

## Analysis of Gentamicin Kinetics in Fluids of the Inner Ear with Round Window Administration

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**Hypothesis:** That a theoretical basis for quantifying drug distribution in the inner ear with local applications can be established.

**Background:** As methods of local drug delivery to the inner ear gain wider clinical acceptance it becomes important to establish how drugs are distributed in the ear as a function of time and for different delivery methods.

**Methods:** The time course of gentamicin concentration in the inner ear fluids was simulated with a program that considered general pharmacokinetic principles and incorporated inner ear dimensions and drug dispersal processes, including diffusion, clearance, and intercompartmental exchange.

**Results:** Cochlear fluid space dimensions of the chinchilla were derived from three-dimensional magnetic resonance images and were incorporated into the simulator. The published time course of gentamicin in vestibular perilymph of chinchillas was closely approximated by the adjustment of parameters

defining round window membrane permeability, clearance, and interscala exchange. To simulate the time course, it was necessary for drug entry into the vestibule to be dominated by interscala exchange rather than longitudinal spread through the helicotrema. The effects of different round window delivery methods were also calculated. Perilymph drug levels and spatial distribution in the ear were shown to be markedly influenced by the time the applied drug remained in the middle ear.

**Conclusion:** The development of local inner ear drug application strategies requires consideration of inner ear pharmacokinetic characteristics, delivery methods, and therapeutic range of the drug. **Key Words:** Cochlea—Gentamicin—Ménière's Disease—Perilymph—Round window—Pharmacokinetics—Inner ear drug delivery.

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There is increasing interest in the local delivery of drugs to the inner ear by applying them to the round window membrane. Most drug application protocols have been empirically based because of technical difficulties in measuring actual drug levels in the ear. As a result, the consequences of changes in delivery method, applied drug concentration, or even small alterations in treatment protocols have been difficult to predict. For example, gentamicin has been topically applied onto the round window membrane by single or repeated intratympanic injection of solution through tympanostomy incisions, tubes, or catheters (1,2), by application onto patches of Gelfoam placed onto the round window mem-

brane (3), by applying the solution onto a wick (4), or by continuous delivery of the substance via implanted catheters and external pumps (5,6). The therapeutic results of these approaches vary, notably the risk-benefit ratio of vertigo control/hearing preservation. The percentage of patients experiencing deterioration of hearing attributable to the treatment is typically approximately 30%, but reports of deafened patients vary from 0 to 80% (2,6-8). Part of the variation between different groups may be attributable to different dosing regimens. The total dose applied is typically between 30 mg and 200 mg, although doses of 0.24 mg to more than 700 mg have been reported (2,5-8). Also contributing to outcome variation may be the application method, although a correlation of outcome to both dosage and application method has yet to be established. These variations underscore the need to understand more about how drugs are distributed within the cochlear fluid spaces, and how drug levels are influenced by the method of application.

Recently, several animal studies have been published in which drugs were applied with different protocols and concentrations measured in the fluids at varying time intervals (9-14). Quantitative interpretation of these data is complicated by the fact that the fluid spaces of the

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inner ear are “unstirred” and that movements of drugs through the fluids by diffusion can be slow. Marker studies suggest that even with prolonged application of drug, concentration gradients remain in the fluids (15).

In the current study we analyzed recently published data documenting perilymphatic concentration of gentamicin in samples taken from the vestibule for different time intervals after gentamicin application to the round window of chinchillas (9–11). Because these experiments were performed in chinchillas, it was necessary to quantify the fluid spaces of the inner ear for this species, because these data were not available.

## MATERIALS AND METHODS

### Imaging the cochlea by magnetic resonance microscopy

Three chinchilla cochleae were fixed by whole head perfusion of 3.1% glutaraldehyde in phosphate-buffered Hanks balanced salt solution after anesthesia by intramuscular injection of 1 ml/kg of a cocktail containing ketamine 40 mg/ml, acepromazine 1 mg/ml, and atropine 0.04 mg/ml. The fixed temporal bones were removed and prepared for magnetic resonance (MR) imaging as detailed elsewhere (16). The specimens were shipped to the Center for In Vivo Microscopy, Duke University, and three-dimensional MR scans were performed with parameters identical to those described in our previous studies (17,18). The protocol for the use of chinchillas in this study was approved by the animal studies committee of Washington University, St. Louis, Missouri (approval number 20000131, Dr. B. Bohne).

