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REVIEW

Intratympanic drug delivery for the treatment of inner ear diseases

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Abstract
Introduction: Intratympanic drug delivery for labyrinth diseases is a non-aggressive outpatient procedure where drugs reach high concentrations in the cochlea and minimum systemic diffusion. The aim of this review is to update the delivery techniques and report on the results obtained with different substances in cochleovestibular disorders. New perspectives in drug development and gene therapy are discussed.
Material and method: We have analysed the literature published to date using the MEDLINE and EMBASE databases. The categories chosen for the review were the delivery techniques, the results using corticosteroids and aminoglycosides (gentamicin) and isolated papers related with new drugs or pathways to introduce the substance in the inner ear.
Results: Intratympanic steroid therapy has been shown to be effective for cochleovestibular symptoms after failure of systemic steroids for sudden deafness and for control of Ménière's disease. Intratympanic gentamicin using a titration method showed vertigo control in 80%of the patients with a 0%25%risk of hearing impairment in Ménière's disease.
Conclusions: Intratympanic delivery is an effective procedure for the control of cochleovestibular disorders such as sudden deafness and Ménière's disease. Future perspectives could increase the indications for steroid and gentamicin treatment and open the door to new drugs and gene therapy.

PALABRAS CLAVE
Hipoacusia neurosensorial;
Sordera súbita;
Enfermedad de Ménière;

Vía intratimpánica en el tratamiento de patología de oído interno

Resumen
Introducción: La vía intratimpánica para el tratamiento de enfermedades laberínticas es un procedimiento poco agresivo y ambulatorio, que maximiza las concentraciones de fármaco en la cóclea y minimiza su difusión sistémica. A través de esta revisión se propone actualizar

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Traumatismo acústico;
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las técnicas de aplicación y los resultados que ofrecen los diferentes fármacos para las enfermedades cocleovestibulares. Se expone nuevas perspectivas futuras en cuanto al desarrollo de fármacos y de la terapia génica.
Material y método: Se analiza la literatura hasta la fecha según las bases médicas MEDLINE y EMBASE. Se ha considerado los artículos relacionados con la técnica de instilación, los resultados en el tratamiento esteroideo y aminoglucósido (gentamicina) y artículos aislados sobre nuevos fármacos o vías de administración.
Resultados: La terapia esteroidea ha demostrado su eficacia en los síntomas cocleovestibulares como pauta de rescate tras corticoterapia intravenosa en la sordera súbita y en el control de la enfermedad de Ménière. La administración de gentamicina intratimpánica en pautas a demanda aporta un adecuado control del vértigo en el 80%de los pacientes y un riesgo de hipoacusia del 0-25%en la enfermedad de Ménière.
Conclusiones: La vía intratimpánica es un procedimiento eficaz en el control de enfermedades cocleovestibulares, como la sordera súbita y la enfermedad de Ménière. Junto con el tratamiento esteroideo y gentamicina, perspectivas futuras podrían ampliar las indicaciones de su uso y un nuevo arsenal terapéutico farmacológico y génico.

Introduction

The increase currently experienced by intratympanic (IT) administration of drugs for the treatment of labyrinth diseases has taken place due to the abundant literature on pharmacodynamics, results and basic research. The reason for this review is to update the different techniques used, the results in various diseases and the future prospects that this approach could offer.

The extensive experience gained with IT gentamicin in Ménière's disease has opened the doors to corticosteroid therapy (dexamethasone and methylprednisolone) for diseases such as sudden deafness (SD), autoimmune inner ear disease (AIED) and Ménière's disease-endolymphatic hydrops (MD-EH). Other substances such as latanoprost or magnesium have also been used occasionally.

The benefits of this approach are numerous. This is an outpatient procedure, performed in consultation. It is simple, well tolerated by the patient and has a direct effect on the affected ear. The drug concentration that reaches the ear is very high compared with systemic administration routes (oral, intravenous). The risk of side effects is very low: the drug concentration that crosses the blood-cochlear barrier is very low and its systemic spread is minimal. The effects on the middle ear are scarcely relevant: discrete mucosal inflammation and risk of tympanic perforation somewhat lower than that observed in myringotomy with tympanostomy drain.

