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Intratympanic gentamicin injection for Meniere's disease

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Meniere's disease is characterized by idiopathic progressive fluctuating hearing loss, tinnitus, and episodic vertigo. Intratympanic gentamicin injection is the preferred therapeutic option for those who have failed conservative management including lifestyle modifications and oral medications. The procedure is simple and can be performed in the outpatient setting under local anesthesia with manageable recovery time. Patients may experience a disequilibrium sensation beginning approximately 3-5 days after injection, which peaks around 10-14 days after injection and fades over the course of several more weeks. The presence of this reaction is an indicator of treatment response. Intratympanic gentamicin injection achieves control of vertigo in 80%-90% of patients. Risks include prolonged imbalance from delayed vestibular compensation after treatment, as well as sensorineural hearing loss, both of which are generally preferable to disabling vertigo attacks.

Introduction

Meniere's disease is a clinical diagnosis of idiopathic progressive, fluctuating hearing loss and episodic vertigo lasting from 20 minutes to 24 hours. The treatment of Meniere's is centered on the treatment of vertigo as there is no convincing evidence that any existing therapies preserve or restore the hearing loss associated with this disease. For some patients, the symptoms of vertigo can be devastating and lead them to seek relief that often cannot be obtained through lifestyle and oral medical therapies alone. For these patients, intratympanic gentamicin has become an attractive therapeutic option, capable of controlling intractable vertigo in up to 95% of patients.[1] The ability to perform this low risk procedure on patients in the clinic makes it an attractive tool for both clinicians and patients. The following chapter describes the technique used to perform intratympanic gentamicin injections, pre- and postprocedural considerations, and the pearls and pitfalls of this therapy.

Preprocedural planning

The clinical features of Meniere's disease include episodic vertigo, hearing loss, and tinnitus. The disease most commonly presents in adults in their fourth or fifth decade of life with a slight female preponderance.[2] According to the American Academy of Otolaryngology-Head and Neck Surgery, the diagnostic criteria for "definite" Meniere's disease includes at least 2 spontaneous episodes of vertigo lasting at least 20 minutes, sensorineural hearing loss of at least 20 decibels, and tinnitus or aural fullness in the affected ear.[3] The symptom of vertigo is characteristically a spinning sensation of 20 minutes to 24 hours in duration and may be accompanied by nausea and/or vomiting. Approximately two-thirds of patients ex-

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perience vertigo attacks in clusters, while the remaining one-third have sporadic attacks.[4] The frequency of vertigo episodes may also decline over time. Hearing loss pattern is variable but often affects low frequencies first, then high frequencies, and finally mid frequencies, resulting eventually in a severe flat audiometric threshold shift.[5] The hearing loss commonly fluctuates, especially earlier in the evolution of the condition and is progressive. The majority of Meniere patients develop a permanent and severe sensorineural hearing loss at all frequencies over an 8- to 10-year period, though there is considerable intersubject variability in the severity and rate of progression.[5] Fluctuations in hearing are usually associated with a sensation of aural fullness or pressure in the affected ear or on the same side of the head. Tinnitus is characteristically a low-pitched roaring sound that may result in auditory distortion.

Physical examination of Meniere's disease patients will show signs and symptoms of a degenerated inner ear, with reduced hearing on the affected side. Tuning fork tests can be normal but with advanced disease usually reveals sensorineural hearing loss of the affected ear. Positive head thrust sign on the affected side is the most common vestibular physical finding and patients may rotate toward the affected side on a Fukuda stepping test. Patients may also tilt or fall to the affected side on Romberg testing or tandem gait testing.[6]

