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Review Articles

Treatment of Ménière's disease by intratympanic gentamicin application

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Abstract

Ménière's disease is a vestibular disorder characterized by episodic vertigo, tinnitus, fluctuant hearing loss, and ear fullness, with vertiginous attacks being the most disabling complaint. The effectiveness of conservative treatment has been variable, while surgical techniques provide more permanent relief from vertigo, but pose possible morbidity and cochlear risk. Intratympanic administration of gentamicin has been proposed as an alternative for patients with debilitating Ménière's disease who have failed to respond to standard medical treatment. The goal of such treatment is to control vertigo by partially or completely destroying the vestibular system, while at the same time maintaining hearing.

In this review we present the current medical literature on pathophysiology, pharmacokinetics, administration methods, dosage, treatment protocols, and problems related to intratympanic administration of gentamicin for patients with MD.

Intratympanic gentamicin administration is a simple medical modality for treatment of persistent vertigo in patients with Ménière's disease. According to recent world research protocols, we propose the instillation of gentamicin by transtympanic injection, as a quick, easy, well-tolerated, ambulatory and cost-effective technique. Drug solution concentrations should be dependent on the frequency, intensity and duration of vertigo spells, as well as the degree of existing hearing loss, thus providing progressive vertigo relief with a low possibility of secondary deafness.

Key words: Gentamicins; Ménière's Disease; Treatment Outcome

Background

Ménière's disease (MD) is a vestibular disturbance with an incidence of 12/1000 people all over the world,[1] characterized by vertiginous attacks, sensorineural hearing loss, tinnitus, and ear fullness. These symptoms, vertigo being the most distressing, are caused by the presence of endolymphatic hydrops. Medical treatment aims at relieving vertigo as well as curing the possible causes of endolymphatic hydrops (autoimmune disease, syphilis, metabolic, and endocrine derangements).[2] Significant control of the disease's symptom complex is accomplished with diuretics and diet restriction of caffeine and excessive salt.[3,4] Treatment for cases refractory to medical therapy includes either surgical procedures or chemical ablation of vestibular function.[5,6]

Aminoglycoside ototoxicity has been implicated in the treatment of intractable MD since the late 1940s. Comparative results have been published on aminoglycosides applied either intramuscularly,[7,8] via the middle ear,[9] or even by intralabyrinthine applications.[10,11] Selective chemical vestibular ablation by intratympanic gentamicin (ITG) application has been practised as a treatment option for patients with debilitating unilateral[12,13] or bilateral[14,15] MD. Such treatment aims at controlling vertigo by partial or complete destruction of the vestibular system while attempting to preserve hearing. Despite the reported encouraging results, ITG therapy has not yet been established as the 'gold' standard for treatment of MD. In this study we present a review of the literature on pathophysiology, pharmacokinetics, administration methods, dosage, treatment protocols, and discuss the controversies of ITG treatment for patients suffering from MD.

History

Byzantine physicians (324–1453 AD) appear to have referred to the deficiency of hearing and deafness as well as vertigo and tinnitus, along with a meticulous description of the suggested treatments.[16] In the late

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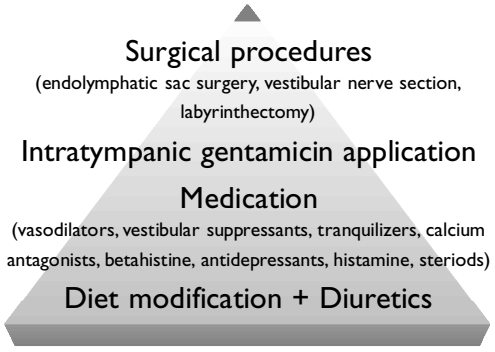

FIG. 1
Therapeutic approach for vertigo in Ménière's disease.

