State-of-the-Art Mini-Symposium: From Bench to Bedside: Latest Advances in Inner Ear Regeneration and Otoprotection

Drug Delivery to the Inner Ear: Pharmacokinetic Principles and Influence of Drug Properties and Delivery Paradigms

Stefan K. Plontke
Department of Otorhinolaryngology, Head and Neck Surgery, Martin-Luther-University Halle-Wittenberg, Germany
Disclosure:

Yes, within the last 12 months, I have/had a financial arrangement or affiliation with commercial interests related to the content of this continuing education activity that requires disclosure.
<table>
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<th>Name of Commercial interest/ Company</th>
<th>Spouse/ Partner</th>
<th>Grant/ Research Support?</th>
<th>Consultant?</th>
<th>Stocks/Bonds? (Exclude mutual funds)</th>
<th>Speakers Bureau?</th>
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Drug movements in the inner ear

Salt and Plontke (2018) Hearing Research
Pharmacokinetic Basis of Drug Delivery to the Inner Ear: LADME

- **Liberation**
  - Controlled release devices

- **Adsorption**
  - RW
  - Oval window, annular ligament
  - Bony wall
  - Blood vessels, mucosa

- **Distribution**
  - Diffusion or active transports
  - Borders between compartments
  - Partitioning, Re-Partitioning

- **Metabolism**
  - (e.g. DexP $\rightarrow$ Dex)

- **Elimination**
  - Clearance from middle and inner ear

Rask-Anderson et. al (2006)

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Rask-Anderson et al. (2006)

Adopted from: Plontke, Wood and Salt (2002)
High variability of intracochlear drug concentration in scala tympani (guinea pig) after RW delivery

- Parnes et al. (1999)
- Bachmann et al. (2001)
- Hahn et al. (2006)
- Plontke et al. (2007), (Gent)
- Plontke et al. (2008), (Dex)
- and others
Low and variable entry rates for dexamethasone after RW- application

<table>
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<th>Study</th>
<th>% of applied concentration*</th>
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<td>Hahn et al. 2006</td>
<td>2.9</td>
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<td>Plontke et al. 2008</td>
<td>1.4</td>
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<tr>
<td>Wang et al. 2011</td>
<td>0.05</td>
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<tr>
<td>Parnes et al. 1999</td>
<td>0.04</td>
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<td>Borden et al. 2011</td>
<td>0.04</td>
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<tr>
<td>Liu et al. 2006</td>
<td>0.005</td>
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<tr>
<td>Chandrasekhar</td>
<td>0.0013</td>
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*Mean maximum as % of applied concentration. Sampling times and sampling methods may vary. Sampling method may cause artefacts in some studies.
Relative gentamicin entry rates at the stapes, apex and RW membrane

Mean: 35.5% 7.2% 57.3%

Note high variation, e.g. at stapes varying from 7% to 65% of the total.

Salt AN, Hartsock JJ, Gill RM, King E, Kraus FB, Plontke SK (2016) Hear Res
Entry of substances into perilymph through the bone of the otic capsule after intratympanic application

Extrapolation from animal experiments to the situation in the human:

No substance entry at the apex of the human cochlea

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Rask-Anderson et al. (2006)

Adopted from: Plontke, Wood and Salt (2002)
High variability of absolute intracochlear drug concentration and Drug gradients along scala tympani after RW delivery

Mynatt, ... Plontke, Salt (2006) JARO
Plontke et al. (2007) Laryngoscope
Plontke et al. (2008) Otol Neurotol
Pharmacokinetic Basis of Drug Delivery to the Inner Ear: LADME

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Adapted from: Plontke, Wood and Salt (2002)
Rapid elimination: Concentration after 120 min delay for different substances

**Elimination t$_{1/2}$ (min):**

- Fluorescein: 54.1
- TMPA: 24.5
- Dex: 22.5

Elimination not uniform throughout the ear, most rapidly from scala tympani.

