Intratympanic treatment for tinnitus: A review

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Abstract

Since the 1940s, various attempts have been made to treat peripheral tinnitus by way of intratympanic injection. This administration procedure requires only low concentrations of medication, thanks to the highly targeted delivery to the site of action and comes with minimal systemic exposure. While different compounds have been tested for their effects on tinnitus by intratympanic injection, there has been no breakthrough so far. Accordingly, the clinical use of intratympanic tinnitus treatments has remained limited to date. A more widespread adoption of this approach will require the development of specific medications for peripheral tinnitus, as well as proof of safety and efficacy, which would be determined from randomized controlled clinical trials.

Keywords: Cochlea, hearing loss, intratympanic injection, round window, tinnitus

Introduction

The interest in intratympanic treatment of inner ear disorders has substantially increased over the past two decades. While a PubMed search for the terms "intratympanic" or "transtympanic" produces just a few "hits" for any given year back in the 1990s,[1] for 2011 already more than 40 publications on the topic are listed – and this only counting those which deal with drug injections into the human middle ear. The rise in interest in this local drug delivery approach may be explained by our increased knowledge and understanding of inner-ear pharmacology and pharmacokinetics from animal studies. However, it probably also reflects a growing awareness among otolaryngologists of the advantages of local therapy for inner-ear disorders, and the increasing comfort level associated with its use. The intratympanic technique (i.t.) today is primarily used for second-line treatment of sudden deafness with glucocorticoids; chemical ablation of vestibular hair cells in Menière's disease with gentamicin; and tinnitus relief with, for example, lidocaine.

The i.t. approach could open up promising new pharmacological treatment options, particularly, in the field of tinnitus therapy. One of its principal advantages is the ability to deliver therapeutic concentrations of a pharmaceutical agent in a highly targeted fashion to the affected inner ear, with only minimal systemic exposure, thus avoiding side effects on the unaffected ear and/or the central nervous system. This article aims to review state-of-the-art i.t. treatment of inner ear disorders and in particular, tinnitus, and to discuss its potential for broader use in this therapeutic field.

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Basic Concept of Intratympanic Injection

The basic concept of i.t. therapy is fairly simple and straightforward: A drug with a target site of action inside the inner ear is injected into the middle-ear cavity, from where the active substance diffuses into the cochlea [Figure 1]. Diffusion occurs across the semi-permeable round window membrane (RWM), driven by the concentration gradient between the middle ear and the perilymph-filled scala tympani on the opposite side of the RWM. The diffusion rate is determined by various factors, such as size/molecular weight, configuration, concentration, liposolubility and electrical charge of the active substance, as well as by the thickness of the membrane.[2] The smaller a molecule and the higher its solubility, the better it crosses the membrane – it will cross the membrane even more readily if, in addition, it has a positive electrical charge.

The RWM consists of three layers: An outer epithelium facing the middle ear, a core of connective tissue, and an inner-ear epithelium bordering the inner ear.[3] It is a tiny structure (the surface in humans measures 1.82-5.25 mm^2),[4] whose real function is the release of mechanical energy[3] in the form of hydraulic pressure. As sound waves enter the cochlea via the oval window and travel through the liquid-filled turns of the cochlea, their energy has to be dissipated somehow because a liquid is not compressible. Since the cochlea itself is embedded in the highly dense temporal bone and is thus not directly accessible, and as a cochleostomy for direct drug

delivery entails a substantial risk of permanent damage, the RWM provides an attractive gateway to the inner ear.

