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# Intratympanic Therapy in Meniere's Disease

The principle of delivering a drug to the middle ear through the tympanic membrane is not new with reports in the literature from the nineteenth century regarding its efficacy as a treatment for 'catarrhal affections of the middle ear'.<sup>1,2</sup> However, the use of this technique in the treatment for inner ear disorders has only been popularised over the past 20 years particularly in treating Meniere's Disease and more latterly sudden sensorineural hearing loss. This article focuses on intratympanic therapies used in the treatment of Meniere's Disease.

## Current delivery methods

Intratympanic therapies aim to deliver a given pharmacological agent to the inner ear via the tympanic cavity and in so doing optimise inner ear dosage and reduce the risk of developing systemic side effects. However, delivery of drugs to the inner ear is challenging. Systemic delivery has significant limitations with variable penetration due to the presence of a blood-inner ear barrier as well as the risk of significant side effects. Similarly, more direct access to the inner ear is limited because the structures within the labyrinth are contained within hard bone and are only accessible through the middle ear via the round and oval windows. Access is made all the more difficult by the fact that minor trauma to the membranous structures of the inner ear can result in acute labyrinthine failure. In addition, there are a number of potential drawbacks to current intratympanic drug delivery strategies including loss of drug down the Eustachian tube as well as poorly understood intracochlear pharmacokinetics. Some have also expressed concern regarding poor absorption of drug through the round window. However, a recent study by Bird *et al.* has suggested that the dose delivered to the cochlea following intratympanic therapy is 260 times greater than the dose delivered by intravenous therapy.<sup>3</sup>

There are a number of different methods of delivering drugs intratympanically.<sup>4</sup> The most common method of intratympanic drug delivery is injection through the tympanic membrane (Figure 1). A typical regimen for this type of administration is shown in Figure 2.

An alternative method of drug delivery is the Silverstein wick.<sup>5</sup> This consists of a grommet that is inserted into the eardrum in the posteroinferior quadrant over the round window niche. The grommet has a porous

sponge running through the central passage and this can be slid down to come in to contact with the round window niche. Drugs can then be delivered into the external ear canal and they soak the sponge and diffuse down to the middle ear (Figure 3).

Some authors have also described the use of fine catheters placed adjacent to the round window membrane via the tympanic membrane in order to allow prolonged or repeated drug delivery. Pump systems that may be either partly or fully implantable may be used to deliver the drug. However, this technique is associated with a high proportion of complications, particularly accidental dislocation of the catheter, and has not entered widespread use in clinical practice.

## Current intratympanic drug treatments in Meniere's Disease

There are currently two main groups of drug used to treat Meniere's Disease via the intratympanic route. They are aminoglycoside antibiotics and steroids.

### Aminoglycosides

Aminoglycoside antibiotics, particularly gentamicin, are commonly used to treat gram negative bacterial and some types of mycobacterial infection. One of their side effects is ototoxicity and this is the basis for their use in Meniere's Disease.

Most are predominantly cochleotoxic, resulting in sensorineural hearing loss in a significant proportion of patients. However, gentamicin is predominantly vestibulotoxic and is less likely to result in hearing loss.

The mechanism of toxicity is unclear. From pathology studies it would appear that they induce hair cell death within the cochlea at high doses.<sup>6</sup> There is probably a preference for outer hair cells. At lower doses,

they appear to damage the stereocilia of both cochlea and crista sensory cells.<sup>7</sup> They probably also have a damaging effect on the otolithic hair cells although this may be less significant. The mechanism by which these changes are produced is not completely clear. Aminoglycosides are actively transported into cells where they bind to iron. This may then form a toxic metabolite that generates free radicals resulting in cellular injury and cell death.<sup>8</sup> There may also be an effect mediated through a reduction in mitochondrial protein production and an associated reduction in ATP production. This is an attractive hypothesis given that mitochondria have many similarities to bacteria.