The disadvantages demonstrated by this technique, in addition to the previously mentioned tympanic perforation, are the appearance of pain or vertigo after drug application, which will depend on the substance used, on concentration, temperature and individual susceptibility, but which are limited to 1-2 h duration. Some cases may suffer acute otitis media, especially if aseptic conditions during instillation are not adequate. The occasional occurrence of hearing loss with IT gentamicin administration is an important side effect that the patient must accept as the lesser evil in treating disabling vertigo.

Permeability of the oval window and pharmacokinetics

Several factors are involved in spreading the medication to the perilymph: permeability and thickness of the round window membrane, presence of fibrous membranes and bridles in cavity, time of exposure, dosage and drug concentration, substance pharmacokinetics (size of the particles to diffuse, medium solution, osmolarity, pH, ionic composition and association with drug transporters), application method, individual sensitivity to drugs (aminoglycosides) and inner ear pharmacodynamics.

Once the drug has penetrated through the round membrane, its longitudinal diffusion takes place throughout the tympanic and vestibular cavities. It also undergoes a process of clearance into the bloodstream through the mucosa of the middle ear, the vestibular and tympanic cavities, the mucosa of the vestibule, the stria vascularis and the spiral ligament.

Application method

IT drug administration is a simple consultation procedure, requiring a microscope and material that is basic in our specialty. The patient should be placed in a chair tilted by 45º, with the ear to be treated in a superior position compared to the contralateral. The first step is to anaesthetise the instillation site in the tympanic membrane. For this purpose, it is possible to use anaesthetic drops with lidocaine, local injection of an anaesthetic in the external ear canal or the application of EMLA® (lidocaine and pilocarpine) on the tympanic membrane. We use phenol at a concentration of 88%[1] A drop is deposited on the tympanum using a 0.5 mm diameter ear aspirator that is not connected to the vacuum system. This generates a whitish area that is the anaesthetized location where the drug should be injected. A single application of the anaesthetic can serve for successive injections. To do this, a No. 22 spinal puncture needle is

used, connected to a 1 ml syringe where we will have the appropriate medication has been loaded previously. Once the membrane has been perforated, the drug is instilled in an amount of 0.4 to 0.6 ml. The appearance of bubbles during injection is a sign that the content is entering the middle ear. Some authors prefer to place a transtympanic drain and instil the drug through it, thus not requiring new injections of local anaesthetic. Next, the patient must maintain the position of 45º rotation with the affected ear in the top position for 20-30 min. The number of injections given depends on the articles reviewed. Patterns are described receiving 2 consecutive injections, separated by 10 min, on several consecutive days; one injection every other day until a maximum of 3; and other authors prefer patterns of weekly doses for 3 weeks or tailored according to the effect obtained.

Other, more sophisticated instillation systems have been developed, to achieve greater comfort in their use (MicroWick™, Micromedics, St. Paul, USA) or to maintain continuous diffusion at a given drug concentration (Microcatheter™infusion pump, IntraEar, San Diego, USA). The first device is made of a spongy material, cylindrical and elongated, which is placed through a tympanostomy drain, so that it connects the external ear canal with the oval window niche. The medication is applied as drops into the canal, and they move to the niche by capillarity, allowing absorption through the membrane of the oval window (OW). The second system, which is more sophisticated, requires tympanostomy surgery to place the infusion catheter in the OW niche. The device has an external pump that delivers medication at a constant concentration, so that there is a continuous drug flow through the pump and the catheter in contact with the OW membrane. These systems are scarcely used at present.