Compared with systemic administration, i.t. injection results in much higher intracochlear drug concentrations. The inner ear is an end organ with regards to its blood supply, and it is protected by a blood-labyrinth barrier similar to the blood-brain barrier,[5] thus requiring considerable systemic doses. It has been demonstrated, for example, that cortisol levels in the perilymph do not increase following intravenous administration of a high dose of prednisolone (125 mg) in comparison with a placebo. A significant increase could only be observed when the dose was doubled,[6] i.e., to a level that is usually reserved for acute conditions such as the treatment of anaphylactic shock or toxic pulmonary oedema. In a direct comparison, intravenous (i.v.) administration of methylprednisolone resulted, adjusted for dose, in a 425-fold lower concentration in the perilymph when compared to an i.t. injection.[7]

Intratympanic Injections in Practice

For the otolaryngologist, i.t. injections are a straightforward procedure. They can be performed under a microscope with the patient sitting reclined on the examination chair or lying on a stretcher. For the procedure, the patient's head is usually placed in a position tilted 45° towards the unaffected ear.[8] This allows for the RWM to be at the lowest point of the middle-ear cavity, and the study medication to collect there and be in physical contact with the membrane. Patients are asked to remain in this position for about 30 min, allowing the active substance to diffuse into the inner ear. In order to avoid loss of medication into the nasopharynx through the Eustachian tube, patients are also asked not to swallow, yawn, sneeze or speak.

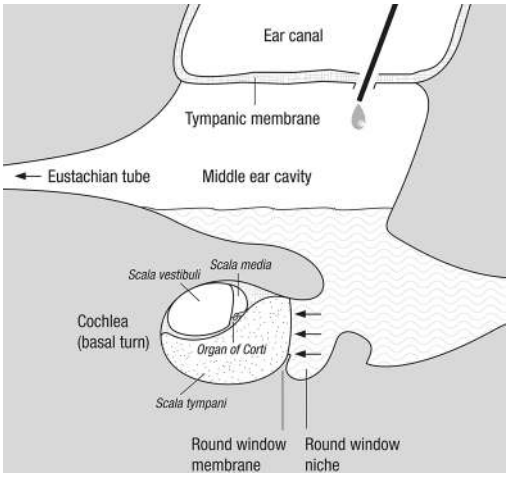

Figure 1: Basic concept of intratympanic treatment. Medication is injected through the tympanic membrane into the middle ear cavity in a quantity that is sufficient to fill the round window niche. The active substance is diffusing across the round window membrane into the basal turn of the perilymph filled scala tympani of the cochlea from where it is spreading further

Following a brief explanation of the procedure to the patient, otoscopy of the ear canal and tympanic membrane is performed. Excessive earwax or debris is cleared and a local anaesthetic applied. Usually, EMLA cream (eutectic lidocaine/prilocaine mixture), xylocaine (4% lidocaine solution or 10% pump spray), or phenol are used. The xylocaine pump spray has a very short induction time of about 1-3 min, while EMLA cream requires 1 h. Phenol numbs the eardrum for up to several days. Once the anaesthesia has taken effect, any remaining anaesthetic needs to be suctioned off prior to the injection to avoid spillage into the middle ear, and avoid vertigo or dizziness. During all these preparations, the drug can be warmed up to about body temperature to prevent caloric vertigo.

For the injection, various techniques and different materials are used. Typically, 1 ml syringes are used – preferably with a luer lock to prevent uncontrolled release of the needle while injecting. Frequently, a spinal needle is used, which may be slightly bent by hand, or a microsuction cannula. Preferably, a short bevel needle is used or, even better, one that is blunt. The injection is frequently performed via the posterior-inferior quadrant of the tympanic membrane, i.e., the area overlying the round window niche [left ear: about 3 o'clock, right ear: about 9 o'clock; Figure 2], close to the limbus. Alternatively, the injection may be performed antero-superior.