The first description of the use of aminoglycosides via the intratympanic approach was by Schuknecht in 1956. He used streptomycin.<sup>9</sup> However, this drug was associated with a very high incidence of sensorineural hearing loss because of its ototoxicity. As a result the popularity of intratympanic injection of aminoglycosides waned until it became clear that gentamicin was equally effective at resolving symptoms but was less cochleotoxic.

There are several papers evaluating the efficacy of intratympanic gentamicin in Meniere's Disease. Unfortunately, the study design and protocols for administration vary widely and this makes comparison of outcomes difficult. Some investigate high dose single injection therapy. Others investigate staged, lower dose administration. This may be given daily, weekly or monthly. Similarly, the end point of treatment varies. This may be the rendering of the labyrinth avestibular or the onset of vestibular symptoms. Onset of hearing should also trigger cessation of therapy.

All studies suggest that intratympanic gentamicin is an effective treatment for vertigo in Meniere's Disease but treatment must balance the need to control symptoms with the potential for cochleotoxicity. The dosage of gentamicin used varies in the literature from 2.4 to 720mg. The effectiveness of intratympanic gentamicin in completely resolving vertigo symptoms in Meniere's Disease varies from 27% to 100% depending on the series.<sup>10-15</sup> A meta-analysis of 27 studies by Chia *et al.* found that the mean complete vertigo control rate for all types of regimen was 73.6%.<sup>16</sup> Low dose staged treatments controlled vertigo completely (AAO vertigo score of 0) in 66.7% of cases. The effective vertigo control rates (AAO vertigo score of 1-40) were 90.2% and 86.8% respectively for all regimens and low dose regimens. The risk of hearing loss (partial and



Figure 1

**A protocol for the administration of intratympanic gentamicin**

- The following procedure can be performed in an out patient setting
- Mix the following in a 2ml syringe:
  - 1.5mls of 80mg/ml gentamicin
  - 0.3mls of water for injection
  - 0.2mls of 84mg/ml sodium bicarbonate
- Place the patient supine with the head flat and turned away from the ear to be injected. Use topical anaesthetic agents such as EMLA or Ametop to anaesthetize the tympanic membrane
- Under the operating microscope, inject the buffered gentamicin through the tympanic membrane in the posteroinferior quadrant just over the round window niche using a spinal needle. The middle ear can be seen to fill up with the fluid
- Leave the patient supine with their head turned away for 40 minutes. The patient may feel some of the drug pass down the Eustacian tube into the nasopharynx
- Repeat injections weekly until they start to experience imbalance as a result of the treatment, their symptoms resolve or if there is a deterioration in their hearing. This is usually 2-3 injections
- Some clinicians prefer to insert a ventilation tube at the time of the first injection in order to avoid the need to facilitate subsequent injections