Although there are no gold standard diagnostic tests for Meniere's disease, workup generally includes audiometry, vestibular testing, laboratory testing, imaging studies, as well as tests for endolymphatic hydrops. Audiometry should be performed in all patients with suspected Meniere's disease, with the most common audiometric pattern in early disease course being a low frequency or combined low- and high-frequency sensory loss with normal hearing in the mid frequencies.[7] Vestibular testing is useful for determining candidacy for interventional treatments or identifying bilateral disease. Standard vestibular evaluation includes video- or electronystagmography (VNG/ENG), rotary chair testing. With disease progression, VNG/ENG and rotary chair test should reveal declining peripheral vestibular function in the affected ear. VNG/ENG is more sensitive for inner balance dysfunction, but rotary chair test is more specific.[7] With regard to laboratory testing, comorbid conditions and other causes of vestibular dysfunction should be ruled out. Imaging studies, such as MRI, are not diagnostic but may be indicated to rule out central nervous system lesions like tumors, aneurysms, posterior circulation lesions, Arnold-Chiari malformations, or demyelinating disease that may produce symptoms resembling those of Meniere's disease.[8] Putative tests for endolymphatic hydrops include glycerine, urea, or sorbitol stress tests and electrocochleography, but these have low sensitivity and specificity and therefore little or no role in diagnosis and management of Meniere patients.[9,10] Vestibular evoked myogenic potential can also be useful for both diagnosis and monitoring of disease progression.[11]

Indications

Intratympanic gentamicin injection is the treatment of choice for patients who have been diagnosed with Meniere's disease who have undergone examination and diagnostic testing to exclude other causes of symptoms, and who have failed conservative, noninterventional management strategies. Such strategies include lifestyle modifications like salt restriction or avoidance of spikes in salt intake, stress avoidance, and reduction in caffeine, alcohol, nicotine, and monosodium glutamate intake, as well as medical management with diuretics, antiemetics, anxiolytics, immunomodulators, and/or antihistamines.[12] In patients who also carry a diagnosis of migraine, it is also prudent to give a trial of migraine prophylaxis before resorting to the destructive and irreversible gentamicin treatment.

Contraindications

The only absolute contraindication to intratympanic gentamicin treatment is allergy to the drug. However, as noted above, this treatment is destructive and irreversible. It causes weakening of the peripheral vestibular input from the treated ear and recovery from treatment depends upon central vestibular compensation.[13] Patients with other sensory or motor impairments or with central nervous system disease or advanced age often have a slower and less complete recovery. Permanent imbalance may be preferable to and less disabling than unpredictable and violent attacks of vertigo but this is something that must be considered carefully and discussed thoroughly with patients prior to treatment.

While control of definitive vertigo attacks is achieved in over 90% of patients treated with intratympanic gentamicin, there is some risk of hearing loss.[1,13] Approximately 20%-25% of patients experience a decrement in hearing of the treated ear.[2] If the affected ear has worse hearing already, this is generally not a great concern in therapeutic decision-making. However, if the patient has active Meniere's in their better-hearing ear or bilateral Meniere's disease, the prospect of worsening the hearing and producing bilateral chronic disequilibrium from bilateral vestibular hypofunction with gentamicin must be considered. Since the alternative method of controlling the vertigo in such cases is vestibular neurectomy, which is a major intracranial surgery that also has about 15%-20% risk of hearing decrement, most patients and physicians will still opt for the gentamicin injection.[14]

Procedure technique

Intratympanic gentamicin injection is performed in the outpatient clinic under local anesthesia. The patient is placed in the supine position with the head turned slightly to the "good" side, placing the affected ear slightly upward. The tympanic membrane is visualized under the operating microscope. Local anesthesia is used to numb the tympanic