The segmentation and quantification of the fluid spaces and the round window of the chinchilla were performed using methods identical to those described previously for other species (16–18). Analysis was performed with NIH Image, available at <http://rsb.info.nih.gov/nih-image>. Fluid spaces or structures were segmented from the original gray-scale image stack, and cross-sectional area of the fluid spaces was measured using an automated algorithm that determined scala length and cross-sectional area of small segments along the scala length. In addition, the round window membrane was segmented, and its surface area and orientation with respect to the scala tympani determined using methods described elsewhere (16).

### Simulation of gentamicin movements in the cochlear fluids

Simulations of gentamicin movements in the cochlear fluids were performed using the Washington University Cochlear Fluids Simulator, version 1.6, a public-domain computer program available at <http://oto.wustl.edu/cochlea/>. The simulator is a finite-element model that incorporates many of the passive physical processes by which solutes spread in the inner ear, and it has been validated by comparisons with direct solute measurements from the cochlea made with ion-selective electrodes (15,19,20). The program takes into account the cross-sectional area of each scala as a function of distance, the area of the round window membrane and its geometric relationship to the scala tympani, the size of the vestibule, the permeability of the round window membrane, the rate of gentamicin diffusion, and the rate of gentamicin clearance to other inner ear or external compartments. Diffusion was calculated for 0.1-second time increments with a distance resolution of 0.1 mm. All other

processes were calculated for 1-second time increments for each 0.1-mm scala segment. Calculated time courses were compared with experimental data by determining sums of squared differences between the measured concentrations ( $C_{\text{meas}}$ ) and those estimated by the simulation ( $C_{\text{est}}$ ). A unique best fit was obtained by systematically changing one parameter while leaving all other parameters constant until the sum of squared differences [ $\sum(C_{\text{est}} - C_{\text{meas}})^2$ ] was minimized.

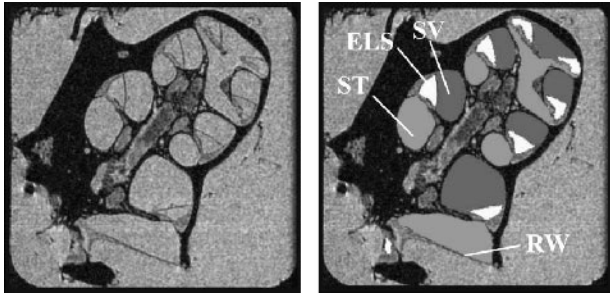
The simulation of gentamicin time course data measured by Hoffer et al. (9,11) and Balough et al. (10) replicated the drug delivery procedures used in their experiments. Specifically, they applied 2.5 mg of gentamicin dissolved in 0.5 ml fibrin glue for volume stabilization, resulting in a concentration of 5 mg/ml. Time courses were calculated representing 10,080 minutes, which is 7 days. The parameters derived from the simulation of this application method were then used to calculate concentration time courses for additional drug application paradigms with a more commonly used gentamicin concentration of 10 mg/ml. One was a brief application of 0.5 ml gentamicin solution without stabilization of volume in the middle ear, comparable to a single transtympanic injection followed by washout from the middle ear cavity after 30 minutes. This has been termed single brief application without volume stabilization. The second paradigm was simulation of a continuous irrigation of the round window membrane such as via a catheter with an attached pump providing a constant concentration of gentamicin solution at the round window for 7 days. This has been termed a continuous delivery. In addition, the single application with volume stabilized was recalculated for 10 mg/ml gentamicin applied to the middle ear. Simulations of one-shot application methods calculated time courses representing 3 days after delivery. Simulation of continuous delivery calculated a 7-day application period followed by 3 days without drug application.

Drug levels were also calculated for cochlear dimensions corresponding to those of the human cochlea, using pharmacokinetic parameters derived from the chinchilla. Scala length, volume, and cross-sectional area as a function of distance for the human were based on those documented by Thorne et al. (18). The area of the human round window was taken as 2.22 mm<sup>2</sup>, which is an average of two published values (21,22). The vestibule was approximated as a volume of 30  $\mu$ l over a length of 6.5 mm (23,24).