In one version, the tympanic membrane is punctured directly with the needle (tympanopunction) and the injection is performed right away. Alternatively, a small paracentesis (myringotomy) is made first, and then the needle penetrates through that incision. This other version allows the RWM patency to be verified by otoendoscopy prior to the injection, and allows air to escape during the injection, thus preventing the build-up of pressure in the middle ear; the Eustachian tube may not always be "open" for air displacement.[9] An outlet for displaced air may also be created through a second

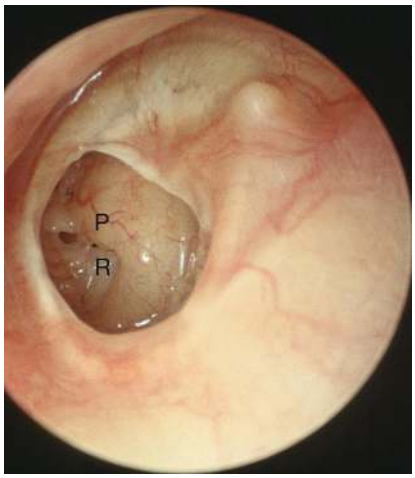

Figure 2: Area of round window visible through mesotympanal perforation in right ear of chronic otitis media patient. P: Promontorium, R: Entrance to round window niche

tympanopunction superior to the first one.[10] However, this may not be necessary if low volumes are injected or if the injection is performed slowly, while observing the fluid level rising to cover the RWM behind the eardrum.[9]

Actually, about 5 µl is usually sufficient to fill the entire round window niche.[11] In a concentration driven drug delivery process, it is much more important how long a drug remains in the round window niche and can diffuse into the cochlea than the volume that is injected into the middle ear.[12] However, since the application of such small volumes is not practical, and as the exact position of the niche cannot be seen while injecting, a much larger quantity is usually injected to amply cover the RWM area – especially since there are usually no safety concerns. Injected volumes in published studies range from <0.3 ml[13] to 1 ml[7,14] at the higher end. Some flexibility in the quantity of administered drug makes sense, as the volume of the middle ear is highly variable between normal hearing ears, measuring between 0.5 ml and 1 ml.[15] An injection volume of 0.2-0.3 ml is probably fully sufficient to cover the target area – any additional quantities are likely to increase the sensation of pressure and possibly, pain in the middle ear, and they would spill back into the ear canal or drain off via the Eustachian tube (occasionally observed in one study with an injection volume of 1 ml).[7]

Early Beginnings of Intratympanic Technique Tinnitus Therapy

While i.t. treatments for sudden deafness or Menière's disease have been the subject of numerous pre-clinical and clinical studies, much less work has been done on their application in the field of tinnitus therapy. This is striking, since, in fact, the first modern attempt at i.t. treatment was, contrary to a widely held belief, not for Menière's disease, but for tinnitus. While Harold Schuknecht proposed the use of streptomycin in Menière's disease as an alternative to surgical labyrinthine ablation in 1956,[1] it was actually Barnard Trowbridge from the University of Kansas School of Medicine in Kansas City who initiated the use of i.t. treatments for tinnitus in the 1940s.

In 1944, Trowbridge wrote a short report, and then in 1949 a detailed paper, on the i.t. treatment of tinnitus with morphine.[16,17] His treatment protocol consisted of repeated i.t. injections of 0.25 ml of a 5% ethylmorphine hydrochloride solution at 4-day intervals using, essentially, the technique that is still applied today. Trowbridge had observed that tinnitus and otalgia often appeared together, and ascribed this to inflammation of the tympanic plexus. With ethylmorphine hydrochloride, an analgesic and vasoactive substance, which at that time had already been used in ophthalmology for removing inflammation products from the eyes, he sought to "calm" the tympanic plexus, thus suppressing tinnitus, and rehabilitate middle-ear tissues. Trowbridge treated 20 patients and claimed complete tinnitus relief in 11 of them, partial improvement in seven and no change in the remaining two: Best results were seen in unilateral peripheral tinnitus up to 1 year from the onset of the tinnitus.

Since no control group was included in Trowbridge's study, it is not known whether there was any real therapeutic benefit. J.F.O. Mitchell from the Royal Infirmary in Edinburgh, UK, failed to replicate Trowbridge's results shortly after their publication, reporting no improvement in the majority of subjects (seven out of 11), and only a slight and transient improvement in the others.[18] However, only four of his subjects suffered from peripheral tinnitus with onset up to 1 year before the conditions best suited for the treatment according to Trowbridge. Since no other references to Trowbridge's therapy can be found in the literature, we must presume that it fell into oblivion.