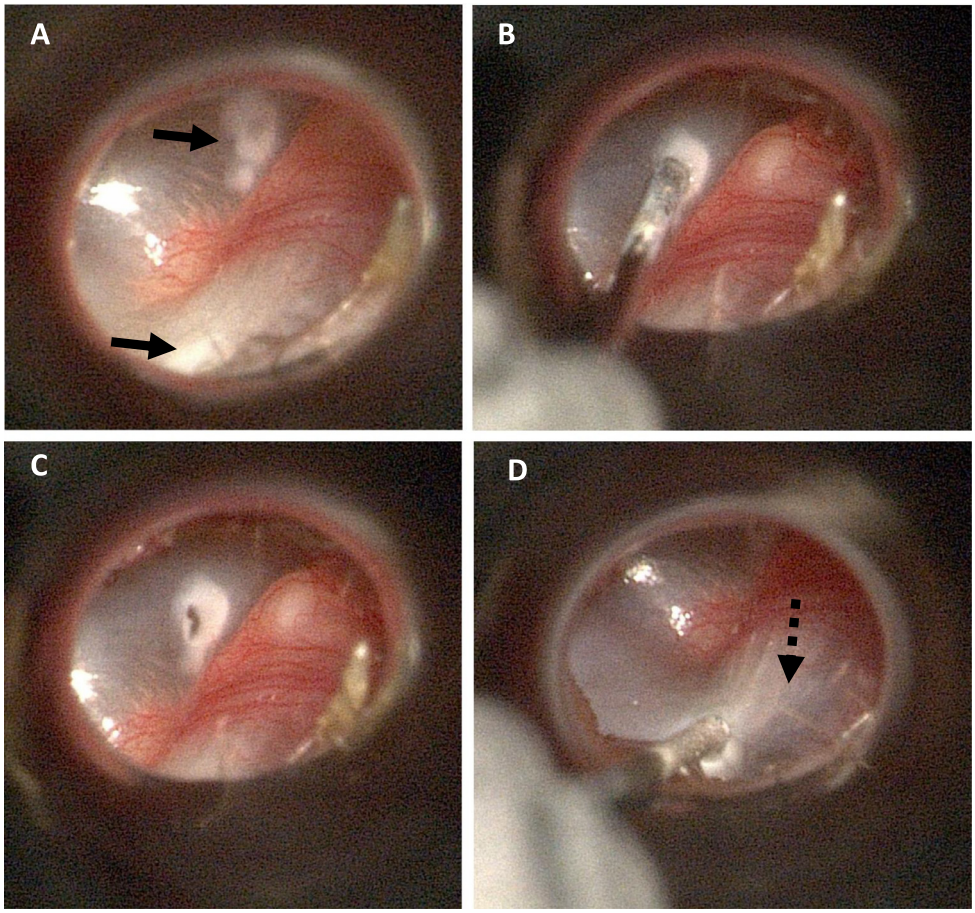

Figure 1 Left ear visualized through an operating microscope and speculum. (A) Topical phenol is applied at 2 points in the anterior-superior quadrant and the posterior-inferior quadrant, blanching the tympanic membrane (solid arrows). (B and C) A spinal needle is used to create a vent hole superiorly. (D) The needle is used to inject 1 cc of gentamicin inferiorly. Note the rising meniscus of fluid visible in the middle ear (dotted arrow).

membrane sufficiently. This can be accomplished with topical 4% phenol solution or 10% lidocaine cream. With phenol, 2 small spots are anesthetized, 1 anterosuperiorly and 1 posteriorly (Figure 1A).[15] If using 10% lidocaine cream, the entire drum is anesthetized. The 40 mg/mL gentamicin solution is warmed to avoid a caloric reaction by placing the vial in a bead sterilizer for a few seconds. One millilitre is drawn into a 1 cc tuberculin syringe. The syringe is fitted with 25 g spinal needle. A "vent" hole is made with the syringe needle in the anterior superior quadrant of the drum to allow air to escape during gentamicin injection (Figure 1B and C).[15] The needle is then used to inject the entire 1 cc volume of gentamicin solution through the posterior or posterosuperior margin of the tympanic membrane (Figure 1D) until the middle ear is completely filled, all air bubbles have been flushed out through the vent opening and all excess gentamicin solution has flowed out of the vent to fill the medial ear canal.[15] Patients remain in this same position for 1 hour to allow the gentamicin to diffuse through the round window membrane and annular ligament of the stapes into the inner ear. Patients sit up and are discharged on 10-14 days of water precautions. The tipsy reaction is often the only indicator that the drug has worked so it is reassuring to confirm that response. A bedside evaluation with head impulse testing may show a new corrective saccade when the head is moved toward the treated ear.[6]