## RESULTS

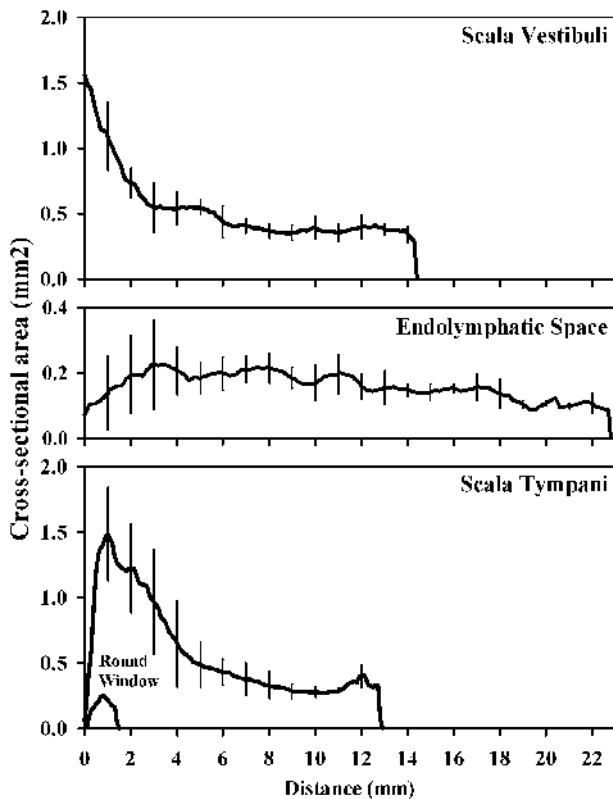
### Quantitative anatomy of the chinchilla cochlea

The resolution of MR images of chinchilla cochleae was sufficient to visualize structures bounding the cochlear fluid spaces, including Reissner’s membrane and the round window membrane, as shown in Fig. 1. Specimens were analyzed by segmenting the fluid spaces in each slice of the specimen, extracting the three-dimensional spiral representing each scala, and then measuring the scala cross-sectional area at small intervals along its length. The scala measurements for the three chinchilla specimens are summarized in Fig. 2. The average scala lengths were as follows: scala tympani, 12.8 mm (SD 0.8); endolymphatic space, 22.7 mm (SD 1.6); scala vestibuli, 14.3 mm (SD 1.5). The endolymphatic space was substantially longer than the perilymphatic (PL) scalae, a finding that is in common with other



**FIG. 1.** *Left:* Magnetic resonance image 114 of the 188 slices representing the three-dimensional structure of the fixed, isolated chinchilla cochlea. The boundaries of all fluid spaces are resolved, including Reissner's membrane and the round window segmented. ST, scala tympani (pale gray); ELS, endolymphatic space (white); SV, scala vestibuli (dark gray); RW, round window membrane

species. The difference occurred because scala length was measured along the midpoint of the endolymphatic space, which occurs more laterally with respect to the modiolus, as seen in Fig. 1, so that the endolymphatic space follows a wider, longer spiral. The average volumes of the scalae were as follows: scala tympani, 7.42

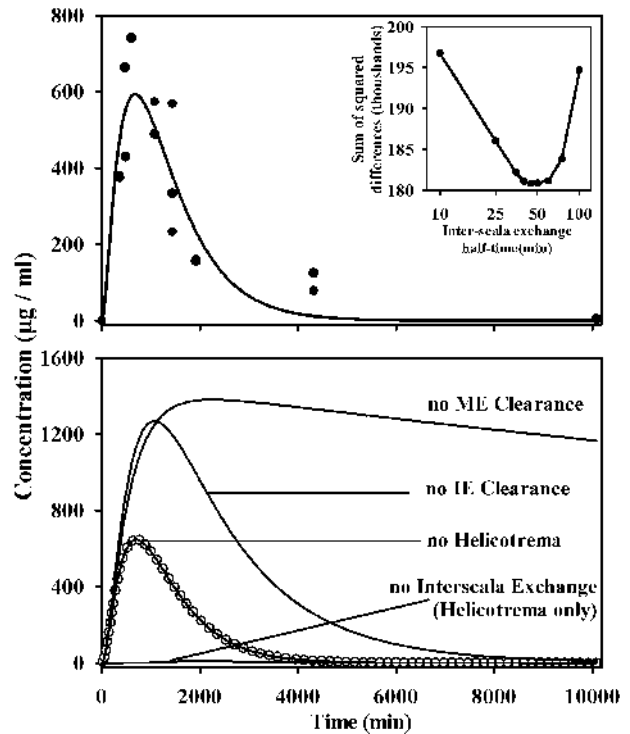


**FIG. 2.** Cross-sectional area as a function of distance for the three fluid spaces of the chinchilla cochlea. Length was measured along the midpoint of each scala. The endolymphatic space is longer than the perilymphatic spaces because it follows a wider spiral around the modiolus. Each curve shows the average of 3 specimens. Bars indicate standard deviation.