Figure 2

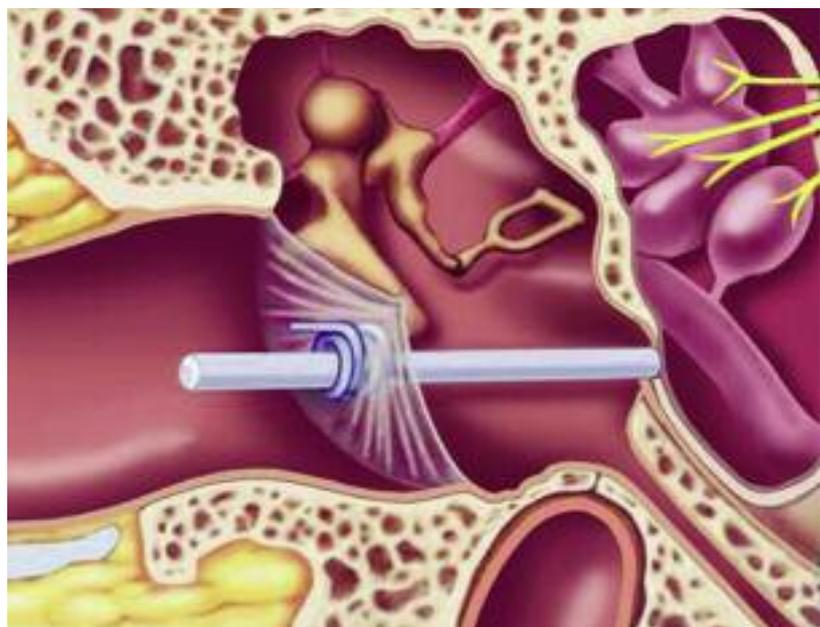


Figure 3

profound) ranged from 0% to 90% but the mean hearing loss for all regimens was 25.1% with low dose regimens producing hearing loss in 13.1%. A recent Cochrane review has further assessed the literature<sup>17</sup> and found only two well designed randomised placebo controlled trials.<sup>10,11</sup> The first study by Stokroos *et al.* suggested that there was a complete resolution of vertiginous symptoms in all patients and that this was significantly greater than placebo. They had no significant hearing deterioration in any patient. The second study by Postema *et al.* showed that vertigo scores reduced from 2.1 to 0.5 in the gentamicin group compared to 2.0 to 1.8 in the placebo group. Average hearing loss in the gentamicin group was 8.1dB compared to 0dB in the placebo group.

From the literature, it would appear that a dose of 30mg/ml administered weekly with end points of resolution of symptoms, onset of vestibular symptoms because of treatment or onset of hearing loss provides the most effective method of symptom control with the lowest risk of hearing impairment.<sup>16,18,19</sup> This may be buffered with 84% sodium bicarbonate in order to reduce discomfort during injection. Between one and four injections may be required to achieve symptom control and further injections may be required in the future. A typical regimen is shown in Figure 1. For low dose treatments, the time taken until further injections are required to control recurrent vestibular symptoms may be in the region of four months.<sup>20</sup>

With regards to modification of other Meniere's symptoms, most studies have found that intratympanic gentamicin does not modify tinnitus but may reduce symptoms of aural fullness.<sup>10,11</sup>

### Steroids

Intratympanic steroid injections have become increasingly popular as a means of controlling vestibular symptoms in Meniere's Disease. They have the potential advantage over gentamicin of not being inherently ototoxic. They are thought to act through an anti-inflammatory effect but may also have an influence on sodium and fluid transport within the labyrinth.<sup>21</sup>

Steroids delivered intratympanically have been used to treat Meniere's Disease since the early 1990s.<sup>22</sup> However, the literature regarding intratympanic steroids in Meniere's Disease is less extensive than that for gentamicin and is

subject to the same limitations of heterogeneous study design.

Intratympanic steroids appear to be effective in controlling vertigo in Meniere's Disease but they are probably less efficacious than gentamicin. The literature would suggest that 41-82% of patients have complete relief of vertigo and 72-91% of patients have adequate control of their vestibular symptoms following treatment. More than four injections may be required in some cases and a proportion require further injections a few months after the original treatment.<sup>23-27</sup> Most studies suggest that hearing is not affected in either a positive or negative way following steroid injection.

There have been no meta-analyses performed investigating the efficacy of intratympanic steroid in Meniere's Disease to date. However, a Cochrane review has been performed by Phillips and Westerberg.<sup>28</sup> They felt that only one randomised placebo controlled trial met rigorous criteria regarding quality. This paper, published by Garduno-Anaya *et al.*, showed that intratympanic 4mg/ml Dexamethasone was an effective treatment in improving vestibular symptoms in Meniere's Disease.<sup>27</sup> Eighty-two per cent of the steroid group achieved complete control of symptoms (AAO class A) compared to 57% in the placebo group. There was no significant change in hearing. There was no significant change in tinnitus.

A number of different steroids have been used in Meniere's Disease. The most commonly used are dexamethasone and methylprednisolone. Doses are very variable between studies. For example dexamethasone doses vary between 1mg/ml and 19mg/ml. Pain may be troublesome following injection although this seems to be less of an issue for dexamethasone. A dose of 4mg/ml of dexamethasone would seem reasonable based on the literature.

