The future of inner ear drug delivery

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Why Controlled Drug Delivery?

Drug concentration at the site of action

- **Uncontrolled release**
- **Controlled release**

**Therapeutic window**

- **Minimal toxic concentration**
- **Minimal effective concentration**

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).

\[ \frac{M_\infty - M_t}{M_\infty} = 1 - \frac{8}{\pi^2} \sum_{n=0}^{\infty} \frac{1}{(2n+1)^2} \exp \left( -\frac{D(2n+1)^2 \pi^2 t}{L^2} \right) \]
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 of Confocal Microscopy with DXM cube]

- DAPI
- DXM
- Phalloidin
- Anti-DXM labeling
- 3 labeling
Results: Specific labeling

Location of anti-DXM labeling in inner hair cells and outer hair cells of organ of corti

*Phalloidin, DAPI, DAPI, anti-DXM labeling, Phalloidin, DAPI, anti-DXM labeling*
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
Drug release mechanisms

Silicone implants loaded with dexamethasone
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.
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?
Confocal microscopy on whole transparent cochlea
Cell population

![Bar graph showing the population of hair cells in different conditions.](image)

- **DXM 1% electrode array**: 83.5 (56-120) hair cells/25000 μm²
- **DXM - electrode array**: 64.2 (52-82) hair cells/25000 μm²
- **Control**: 74.6 (68-88) hair cells/25000 μm²

**Legend**:
- **Inner ear hair cells**
- **Outer ear hair cells**
The drug loading was 10 and 30% dexamethasone.

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!)
  – other intracochlear phenomenons (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
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The authors are very grateful to the ANR (The French National Research Agency) for their financial support (N° ANR-15-CE19-0014-01) and Oticon medical