$\mu\text{l}$  (SD 1.88); endolymphatic space, 3.59  $\mu\text{l}$  (SD 0.73); scala vestibuli, 7.67  $\mu\text{l}$  (SD 1.43). The round window membrane areas averaged 2.33  $\text{mm}^2$  (SD 0.17,  $n = 3$ ). In one specimen, the entire vestibule was present and was analyzed, with a volume estimated to be 5.1  $\mu\text{l}$  distributed over a distance of 2.4 mm. Finally, round window orientation with respect to the scala tympani was established, and the round window was found to extend 1.4 mm along the scala tympani, as shown in Fig. 2. These data defining the cochlear fluids of the chinchilla were incorporated into version 1.6 of the simulation program.

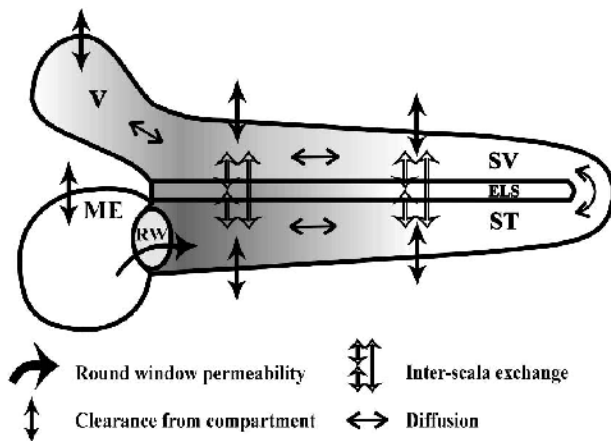
**Simulation of gentamicin entry into the cochlea after a single application**

Experimental studies have quantified gentamicin levels in perilymph after its application to the round window (9–11). In each of these studies, similar time courses were presented, although slightly different data sets were given in each publication. For our analysis, we combined the three data sets as replotted in Fig. 3 (upper panel, symbols). Important features of the observations in-



**FIG. 3.** *Above,* full circles: Experimental measurement of gentamicin levels in perilymph samples taken from the vestibule after application to the round window. Data are replotted from Hoffer et al. (9,11) and Balough et al. (10). Solid line: Best fit of the concentration time course established by the simulator based on physical processes of solute movement. The curve represents the calculated concentration of a simulated 15- $\mu\text{l}$  sample taken from the vestibule, as described in the text. Inset graph: A unique best fit using methods described in the text was found to occur with an interscala exchange half-time of 45 minutes. *Below,* Calculated gentamicin time course in the vestibule with best fit parameters (open circles) and with specific processes in the simulator disabled (solid lines).

cluded the delayed timing of the peak ( $T_{\max}$ ), which occurred at approximately 600 to 700 minutes, and the relatively rapid buildup and decay from this peak. We found that this time course could be generated only with the model parameters set within a limited range. The physical processes incorporated into the model are shown schematically in Fig. 4 and include round window properties, local interscala exchange, clearance from each compartment, and drug diffusion. The diffusion coefficient used for gentamicin was  $0.72 \times 10^{-9} \text{ m}^2/\text{s}$ , based on a mean formula weight of 466 for component fractions in the commercial drug. Because gentamicin has been shown to enter the endolymphatic space (25), and local communication between the scala tympani and the scala vestibuli has been demonstrated (19,26), local interscala communications between the endolymphatic space and scala tympani, the endolymphatic space and scala vestibuli, and the scala tympani and scala vestibuli were included. Identical half-times were used for each of these processes because there is no evidence that any one occurs preferentially. Solute clearance from each compartment was also incorporated into the analysis with the rate for each set equal. Simulations, therefore, depended on three unknown parameters: round window permeability, clearance, and interscala communication. It was also necessary to consider the specific regions contributing to the 15- $\mu\text{l}$  perilymph sample taken from the vestibule in the experimental studies. It is known that when perilymph is withdrawn from the inner ear it is replaced by cerebrospinal fluid entering through the cochlear aqueduct near the base of the scala tympani (27). We calcu-



**FIG. 4.** Schematic of the physical processes incorporated into the simulation program. The compartments shown include the middle ear (ME), scala tympani (ST), cochlear endolymphatic space (ELS), scala vestibuli (SV), and vestibule (V). Drug enters through the round window (RW) in an amount depending on the permeability and spreads longitudinally by diffusion. Local interscala exchange allows drug to spread to the endolymphatic space and the scala vestibuli, and from there to the vestibule. Drug clearance (losses to other compartments such as to blood) occurs from each compartment. Diffusion, clearance, and interscala exchange are calculated for each 0.1-mm segment of the fluid space.

