on where the drug enters the ear, whether by systemic or local application, and whether the drug can pass through the tight, cellular endolymph-perilymph barrier. In the cochlea, distribution of charged molecules between endolymph and perilymph is also influenced by the endocochlear potential. Fluid spaces in the bone of the otic capsule also interact with perilymph, with incomplete bone-lining cells (Chole and Tinling, 1994) and a lacuno-canalicular system in the bone in open fluid communication with perilymph (Zehnder et al., 2005).
3) *Cranium.* Perilymph is in open fluid communication with cerebrospinal fluid (CSF). The endolymphatic sac also contacts the dura mater in the posterior fossa. These communications raise the possibility that substances applied to perilymph may gain access to the brain. In rodents, where the cochlear aqueduct is relatively large, passage of drugs through the aqueduct is largely mitigated by the high rate of CSF turnover. While the CSF may be providing a sink to which perilymphatic drugs are lost (Salt et al., 2015), drug accumulation in CSF is generally low. Although in humans the aqueduct is longer and narrower, there are instances of hearing loss after intrathecal administration of ototoxic drug (Maarup et al., 2015). The passage of drugs from the ear to the brain via the auditory and vestibular nerves has also been proposed (Praetorius et al., 2007; Zhang et al., 2012).
4) *Vasculature.* For the inner ear the vasculature represents a large sink to which drugs can be lost (or gained following systemic applications), impeded by the tight blood labyrinth barriers. This includes the blood-perilymph and blood-strial barriers which may have different characteristics. Each of the tissues of the middle and inner ear, including the bone of the otic capsule, has an associated vasculature that may contribute to the overall pharmacokinetics of the inner ear. It should also be borne in mind that any barrier is only as good as its weakest segment, with pharmacokinetics potentially influenced by local defects in the barrier.

A schematic of the main processes and compartments underlying inner ear pharmacokinetics with intratympanic drug applications is shown in Fig. 1. The figure shows a drug-containing formulation injected through the tympanic membrane into the middle ear cavity. Drug enters the inner ear through multiple pathways, including through the round window (RW) membrane and the stapes (King et al., 2011; Salt et al., 2012a). Drug is lost from the middle ear by multiple mechanisms, as discussed above. As the drug enters perilymph it initially distributes throughout the fluid and tissue spaces of basal turn and vestibule, with spread along the scalae towards the cochlear apex occurring more slowly. In the basal turn of ST, drug levels are diluted by CSF, either entering through the cochlear aqueduct as a volume flow, or as a CSF-

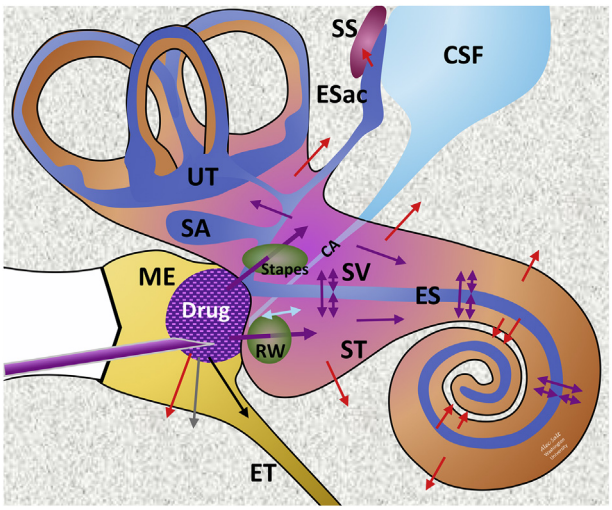

Fig. 1. Schematic of drug applied intratympanically to the inner ear. Colored arrows indicate movements of drug; Purple: Distribution; Red: Elimination to blood; Cyan: CSF-Perilymph fluid exchange; Gray: Elimination to lymphatics; Black: Elimination via the Eustachian tube. Abbreviations are: CSF: Cerebrospinal Fluid; CA: Cochlear aqueduct; Esac: Endolymphatic Sac; ES: Endolymphatic Space; ET: Eustachian tube; ME: Middle Ear; RW: Round Window; SA: Saccule; SS: Sigmoid Sinus; ST: Scala Tympani; SV: Scala Vestibuli; UT: Utricle. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

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