More than 10 years before Trowbridge published his results with i.t. morphine treatment, Nobel Prize winner Robert Bárány of the University of Uppsala, Sweden, had discovered serendipitously that tinnitus was occasionally suppressed in some patients for a variable length of time when procaine, a local anaesthetic, was administered during intranasal surgery.[19] This clinical observation prompted Robert Lewy of Chicago in 1937 to perform the first study of the use of local anaesthetics for tinnitus relief in 1937, using 75 subjects.[20] Following i.v. administration of procaine, dibucaine or quinine combined with urethane, he observed tinnitus suppression or attenuation in the majority of cases, with effects lasting between a few minutes and a few weeks.

Further Exploration of Pharmacological Targets for Tinnitus Treatment

From Trowbridge's work, it took several decades for the concept of i.t. tinnitus therapy to resurface. Firstly, lidocaine, another local anaesthetic which acts as a sodium-channel blocker, was tested by several groups in the treatment of Menière's disease by way of systemic administration.[21,22] Then, in the 1970s, Eiji Sakata of the Saitama Clinic in Japan started administering lidocaine and dexamethasone intratympanically.[21,23] Since lidocaine has a cardiac depressant effect, giving rise to safety concerns, local administration seemed to offer a much better risk/benefit ratio. For i.t. lidocaine, Sakata reported that tinnitus diminished in 48 of 58 patients (82.8%) after i.t. injection.

When Coles *et al*., (1992) tested i.t. dexamethasone in a small number of tinnitus patients, they found no therapeutic benefit; treating them subsequently with i.t. lidocaine injections led to violent vertigo in all of them, which in some cases necessitated hospitalization.[21] Since a therapeutic effect from i.t. lidocaine was seen in just one patient, and only in a transitory fashion, they concluded that neither treatment warranted a further clinical use. While Sakata's group later reported impressive efficacy data with i.t. lidocaine in almost

300 patients, though almost all of them experienced vertigo at the same time,[24] lidocaine is hardly ever used for tinnitus management currently due to its unacceptable side effects and only transitory efficacy.[22]

In the period that followed, the focus of research in i.t. tinnitus treatments shifted towards glucocorticoids. Starting in the 1990s, steroid drugs were evaluated in an increasing number of clinical studies for Menière's disease and sudden deafness, although in most cases not specifically for tinnitus control. Substantial reductions in tinnitus were reported from a variety of studies (e.g., 75% improvement with i.t. dexamethasone reported by Sakata).[25] However, these results should be viewed with caution, because most of them were retrospective and had no controls.[22] A high-rate of spontaneous recovery of hearing loss and accompanying tinnitus is a hallmark of sudden deafness, which necessitates appropriate controls, and there is already no clear evidence of a therapeutic benefit of steroids with regard to hearing loss.[26,27]

Prospective randomized studies indeed cast doubt on the efficacy of i.t. steroid treatments for tinnitus [Table 1]. In a placebo-controlled, double-blind crossover study in 20 patients with unilateral Menière's disease, three consecutive daily i.t. injections of dexamethasone in a hyaluronate formulation showed no better effect on tinnitus than a placebo.[28] In a single-blind placebo-controlled study of 36 patients with severe, disabling tinnitus, substantial improvement was observed immediately after completion of the treatment in around 30% of subjects in both the i.t. dexamethasone and the saline control groups, but there was no statistically significant difference, and the effect waned over time.[29] A similar result was obtained in a single-blind placebo-controlled study with methylpredisolone in 70 patients suffering from inner-ear tinnitus refractory to medical treatment: two weeks after treatment, subjects in both the placebo and the active groups rated their tinnitus as lower, but the difference was not statistically significant.[10] Another study found no significant differences between i.t. methylprednisolone, i.t. dexamethasone and oral carbamazepine.[30]