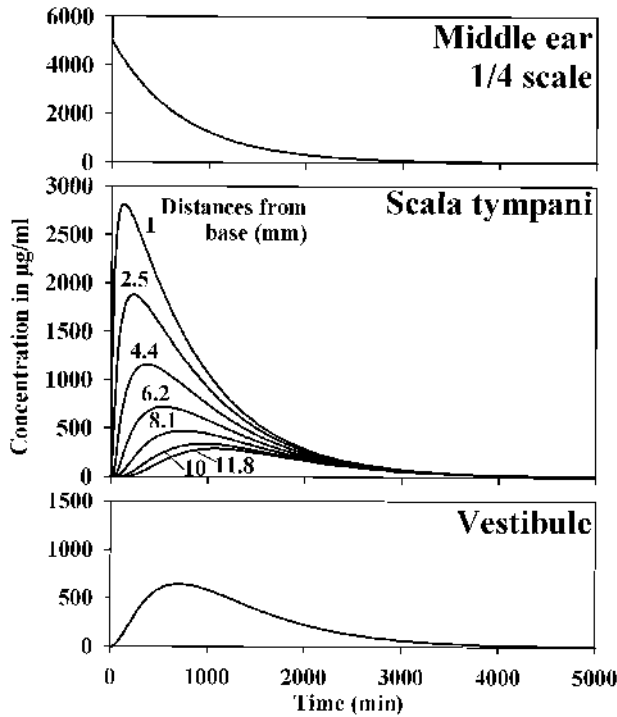
lated that the 15- $\mu\text{l}$  sample taken from the vestibule would represent the cumulative volume of perilymph in the vestibule (5.1  $\mu\text{l}$ ), that in the scala vestibuli (7.6  $\mu\text{l}$ ), and 2.3  $\mu\text{l}$  from the apical region of the scala tympani.

Initial simulations showed that changing round window permeability or clearance while holding interscala exchange constant influenced the calculated time courses differently. Increasing round window permeability increased concentration and moved  $T_{\max}$  earlier. Slowing clearance (increasing half-time) increased concentration but made  $T_{\max}$  later. Thus, by systematically varying round window permeability and clearance, it was possible to obtain a unique best fit for one rate of interscala exchange. This fitting procedure was then repeated for different rates of interscala exchange, and the overall minimum sum of squared deviations was established, as shown in the inset of Fig. 3. The parameters giving the best fit to the data were 45 minutes interscala exchange half-time,  $0.38 \times 10^{-9} \text{ m/s}$  round window permeability, and 505 minutes clearance half-time, which generated the gentamicin time course of the simulated 15- $\mu\text{l}$  sample indicated by the solid curve in Fig. 3 (upper panel). The process of systematically changing parameters provided a better understanding of each specific factor's influence that can only partially be presented graphically. The examples shown in Fig. 3 give calculated time courses for vestibular concentration when single specific processes were excluded from the simulation. It is noted that while excluding communication through the helicotrema had no influence on vestibular concentration, excluding middle ear clearance, inner ear clearance, and interscala exchange each substantially changed the calculated time course.

Calculations showed that the distribution of gentamicin in the ear was not uniform, as summarized in Fig. 5. The concentration in the middle ear decayed from the applied value, in part because of gentamicin flux into the cochlea from the finite volume (0.5 ml) applied and because of assumed clearance to other compartments such as the blood. When clearance from the middle ear was excluded, the observed rate of decline of gentamicin concentration in the inner ear fluids could not be achieved (Fig. 3). Fig. 5 shows the time courses for different locations in the scala tympani. Locations close to the round window (1 mm) showed higher concentrations and earlier  $T_{\max}$ , compared with more apical locations (11.8 mm), reflecting the slow rate at which drugs diffused the length of the cochlea. The vestibule showed a time course similar to, but not identical with, the curve fitted to the experimental data (Fig. 3). The difference was that the curve fitted to the data combined the solute concentrations in the vestibule, the scala vestibuli, and the apical regions of the scala tympani, corresponding to the aspirated 15- $\mu\text{l}$  sample.