As with gentamicin, it would appear that intratympanic steroids do not significantly modify tinnitus associated with Meniere's Disease.<sup>29</sup>

### Failure of intratympanic treatment

It remains unclear why some patients do not respond to intratympanic therapy but there is some evidence that it may reflect ineffective delivery of drug in a significant proportion of cases. Some authors have noted a high incidence of

adhesions or round window thickening in those who fail this form of therapy. In this situation exploration of the middle ear to improve access to the round window followed by direct placement of gentamicin on a pledget onto the round window resolves symptoms in the majority of initial treatment failures.<sup>30</sup>

### When to use intratympanic therapy

Intratympanic treatment with gentamicin or steroid has become the first line of treatment following failure of conservative management in Meniere's Disease. This is because of the documented effectiveness of these drugs and because of the simplicity and safety of the procedure. However, there are very few studies comparing outcomes of these two types of drug. Sennaroglu *et al.* have shown effective vertigo control in 72% of patients with intratympanic dexamethasone, 75% of patients with intratympanic gentamicin and 52% for endolymphatic sac surgery.<sup>24</sup> Other studies are ongoing (Bronstein *et al.* unpublished).

The decision to use gentamicin or steroid is dependent on the amount of hearing remaining in the ear to be treated and on the status of the opposite ear. If there is serviceable hearing in the ear to be treated and the opposite ear has poorer hearing or evidence of significant vestibular impairment then steroid is the drug of choice as it is unlikely to render the patient deaf or avestibular. If the ear to be treated has poor hearing and the opposite ear is healthy then gentamicin is the drug of choice. However, it is important to bear in mind that around 20% of patients will develop Meniere's Disease in the opposite ear at some point.

### Cochlear hydrops

There are a number of papers that have investigated the response of fluctuating sensorineural hearing loss seen in cochlear hydrops to intratympanic steroid injection. The proportion of patients who have an improvement in their hearing is lower than the proportion of patients that get an improvement in their balance symptoms and ranges from 40 to 74% depending on the series.<sup>31,32</sup> Care must be taken when interpreting this data however, as by its very nature the hearing loss is fluctuating and certainly a significant proportion may have improved spontaneously without intervention. Nevertheless, intratympanic steroid injection should be considered for the management of acute hearing loss resulting from cochlear hydrops.

## The future of intratympanic therapy Drug delivery systems

Given the challenges of access to the inner ear, a number of techniques are currently being developed for the delivery of drugs not just via the middle ear but directly to the inner ear.

Microcatheters that deliver drugs directly into the inner ear are currently under development. These have been used in conjunction with pump systems such as osmotic pumps or reciprocating perfusion systems.<sup>33</sup>

One of the primary limitations of current intratympanic therapy techniques is the limited exposure that the round window has to the drug being delivered because of its low viscosity. Hydrogels that can be loaded with a drug and placed over the round window have been demonstrated to improve exposure to the round window by maintaining contact with the drug for a prolonged period.<sup>34</sup>

Vectors such as viral particles or nanoparticles are showing promise as techniques for delivering drugs into the inner ear.<sup>35</sup> The particles can be filled with a 'cargo' such as a drug or gene plasmid and injected into the middle or inner ears. Their delivery to a specific site can be facilitated by the addition of ligands to their surface that aid in transmembrane transport or binding to the target tissue.

## Pharmacological agents

In addition to steroids and gentamicin, therapeutic agents for inner ear disease currently under investigation include anti-oxidants that may confer a protective effect in the prevention of noise induced hearing loss,<sup>36</sup> neurotrophins such as neurotrophin-3 that may stimulate regeneration of cochlear nerve fibres or hair cells,<sup>37</sup> genes that could be spliced into the genome of inner ear cells to stimulate the production of a deficient protein product<sup>38</sup> and stem cell therapies.

## Conclusions

Current intratympanic therapies are effective in treating a significant proportion of patients with Meniere's Disease. Gentamicin is probably more effective than steroids but has a small risk of inducing sensorineural hearing loss. There are many new drug delivery systems and pharmacological agents under development and these may result in the ability to prevent and even reverse Meniere's Disease in the future. ■

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