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Local Inner Ear Drug Delivery and Pharmacokinetics

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Summary

A number of drugs are in widespread clinical use for the treatment of inner ear disorders by applying them directly to the inner ear. Many new substances and drug delivery systems specific to the inner ear are under development, and in some cases are undergoing evaluations in animal experiments and in clinical studies. The pharmacokinetics of drugs in the inner ear, however, is not well defined and the field is plagued by technical problems in obtaining pure samples of the inner ear fluids for analysis. Nevertheless, a basic understanding of the mechanisms of drug dispersal in the inner ear has emerged that facilitates the design and interpretation of future pharmacokinetic studies.

Introduction

In recent years there has been increasing interest in the treatment of inner ear disorders by local rather than systemic application of drugs. Substances are applied intratympanically, i.e. injected through the tympanic membrane into the middle ear cavity. This procedure is based on the premise that the drug will contact the round window membrane (RWM) of the cochlea, enter the scala tympani (ST) and spread throughout the ear. The target tissues of such treatments may include the sensory hair cells, the afferent nerve fibers and supporting cells of the cochlea (hearing) or vestibular (balance) portions of the inner ear. The idea of a topical application of medicine to the inner ear is not new. Local anaesthetics and aminoglycosides were applied decades ago to treat inner ear disorders (1,2,3). The present, most widely used form of intratympanic therapy is the injection of gentamicin into the middle ear in patients with Menière's disease (3,4,5,6,7,8). Gentamicin is toxic to the sensory cells of the balance system and thereby suppresses the vertigo in these patients by partially ablating their vestibular system. There are also an increasing number of clinical reports related to the local application of glucocorticoids for acute hearing loss (9,10,11,12,13,14,15,16), glucocorticoids for Menière's disease (17,18,19,20) or for tinnitus (21,22,23,24,25). Other substances that have been tested in humans include local anaesthetics, neurotransmitters and neurotransmitter antagonists (26, 27). There is also interest in the use of growth factors, antioxidants, apoptosis inhibitors and antisense-oligonucleotides. Animal experiments have shown promising results using locally applied drugs to provide otoprotection from noise and drug toxicity (28,29,30,31,32,33,34, 35,36). One extension of such studies is local viral and non-viral gene transfer for the sustained treatment of inner ear disorders (37,38,39,40,41,42). It has recently been shown that Atoh1, a gene also known as Math1 and a key regulator of hair cell development, induces regeneration

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Teaser

Even though locally applied drugs are often used to treat inner ear disorders, the pharmacokinetics of drugs in the inner ear fluids remains uncertain due to technical difficulties.

of hair cells and substantially improves hearing thresholds in the mature deaf inner ear after delivery to nonsensory cells through adenoviral vectors (43). While many of the above examples show that local therapy has many advantages over systemic therapy, it should be noted that no medicine to date is approved anywhere in the world for local application in the treatment of inner ear disorders.

Local application of drugs to the inner ear is based on the rationale that despite the lower total amount of drug given, medications applied topically to the RWM can result in higher concentrations in the inner ear fluids than would be the case with systemic application. Pharmacokinetic studies have confirmed this principle (9,34,44,45,46,47). Potential side effects of systemic treatment and complications from a long lasting, higher dose therapy can be avoided through topical application therapy. Substances applied locally at a low dose can be administered where there are major restrictions or even contraindications associated with systemic application.

While in theory, the local application of drugs to the inner ear has great potential, in practice there are numerous technical difficulties to overcome. Important issues that have so far received only limited consideration are:

- i. Where in the ear do drugs reach, in what concentration and with what time course?
- ii. How do different delivery methods or application protocols influence the drug levels and time courses achieved at different locations in the ear?
- iii. How variable are the drug levels achieved with different delivery protocols and what are the major sources of variation?

Currently, the applied doses, application protocols and application systems are empirically justified. This approach has led to varying results in the therapy of Menière's disease by intratympanic gentamicin application, which serves as an example of the uncertainties associated with different application strategies. While some studies reported few patients with deafness as an unwanted side effect of local gentamicin treatment (7) others found complete deafness of the treated ear in more than 20 % of patients (48) and in one study, in which drugs were applied for a prolonged period, 80% of the patients were deafened (49). It is therefore necessary to acquire an understanding about the quantitative drug distribution in the inner ear fluids when medications are locally applied with different delivery protocols.