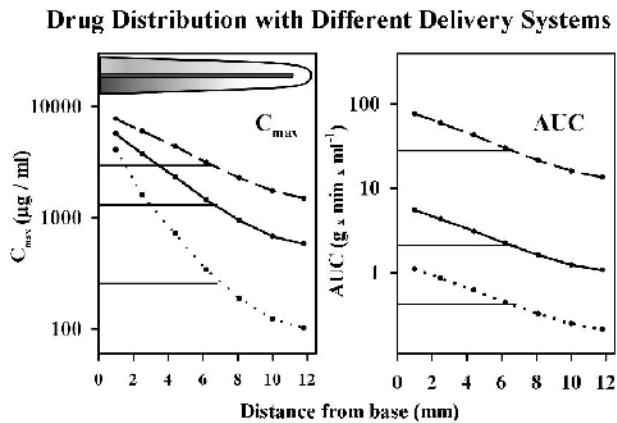
#### Distribution of drugs in the ear using different drug delivery systems

Using parameters that define the processes of gentamicin distribution in the ear, it is possible to compare



**FIG. 5.** Concentration time courses for different regions of the inner ear calculated during the simulation that best fits the data, as shown in Figure 3. There are considerable differences in the amplitude and time course of drug in different regions, especially when basal and apical regions of scala tympani are compared.

theoretically the influence of different drug delivery strategies, as shown in Fig. 6. The curves show peak gentamicin concentration and the area under the curve as a function of distance along the scala tympani and for the

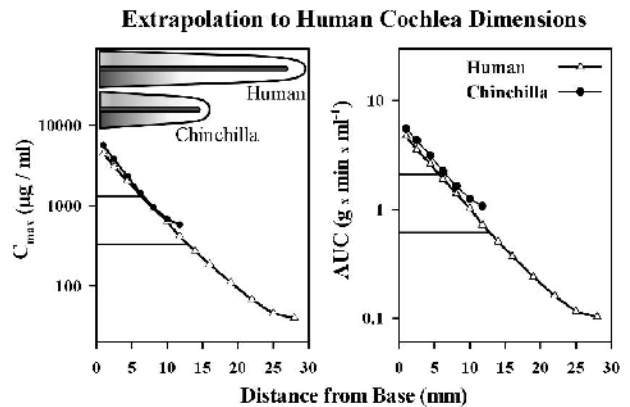


**FIG. 6.** Comparison of the drug distribution along the scala tympani (ST) for application by three delivery systems each using 10 mg/ml gentamicin. Left: Maximum concentration ( $C_{max}$ ). Right: Area under the curve (AUC). Solid line: Single drug application with volume in the middle ear stabilized (such as by fibrin glue). Dashed line: Continuous delivery. Dotted line: Single brief application followed by a washout from the middle ear. Thin horizontal lines represent the values for vestibular perilymph.

vestibule. It is apparent that the basal region of the cochlea was exposed to higher gentamicin levels than the vestibule, whereas the apical regions of the cochlea were exposed to lower levels.  $C_{max}$  and area under the curve (AUC) plots are also given for simulated continuous delivery for 7 days and for a single brief application without volume stabilization. Continuous delivery resulted in substantially higher  $C_{max}$  and AUC, whereas the brief one-shot application gives substantially lower absolute drug levels. In addition, the relative distribution of gentamicin, as quantified by  $C_{max}$ , depended on the application method. For the brief, one-shot application, the basal-apical gradient of  $C_{max}$  was high, whereas for continuous delivery, the basal-apical gradient for  $C_{max}$  was lower. By contrast, comparison of the AUC curves shows them to be displaced in a parallel manner, indicating that the application method had little influence on the relative distribution of drug.

