The future of inner ear drug delivery

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Inserm U1008: Controlled Drug Delivery Systems and Biomaterials
Why Controlled Drug Delivery?

Drug concentration at the site of action

Efficacy & Safety

Uncontrolled release

Minimal toxic concentration

Controlled release

Minimal effective concentration

Therapeutic window

Efficacy & Safety

Efficacy & Safety

Efficacy & Safety

Efficacy & Safety
Drug delivery to the inner ear

General administration

Intra-cochlear administration
Blood-Cochlear barrier

1- Middle ear administration and cochlear diffusion via the round window

2- Cochlear injection

3- Cochlear administration with controlled diffusion: drug eluting devices
Intracochlear devices

Extracochlear devices
Ear Cubes for local controlled drug delivery to the inner ear

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Results: DXM Release

Silicone-based implants

Drug release was prolonged and continuous during the observation period (90 days for implants).

\[
\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2} \sum_{n=0}^{\infty} \frac{1}{(2n+1)^2} \exp\left(-\frac{D(2n+1)^2 \pi^2 t}{L^2}\right)
\]
Materials and methods: Implantation

12 Mongolian gerbils implanted bilaterally

Risoud et al, Hear res, 2016
Materials and Methods

- Cochlea preparation: dissection, fixation (and decalcification for the whole cochlea)

organ of Corti

whole transparent cochlea
Controls

Positive: DXM intratympanic injection

Negative: saline & unloaded ear cube
Results: Confocal Microscopy with DXM cube

Detection of specific anti-DXM fluorescence (green labeling) in the hair cells

[Image: Confocal microscopy images showing DAPI, DXM, Phalloidin, and 3 labeling]
Results: Specific labeling

Location of anti-DXM labeling in inner hair cells and outer hair cells of organ of corti
Results: Staining intensity

Detection of anti-DXM labeling inside hair cells 20 min post-implantation and even at day 30. Climax for the cochlea collected at day 7 post-implantation.
Conclusion

- A new device for local drug delivery into the inner ear using a non-degradable polymeric silicone matrix placed at the level of the oval window

- Continuous and prolonged release from DXM-loaded implants for 90 days adapted for chronic ear disease treatment

- Carrier for other drugs or therapies (e.g. gentamycin, diuretics...).

Intracochlear devices

Extracochlear devices
Modified electrode: Drug is added to the silicone matrix

Intra-cochlear implants
Physical state of the drug: SEM of cross sections

- Surface of a polymeric film loaded with 10 % DXM
- Cross section of an extrudate loaded with 1 % DXM
- Cross section of a polymeric film loaded with 10 % DXM
- Cross section of an extrudate loaded with 10 % DXM.
Drug release mechanisms

Silicone implants loaded with dexamethasone
Implantation of DXM+ and DXM - electrodes

• Pre-op hearing testing

• Implantation of 20 gerbils:
  – one ear with a DXM+ electrode (1 & 10 %),
  – the other with a DXM- electrode

• Post-op hearing testing @ 1 month and 1 year
In vivo study

- Active dexamethasone electrode array with controlled release allows a better conservation of hearing thresholds at 1 month for 500, 1000, 2000, 4000 and 16000 Hz and at 1 year for 16000 Hz in our gerbil model.

Krenzlin et al, J Control Release (2012)
Douchement et al, Cochlear Implants Int (2014)
Cochlear implants: long term safety?
Cell population

![Graph showing cell population for different cochlear conditions: DXM 1% electrode array, DXM - electrode array, and Control. The graph compares inner ear hair cells (blue) and outer ear hair cells (orange).](image)
DXM + electrode & chronic implantation

• Change in the electrode/tissue interface
• Lower impedances than compared to the DXM – side
• Imaging of transparent whole cochleas
  – confocal microscopy
  – lightsheet microscopy
• Study large surfaces and volumes
  – fibrosis: lower impedance=less fibrosis (to be confirmed on a long term basis!)
  – other intracochlear phenomenoms (apoptosis...)
• Difficult to obtain statistical significance (more animals)
Preservation of cochlea after cochlear implantation

• Preservation of structure
  – less invasive electrode
  – better preoperative analysis of the cochlea
  – better control of insertion, better quality control

• Preservation of function
  – drug eluting electrodes
  – DXM is a starting point (”cochlear cocktail”?)
  – Controlled drug delivery is mandatory
Inserm U1008: Controlled Drug Delivery Systems and Biomaterials: J. Siepman, C. Vincent

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