In addition to glucocorticoids, a small number of other molecules have also been evaluated in recent years as potential i.t. treatments for tinnitus. In a single-blind placebo-controlled clinical trial with i.v. administration of caroverine, an AMPA receptor antagonist (and NMDA receptor antagonist at higher concentrations), 48% of patients reported a treatment benefit (vs. 3% for saline).[31] However, an independent attempt to replicate these results in an open trial failed.[32] The compound was then tested again in a non-controlled trial through administration of eardrops twice a day for 2 weeks. A clinically relevant improvement (reduction of at least 2 points on a 10-point numerical rating scale for tinnitus severity) was claimed in 57% of cases.[33] AM-101, an NDMA receptor antagonist formulated in a hyaluronic acid gel, was evaluated for safety in a small double-blind placebo-controlled dose-escalation trial. In addition to good tolerance, the study showed trends for improvement in tinnitus status.[13] An open trial with i.t. administration of the muscarinic receptor agonist pilocarpine and the muscarinic and nicotinic receptor agonist carbachol showed a transient effect on the tinnitus minimum masking level.[34]

Table 1: Safety and efficacy data from i.t. tinnitus treatment studies. Frequency of adverse events is expressed in % of treated ears/ patients

Study	*N*	Rx	Dose regimen	Efficacy outcomes	Local safety outcomes
Arajúo *et al*., 2005	21 (ears)	DEX 4 mg/ml	1 × 0.5 ml weekly 4 wks	Tinnitus intensity on 10 pt. scale −1.14 (−14%) for verum, −1.36 (−18%) placebo; all improvements reversed 13-31 months later	Vertigo 10%
	14 (ears)	Saline ctrl			Vertigo 14%, ear pain 7%
DeLucchi, 2000	46	Pilocarpine 1% Carbochol 2%	1 × ? ml	MML −20 dB, effect lasting only 24-72 h, carbochol > pilocarpine	Rotatory vertigo (in all?)
Ehrenberger, 2005	77	Caroverine 1%	Eardrops b.i.d. 2 wks	Tinnitus severity −3.4 pts. on 11 pt. scale at end of Rx, baseline unknown	Transient itching
Mühlmeier *et al*., 2011	16	AM-101 0.03-0.81 µg/ml	1 × 0.25 ml	Gradual trend for better improvement in MML and tinnitus loudness in verum pts. 60 days post Rx	Ear pain: 6%, vertigo 6%
	8	Placebo			Otitis media: 12%
Sakata *et al*., 2001	292 (369 ears)	LID 4%	4 × 1 ml every 2 days	81% of ears with at least 70% reduction in tinnitus intensity at hospital discharge	Vertigo and nausea: almost all, otitis media: 0.1%, eardrum perf. 0.1%, transient hearing loss <10 dB and recruitment ?%
She *et al*., 2009	35 ears	MP 0.25 mg/ml	2 × 0.5 ml 1st week, 1 × 0.5 ml next 2 wks	Tinnitus loudness decreased by ≥5 dB (SL): 48.6% MP group, 37.5% DEX group, 44.0% carbamazepine group; statistically not different	No side effects
	24 ears	DEX 5 mg/ml			
	25 ears	Carbamazepine	300 mg/day 4 weeks		
Topak *et al*., 2009	30	MP 62.5 mg/ml	0.3-0.4 ml weekly 3 weeks	Tinnitus loudness on 11 pt. scale −1.58 (−21%) for verum, −1.47 (−22%) for placebo. No signif. change in tinnitus severity index	Ear pain: 57%, injection pain 67%, vertigo 57%
	29	Saline ctrl			Ear pain: 17%, injection pain 52%, vertigo 38%

DEX = Dexamethasone, MP = Methylprednisolone, LC = Lidocaine, Rx = Treatment, wks = Weeks, MML = Minimum masking level, SL = Sensation level, perf = Perforation