General principles of drug distribution in the inner ear

The inner ear represents a geometrically complex structure, with characteristic large fluid-filled extracellular spaces (scalae), each with multiple interfaces with other scalae and with outside compartments, such as the systemic blood circulation and the middle ear cavity (Figure 1). ST and SV contain perilymph, a fluid similar in ionic composition to other extracellular fluids, while the endolymphatic space contains fluid with a unique, high-potassium composition. In contrast to most other body fluids, the inner ear fluids do not move or flow appreciably and are not actively "stirred". As a result, the spread of locally applied drugs through the ear occurs only slowly and predominantly by passive diffusion (50,51). The diffusion coefficient, which governs the rate at which drugs spread, depends on the physical characteristics of the diffusing particles or molecules, with the molecular weight playing a major role (52).

Transfer of substances through the RWM to the ST of the inner ear also appears to be primarily a passive process. Active transport processes have been assumed particularly for larger molecules and particles, but have not been confirmed so far (53). The rate at which medications cross the RWM to the inner ear depends on the size, geometry and tissue permeability characteristics of the RWM. Animal experiments have shown that, despite its three-layered

nature, the RWM behaves as a semipermeable membrane. Many agents have been applied to the RWM and their transition into ST have been assessed either by histological methods, by direct measurement of concentrations, or by indirect methods such as through an influence on hearing thresholds (53). The permeability of the RWM may also be influenced by simultaneous application of other substances (54,55) or by intracochlear pressure changes by altering the distension of the membrane (56).

The processes underlying drug distribution in the ear have been subdivided into “radial” (with respect to the modiolus, the central core of the cochlea) and “longitudinal” processes as shown in Figure 1 (51,57,58). Radial distribution processes include communications between the parallel scalae of the same turn (open arrows) and communications with the vascular system (closed arrows). Communication between ST and SV via the lateral wall (the tissues at the right of Figure 1A) appears to be particularly rapid (58,59,60). Communication with the blood is through the endothelial cells of the capillary beds in the lateral wall which provide a tight “blood-labyrinth barrier”, comparable to the blood-brain barrier. Longitudinal processes include diffusion and longitudinal flow along the scalae. In the normal, unopened cochlea the flow rates of endolymph and perilymph are extremely low so the effect of flow on can be regarded as negligible compared to diffusion (57,61). Other longitudinal communications include those between ST and SV through the helicotrema at the cochlear apex and the open communication between the basal part of SV and the vestibulum.

A major process that influences drug distribution in the inner ear is that of clearance, which refers to the removal of substance from the cochlear fluids via the capillary beds in the lateral wall and modiolus. Broadly speaking, clearance includes all processes that lead to the reduction of substance levels in the cochlear fluids, which includes losses to the fluid spaces of the modiolus, uptake into intercellular spaces, and inactivation of the applied drug by metabolism or by binding to tissues. The interplay between diffusion and clearance is key to determining the distribution in the inner ear of substances applied to the RWM. Substances cleared from the fluids at high rates will rapidly reach a steady state in which drug diffusion is balanced by clearance, so the drug may never reach the apical regions of the cochlea in appreciable concentration. Substances with slower clearance rates will diffuse further along the cochlea. The magnitude of longitudinal drug gradients following local delivery is therefore highly dependent on the rate the drug is cleared from perilymph. The greatest technical problem associated with local drug administration is the large gradients of drug concentration, with highest levels near the site of application and decreasing levels at more distant sites. These gradients can be predicted by computer simulations (59,62) and have been demonstrated experimentally by ion-electrode measurements (50) and by histological methods (41,63).

Pre-clinical studies of pharmacokinetics in the inner ear

The development and approval of medications and drug application systems requires the study of the pharmacokinetics, toxicity and efficacy of medications applied locally to the RWM. Preclinical animal studies lay the foundation for introducing specific drug delivery protocols into clinical practice. Only a few studies have quantitatively studied drug concentrations in the inner ear fluids (9,34,45,46,63,64,65). However, data from two of these studies show very different perilymph concentrations of a drug after using similar application modes (9,46). Large deviations in pharmacokinetic profiles in animal experiments considerably limit their applicability to the human situation. For this reason, it is important to understand some of the technical problems associated with pre-clinical pharmacokinetic studies of the inner ear.