Salt, Hartsock, Gill, Piu, Plontke (2012) JARO
Clinical Trade-off Between **Control of Drug Level** and **Risk**

- **High Risk**
  - Improve the safety of quantitatively reliable intralabyrinthine applications
- **Acceptable Risk Level**
  - Improve the quantitative reliability of safe intratympanic applications
- **Low Risk**
  - Drops in Ear Canal + Tympanostomy
  - Microwick
  - One Shot Intratympanic Injection
  - Biopolymer in RW niche
  - Continuous application to RW niche via catheter
  - Intracochlear injection into "intact" ear
  - Intracochlear delivery combined with implant

**Target zone**

**Control of Perilymph Drug Concentration**

Salt & Plontke, Audiol Neurotol (2009)
Obstruktionen im Bereich der Rundfensternische


Obstruktionen gesamt

33.2%

Zusätzliche Membran

21.3 %

Bindegewebe

10.4 %

Fettgewebe

1.5 %
Review Article

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

Alec N. Salt a, *, Stefan K. Plontke b

a Department of Otolaryngology, Washington University School of Medicine, St. Louis, MO, USA
b Department of Otorhinolaryngology, Head and Neck Surgery, Martin Luther University Halle-Wittenberg, Halle (Saale), Germany
Membrane permeation-related characteristics, WLOGP (lipid solubility, Y-axis) and TPSA (topological polar surface area; X-axis) for a number of drugs calculated by the SwissADME website (http://www.swissadme.ch). The yellow ellipse bounds the statistical range for molecules that pass through the blood-brain barrier and the white ellipse bounds the range for molecules that permeate the gut (Daina and Zoete, 2016; Daina et al., 2017). Based on this analysis, dexamethasone and methylprednisolone would be expected to permeate membranes more readily than dexamethasone-phosphate, methylprednisolone-hemisuccinate, and methylprednisolone-succinate. Gentamicin would be expected to be substantially less permeable than all forms of the steroids.
Clinical Trade-off Between Control of Drug Level and Risk

- High Risk
- Acceptable Risk Level
- Low Risk

Control of Perilymph Drug Concentration

- Poor
- Excellent

Hearing Risk from Drug Application

- Low Risk
- High Risk

- Intracochlear injection into “intact” ear
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- One Shot Intratympanic Injection
- Microwick
- Drops in Ear Canal + Tympanostomy

Target zone

Salt & Plontke, Audiol Neurotol (2009)
Biodegradable Polymer Drug Delivery - System in the RW niche of humans – first experience

0.7 mg Dexamethasone in PLGA Polymer matrix (arrow head) in the RW niche

Plontke et al. (2014) Otology & Neurotology
Clinical Trade-off Between Control of Drug Level and Risk

- **High Risk**: Intracochlear injection into “intact” ear
- **Acceptable Risk Level**
  - Intracochlear delivery combined with implant
  - Continuous application to RW niche via catheter
- **Low Risk**: Biopolymer in RW niche
- **Control of Perilymph Drug Concentration**
  - **Poor**
    - Drops in Ear Canal
    - Microwick
    - One Shot Intratympanic Injection
  - **Excellent**

Salt & Plontke, Audiol Neurootol (2009)
Normal sensitivity is well-maintained with artificial perilymph (AP) injection and high frequency sensitivity is suppressed by salicylate.
Clinical Trade-off Between Control of Drug Level and Risk

- High Risk
  - Intracochlear injection into "intact" ear
  - Intracochlear delivery combined with implant
  - Continuous application to RW niche via catheter
- Low Risk
  - Biopolymer in RW niche
  - One Shot Intratympanic Injection
  - Microwick
  - Drops in Ear Canal + Tympanostomy

Control of Perilymph Drug Concentration

- Poor
  - Hearing Risk from Drug Application
- Excellent
  - Target zone

Salt & Plontke, Audiol Neurootol (2009)
Drug Delivery with Cochlear Implants

Possible ways of implementing drug delivery from cochlear implant electrode carriers

„Dissolved drug“  „Coating“  Drug Delivery Channel and (external?) drug reservoir
Calculated pharmacokinetics in scala tympani

Daily injections 5x total (Dex-P 4mg/ml; 0.3mL; 30min)

Controlled release drug delivery system (OZURDEX®) intracochlearly next to CI-electrode in ST (Dex-base 0.7mg)

from Plontke et al. (2016) HNO
Acknowledgements

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Thank you for your ear!
Welcome to the 100th anniversary of the German Society of Otorhinolaryngology, Head and Neck Surgery
May 2021
Berlin, Germany