Development Issues with I.T. Treatments

Besides finding the right molecule, the development of future tinnitus therapies based on i.t. injections will also have to address a number of anatomical and physiological factors that tend to produce variability in therapeutic outcomes. Probably, the most important source of variability arises from the fact that the RWM is anything but a standardized "drug delivery port". Its thickness (on average 70 µm) and, especially, its size varies widely in humans[3] and in some cases, it is also covered or obstructed by an extraneous "false" membrane stretching across the opening of the niche in front of the RWM, or by fibrous or fatty plugs within the niche itself.[35] A drug may thus diffuse much better into the inner ear of a patient with a thin RWM, which has a large surface area than in another patient, whose RWM is covered by a dense false membrane, resulting in substantial differences in perilymph concentrations.

The presence of round window niche obstructions is impossible to detect through the closed tympanic membrane. Temporal bone studies have revealed the presence of false membranes in more than 20% of cases, and a lower prevalence of fibrous and especially fatty plugs; overall, the prevalence of RWM obstructions is thought to be up to 32%.[35,36] Using middle-ear endoscopy, other authors have reported partial and complete obstructions in 17% and 12% of cases, respectively,[37] while others have found – in a relatively young population – no such obstructions at all.[13] The presence of an obstruction does not preclude diffusion in all cases. False membranes are sometimes perforated or reticular,[38] thus merely impeding diffusion of a drug rather than blocking it entirely. Magnetic resonance imaging following i.t. injection of the paramagnetic contrast agent gadolinium showed no round window permeability in 5% of ears, and poor permeability in 13%.[39]

Once the pharmaceutical agent has been absorbed into the inner ear, another source of variability comes into play in the form of a concentration gradient from the basal turn of the cochlea (the location of the RWM) to the apex. Distribution of drugs within the perilymph-filled scala tympani of the cochlea is dominated by passive diffusion, with slow substance movement and increasing loss through distribution into adjacent fluid spaces and tissue compartments, and elimination along the length of the cochlea.[12] Animal data shows basal-apical concentration differences of over 1000-fold.[12] However, this cannot be generalized to humans easily due to important anatomical differences. While direct determination of the gradient in a human cochlea is usually not feasible, it has been estimated in a computer-based simulation for i.t. gentamicin at around 100:1 (basal to apical levels).[40] Such a gradient can be of importance if a drug has concentration-dependent side effects in the inner ear, e.g., reaching a target concentration at a more apical target site may require the administration of a dose that is ototoxic in the basilar part.

Since the sampling of inner ear fluids places hearing at risk,[41] drug concentrations in the perilymph following i.t. administration have only been determined in small groups of patients undergoing surgical procedures, where hearing preservation did not matter. Three studies with patients undergoing cochlear implantation, labyrinthectomy or translabyrinthine surgery found that perilymph concentrations varied significantly following i.t. injections of methylprednisolone,[7] dexamethasone[42] or gentamicin.[43] The authors, however, cautioned that it was not possible to quantify precisely the quantity of drug that was effectively in contact with the RWM and that some of the perilymph samples were quite small.[7]

Dealing with the Sources of Variability

For the development of i.t. tinnitus treatment, various conclusions can be drawn from the aforementioned sources of variability. First of all, it is evident that, for safety reasons, i.t. injections are best suited for drugs with a wide therapeutic range.[44] Secondly, i.t. treatments targeting a site of action in the basal part of the cochlea, i.e., in the higher hearing frequencies, are easier to accomplish than therapies with a site of action in the apical part. This means, for example, that the feasibility of i.t. treatments for noise trauma or inner-ear tinnitus, which most often affect high-frequency regions of the cochlea, is *a priori* more easily given than those for Menière's disease, which affects the low frequencies. Thirdly, if the target site of action is located in the middle or apical turns of the cochlea, continuous perfusion or repeated i.t. injections may be required to raise concentrations high enough.[12] Fourthly, when evaluating the dose response effect of an i.t. treatment, larger dose-step increments than the factors (×2 or lower) commonly applied in dose escalation studies should be used. In order to obtain clear signals, a factor of 3 seems much more appropriate; this factor is frequently used in dose escalation studies with intranasal drug application to take account of the variability in absorption through mucosal tissue.