**Extrapolation to human cochlea dimensions**

Using parameters derived from simulations of chinchilla data, curves relating  $C_{max}$  and AUC were calculated for fluid space dimensions corresponding to the human, as shown in Fig. 7. These simulations used a single application with volume in the middle ear stabilized. Chinchilla curves are also shown for comparison. The simulations show that even with consideration of different scala sizes, predicted  $C_{max}$  and AUC at the base of the human and chinchilla cochlea are similar. The major difference is related to the length of the human cochlea, with scala tympani length approximately twice that of the chinchilla. Drug levels reaching the apex of the chinchilla cochlea are low, with  $C_{max}$  being lower by a factor of 10 and AUC lower by a factor of 5.2 at the



**FIG. 7.** Calculated drug distribution for cochlear dimensions representing the human, using parameters derived from chinchilla experiments. Profiles are calculated for single drug application with volume in the middle ear stabilized. Curves for the chinchilla (filled circles), taken from Figure 7, are shown for comparison. For both maximum concentration ( $C_{max}$ ) and area under the curve (AUC), larger gradients along the scala tympani are present in the human because the spread of drug is dominated by diffusion, and the scala tympani is more than twice the length in the human.

apex compared with the base. This situation is even more pronounced for cochlear dimensions corresponding to the human, in which it is calculated that  $C_{\max}$  is 100 times lower and AUC is 40 times lower at the apex than at the base. It is also notable that vestibule gentamicin levels quantified by  $C_{\max}$  or AUC are calculated to be lower by a factor of approximately 3 for the human.

## DISCUSSION

Topical application onto the round window membrane is a promising way of getting drugs to target structures within the inner ear. Using different application systems, drugs can be delivered that cannot be given systemically because of unfavorable risk-benefit ratios or systemic side effects. At present, however, it is difficult to compare different delivery systems, doses, and timing protocols used for local drug application to the inner ear in humans. Simulations of drug movements in the inner ear can potentially provide a basis by which different treatment protocols can be compared and the effects of changes in treatment protocols estimated. To our knowledge, the current study is the first to consider movements of the clinically relevant drug gentamicin in the inner ear fluids as a function of location and time. The study used a simulator that incorporated many factors, of which some were held constant (scalae dimensions, round window membrane area, diffusion coefficient for gentamicin, initial concentration, and applied volume) and a limited number varied (round window membrane permeability, local interscala communication rate, and clearance). From the simulation of experimental data and consideration of which parameters are of greatest importance, conclusions regarding the design and the interpretation of clinical and animal experimental studies can be drawn.

We can conclude that entry of drug into the vestibule does not occur by diffusion along the perilymphatic scalae, passing through the helicotrema. Because of the distances involved, the predicted time course would be slower and the calculated peak concentration could not reach the levels reported (Fig. 3). 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 (19,26). We cannot at present differentiate between local communication between the perilymphatic scalae, or communication of each perilymphatic scala with the endolymphatic space, but the simulations demonstrate that gentamicin must cross readily between the scala tympani and the scala vestibuli, and from there diffuse into the vestibule. This may partially account for the known vestibulotoxicity relative to cochleotoxicity.

It can also be concluded that 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 to generate the observed time courses. Disabling clearance from either the middle ear or co-

chlear fluids resulted in a very slow decline of drug after the peak, quite unlike that documented by Hoffer et al. (9,11) and Balough et al. (10) (Fig. 3). Again, because of the limited data available, we could not differentiate numerically between rates of clearance at different sites. Instead we used a pooled value representing all sites.

Several implications arise from the high rate of local interscala communication relative to the slow rate that gentamicin diffuses longitudinally along the scalae. When drugs are applied to the round window membrane, they do not become uniformly distributed throughout the inner ear fluid compartments. The drug concentration time course (defined by its shape,  $C_{\max}$ ,  $T_{\max}$ , and AUC) varies throughout the inner ear. Peak concentration levels ( $C_{\max}$ ) and dose (AUC) exhibit longitudinal gradients along the cochlear scalae and differences between various fluid compartments (Figs. 5 and 6). The simulations predict that the basal region of the cochlea is exposed to higher gentamicin levels than the vestibule, whereas the apical regions of the cochlea are exposed to lower levels. Similar concentration gradients along the scala tympani have been demonstrated in experiments using ionic markers (15). Differences in toxicity to vestibular and cochlear hair cells cannot necessarily be inferred from such plots because it is likely that the sensitivities of cochlear and vestibular hair cells to gentamicin are not equal. Nevertheless, the quantification of drug level differences is important to an understanding of the general patterns of effects of drugs on different target structures within the inner ear.