1940s it was noticed that patients receiving streptomycin systemically by intramuscular injection for tuberculosis experienced ablation of peripheral vestibular function with potential hearing damage. In the following years a number of investigators reported on systematically administered streptomycin for patients suffering from both unilateral and bilateral MD.[7,8,17] Intratympanic administration of aminoglycosides in patients with unilateral MD was first performed by Schuknecht in 1956.[18] Lange resurrected this therapy in 1968, again using streptomycin.[19] There was little further interest in the technique until Beck and Schmidt published their results on intratympanic gentamicin treatment in 1978, reporting successful control of vertigo in over 90 per cent of patients and preservation of hearing in 42 per cent of cases.[20]

Discussion

Ménière's disease is a clinical disorder characterized by acute episodes of vertigo lasting minutes to hours, accompanied by fluctuant hearing loss, aural fullness, and tinnitus. Definite curative treatment for MD does not currently exist and the therapeutic procedure is mainly aimed at the relief of vertigo, that in the majority of cases seems to be the most distressing symptom. At least 70 per cent of patients treated with diuretics and diet restriction from caffeine and excessive salt obtain significant control of their symptoms. The remaining 30 per cent receive other medication, including vasodilators, vestibular suppressants, minor tranquilizers, calcium antagonists, betahistine, antidepressants, histamine, and occasionally steroids. Patients suffering from recurrent vertigo uncontrolled by conservative medication are candidates for further intervention. (Figure 1).[3,6,21]

Surgical intervention may include conservative procedures, which maintain vestibular function and/or hearing, and radical techniques that ablate residual balance control.[6,22] Endolymphatic sac surgery is the main conservative surgical treatment; it does not comprise inner ear function.[23–25] while vestibular nerve section and labyrinthectomy destroy residual vestibular function, the latter with concomitant hearing loss.[5] Complete or substantial control of vertigo by the various surgical procedures in patients with MD has been reported to range from 70 to 97 per cent.[14,26–29] Nevertheless, considerable morbidity is associated with surgical treatment including immediate sensorineural hearing loss,[30,31] facial nerve injury,[24] cerebrospinal fluid leak,[32] protracted headaches, epidural bleeding, seizures, and temporal lobe injury.[33]

Aminoglycosides have been exploited to provide partial or complete destruction of vestibular function while minimizing the risks associated with surgical procedures. Several investigators have studied the possibility of achieving a functional labyrinthectomy with preservation of hearing by ITG administration.[9,13,22,34–47] Reports on successful vertigo control using ITG in patients with MD have ranged from 71.4 to 100 per cent (Table I), while a recent study has also suggested ITG application in selected patients suffering from persistent vertigo even after endolymphatic surgery.[48] In cases of bilateral MD, intramuscular streptomycin administration has been reported to provide satisfactory results in controlling vertigo, with the possibility of hearing deterioration, oscillopsia, ataxia and renal insufficiency. In addition, systematically administered streptomycin affects both ears with the existing danger for the

TABLE I
TREATMENT OF MÉNIÈRE'S DISEASE BY INTRATYMPANIC GENTAMICIN APPLICATION

Study	Number of patients	Protocol type	Administration route	Dosage	Duration of treatment	Vertigo improvement	Hearing deterioration
Kaasinen *et al.*[60]	93	Fixed	Injection	9–15 mg/d	1–4 days	92%	39%
Mc Feely *et al.*[14]	25	Fixed	Ventilation tube	26.7 mg tpd	4–5 days	100%	20%
Quaranta *et al.*[39]	11	Fixed	Injection	40 mg/weekly	2 weeks	100%	27%
Silverstein *et al.*[42]	10	Fixed	Injection	5.34–8.01 mg	Single dose	77.8%	10%
Silverstein *et al.*[42]	10	Fixed	Injection	5.34–8.01 mg	2 doses 5 days apart	71.4%	20%
Silverstein *et al.*[42]	12	Titration	Injection	5.34–8.0 mg	Undefined	75%	None
Kaplan *et al.*[37]	90	Fixed	Ventilation tube	18.7–21.4 mg tpd	4 days	93.4%	25.6%
Charabi *et al.*[35]	14	Titration	Microcatheter	4–14 mg	Undefined	93%	7%
Hone *et al.*[36]	103	Fixed	Ventilation tube	26.7 mg tpd	4 days	Undefined	18%
Leone *et al.*[22]	29	Fixed	Injection	16 mg/weekly	2–3 weeks	100%	20%
Longridge *et al.*[38]	23	Fixed	Various	13.5 mg/d	2 days	Undefined	4.3%
Thomsen *et al.*[43]	27	Titration	Microcatheter	0.24–90 mg	1–100 days	81%	22%
Quaranta *et al.*[40]	15	Fixed	Injection	10 mg/bpd	1 day	93%	7%
Schoendorf *et al.*[41]	11	Titration	Microcatheter	40 mg/d	6.7 days	72.7%	81.8%
Sennaroglu *et al.*[6]	16	Fixed	Ventilation tube	20 mg/tpd	7 days	73%	35%
Hoffer *et al.*[47]	27	Fixed	Microcatheter	1.25 mg/weekly	2–3 weeks	92.6%	3.7%