The anatomical differences in RWM size and thickness, as well as the existence of basal-apical concentration gradients, cannot be removed as sources of variability. The process of drug delivery, however, offers various possibilities for optimization. Formulations or devices that ensure retention and facilitate physical contact with the RWM are preferable to solution-based formulations, which can easily get lost through the Eustachian tube. This may be achieved by injecting viscous gel formulations, or by placing wicks, microcatheters or drug-eluting implants (stabilizing matrices)[45] into, or close to, the round window niche. The latter approaches typically require more invasive administration procedures than i.t. injections, and are beyond the scope of the present review.

For gel-based formulations, there are a large number of biocompatible polymers that have already been used, or at least proposed, for i.t. injections. They include hyaluronates[13,46] collagens,[47] chitosans,[48] fibrins,[49] starch,

celluloses, gelatines,[50] poloxamers,[51] and many others. Some of them, like hyaluronates and gelatine, are natural products frequently used in otolaryngology for other clinical purposes, and whose safety has been extensively studied.[46] Most of them are hydrogels, i.e., water-absorbing polymers, which release the active substance by enzymatic hydrolysis of the polymeric matrix, or basic diffusion out of the matrix.[52] The viscosity of the gel formulation is typically chosen as a trade-off between injectability (favouring lower viscosity) and middle-ear retention capacity (favouring higher viscosity). Viscosity that is too high may also result in the formation of an air bubble on the RWM [Figure 3], thus preventing effective diffusion, or temporarily impact the free movement of the ossicular chain, resulting in transient conductive hearing loss, as observed, for example, with a poloxamer gel.[51]

It seems tempting, of course, to enhance RWM diffusion of a drug by incorporating excipients into the formulation that are known to enhance permeability, such as histamine or dimethylsulfoxide (DMSO),[53] prostaglandins or leukotrienes,[3] or to use microsphere or nanoparticle formulations.[45] Adding mannitol, which is well known for shrinking endothelial cells and stretching tight junctions between them, or the preservative benzyl alcohol, has a dramatic effect on RWM permeability.[54] Permeability enhancement should, however, not come at the expense of safety: DMSO, for example, has been shown to be cytotoxic in cochlear organotypic cultures at concentrations between 0.5% and 6%.[55] It may also lead to reduced permeability for later i.t. treatment, due to thickening and scarring of the RWM or increased susceptibility of the inner ear to toxins that are present in a non-sterile middle-ear space.[54]

Ensuring Patient Acceptance

For patients, i.t. treatments are attractive if they allow for short, effective therapies with fewer drug side effects than with systemic administration, and if they don't entail unacceptable procedure-related side effects. Most patients understand the concept of i.t. injection, and readily accept the proposed therapy,[8] recognizing the benefits of a targeted treatment. Compared with infusion therapy, which sometimes even requires hospitalization, i.t. therapy is certainly much shorter and can be performed on an outpatient basis. The whole procedure, comprising otoscopy, local anesthesia of the eardrum, preparation for the injection, drug administration and the following resting period, takes less than one hour in the hands of an experienced otolaryngologist.

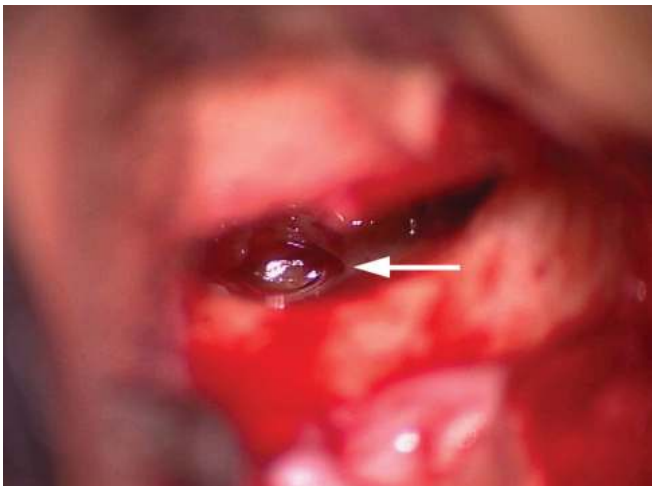

Figure 3: Air bubble (arrow) in highly viscous hyaluronic acid formulation on round window membrane, impeding effective diffusion into the cochlea. Image courtesy of Prof. M. Suckfuell, Munich (Germany)

