Meniere's Disease

Aminoglycoside ear-drops for treatment

Dr Kevin B K Soh
Consultant Otolaryngologist
Gleneagles Medical Center

Meniere's disease or endolymphatic hydrops is caused by excessive buildup of endolymph in the inner ear, due to either excessive secretion or inadequate drainage. It produces symptoms of hearing loss, spontaneous vertigo, tinnitus and aural fullness. The membranous labyrinth dilates and swells, giving rise to a situation that is analogous to "glaucoma of the ear". When the thin delicate walls of the membranous labyrinth breaks, sodium rich endolymph leaks into the perilymphatic space, mixing with the potassium rich perilymph. The electrical potential that exists between the endolymph and perilymph discharges, resulting in a sudden loss of function of the inner ear, precipitating an attack of Meniere's disease.

Meniere's disease is a progressive disease which causes a gradual decline in vestibular function and hearing over time. In 10% to 60% of patients, the condition is bilateral. Vertigo, deafness and tinnitus from Meniere's disease are important causes of functional impairment, emotional problems, diminished quality of life and inability to maintain employment. Patients also suffer from chronic dysequilibrium and motion intolerance that results from a general reduction of vestibular function.

Medical and surgical management of Meniere's disease

Up to 95% of patients with Meniere's disease obtain relief with simple conservative measures and medications. But 5% of patients will need surgical therapy. Surgery attempts to control vertigo in one of 2 ways: 1) drainage procedures that relieve the pressure buildup in the endolymphatic system, and 2) destructive procedures that ablate the vestibular end organ or sever its afferent neural connections.

The cochleosacculotomy operation controls endolymphatic hydrops by puncturing the endolymph system whenever a hydropic state appears. The pressure buildup is allowed to discharge in a controlled manner, thus preventing membranous tears from taking place. Endolymphatic sac decompression and shunt procedures relieve pressure buildup by uncapping the bony walls of the mastoid bone to allow it to undergo volume expansion in response to pressure buildup. A shunt is also inserted to allow endolymph to drain more easily. Unfortunately, both options are fraught with problems, and have fallen out of favor with clinicians. First, there is a very high risk of severe sensorineural hearing loss with the cochleosacculotomy operation. Second, endolymphatic sac operations are associated with a high rate of failure to control vertigo.

Disadvantages of conventional ablative surgery

Destructive surgical procedures like labyrinthectomy or vestibular neurectomy are the gold standards in the management of intractable Meniere's disease. Both have a vertigo control rate of more than 90%. In labyrinthectomy, the whole bony and membranous labyrinth is extirpated through a mastoidectomy approach, and the neuroepithelium of the vestibular system is completely removed. Unfortunately, complete loss of hearing is a usual consequence of the procedure. Vestibular neurectomy is an intracranial operation that aims to sever the vestibular nerves to prevent the reception of anomalous vestibular signals from the inner ear. It is an intracranial operation that involves creating a craniotomy through the middle fossa or retrolabyrinthine approach. Despite a deliberate attempt to conserve hearing function, there is still a 2% to 10% risk of deafness. Other risks include injury to the facial nerve, anterior inferior cerebellar artery, and temporal lobes.

Harnessing the ototoxic effects of aminoglycoside antibiotics

The ototoxic effect of aminoglycosides became evident when tuberculosis patients treated with systemic streptomycin developed bilateral vestibular hypofunction, unsteadiness, motion intolerance and oscillopsia. Streptomycin was deliberately used in 1948 to ablate the vestibular system of vertigo patients.

Gentamicin is preferred to streptomycin for intratympanic administration because it is less toxic to the cochlea. When gentamicin is infused into the middle ear, it diffuses passively through the round window membrane to reach the inner ear.

Differential ototoxic susceptibility in the cochlea and vestibule

In the inner ear, gentamicin affects 3 different structures:

- vestibular dark cells that secrete endolymph,
- vestibular sensory hair cells, and
- cochlear sensory hair cells.

The dark cells are most susceptible to the ototoxic effects of gentamicin. Even at low doses, gentamicin is able to normalize the hyper-secretory state of the dark cells, causing a reversal of the hydropic state of the inner ear. The ototoxic changes in the dark cells precedes the onset of changes in the sensory epithelium of the vestibular system and cochlea. As gentamicin is administered at higher concentrations or at more frequent intervals, the vestibular sensory hair cells are affected, causing a reduction in responses to bithermal and ice-water caloric stimulation. At even higher doses of gentamicin, the ototoxic effects manifest on the cochlear hair cells, giving rise to sensorineural hearing loss. (Fig. 1)

Both the reduction of dark cell and vestibular sensory hair cell function are effective in alleviating the acute rotatory attacks of Meniere's disease. But they do so by different mechanisms, giving rise to dissimilar consequences. When dark cell function is controlled, the pressure buildup and dilatation of the membranous labyrinth of endolymphatic hydrops is reversed. The inner ear returns to its premorbid state before the onset of Meniere's disease. Because the basic pathologic situation of hydrops is reversed, symptoms of vertigo, hearing loss, aural fullness and tinnitus are controlled. Hearing may also be expected to improve with the control of endolymphatic hydrops. Furthermore, vestibulo-ocular and vestibulo-spinal reflexes in the treated ear continue to serve the important function of maintaining ocular stability with changes in head position and gait equilibrium.