Intratympanic corticosteroid therapy

Mechanisms

The effects of inner ear corticosteroid therapy are based on their anti-inflammatory and immunosuppressive power. The immunological mechanisms are involved in the alterations of many inner ear diseases: endolymphatic hydrops and Ménière's disease, otitis media, acoustic trauma, ototoxicity, ischemic processes and systemic inflammatory diseases. Another effect of corticosteroids is their regulatory role in ionic homeostasis. They have an effect on potassium transport, which is altered in lesions of the endocochlear barriers. The mineralocorticoid effect increases the synthesis of aquaporin and ion channels, thus improving inner ear water balance.

Intratympanic administration of corticosteroids increases their perilymphatic concentration much more than systemic administration (oral or intravenous).[2,3] IT application shows minimum drug concentration in the blood compared to intravenous application.

Most studies used dexamethasone (DXM) or methylprednisolone (MTP) as corticosteroids of choice. In a pharmacokinetic study of the profile of both drugs, Parnes noted a significantly higher MTP concentration in the perilymph and endolymph after IT administration, compared with DXM and hydrocortisone. This study has had a major influence on the choice of either drug.[3] For other authors,[4] DXM spreads more quickly to the extracellular fluid and, therefore, to the cochlear cells than MTP, and this might explain the lower DXM concentrations in the endolymph compared with MTP. The doses used have also increased gradually to the extent that no side effects have been reported with their application.

DXM is applied in doses of 24 g/ml, while MTP is used in concentrations of 40 mg/ml. We use MTP at 40 mg/ml in a preparation of 0.9 ml, together with 0.1 ml of 1% lidocaine, to reduce the pain caused by MTP on the middle ear mucosa and the Eustachian tube. Chandrasekhar proposes the combination of corticosteroids and other substances that facilitate transport across the OW membrane. In a comparative study, he showed a significantly higher DXM concentration in the perilymph when it was associated with histamine, and to a lesser extent with hyaluronic acid.

Corticosteroid therapy in sudden deafness

Numerous publications and several randomised clinical trials (RCTs) have shown the therapeutic benefit of IT corticosteroid therapy as salvage treatment for patients who do not improve following systemic corticosteroid application (Table 1).[3,5,22-34] Battaglia et al. designed an RCT with three patient groups. Some received 60 mg oral prednisone for 7 days and IT DXM at 12 mg/ml, 1 injection per week, for 3 weeks (CSCIT). The second group received the oral corticosteroid, but an IT placebo (CS), while the third group received the IT DXM with oral placebo (CIT). Significant differences were obtained in the improvement of hearing thresholds with respect to the pre-treatment values. The greatest response was obtained in the CSCIT combined group: 44% improvement in verbal reception threshold and 40 dBHL in average conversational frequencies, pure-tone average (PTA). The second most effective group was the CIT; there were significant differences between the CSCIT combined group and the third in efficacy, the CS.[35]

Significant results with a control group were also described by Xenellis (47% improvement versus 0% in the control group)[32] and Van Wijck (66% versus 0% in control, using the SIverstein MicroWick™).[34] In one RCT published by our group, 18 patients with partial or no response to intravenous steroid treatment were offered the IT salvage pattern; 9 of them accepted and the remaining 9 formed the control group. Improvement was shown by 55% of patients with IT administration, compared to 0% in the control group after one month of treatment. The improvement was of 33 dBHL PTA, and 60% of patients reported significant improvement in tinnitus intensity, compared with 10% in the control group.[5]

Parnes has described the utility of IT steroids as an initial treatment of choice in sudden deafness. Through the use of 0.9 ml of MTP at 40 mg/ml and 0.1 ml of lidocaine at 1%, 2 injections per week until achieving hearing stability, the author shows an improvement in 23.3 dBHL PTA, 27.5 dBHL in verbal reception threshold and 26.2% in maximum discrimination in the pre- and post-treatment results in 19 patients (personal communication). The lack of a control group makes us regard these results with caution. A multicentre RCT is currently being carried out in the USA to

Table 1 Results obtained using intratympanic corticosteroid therapy as salvage treatment in sudden deafness

