

Section 21: Drug Discovery/Delivery

Pharmacokinetic Considerations of Local Drug Delivery to the Inner Ear by Round Window Application

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Although there is increasing interest in the local delivery of drugs to the inner ear by applying them to the round window (RW) membrane, most drug application protocols have been empirically-based. As a result, consequences of changes in delivery method, applied drug concentration or even small alterations in treatment protocols have been difficult to predict. Since direct measurements of drug concentration time courses (as required in phase I clinical studies) are not presently possible in the human inner ear, computer simulations provide a valuable tool for estimating drug concentrations in the inner ear for phase II clinical studies. The ultimate goal is to simulate drug movements in the inner ear sized appropriately to the human after topical application to the RW membrane.

In animal experiments it has been shown with ionic markers that following RW drug delivery, a concentration gradient is set up along the cochlea, with higher levels near the base and lower levels in more apical turns. Even after prolonged applications, a gradient will persist.¹ As these gradients are of fundamental scientific and clinical importance, it is necessary to experimentally demonstrate the existence of gradients for physiologically-relevant drugs.

Methods

Models of drug dispersal in the cochlea

Using a 1D finite element computer model (Washington University Fluid Simulator, <http://oto.wustl.edu/cochlea/>) we have analyzed published data on gentamicin concentration time course in the chinchilla after RW application.² Although the 1D simulation model provides a good representation of the longitudinal distribution of drugs, its ability to accurately predict the radial distribution of drugs (across and between scalae) is limited. A three-dimensional model has therefore been developed which better represents the complex geometry of the inner ear and is better able to represent radial drug movements from scala tympani (ST) towards the vestibule.³ The 3D-structure was constructed from 80,000 finite elements with 100,000 nodes taking geometric dimensions from the guinea pig cochlea. The RW was placed in a plane perpendicular to the length axis of scala tympani to simplify mathematical modeling. Drug propagation along and between compartments was described by passive diffusion. The 3D-model was implemented in a commercial software package for finite-element calculations (ANSYS®, ANSYS Inc., Canonsburg, USA).

Measurement of drug gradients along scala tympani following local applications

Experiments were performed in guinea pigs in vivo using a ventrolateral surgical approach (for procedure and anesthesia, see¹). Gentamicin (40 mg/ml) was administered to the RW niche for 2 hrs after which perilymph (PL) was sampled from the cochlear apex. Immediately following perforation of the apex, 10 fluid samples, each with a volume of 1µl, were collected into calibrated capillary tubes. Samples were diluted in buffer and gentamicin concentrations were measured using a Fluorescence Polarisation Immunoassay (Abbot TDx/FLX Analyzer, Abbot Laboratories, USA). Individual experiments were analyzed using the 1D finite element model, which permits the volume and the collection time of each individual sample to be incorporated. Drug diffusion, including that occurring during the sampling procedure, is incorporated into the model. By modeling the sample concentration data it is possible to establish the drug profile along the cochlea at the time of sampling.

Results and Conclusions

When drugs are applied to the round window membrane they do not become uniformly distributed throughout the inner ear fluid compartments. Computer simulations with 1D and 3D models predict that the basal region of the cochlea is exposed to higher gentamicin levels than the apex and the vestibule (Figure 1 and 2).

Other conclusions from the simulations (data not shown) are: that (1) entry of drug into the vestibule does not occur by diffusion along the perilymphatic scalae, passing through the helicotrema. Rather, the observed time course is consistent with the presence of local communication between scalae in all segments of the cochlea, as supported by previous anatomic and physiologic studies. (2) Loss of drug from the middle ear (to the cochlea and to the middle ear mucosa and vasculature) and clearance of drug from the inner ear fluid compartments (to tissues and to the vasculature) must both occur in order to generate the observed time courses. (3) Different delivery systems most likely create substantially different pharmacokinetic profiles in the inner ear, resulting in differences in absolute and relative drug levels and time courses. (4) Because the relative distribution of drugs along the ST is determined predominantly by rates of diffusion and clearance, the above conclusions are expected to be more significant for cochleae of larger size, as in the human.^{2,4}

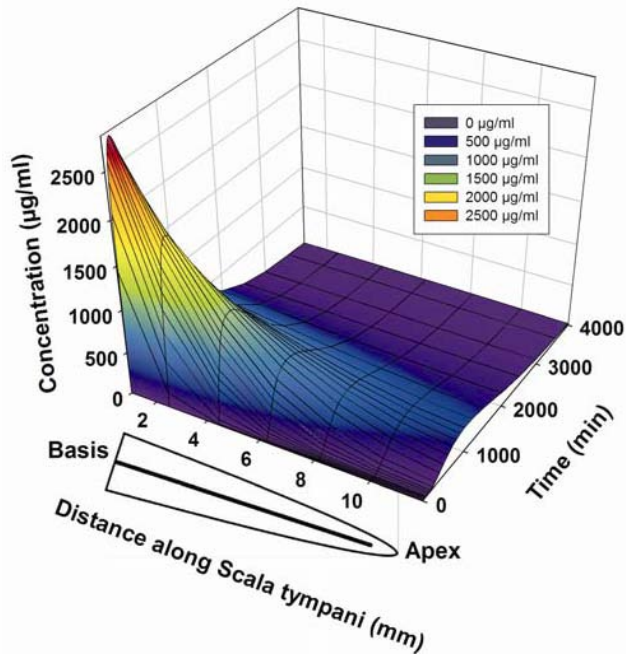


Figure 1 The calculated concentration time course of gentamicin in ST of the chinchilla cochlea after single application with volume stabilization in fibrin glue reveals high peak concentrations at the base at an early stage after the onset of application to the RW niche. A uniform concentration distribution in the cochlea is achieved only very late on and at a very low level (data from³).

