Intratympanic Drug Delivery

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Advantages of intratympanic delivery

- Higher concentration of drug at site of action
- Avoid systemic effects
  - May be able to use some medications that would not be tolerated if delivered systemically (e.g. neurotransmitter antagonist)

Drug delivery to the inner ear

Requirements for effective drug delivery via intratympanic

- Drug must cross round window membrane
- Drug is tolerable when injected into the middle ear
- Can achieve adequate concentration in middle ear

Drug delivery to the inner ear

Indications for intratympanic drug delivery

- Otitis media with perforation or tube
- Meniere disease
- Idiopathic sudden sensorineural hearing loss
- Tinnitus
- Chronic unremitting otalgia-diagnostic
- Autoimmune inner ear disease
- Noise induced hearing loss
**Intratympanic medications**

- Aminoglycosides (e.g. gentamicin) - ablate vestibular function, cytotoxic
- Steroids (e.g. dexamethasone) - modulate inflammatory or immune responsive, cytoprotecive
- Neurotransmitters and antagonists - tinnitus
- Monoclonal antibodies - autoimmune inner ear disease
- Apoptosis inhibitors (e.g. AM-111) - noise induced hearing loss

**Intratympanic Drug Delivery**

- Single or repeated injections
- Via tympanostomy tube or wick
- Microcatheter

**Set up for intratympanic injections**

**Intratympanic injections**

**Microcatheters for drug delivery**

**Hypothesis of Meniere’s disease**

Multiple factors contribute to the development of endolymphatic hydrops which in turn causes symptoms of Meniere’s disease.
Endolymphatic hydrops (Meniere disease)

Management of Meniere disease

- Low salt diet
- Diuretics
- Steroids (systemic or intratympanic)
- Surgery for intractable cases (<30%)

Surgical management of intractable Meniere’s disease

- Endolymphatic shunt - placement of silastic shunt into endolymphatic sac
- Controversial - 70% success rate
- Non-destructive - outpatient with short recovery period

Surgical management of intractable Meniere disease

- Labyrinthectomy - destruction of vestibular organs, requires period of compensation (3-6 weeks)
  - Surgical - >95% success rate, total hearing loss - best for individuals with poor hearing.
  - Chemical (gentamicin) - 70-85% success rate, 10-20% hearing loss, long term compensation sometimes not complete.
<table>
<thead>
<tr>
<th><strong>Surgical management of intractable Meniere disease</strong></th>
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<tbody>
<tr>
<td>• Vestibular nerve section- most complex procedure, requires craniotomy</td>
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<tr>
<td>• 90-95% success rate, 5% hearing loss</td>
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<td>• Best for young patients with good hearing</td>
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<td>• 3-6 weeks recovery period</td>
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<th><strong>Intratympanic medications used to treat Meniere disease</strong></th>
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<td>• Aminoglycosides (e.g. gentamicin)- ablate vestibular function, cytotoxic</td>
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<th><strong>Aminoglycosides for Meniere disease</strong></th>
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<tr>
<td>• Gentamicin and streptomycin are preferentially toxic to vestibular hair cells</td>
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<tr>
<td>– Neomycin and kanamycin are preferentially toxic to auditory hair cells</td>
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<tr>
<td>• Response is individual—genetic susceptibility (12S rRNA mutation)</td>
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<tr>
<td>• Gentamicin 40 mg/ml (intravenous preparation)</td>
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<tr>
<td>• Buffered with 8.4% sodium bicarbonate</td>
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<tr>
<td>• Final concentration- 26.7 mg/ml, pH of 6.4</td>
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<td>• Multiple dosing schemes</td>
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<tr>
<td>– Single injection</td>
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<td>– Multiple injections (2-4)</td>
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<td>– Tube or wick application</td>
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<tr>
<td>• Generally accepted to be therapeutically</td>
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<td>– Vertigo control: 75-90%</td>
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<td>– Hearing loss 5-30%</td>
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<td>• More difficult recovery (compensation) in elderly patients</td>
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<th><strong>Multiple gentamicin injections to control Meniere disease</strong></th>
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<td>• Criteria for repeated injections</td>
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<tr>
<td>– Persistent vertigo</td>
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<tr>
<td>– Residual caloric response</td>
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<td>– Stable hearing</td>
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Intratympanic steroids for Meniere disease

- Advantages
  - not cytotoxic
  - minimal risk of HL
  - doesn't require recovery period
- Multiple delivery and dosing schemes
- Other studies with variable outcomes

Sudden SNHL (SSNHL)

- 30 dB or greater SNHL over at least three contiguous audiometric frequencies occurring within 3 days or less
- Likely viral or vascular etiology when other causes (barotrauma, PLF) eliminated
- Treatment more effective if started within first 2 weeks

Asymmetric SNHL or tinnitus: Diagnostic Testing

- 1-2% of patients with asymmetric SNHL or tinnitus have a retrocochlear lesion
  - MRI:
    - Thin cuts through IAC
    - Most sensitive with gadolinium, heavily weighted T2 images (CISS, Fiesta) are adequate if contrast is a concern
  - Auditory brainstem response (ABR) very sensitive for medium to large tumors, may miss small tumors
    - Use in older patients

Acoustic Neuroma/Vestibular Schwannoma

SSNHL: Treatment

- Proposed treatment modalities
  - Anti-inflammatory – steroids, cytotoxic agents
  - Antiviral agents
  - Apoptosis inhibitors, free radical scavengers
  - Diuretics
  - Vasodilators
  - Volume expanders/hemodilutors
  - Defibrinogenators
  - Carbogen

Intratympanic steroids for ISSNHL

- At least 25 studies since 1996
- Most report improvement
- All complicated by enrollment biases, lack of ideal control group
### Other uses for intratympanic drug delivery

- **Intractable otalgia**
  - Lidocaine - diagnostic
- **Tinnitus**
  - Multiple drugs including neurotransmitter antagonists (e.g. glutamate)
- **Autoimmune inner ear disease**
  - Steroids
  - Therapeutic monoclonal antibodies
- **Noise induced sensorineural hearing loss**
  - Steroids
  - Anti-apoptosis
  - Free radical scavengers

### Summary

- Intratympanic gentamicin is standard therapy for intractable Meniere disease
- Other uses of intratympanic medicines are less well established
  - Steroids commonly used to treat Meniere disease and sudden hearing loss
- Several promising new therapies are under investigation for a variety of inner ear disorders