It can also be concluded from our simulations that different delivery systems may create substantially different pharmacokinetic profiles in the inner ear, resulting in differences in absolute and relative drug levels and time courses (Fig. 6): a conclusion that has been generally supported by recent experimental studies (13). A single brief application without volume stabilization is expected to result in low absolute drug levels in the inner ear. It is noteworthy that in the clinical literature, single or repeated intratympanic injections of gentamicin are now commonly used in the treatment of Ménière's Disease (28). This analysis did not include simulations of repeated intratympanic injections because clinical protocols can vary between multiple applications per day (2,8) and applications once or twice per week (7,28). Specific protocols can, however, be simulated using the computer program, which is available to the public as described in Materials and Methods, in conjunction with the parameters used in this study.

The single drug application with volume in the middle ear stabilized is calculated to cause higher absolute drug levels in the inner ear if compared with a single brief application without volume stabilization. This demonstrates that drug levels in the inner ear depend highly on how long the applied substance remains in the middle ear. For clinical treatment, it is therefore important to closely control the time the drug persists in the middle ear. This has already been attempted in clinical settings, for example by applying drugs onto patches of Gelfoam

(3) or via a wick (4). The highest inner ear drug levels would be reached with continuous drug delivery.

We found that the gradient of  $C_{\max}$  from the basal to the apical region of the scala tympani was highest for a brief intratympanic injection followed by washout of the middle ear.  $C_{\max}$  was most evenly distributed among the cochlear fluid spaces for continuously delivered drugs (Fig. 6). One consequence of the dependence of  $C_{\max}$  on the delivery system is that to achieve a similar  $C_{\max}$  in the vestibule, the very basal region of the scala tympani would be exposed to far higher levels with the single brief one-shot than it would be with continuous delivery. Thus, if the effect of the drug is dominated by  $C_{\max}$ , then the chosen application method would be expected to influence toxicity patterns along the cochlea. The model also predicts that although the absolute dose, as quantified by AUC, varies with delivery method, the relative distribution of the drug dose is independent of the delivery method (Fig. 6). Thus, if drug effects are dominated by the AUC, then the chosen application method is predicted to have a negligible influence on relative toxicity patterns.

Because the relative distribution of drugs along the scala tympani is determined predominantly by rates of diffusion and clearance, the above conclusions are expected to be more significant for larger cochleae, as in the human. One major factor in attempts to extrapolate results from animal experiments to humans is the need to consider the larger size of the human inner ear. Simulations using anatomic parameters appropriate for the human permit the influence of cochlear dimensions to be assessed. Our analysis indicates that the gradients of  $C_{\max}$  and AUC are greater for human inner ears than chinchillas. Because vestibule gentamicin levels are calculated to be lower by a factor of approximately 3 for the human inner ear, it is suggested that higher drug levels in the basal turn of the human cochlea may be required to achieve a similar drug concentration in the vestibule. Comparisons of relative vestibulotoxicity and cochleotoxicity performed in animals may need to consider such anatomic differences.

The simulations presented here are not intended to provide a quantitative estimation of drug levels in the human ear. Simulations are limited by presently unknown pharmacokinetic parameters for the human, such as round window permeability and clearance rates. Rather, this analysis is intended to focus attention on the general principles that likely underlie drug dispersal in the ear, and on the relevant parameters that must be estimated to make accurate predictions. Some uncertainty in the simulations may also be attributable to the experimental data on which they are based. Although the experimental time courses are based on extensive and technically difficult studies in a large number of animals, the fact that only a single measurement can be made from each animal makes the derivation of the time course difficult and subject to interanimal variations. Nevertheless, it is apparent that a close approximation to the experimental time course is possible using calculations

based entirely on general pharmacokinetic principles and the passive physical processes of drug movement.

## CONCLUSIONS

Because direct pharmacokinetic studies cannot be performed with the human inner ear, an alternative is to predict drug levels with mathematical simulations based on general principles of drug dispersal derived from animal studies. Such simulations are especially useful because they permit different treatment protocols to be compared. Our analysis demonstrated that gentamicin applied to the round window membrane readily spread to the vestibule by local communication between the scala tympani and the scala vestibuli in the basal turn and not by diffusion via the helicotrema. Drug levels and spatial distribution were markedly influenced by the time the applied drug remained in the middle ear. Absolute drug levels in the inner ear and the relative distribution as quantified by peak concentration were highly influenced by the delivery method. This needs to be considered in conjunction with the therapeutic range of the drug when choosing a specific delivery strategy. Because the relative distribution of drugs along the scala tympani is determined predominately by rates of diffusion and clearance, basal-apical gradients are larger for cochleae of human size than for experimental animal cochleae, which typically have smaller dimensions. These differences affect the application of results from animal experiments to clinical practice.

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