The withdrawal and analysis of samples from the inner ear both represent a considerable technical challenge because the fluid volumes in the inner ear are extremely small. For example, the entire perilymph volume in the cochlea of the guinea pig is less than 10 μ l (66,67). In

previously-published studies, sample volumes were withdrawn that approach, or in some cases exceed, the cochlear perilymph volume in order to provide adequate sample volumes for pharmaceutical analysis (9,34,45,46,64,65). When fluid is aspirated from the basal turn of ST, such as through the RWM, it is replaced by cerebrospinal fluid (CSF) which enters ST through the cochlear aqueduct and contaminates the perilymph (56,60,68,69). As greater volume is taken, the sample will contain an increasing amount of CSF so that the volume taken no longer represents pure perilymph. In one study, multiple samples, each larger than the cochlear perilymph volume were taken over time (9). The assessment of pharmacokinetic profiles based on such fluid samples can therefore be misleading. In a recent study using a chemical marker, the marker concentration of fluid samples taken through the RWM was compared with the perilymph concentration of the marker measured prior to sampling with an ion-selective microelectrode sealed into the scala. It was calculated that even a 1 μ L sample taken through the RWM was contaminated with 20% CSF (56). Larger sample volumes, such as the 10 μ L samples used in some prior studies, were estimated to contain less than 15% perilymph and over 85% CSF. A consequence is that the drug levels reported in some pharmacokinetic studies do not accurately represent the real drug concentration in the perilymph. It is therefore important to scrutinize carefully the methodology used before accepting that published values described as “perilymph concentrations” are reliable.

Interpretation of specific delivery and sampling protocols is aided by a finite-element computer model (<http://oto.wustl.edu/cochlea/model.htm>) that considers the anatomy of the inner ear, general pharmacokinetic principles and solute distribution processes. This model allows the calculation of solute movements associated with a variety of drug delivery protocols. It also simulates a number of measurement methods, including measurement at a specific point (comparable with an ion-selective microelectrode), and a number of fluid sampling techniques, including microdialysis. Volume flows associated with the aspiration of samples are incorporated into the simulations. This simulator is therefore useful for the interpretation of a variety of experimental configurations. A detailed analysis of the repeated sampling study mentioned above (9) has shown that perilymph concentration of methylprednisolone in ST must have been more than 10 X higher than the presented sample concentrations, as shown in Figure 2 (60). This analysis goes a long way to reconcile the disparate concentrations of steroids in the ear reported by different studies (9,46,60). It also confirms that the major hazard of sampling perilymph from ST is that the actual perilymph drug levels may be substantially underestimated by the concentrations detected in samples.

Other studies, in which perilymph was sampled from the vestibule (52,70,71) are more readily interpretable in terms of the basic mechanisms by which drugs distribute within the inner ear fluids. The amount and time course of gentamicin concentration change in the vestibule is consistent with drug entering the basal region of ST and spreading quickly to SV and the vestibule by radial diffusion pathways across the membranous structures (59). The amount of drug reaching the apical regions of the cochlea was predicted to be substantially lower than that at the base, which is consistent with the limited hearing loss seen when moderate gentamicin doses are applied locally. Other studies have adopted sampling methods in which the animal was first sacrificed, the temporal bone removed and then the fluids aspirated from the cochlea. In this method, the perilymph withdrawn is replaced by air, so that sample contamination with CSF cannot occur (46). The choice of sampling location is constrained by the focus of the study, specifically those studies that are interested in the vestibular effects of drugs need to sample from the vestibule, while for studies focused on the auditory effects of drugs, the drug concentration in ST is of greater relevance.

One alternative to fluid sampling from the cochlea has been the use of microdialysis, which involves sealing a permeable probe into the scala, through which fluid is continually perfused. Analysis of repeated samples of fluid efflux from the probe allows a drug concentration time

course in the cochlea to be monitored without volume disturbance. Time courses for a number of substances including gentamicin and dexamethasone following application to the RWM have been presented (47,72,73). Although this is an excellent method to quantify RWM permeability, the drug time course measured with this technique also does not accurately represent the true perilymph kinetics. This is because the leakage of drug from perilymph into the dialysis probe (which is an essential part of the method) represents a non-physiologic clearance of the drug from the cochlea fluid spaces. It has been demonstrated that dialysis of small compartments *in vitro* caused rapid clearance of solute from the compartment that could be accurately modeled (72). In a subsequent analysis of *in vivo* dialysis experiments using dexamethasone and fluorescein it was further demonstrated that the dialysis probe significantly contributed to solute clearance from perilymph (74), making it impossible to define the physiologic rate of drug clearance. The high rates of drug clearance reported in prior dialysis studies are therefore unlikely to represent the perilymph kinetics that would exist in the absence of dialysis. It is unfortunate that the errors in both dialysis and sampling studies both underestimate both the drug concentration and the time the drug remains in perilymph.