Author(s)	Previous treatment	Year	Patients, n	Improvement (patients, %)	Average improvement, dB
Parnes et al.[3]	o.	1999	13	46	62
Chandrasekhar et al.[22]	o.	2001	10	70	33
Gianoli et al.[23]	i.v.	2001	23	44	15
Ho et al.[24]	o.	2004	15	53	28
Banerjee et al.[25]	–	2005	26	50	27
Battista[26]	o.	2005	25	12	17
Gouveris et al.[27]	i.v.	2005	40	62	15
Herr et al.[28]	i.v.	2005	17	53	24
Lautterman et al.[29]	i.v.	2005	13	30	11
Slattery et al.[30]	o.	2005	20	55	8
Plaza et al.[5]	i.v.	2005	9	55	33
Haynes[31]	o.	2006	40	40	15
Xenellis[32]	i.v.	2006	19	47	15
Fitzgerald[33]	o.	2007	21	67	26.6
Van Wijck[34]	i.v.	2007	12	66	24.5

i.v. indicates intravenously; o., orally.

compare the effectiveness of IT MTP (4 doses) as a treatment of choice in SD, compared with that of oral prednisone (60 mg for 2 weeks). The results of this study could produce a major shift in how to handle SD in our clinical practice.

Corticosteroid therapy in Ménière's disease

The positive effect of oral corticosteroid treatment in MD has opened the door to potentially greater control of the disease with the IT approach.[6] Garduño et al.[7] published an RCT comparing IT DXM (4 mg/ml daily injection for 5 consecutive days) and placebo IT. The results at 2 years showed a significant control of vertigo of 100% in the treated group, compared with 64% in the placebo group. Hearing improved in 35% versus 10%, although there were no significant differences in PTA values. Regarding tinnitus, 48% of patients in the IT DXM group improved in intensity, compared to 20% of those in the placebo group. There were no significant differences in the Tinnitus Handicap Inventory (THI). Boleas-Aguirre et al.,[8] with a group of patients who were offered ablative treatment for disabling vertigo (IT gentamicin, neurectomy or labyrinthectomy), reported that 91% of patients refused ablative treatment and showed an acceptable control of vertigo at 2 years after IT DXM (12 mg/ml, 3 doses). In our series of 54 patients, 62% improved their PTA hearing thresholds (10 dBHL on average) at 6 months. The number of vertigo crises was significantly reduced from 4.4 to 1.5 and tinnitus improved in 72% of the cases after 3 applications of IT MTP.[9] Other authors publish descriptive studies with hearing improvement in 18%–67% of cases and control of vertigo in 50%–70% (Table 2).[7,35–42]

Other applications of IT corticosteroid therapy

The results of IT steroids in acute acoustic trauma are limited to animal testing. The different series published show a significant improvement over placebo in hearing thresholds and number of damaged cells.[10,11] The application of IT corticosteroids at our centre for other diagnoses is shown in Table 3.

Intratympanic gentamicin

The objective of the applying IT gentamicin (GNT) is the control of vertigo in Ménière's disease and minimising cochlear damage. This medication produces a lesion on the ciliated cells (more selective on the vestibular than on the cochlear) and the pigmented cells of the stria vascularis, which are in charge of perilymphatic fluid production. Studies with GNT are numerous, but with little consensus on the dosage schedule, total dose administered, method and mode of result assessment. Nevertheless, several meta-analyses support the efficacy of this treatment in the control of vertigo in MD (Table 4).

The RCT published by Stokroos et al.[12] shows that, at 6 months, IT GNT is effective in the control of vertigo in 100% of cases, compared with placebo (60%). A study by the University of Navarra on 71 patients shows class A vertigo control in 69% of cases, and class B vertigo control in 14%. The schedule applied consisted of daily GNT injections (26.7 mg/ml buffered to pH 6.4) until the appearance of vestibular ablation symptoms. A worsening of their hearing loss at 2 years of instillation was shown by 15.5% of cases.[13] Similar results in the control of vertigo (86%) but lower incidence of hearing loss were published by Harner et al.[14], using a single dose of GNT. The 980-patient meta-analysis published by Chia et al.[15] evaluated which pattern to use to obtain more effect with less cochlear damage (several daily doses, weekly doses, single doses, continuous administration or treatment "on demand" until the onset of vestibular dysfunction symptoms). The conclusions of the analysis show that the "on demand" pattern obtained better results, although all showed good control of vertigo. Hearing loss was also lower

