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Rapid clearance of methylprednisolone after intratympanic application in humans

The study by Bird and co-authors (1) is extremely important to the field of drug delivery to the inner ear as it provides the first measurements of human perilymph levels of a glucocorticoid (methylprednisolone, MP) following local intratympanic application. Perilymph samples were taken at various times (20 min to 3 hrs) after application and the measurements tabulated. However, because of the variability they observed, the authors chose to pool their data which were presented as a simple scatterplot. We re-analyzed the raw data taking into account the timing of the samples, from which we have been able to derive important pharmacokinetic parameters for MP entry into the inner ear. The symbols in Figure 1 show Bird et al.'s data re-plotted based on the sample timing information. It is apparent that samples taken at 1 hour show consistently higher levels than samples taken at longer times (2 hrs, 3 hrs) that are uniformly low. We have used computer simulation methods (2) to calculate expected sample concentration time courses as kinetic parameters were varied. The most important variable affecting the time course is the rate of drug clearance from the system. The rate of clearance was varied while calculating the sum of squares of deviations between calculated sample values and those obtained experimentally. The lowest sum of squares, indicating best fit, was found with a clearance half-time of 27 min. This estimated rate of clearance for MP was somewhat faster than that calculated for prednisolone based on prior experiments in guinea pigs, which occurred with a half-time of 130 min (2;3).

Bird et al.'s data show that MP is rapidly eliminated following a single intratympanic application in humans. We believe the time course results from two competing processes. Initially, MP perilymph concentration increases as a function of application time. As time progresses, clearance of drug from the middle ear and perilymph counteracts the increase and results in declining concentration with time. Due to this rapid rate of clearance, in order to maximize glucocorticoid levels in the inner fluids and tissues, the drug concentration in the RW niche needs to be maintained.

Even considering the likely time course followed, the variation of samples values is large, as correctly pointed out by the authors. However, the degree of variation is comparable to that observed with round window (RW) delivery of dexamethasone in animals (3-5). Our calculations show that the perilymph drug level achieved is highly dependent on the time of contact of drug with the RW membrane. In contrast, the applied drug volume plays a lesser role. Based on the RW membrane permeability, the amount of drug entering the cochlea is a small proportion of that applied. Loss of drug from the RW niche to regions other than the cochlea is of far greater significance. This can occur either by the loss of volume from the middle ear, such as loss through the Eustachian tube, or as adsorption by the mucosa, which can cause drug concentration to decrease without an associated volume change. The important

Details of simulation parameters: The simulation program (available at <http://oto.wustl.edu/cochlea/>) was set with cochlear dimensions appropriate to the human and a diffusion coefficient for MP of $0.784 \cdot 10^{-9} \text{ m}^2/\text{s}$. Simulation of the application to the RW niche used an applied volume of 1 ml at a concentration of 40 mg/ml. It was assumed that the 20 μl sample volume taken experimentally originated from the most basal 12 mm of scala tympani which, based on the scala cross-sectional area data, makes up this volume. As the sites of clearance cannot be definitively established, the same rates were used to define clearance from the middle ear and the cochlear fluids. A RW permeability of $7.8 \cdot 10^{-9} \text{ m/s}$ and clearance half time of 27 min generated the best fit curve.

conclusion is that a high concentration on the RW membrane must be maintained in order to maximize drug entry into perilymph either by replacing the drug solution at intervals or by using a sustained delivery vehicle.

Reference List

1. Bird PA, Begg EJ, Zhang M, et al. Intratympanic Versus Intravenous Delivery of Methylprednisolone to Cochlear Perilymph. *Otol Neurotol* 2007;28:1124–1130. [PubMed: 18043438]
2. Plontke SK, Salt AN. Quantitative interpretation of corticosteroid pharmacokinetics in inner ear fluids using computer simulations. *Hear.Res* 2003;182:34–42. [PubMed: 12948599]
3. Bachmann G, Su J, Zumege C, et al. Permeabilität der runden Fenstermembran für Prednisolon-21-Hydrogensuccinat. *HNO* 2001;49:538–542. [PubMed: 11486587]
4. Hahn H, Kammerer B, DiMAuro A, et al. Cochlear microdialysis for quantification of dexamethasone and fluorescein entry into scala tympani during round window administration. *Hear.Res* 2006;212:236–244. [PubMed: 16442251]
5. PlontkeSKBiegnerTKammererBDexamethasone Concentration Gradients Along Scala Tympani After Application to the Round Window Membrane. *Otol Neurotol*2008;Epub ahead of print Feb 11.

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Solid symbols: Measured MP concentrations reported by Bird et al. (1) plotted as a function of the time between drug application and sampling. **Lines:** Predicted time courses derived from simulation of the application and sampling protocol. The solid curve shows the best fit to the data, derived by minimizing the sum of squares of differences between measured and calculated values (inset graph). Dashed lines show curves calculated for 0.5x (13.3 min) and 2x (54 min) clearance values and scaled to the same peak amplitude, to demonstrate the expected time course as clearance rates were varied.