There are only few pharmacokinetic studies using fluids samples taken from the inner ear of man. In patients undergoing labyrinthectomy, perilymph was sampled from the vestibule at various times following local delivery of gentamicin to the middle ear (75). Such data will be valuable in the extrapolation of pharmacokinetic studies in animals to the situation in the human.

Drug application systems

As more candidate substances for the treatment of inner ear disorders are being discovered, it is necessary to develop appropriate strategies for their delivery in the least invasive manner possible. In **controlled release systems**, the rate of release is determined largely by the design of the device itself (e.g. an implantable or external pump or biopolymer) and is not dependent on environmental conditions. In contrast, **sustained release systems** provide prolonged release but the release rate is significantly affected by environmental conditions (76). For the local drug delivery to the inner ear, a variety of strategies exist ranging from intratympanic injections of fluids to the use of pumps, polymers and gels.

i) Single or repeated intratympanic injection with or without volume stabilisation and with or without visualization of the round window membrane

The most frequently used means for local drug application is an intratympanic injection of drug solution (1,26,77,78). The limitation of this method is the lack of control of both the drug concentration reaching the RWM and the duration of contact of the drug with the RWM, both of which are important factors in determining the drug level achieved in the cochlea. During and after injection the patient usually lies with the treated ear upwards. The time the drug remains in the middle ear is uncertain, however, as drug is lost by drainage of the solution via the eustachian tube (during swallowing) or by resorption through the middle ear mucosa. A number of methods have been developed to increase the time drugs remain in the middle ear. In animal experiments, fibrin glue was employed to stabilize the applied volume as a gel (45), while in man hyaluronic acid (14,79,80) or resorbable gelatine-sponges (81) have been used. Despite this, the doses, dosing intervals and therapeutic durations required to achieve a specific therapeutic goal are hard to predict. Other factors that contribute to variation include anatomic obstacles, such as plugs of connective or adipose tissue, or so-called pseudomembranes of the RW niche. It has been estimated that approximately one third of patients have obstructions of the RWM (82). Inspection of the RWM before drug application is possible using a microotoscope (explorent® GmbH, Tuttlingen, Germany) (83). Another approach to maintaining drug in contact with the RWM is the use of the “microwick” (84), in which a “wick” is positioned in the RW niche via a tympanostomy tube. The external end of

the wick is located in the external auditory canal, to which the patient can intermittently apply medications. While it is possible that the device acts as a wick when it is initially placed and is dry, it remains uncertain how much volume flows along the wick when the fibers are already fluid-saturated. It is more likely that drug diffusion within the fluid spaces of the wick will dominate drug movement towards the inner ear, and this is likely to be a slow process.

ii) Continuous or discontinuous drug application via partly or fully implantable pump systems

During brief drug applications, small permeability variations in the face of large drug gradients across the RWM, combined with variations in the brief application time, contribute significantly to variations of perilymph drug levels. In an attempt to better control the drug level at the RWM, continuous drug application has been employed, via partially or fully implantable catheter systems and pumps. In animals, the mini-osmotic ALZET-pump (DURECTTM, Co., Cupertino, USA) has been widely used both for drug delivery to the middle ear (85) and for intracochlear delivery of drugs (29,36,86).

A device for discontinuous drug delivery which has been evaluated in animals, but which is not yet approved for the use in humans, is the TI-DDS® (Totally Implantable Drug-Delivery-System) (87,88). The manually operated pump releases a defined volume of 5 or 10 µl upon push-button activation. A subcutaneously implanted reservoir can be refilled transcutaneously.

In humans, although a variety of experimental catheter systems have been employed, the round window microcatheter from DURECT (RWµCathTM, DURECTTM, Co., Cupertino, USA) represents the best characterised system to date (10,13,27,48). In a recent nonconcurrent cohort study it was found that local continuous glucocorticoid delivery via the µCath in patients with acute severe or profound hearing loss and failure of standard systemic therapy showed a significant improvement in hearing compared to a historical control group without local treatment (16). However, for unknown reasons, commercial production of the Durect RWµCath was halted in 2004.

There remains an intense interest in the development of safe, effective and minimally-invasive drug delivery systems for the inner ear, with a number of groups working on intracochlear catheter-based application systems. One approach has been to combine drug delivery with an existing device, such as by incorporating a drug delivery cannula into a cochlear implant electrode (89). Other groups are working on specific implantable drug delivery devices usable in normal ears (90). This group is hoping to combine developments in biomedical engineering that will allow the incorporation of more elements from micro- and nanotechnology (sensors, processors, effectors and actuators) into a delivery device specifically for the inner ear.

iii) Biodegradable biopolymers

In addition to the use of gels to stabilize the volume of drug-containing solutions in the middle ear, there is also enormous interest in the use of biodegradable biopolymers for the controlled delivery of substances to the inner ear. The two main roles of these polymers are diffusion control of active agents and disintegration control of the polymer, which results in release of the active agent.