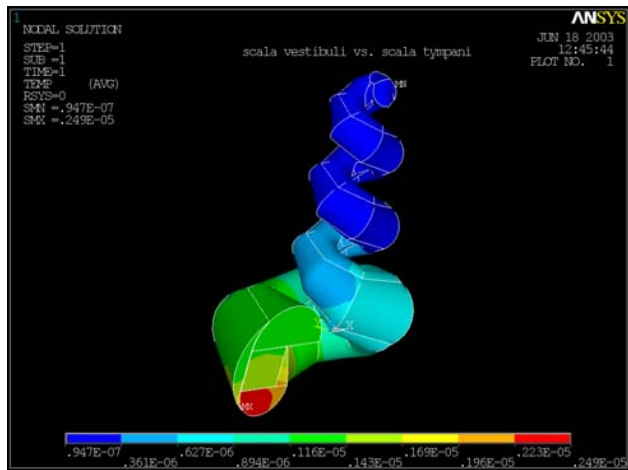


Figure 2 Preliminary calculations with a 3D model using pharmacokinetic parameters derived from the 1D simulations show significant concentration gradients along the length of the cochlea. Radial concentration gradients across the scalae and the spiral ligament are also apparent.

The predicted concentration gradients between the cochlear base and apex for gentamicin after RW application were now demonstrated experimentally for the first time. Figure 3 shows the expected dependence of sample concentration on the sample sequence number for two fundamentally different drug distributions: a uniform distribution of drug throughout ST and for a basal-apical

concentration gradient as well as the sample concentrations measured experimentally. It can be clearly seen that the measured data correspond to the expected curve for a gradient along the cochlea. The first sample, being composed of perilymph from the apical turns shows a low drug concentration. As more samples are taken, perilymph that was previously in the basal turn near the RW and therefore highest in drug concentration will be collected (samples 3 and 4). Later samples contain increasing amounts of CSF and will show low concentration (samples 5-10). In the example, we found a ratio between sample 1 (apical perilymph) and sample 4 (basal perilymph) of approximately 12, which compares with a sample ratio of 46, suggested by the model with this application protocol. Both of these sample ratios underestimate the actual longitudinal drug gradient from base to apex, calculated to be 3×10^6 by the model. We are continuing to fine-tune the model, to better reflect these experimental data.

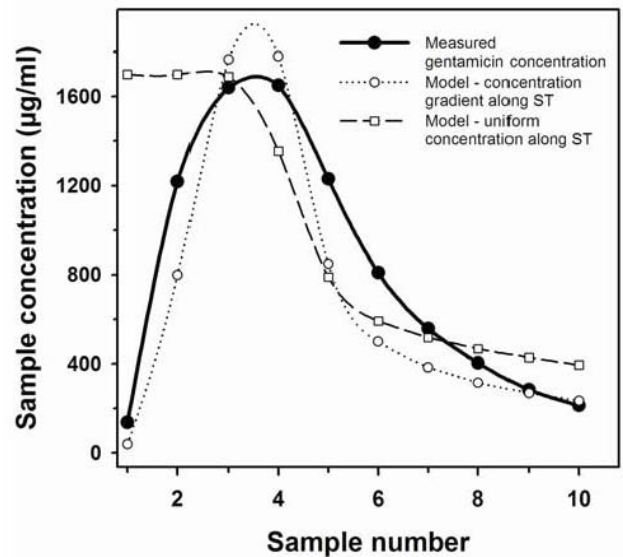


Figure 3 Measured and calculated gentamicin concentrations in sequential samples from the cochlear apex: The expected dependence of sample concentration on the sample sequence number is shown for a uniform distribution of the drug in ST (open squares) and for a basal-apical gradient (open circles). The measured sample concentrations (full circles) are consistent with a drug gradient within ST.

Simulations of drug movements in the inner ear and the experimental testing of the hypothesis generated with these computer simulations are of high importance for clinical studies using local drug delivery to the inner ear.

Acknowledgments

We thank Mr. Shane Hale for his assistance with the animal surgery. Grant support: BfR/ZEBET WK 1-1328-162+171 and UKT-AKF 50-1-0 (SP) and NIDCD DC01368 (ANS).

References

1. Salt AN, Ma Y. Quantification of solute entry into cochlear perilymph through the round window membrane. *Hear Res* 2001 Apr;154(1-2):88-97.

2. Plontke SK, Wood AW, Salt AN. Analysis of gentamicin kinetics in fluids of the inner ear with round window administration. *Otol Neurotol* 2002 Nov;23(6):967-74.
3. Plontke S, Siedow N, Hahn H, et al. [1D-and 3D- computer simulation for planning and interpretation of pharmacokinetic studies in the inner ear after round window drug delivery]. *ALTEX* 2004;21 Suppl 3:77-85.
4. Plontke SK, Salt AN. Quantitative interpretation of corticosteroid pharmacokinetics in inner ear fluids using computer simulations. *Hear Res* 2003;182:34-42.