Table 2 Results in the various series on applying intratympanic corticosteroid therapy in Ménière's disease

Author(s)	DXT dose, mg	Sessions, n	Patients, n	Control of vertigo	Control of tinnitus	Improvement in hearing loss
Itoh-Sakata,[36] 1991	4	4-5	61	78%	74%	(?)
Shea et al.,[37] 1996	2-8	3	28	96%	82%	67%
Silverstein,[38] 1998	3-4	3	17	NS	NS	NS
Sennaroglu,[39] 1999	1.25	4-5	24	72%	(?)	17%
Hirvonen,[40] 2000	2-4	3	15	76%	40%	13%
Hillman,[41] 2003	16	1-3	50	(?)	(?)	40%
Dobson,[42] 2004	5-10	1-5	22	54%	(?)	18%
Garduño,[7] 2005	4	5	22	82:57%	48:20%	35:10%
Boleas,[43] 2008	12	1-4	129	91%	(?)	(?)

DXT indicates dexamethasone; IT, intratympanic, NS, not statistically significant.

*91% of patients who were proposed ablation treatment (IT gentamicin) obtained sufficient control of vertigo with IT DXT so as not to require it.

Table 3 Results obtained at our hospital with intratympanic methylprednisolone in other diagnoses

	Patients, n of tinnitus[a]	Improvement in hearing loss[b]	Improvement
Endolymphatic hydrops secondary to otosclerosis	4	3/4	3/4
Labyrinthitis after stapedotomy			
2 months later	1	0	0
6 months later	1	0	0
18 months later	1	0	0
Barotrauma (treatment 2-3 months later)	2	1/2	1/2
Rapidly progressive hearing loss (AIED?)			
Bilateral	1	1	1
Unilateral	2	2/2	1/2
SLE (unilateral)	1	1	1
Retinitis pigmentosa (bilateral)	1	1	1
Progressive hearing loss	4	2/4	1/4
Labyrinthitis after AOM	4	2/4	2/4
Labyrinthine trauma	2	1/2	1/2
Ototoxicity (HIV)	1	0	0
Acute acoustic trauma	1	1	1
Somatosensory tinnitus (whiplash)	1	0	0

AIED indicates autoimmune inner ear disease; AOM, acute otitis media; HIV, human immunodeficiency virus; SLE, systemic lupus erythematosus.

[a]We considered improvement as a reduction of 2 points or more on an analogue scale of 1-10.

[b]We considered improvement as a reduction of hearing loss of 15 dBHL or more in any frequency.

in the "on demand" pattern, although the low dose patterns did not show clearly worse hearing loss data than the other patterns. The 627-patient meta-analysis by Cohen-Kerem showed complete or substantial control of vertigo (class A+B) in 92.7% of patients. The success rate and the risk of hearing loss (0%25%) did not depend on the pattern used, although it is suggested that the safest schemes are those with shorter patterns at higher doses. This recommendation is also supported by the studies of Salt et al.[16] in computer models, who noted that patterns of single doses had a lower risk for hearing and proposed audiometric control as a safety parameter in IT GNT application.

Future perspectives in intratympanic treatment

The future of IT treatment depends on the development of more direct and controlled implementation mechanisms, on more effective drugs and on gene therapies.