Advantages of polymeric controlled release devices include a specific release kinetic for prolonged delivery and the possibility of drug targeting, i.e. the delivery of drugs to a target site where they are released. Of special interest are so-called “smart polymers” that are able to respond to chemical or physical changes of the environment such as pH, temperature, and electric field that may allow them to be incorporated into auto-regulated implantable drug

delivery systems. Disadvantages are the limited amounts of drug that can be incorporated in a given application form (76,91,92).

Two recent publications have reported on the use of biopolymers for local drug delivery to the inner ear (65,93). Another application in this area is the coating of cochlea implant electrodes with biodegradable carrier substances to release drugs. In this application, glucocorticoids, antioxidants, apoptosis inhibitors or neurotrophins could be employed to counteract side effects of electrode insertion, to aid survival of the spiral ganglia, or to stimulate neurite growth towards the implant electrodes (94).

iv) Influence of the application system on pharmacokinetics with round window application

Based on analyses and simulation of experimental inner ear pharmacokinetic studies in animals (59,60) it has been established that the application protocol is a major factor in determining the absolute drug level reached in the inner ear. The time that the drug remains in the middle ear plays a primary role, with highest intracochlear drug levels found with continuous delivery and lower levels found with brief applications. In addition, the relative distribution of drugs in the ear varies with application protocol, due to the interactions between the duration of application with clearance processes.

Conclusions for clinical applications

The applied concentration of drug and the delivery protocol required to achieve a specific goal in humans, is likely to differ substantially from that demonstrated in experimental animals. As drug concentrations in the inner ear fluids depend on dispersal by diffusion, they are influenced by the differing scala lengths and volumes of the inner ear in different species. For example, to achieve the same active dose in the vestibule of humans, higher middle ear and basal turn drug levels will be required compared to experimental animals with smaller cochlear fluid volumes. This is particularly important in the therapy of Menière's disease by intratympanic drug application, where one also has to consider the relative vestibulotoxicity and cochleotoxicity of specific protocols. A major factor affecting the drug level in the ear is the time the drug remains in the middle ear. It is therefore of major importance that application methods are developed in which the amount of drug in the middle ear and the application duration are closely controlled.

Basal to apical concentration gradients generated by local drug application are also of clinical relevance. Concentration gradients will be greater in the human cochlea than in experimental animals due to the longer cochlear spiral of the human. While drug applied to the RWM of the mouse will readily reach the cochlear apex, the same is not true for the human, as the cochlea is substantially longer. Gradients in drug concentration between the basal (high frequency) regions compared to apical (low frequency) regions of the cochlea partially account for the limited hearing loss in humans with Meniere's disease treated with vestibulotoxic levels of gentamicin. Drug gradients can be exploited for the treatment of other inner ear disorders, such as high-frequency tinnitus and high-frequency hearing-loss. In contrast, it will be difficult to treat hearing disorders in the middle and lower frequency range by present-day intratympanic drug application methods.

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Abbreviations

RW

	round window
RWM	
	round window membrane
ST	
	scala tympani
SV	
	scala vestibuli
CSF	
	cerebrospinal fluid

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Figure 1.

Principles of substance distribution in the inner ear: (A) Cross section through the guinea pig cochlea with an enlarged section of one turn showing the “radial” exchange between compartments (open arrows) and the clearance from the scalae to the blood circulation or to the modiolus (solid arrows). ST: scala tympani, SV: scala vestibuli, EL: endolymph space. (B) Schematic of an “unrolled” cochlea showing the “longitudinal” processes of solute movement. Longitudinal processes must take into account changes of scala dimensions, diffusion and flow along the scalae, and the contributions of the helicotrema and vestibulum (V). The shading in the figure depicts the spread of drug following local delivery to the round window (RW) membrane, which is dominated by radial exchange processes.

Figure 2. Calculation of the methylprednisolone (MP) concentration in the basal turn of scala tympani in the absence of sampling that would account for the amount of MP detected in the four, 10 L samples taken through the RW membrane by Parnes et al., 1999. Note that the perilymph MP level must be substantially higher and the MP must remain in the fluid space for longer time than the sample measurements alone suggest (data from 60).