In contrast, ablation of vestibular sensory hair cell function results in a measurable reduction of bithermal and ice-water caloric responses. Although effective vertigo control is obtained, the basic pathologic processes and hydropic state continue unchanged. Electrolyte disturbances that result from the mixing of endolymph and perilymph still exist. The only difference is with perception: the vestibular hair cells are unable to relay the message of an upheaval that is taking place in the inner ear back to the vestibular centers of the brain. Other symptoms like hearing loss, aural fullness and tinnitus remains. If the ablation of the vestibular hair cells is complete, and the vestibulo-ocular and vestibulo-spinal reflexes abolished, patients may develop oscillopsia, chronic vestibular insufficiency and dysequilibrium. In young patients with good compensatory abilities, this is a less problematic situation. But chronic vestibular insufficiency is incapacitating in the elderly and in patients with bilateral Meniere's disease.

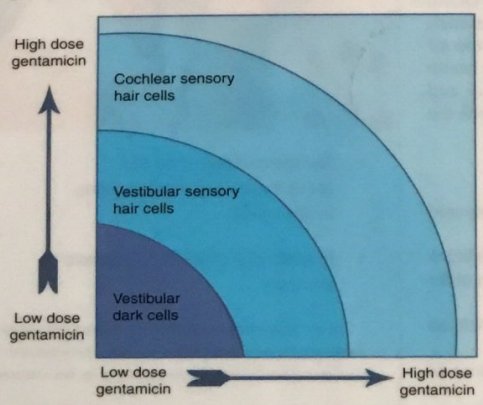

Diagram 1: *Schematic diagram showing that the vestibular dark cells are most susceptible to gentamicin ototoxicity, followed by vestibular and cochlear sensory hair cells. This differential susceptibility creates the opportunity that allows gentamicin to control vertigo and reverse endolymphatic hydrops while sparing residual vestibular function and hearing.*

Gentamicin should be administered in just enough quantity to ablate dark cell function, while preserving the sensory hair cells in the vestibular system and cochlea. By capitalizing on the differential susceptibility of the target organs in the inner ear, control of vertigo may be achieved without sacrificing hearing and vestibular function. Administration of high doses of gentamicin will carry a significant risk of destroying hearing acuity and impairing vestibular function.

What is the right dose? Shotgun vs titration therapy regimes

Early proponents of intratympanic gentamicin administration believed that in order to control vertigo, complete chemical ablation of vestibular function was essential. This is referred to as shotgun therapy. The goal was to maximize toxicity to the vestibular end organ without regard to salvaging hearing function.

Shotgun therapy is achieved by using an aggressive dosing protocol ranging from 5 times daily to once a day. Because of the long half-life of gentamicin in the inner ear, a daily dosing schedule gives little time for gentamicin to clear from the inner ear before the next dose. The concentration of gentamicin in the inner ear will therefore accumulate to high levels, giving it the ability to completely wipe out vestibular function.

Although shotgun gentamicin therapy is extremely effective in controlling vertigo, they also destroy hearing ability with equal facility.

Titration therapy saves hearing and vestibular function

Later investigators noted that by reducing the frequency and number of times that gentamicin was administered, they could achieve similar rates of vertigo control without compromising hearing function. Good control of vertigo could be achieved without sacrificing hearing.

Animal experiments have demonstrated that gentamicin has a half-life of a few days in the inner ear. After a single dose of intratympanic gentamicin, the ototoxic effects progress over several days to reach a maximum level at approximately day five. A daily dosing regimen will therefore not allow sufficient time for gentamicin to clear from the inner ear. This will result in an accumulation of gentamicin in the inner ear, exposing the cochlea hair cells to high levels of ototoxicity. The rationale for a weekly dosing schedule is that it allows time to elapse before the effects of the initial dose is evaluated. Furthermore, gentamicin from a previous dose has time to clear from the inner ear before more is given, preventing it from accumulating in the inner ear.

An important advantage of titration therapy is that some residual vestibular function is preserved. Total ablation of caloric responses is not necessary for the control of vertigo. The preservation of vestibular function reduces the risk of chronic vestibular insufficiency. Using a subablative dose of gentamicin not only alleviates vertigo, but also leaves behind some residual vestibular function. Unlike with shotgun therapy, the goal of titration therapy is to avoid total abolition of the caloric responses. Preserving some vestibular function will allow retention of the vestibulo-ocular and vestibulo-spinal reflexes in that ear, allowing a much faster recovery and compensation after gentamicin treatment. There are also less problems with chronic dysequilibrium.

Preserving some residual vestibular function is a critical factor for recovery in elderly patients who have central vestibular dysfunction or impairment of the opposite peripheral vestibular system. Patients who later develop Meniere's disease or some other vestibular paralytic lesion in the other ear are also at risk of chronic vestibular insufficiency if a complete ablation with gentamicin had been carried out.

Treatments that ablate the vestibular system in a short time, such as shotgun gentamicin therapy, labyrinthectomy and vestibular neurectomy cause acute symptoms of giddiness and dysequilibrium. Titration therapy reduces vestibular function in a gradual, controlled and step-wise manner. This allows central compensation to progress in tandem with the reduction of vestibular function.

Patients who are treated with conventional surgery like labyrinthectomy or vestibular neurectomy do not have the option of leaving behind some residual function. These operations aim to completely ablate the vestibular function of the affected ear. They are all-or-none procedures. Any attempt to leave behind some residual function will result in a surgical failure and recurrence of vertigo. The postoperative severity of chronic vestibular insufficiency would be similar to shotgun gentamicin therapy. Titration gentamicin treatment is able to control vertigo while at the same time retain some residual function because it exerts a differential ototoxic effect on the structures in the inner ear. By controlling endolymph secretion by the dark cells but protecting the vestibular and cochlear hair cells, vertigo may be controlled without compromising hearing and vestibular function.

Six reasons for titration gentamicin therapy

1. Gentamicin therapy is cheap:
   The procedure is performed under local anesthesia in the office. There is no need for an expensive surgical procedure or hospitalization.

2. Gentamicin therapy is easy to perform:
   It is a simple office procedure that an ear surgeon can perform. No [illegible] required.