Historically, a number of different dosing schemes have been utilized and promoted.[16] Because of the obvious desire to optimize treatment efficacy while minimizing adverse effects, presently most authorities favor a single dose administered as described above.[1] Patients are re-examined 4 weeks after treatment. Approximately 70% will exhibit the expected disequilibrium caused by the drug and are considered adequately treated. Those who return for 4-week follow-up and have had no experience of labyrinthine upset are recommended to have a second dose.[15] Even in cases with good initial treatment response, repeat treatment is an option if patients' vertiginous episodes return in the future.[6]

Early response

Aside from the possibility of a caloric reaction if the drug solution is too warm or cool, there is no immediate effect of the gentamicin injection. Based on extensive clinical experience with this method, we have observed that patients begin to notice onset of a tipsy disequilibrium approximately 3-5 days after the injection. They report a heavy-headed imbalance and a feeling that head and eye movements are "out of sync", confirming that their vestibulo-ocular reflexes are impaired by the degenerating vestibular hair cells on the treated side. This disequilibrium is relatively constant and intensifies daily to a peak around 10-14 days after injection. At the peak, it is not unusual for patients to spend a day or 2 in bed. Around the peak, it is not unusual for patients to avoid driving because the side-to-side head movements make them dizzy and nauseous. Once the drug reaction peaks, it begins to fade. On average, this takes an additional 4 weeks, so the entire tipsy drug reaction is about 2 weeks "coming" and 4 weeks "going" for a total of 6 weeks of imbalance. Some patients go through this more quickly and some more slowly. The more active the patient, the more quickly and more completely they compensate. Elderly patients and patients with obesity or sensory or motor impairments that predict poor vestibular compensation benefit from early physical therapy intervention. However, most patients make an excellent recovery without the need for physical therapy.

Complications

The primary complication of intratympanic gentamicin treatment is deterioration of sensorineural hearing as a result of gentamicin's ototoxic action. Although gentamicin is more vestibulotoxic than ototoxic, some studies have demonstrated considerable hearing loss in the treated ear with high dose regimens.[2,13,17] Evidence indicates that the risk of sensorineural hearing loss can be reduced with a low dosage of gentamicin and longer time interval between repeated injections.[13,18,19] It is important to note that hearing also deteriorates during the natural course of Meniere's disease, and it is often an individual decision weighing the benefits of vertigo control compared with the risk of worsening hearing loss in an ear. Other risks include persistent tympanic membrane perforation, seen in less than 1% of cases, and failure of central vestibular compensation resulting in chronic disequilibrium and gait instability.[2] This latter issue, failed or inadequate vestibular compensation, is of particular concern in patients with uncontrolled migraine or other sensory and/or mobility impairments such as obesity, low vision, lower extremity peripheral neuropathy, spinal stenosis, and joint replacement of hips or knees.

There are some patients and physicians who voice concern regarding the long-term consequences of developing Meniere's in the second ear if the first ear has had intratympanic gentamicin (ITG) treatment. There are at least 3 reasons why this concern is not relevant to treatment decision-making in cases of unilateral Meniere's disease: (i) regardless of whether the first ear receives ITG, the balance organs of that ear will continue to degenerate so activation of disease in the second ear will lead to bilateral vestibular hypofunction whether or not the first ear is treated; (ii) there is no evidence to suggest that ITG treatment has any effect on the fate of the second ear—it neither increases nor decreases risk of future bilateral Meniere's disease; and (iii) it is the present vertigo attacks that are disabling and must be treated—one can neither predict possible future involvement of the second nor predict what future treatments may be available at that time. Thus, the patient is best served by offering treatment for control of the problem at hand.

Results

Studies have found that intratympanic gentamicin injection controls symptoms of vertigo in up to 80%-90% of patients with Meniere's disease.[1,20] Randomized control trials have found that intratympanic gentamicin is effective in significantly reducing vertiginous attacks compared to placebo, but the treatment does not address ear fullness, hydrops, hearing fluctuations, or sensory loss.[21] With regard to treatment frequency, there is little consensus at this time over the optimal dosage and protocol for intratympanic gentamicin administration. One meta-analysis found that titrating repeated doses until a vestibular response is achieved was superior to other treatment regimens, while other studies demonstrated that no difference existed between fixed dose and titration regimens.[16,20] Long-term follow-up shows that low dose intratympanic gentamicin injection resulted in good control of vertigo symptoms in the majority of patients followed for 4 or more years, with minimal cochlear loss.[22] However, a second injection may be required for some patients on low dose regimens.[22]