(d: day; bpd: twice daily, tpd: three times per day)

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better-hearing ear to be damaged inadvertently, and duration of treatment (two to four weeks) is difficult for the patients to tolerate. Endolymphatic sac surgery may be an alternative, while destructive procedures are not implicated in bilateral disease. Intratympanic gentamicin administration has been reported to have satisfactory results in cases of bilateral disabling MD and is proposed as a treatment choice only to the ear responsible for the distressing symptomatology.[14,15]

Pathophysiology

Several studies have shown that the possible mechanism of gentamicin inner ear ototoxicity may be the damage generated to the vestibular dark cells.[9,49–51] These cells are present in every vestibular organ except the saccule, and are considered responsible for the production of endolymph.[52] Their destruction is proposed to lead to reduction of the volume of endolymph, with a concomitant beneficial effect on MD,[50,51,53] although a vestibular response would still be present by caloric testing.[42] Animal studies have shown that intratympanic gentamicin causes changes in dark cells prior to the alterations seen in sensory neuroepithelium.[50,51] However, it is not certain that selective dark cell damage occurs in humans as well.[36,41,43] Recent publications report no selective vestibular end-organ damage in animals and indicate that the amount of any damage may be consistent in both cochlear and vestibular hair cells.[54,55] The spiral ganglion may also be the primary site of action of locally delivered gentamicin as recently demonstrated by Hoffer *et al*.[56]

Pharmacokinetics

Various theories exist on the mechanism of inner ear gentamicin absorption after middle-ear instillation. The drug may enter the inner ear through the round window membrane,[57] the annular ligament of the oval window, blood or lymph vessels, and small lacunae in the otic capsule.[20] The round window is the most probable entry site given the relatively thin barrier posed by the lamina propria and epithelial membranes.[4,58] Accumulation of gentamicin in the inner ear continues to increase after instillation, with the peak concentration being achieved at approximately two days after injection. Opinions differ on the time duration of gentamicin remaining in the perilymph. In one study the concentration of gentamicin within the perilymph seemed to decrease slowly with a long half-life of 10 to 12 hours,[59] due possibly to the specific binding of gentamicin to the sensory cells of the inner ear.[60] Another recent study reported that the elimination of gentamicin from the perilymph is extremely fast (a half-life of 75 minutes), suggesting that a high drug concentration depends mainly on large dosages or the use of sustained release vehicles, such as fibrin glue.[61]

There is considerable variability among patients regarding their susceptibility to the medication. The dose administered to the middle ear after ITG injection is known but the amount of drug actually in contact with the round window membrane and the duration of contact cannot be predetermined. Factors influencing gentamicin absorption into the inner ear include the thickness of the round window membrane, scarring or adhesions that may be present near the round window niche, patency or obliteration of the cochlear aqueduct,[62] position of the head, and patency of the eustachian tube.[21] Therefore, certain manoeuvres, such as turning the head in the direction away from the treated ear,[35,43] as well as removal of the mucous membranes in the round window niche have been proposed to prevent loss of drug via the eustachian tube and to enhance drug contact to the round window.[35,42,63,64] The rate of turnover of perilymph and endolymph within the otic capsule could also affect the clearance of gentamicin from the inner ear.[21] Although experimental obliteration of the cochlear aqueduct in animals[65] or occlusion in humans[66] have not resulted in any morphological or functional alterations, it has been suggested that, since the internal orifice of the aqueduct is close to the round window, hindrance of perilymph flow through the aqueduct will preserve the ototoxic drug in the cochlea.[62] Asymmetry in the cochlear damage after systemic aminoglycoside administration could be explained by such a mechanism.