Table 4 Results in the different series on applying intratympanic gentamicin in Ménière's disease

Author	Pattern	Dose, mg/ml	Sessions, n	Patients, n	Control of vertigo A	Control of vertigo A+B	Hearing before, dB PTA	Hearing afterwards, dB PTA
Rauch,[44] 1997	On demand	40	2-24	12	58%	58%	52	47
Hirsch,[45] 1997	On demand	30	1-6	15	71%	93%	52.6	53
McFeely,[46] 1998	Fixed	26.7	12	11	27%	91	57.5	50
Kaasinen,[47] 1998	On demand	30	1-4	93	79	79	59.1	67.9
Kaplan,[48] 2000	Fixed	26.7	12	90	84	93	58.3	64.5
Longridge,[49] 2000	On demand	27	1-4	23	30	83	49	47.3
Harner,[14] 2001	On demand	40	1-4	56	67	84	56	57
Quaranta,[50] 2001	On demand	80	2	15	87	93	59.1	55.4
Abou' Halawa,[51] 2002	On demand	40	1-8	43	74	98	58.6	60
Pérez,[52] 2003	On demand	26.7	1-2	71	79	95	67.3	68.4
Wu,[53] 2003	On demand	26.7	1-3	34	88	97	60	59
Stokroos,[12] 2004	On demand	30	1.5:2.8	22	100%[a]	100%[a]	60[b]	54[b]

PTA indicates pure-tone average.
[a]With significance compared to placebo.
[b]Without significance compared to placebo.

At present, different mechanisms are being developed to improve diffusion and control in the drug concentration that reaches the labyrinth. Small osmotic pumps could provide continuous drug diffusion, although the problem lies in where to place these devices. The development of nanoparticles that disseminate without problem at the OW membrane and, above all, the dilution of the drug in polymers and hydrogels that can be deposited in the OW niche, would allow a longer duration of the drug-gel contact with the OW membrane. In this way, we could obtain more continuous, prolonged diffusion.[17] Lee et al.[18] have tested such maintained release using a gelatin hydrogel containing an experimental drug (rhIGF-1) for the treatment of acoustic trauma.

Research on new drugs with an effect on pathological inner ear processes has a special target in acoustic trauma. In animal experiments, insulin-like growth factor 1 demonstrated an improvement in hearing and a reduction in the number of damaged cells in an RCT after acoustic trauma.[19] Inhibitors of calpain protease and lipid peroxidation have also been used.[20] In humans, the Phase I/II RCT of the c-Jun N-terminal kinase inhibitor (AM-111) seems to show some efficacy when applied within 24 hours after acute acoustic trauma.[21] We must await the final results to evaluate its effectiveness.

Gene therapy proposes introducing genes using viral vectors (adenovirus, lentivirus). This promising technique must solve, at present, two important issues before it can become widespread: distributing the vector and gene throughout the entire cochlea and isolating the treatment in the target tissue (labyrinth) to prevent its systemic dissemination and the appearance of side effects. Introducing neural lineage stem cells into the inner ear has also been tested, obtaining diffusion from the scala tympani to the organ of Corti, along with replacement of the different types of damaged cells.

The future of local treatment for cochlear diseases involves avoiding the intermediate station of the middle ear and the OW membrane, applying the drug directly in an intracochlear manner. Different techniques are being designed to this end, such as direct injection on the oval window, the endolymphatic sac and the perilymphatic space in the scala tympani or scala vestibuli. Performing a cochleostomy in the basal zone of the scala tympani appears to be a relatively safe method that allows introducing needles and infusion pumps. Other authors use a diffusion catheter through the cochlear implant electrode, in cases where the implant is indicated. All these possibilities may provide us, in a not too distant future, with more effective treatments for labyrinthine affections.

Conclusions

The intratympanic route for the treatment of labyrinthine affections is a procedure that maximises drug concentrations in the cochlea and minimises systemic dissemination. Steroid therapy has proven effective with cochleovestibular symptoms as a salvage pattern after intravenous corticosteroid therapy in sudden deafness and in the control of Ménière's disease. The administration of

intratympanic gentamicin in "on demand" patterns provides adequate control of vertigo in 80%of patients and a risk of hearing loss between 0%25%in Ménière's disease. Future perspectives, through this approach route, could extend the indications for its use and offer a new pharmacological and gene therapy arsenal.

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