Depending on the dosage and administration regimen, treatment can be associated with a moderate risk of irreversible sensorineural loss in the affected ear. In single injection treatment regimens, significant hearing loss can occur in 5% of patients.[18] By contrast, a weekly injection regimen until indications of vestibular hypofunction in the treated ear can result in up to 32% incidence of hearing deterioration.[6,23] Notably, there has also been evidence suggesting that hearing loss may be transitory, as one study found decreasing rates of hearing loss comparing immediately post-treatment to 3 months post-treatment and to 2 years post-treatment.[13] In fact, some believe that a degree of hearing loss may be necessary for control of vertigo symptoms, as those patients experiencing no change in level of hearing during treatment often need more courses of injections and had poorer overall control of their vertigo symptoms.[13] Long-term hearing outcomes in patients treated with multiple gentamicin injections are generally in a distribution similar to that in Meniere's patients managed

with medical measures, indicating that intratympanic gentamicin is not overly detrimental in causing hearing loss.[17]

There are a number of other reasons why intratympanic gentamicin treatment could fail to provide the intended benefit. First, the diagnosis could be wrong; intratympanic gentamicin would not be expected to treat disorders of the central nervous system or disorders of the vestibular nerve. Patients with bilateral Meniere's disease may also experience a limited effect of treatment. Problems in delivery of the drug to the inner ear could also result in ineffective treatment, such as adhesions over the round window or the drug exiting the ear inadvertently through the Eustachian tube. Some individuals may also have idiosyncratic susceptibility or resistance to the effects of gentamicin. Recovery of hair cells after incomplete ablation is another possibility.

Recently, there has been growing interest in the use of other intratympanic medications such as steroids (methylprednisolone, dexamethasone), latanoprost, and gancyclovir. Double blind trials have been conducted on the efficacy of steroids vs gentamicin in treating Meniere's disease as well as studies with long-term follow-up of these 2 medications.[24,25] A recent systematic review of 9 studies suggest that, while gentamicin is the most efficacious medication overall, there was no significant difference in efficacy between gentamicin and methylprednisolone when outcomes from studies with follow-up greater than or equal to 24 months were analyzed.[26] Further research is needed into the different classes of medications that may be useful in Meniere's disease.

In summary, intratympanic gentamicin can effectively treat vertigo in patients with Meniere's disease. However, this treatment often does not change the associated aural fullness, hearing fluctuations, and progressive hearing loss that patients with Meniere's disease experience. Treatment regimens with less frequent gentamicin administration also have a lower risk of hearing loss than those involving more frequent administration. Nevertheless, intratympanic gentamicin is now widely accepted as the treatment of choice for most patients with intractable vertigo and significant hearing loss in the affected ear who have failed diet and diuretic therapy.

Pearls

1. Intratympanic gentamicin is the treatment of choice for Meniere's disease patients with intractable vertigo and significant unilateral hearing loss who have failed lifestyle, pharmacologic and nonototoxic intratympanic therapy.
2. The procedure is simple and can be performed in the outpatient clinic with minimal recovery time, with the primary relative contraindications to treatment being concerns about impaired sensory or motor function or impaired capacity for central vestibular compensation, especially including uncontrolled migraine. The presence of bilateral Meniere's disease may also put the patient at risk for severe bilateral chronic disequlibrium.
3. Delayed vestibular compensation after treatment usually responds positively to vestibular rehabilitation and adaptation exercises.
4. Low-dose treatment regimens (with repeated injection only with recurrence of symptoms) minimize risk of treatment-related sensorineural hearing loss without compromising treatment effectiveness for vertigo control.

Pitfalls

1. Failure to appreciate barriers to vestibular compensation may lead to prolonged or permanent disability.
2. Intensity and duration of postinjection disequilibrium are not predictable.

Special instruments needed

None.

Disclosures

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Suggested reading

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