Drug administration modalities

Different methods have been used to apply gentamicin to the middle ear, including injection through the intact tympanic membrane,[22,40,44,60] administration via a tympanostomy tube,[6,12,14,37] injection through microcatheters,[13,35,41,43] use of sustained release vehicles,[42,46,47,56] and retrograde delivery through the eustachian tube.[67] Selection of a certain delivery technique is usually dependent on the frequency of instillation and convenience of the patient. A transtympanic catheter or a tympanostomy tube is more convenient for the patient and the physician when delivering therapy several times daily, despite the existing danger of residual tympanic membrane perforation. Instillation may be performed by the doctor, by the patient's relatives[14,37] or by a micro-infusion pump.[35,41,43] Transtympanic injections are quick, easy to perform and of low cost. This technique is more appropriate for patients receiving once-weekly treatment as well as patients having to travel a long distance to reach the doctor,[37] it does not require hospitalization and the patient may well continue their everyday activities. Sustained release vehicles (fibrin glue, Gelfoam® , or active delivery devices) provide the doctor with the ability to apply gentamicin in close contact with the round window, thus producing the desired effect while minimizing cochlear damage.[56] Nevertheless such a modality requires skill and experience by the doctor and is not always well tolerated by the patient.[42,46,47]

Optimal dosage of ITG administration has not yet been decided. A significant reduction in the risk of hearing deterioration has been obtained by applying very low doses of gentamicin (four to 40 mg) (Table I). The concentration of gentamicin solution used for

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chemical ablation of vestibular function varies according to the investigator and has ranged between 10 mg/ml and 40 mg/ml.[35,47]

Two protocols for ITG instillation treatment for MD have been applied, the titration (variable-end-point)[35,41–43] and the fixed (predetermined-dose) technique.[6,22,36,38–40,42,44,47] A distinction is sometimes difficult, as titration protocols may include a small number of injections and require repeating them as necessary, while, a fixed protocol may be also re-applied. Both modalities have been performed using different time intervals between injections, although in fixed protocols gentamicin is administered at least once daily, whereas in titration protocols it is usually delivered on a weekly basis. Serial injections may allow for a more concise titration, as well as better detection for initial signs of vestibular or cochlear toxicity, although a greater number of injections may be necessary resulting in a prolonged treatment time.[68] Therefore, a titration protocol may prove impractical for individuals having to travel a long distance for treatment sessions, and subjects with nonserviceable hearing.[14]

Regardless of the type of protocol, considerable difficulty exists in defining a safe treatment end point, and consequently in deciding on retreatment. In titration protocols, the maximum *in vivo* gentamicin concentration is usually reached several weeks or longer after the last dose has been administered in contradistinction to a fixed protocol in which treatment is defined over a matter of days. Symptoms and signs associated with inner ear dysfunction (i.e. disequilibrium, motion intolerance, ataxia and nystagmus) are used as clinical criteria for determining the treatment end point.[20] Nevertheless, accurate evaluation is extremely difficult in everyday medical practice, since caloric stimulation provides an estimation of horizontal semicircular canal function only, without any consideration for responses from the remaining semicircular canals, saccule, and utricle.[9,60,68,69]

Patient instructions

Gaining good postural control is the most significant factor determining the outcome of ITG treatment in unilateral as well as bilateral MD.[15] Older patients have more problems with deteriorated posture than younger ones; this may be explained by the longer duration of MD. Vestibular rehabilitation including movement therapy, the patient being alone or in groups, should be provided by the physician or preferably by an experienced physiotherapist together with written exercise programmes.[60,70,71] Special post-treatment care should be taken in cases of older people, who have an increased possibility of a life-threatening accident, difficulty in self-service and various concurrent systemic diseases (i.e. of the cardiovascular or supporting systems), thus compromising their ability to follow-up a strict but potentially helpful post-ITG treatment rehabilitation programme.

Patients must be warned about the possible occurrence of prolonged and severe vestibular disturbance, that can be delayed for up to two weeks following treatment. This is a sign of gentamicin-related vestibular deafferentation, different in sensation from the acute spells of MD. In such a case, vestibular sedatives, support of a family member, and the ability to reach the ENT unit by telephone may be especially helpful.[16,18,45] Patients must also be informed about the possibility of head movement-induced lightheadedness, that is considered a consequence of incomplete central compensation after unilateral vestibular loss.[21,37]

Different theories have been suggested to explain patients' relatively fast compensation following ITG therapy. At first, long-lasting decreased vestibular function may have allowed for significant central compensation before initiation of therapy. Secondly, the selective effect of gentamicin on the vestibular system, damaging the dark cells before altering the sensory neuroepithelium, may provide relief of hydrops.[51] Finally, slow destruction of the vestibular end organ with ITG may allow the central vestibular system to compensate more effectively.[34]

Controversies

Despite the successful results reported for ITG administration, this modality has not yet become the standard treatment for patients with incapacitating unilateral or bilateral MD. This may be due to the lack of uniformity in treatment protocols as well as the fact that success of any treatment for MD is difficult to judge in the short-term due to the variable natural history of the disease, which can involve symptom-free periods of many months or even years. ITG application may also be proven unsuccessful in cases where the diagnosis of MD is incorrect, therefore, a retrocochlear lesion should always be excluded before initiation of therapy. Effectiveness of ITG therapy is strongly dependent on the successful absorption of gentamicin into the middle ear, possibly occurring by pinocytosis via the round window.[4] Thus, fibrosis or any other factors affecting the round window niche may reduce absorption, leading to treatment failure.[13,35,43,62] Difficulties regarding the administration technique may also be encountered. Stability of the gentamicin solution is unknown, therefore an immediate preparation is needed in order to obtain a freshly prepared solution for patients for whom pre-arrangements have not been made, as well as patients scheduled to be re-injected.[21]

Intratympanic gentamicin administration bears potential complications that, apart from sensorineural hearing loss, include residual tympanic membrane perforation, irritative spontaneous nystagmus, and a temporary acute unilateral vestibular deafferentation syndrome involving vertigo, nausea, oscillopsia, and disequilibrium. Nevertheless, these symptoms are minimal considering the possible total or near total disability from the disease.[38] The risk for vestibular and cochlear toxicity may be related to the duration of therapy, age of the patient, total

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dose, individual susceptibility, renal function, and concomitant noise exposure.[21] Occurrence of dead ears could be explained by a lesion of the round window membrane, the patients' genetic priming,[72] or patency of the cochlear aqueduct. Cochleotoxicity has been reported as a mutant mitochondrial DNA-associated form of ototoxicity. Aminoglycoside ototoxicity is closely associated with mitochondrial activity, since gentamicin has been shown to instigate the release of iron from mitochondria and to enhance the generation of hydroxyl radicals.[73] Mutation of mitochondrial DNA, with an A to G transition at nucleotide 1555 within the 12S ribosomal RNA gene, has been associated with a high susceptibility to aminoglycoside ototoxicity, exhibiting a maternally inherited pattern in affected Asian pedigrees.[74] Nevertheless, it has not yet been defined whether cochleotoxicity from aminoglycosides is stronger in the mutant or whether post-treatment hearing loss is intensely highlighted due to its devastating effect on a patient already suffering from severe MD. Patency of the cochlear aqueduct would allow an unobstructed flow of cerebrospinal fluid and perilymph, while a closed aqueduct would raise the possibility of damage by even a small amount of gentamicin.[43,62] In bilateral MD low-dose ITG treatment has been reported to bear satisfactory results while the difficulty of choosing the more severely affected ear always exists.[14,15]

Conclusion

Transtympanic instillation of gentamicin for treatment of intractable vertigo in MD provides the otolaryngologist with an effective method of chemical vestibular ablation. This treatment may serve in cases where medical therapy has failed, without the potential morbidity associated with surgical modalities. ITG treatment may fail if the diagnosis of MD is incorrect and a small but clear risk of sudden hearing loss following ITG administration is always present. Although sensorineural hearing loss tends to progress over time in the natural history of MD, sacrifice of residual useful hearing in order to control or eliminate symptoms of vertigo unresponsive to medical therapy, as well as the hearing status in the contralateral ear, must be seriously considered when deciding treatment options.

Several questions need to be answered before a successful treatment protocol is established, including choice of medication with the fewest side-effects, concentration of solution, method of application, duration and frequency of instillation, and the point at which treatment should be terminated. Precise evaluation methods for adequate vestibular ablation also need to be well defined. Development of more selective vestibulotoxic drugs could mean that chemical labyrinthectomy will become a safe, simple and ultimate treatment for disabling MD.

Finally conclusions are that intratympanic gentamicin administration is a simple medical treatment modality for cases of intractable Ménière's disease. Transtympanic instillation of gentamicin by injection is a quick, easy, well tolerated, and cost-effective technique. It does not require hospitalization and provides the patient with the possibility to continue their everyday activities.

According to recent world research protocols on treatment of persistent vertigo in patients with Ménière's disease, we would propose gentamicin instillation by injection of the tympanic membrane in drug solution concentrations of 10–40 mg/ml (dependent on the frequency, intensity and duration of vertigo spells, as well as the existing degree of hearing loss), thus generating chemical ablation of the posterior labyrinth and progressive vertigo relief with a low possibility of secondary deafness.

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