Table 1 shows safety data from a number of studies with i.t. treatments. The results are not directly comparable due to differences in treatment protocols (number of injections, inclusion of placebo, etc.), data collection and size. They show important drug-related side effects in the case of i.t. lidocaine therapy (transient vertigo in almost all cases),[24] and i.t. methylprednisolone therapy (high incidence of ear pain or injection pain).[10,14,56] I.t. dexamethasone seems to be a steroid which is tolerated better,[8] unlike hydrocortisone, which has led to RWM inflammation after topical instillation in spite of its anti-inflammatory properties, and being well tolerated in animal studies.[57] It is worth noting that none of the medications that are frequently used off-label for i.t. injection have been developed for optimum local tolerance: Gentamicin is acidic, while dexamethasone is basic; both gentamicin and dexamethasone are hypotonic, while methylprednisolone is highly hypertonic.[54]

Local side effects, i.e., procedure-related adverse events of i.t. treatments, may include ear or injection-site pain, dizziness, caloric vertigo, infection, persistent tympanic membrane perforation, or possible vasovagal or syncopal episodes during injection.[8,14,58] In practice, relatively few procedure-related side effects have been observed. Usually, they are of a transient nature, and their risk of occurrence can be reduced in most cases through simple measures. Sufficient warming of the drug, the use of fine needles and appropriate local anaesthesia, a gentle rate of injection, and avoidance of excessive injection volumes seem to be key factors for good local tolerance. Strikingly, in a comparative study using 27G needles for i.t. administration of methylprednisolone or gentamicin, transient pain was rated similarly by patients with our without any local anaesthesia.[56]

A healthy tympanic membrane should close quite rapidly, although data on cicatrisation times are hard to find in the literature. From discussions with otolaryngologists, it would seem that closure can be expected in the majority of cases in between 2 and 5 days. In a small study involving single-dose injection through a paracentesis (and following otoendoscopy), the tympanic membrane was found to be closed 7 days later in 21 out of 24 patients.[13] Sometimes a small blood crust from wound healing will remain on the tympanic membrane:

It will either fall off after some time or may be removed by the otolaryngologist. Where there has been repeated drug administration, subsequent injections are preferably performed at the site of the initial tympanopunction, respectively paracentesis. As long as the tympanic membrane is open, the patient should avoid exposing the treated ear to water.

Following the treatment administration, the otolaryngologist should remind the patient that once he or she gets up small quantities of the study drug may drain down the Eustachian tube and the nasopharynx, and that the perception of sound, including pre-existing tinnitus, may change while the eardrum remains open.

Conclusions

The use of i.t. injections seems conceptually well suited for the treatment of inner-ear disorders such as peripheral tinnitus thanks to the highly targeted delivery of medication to the cochlea. Systemic exposure is minimal, the procedure is simple and straightforward to carry out, and usually well tolerated in patients. Appropriate information prior to the procedure, the use of fine needles and adequate local anaesthetics with short induction times, a gentle flow rate and moderate injection volumes, as well as a sufficiently warmed drug, reduce the likelihood of adverse events, and enhance patient acceptance. The variability in intracochlear drug concentrations can be addressed at least partially through formulation development, in particular, the use of gels.

In spite of a growing interest in the concept, i.t. injections still remain rather the exception than the rule in today's otolaryngology practice, and the studies conducted so far have not resulted in any breakthrough therapy. The lack of specific effective drugs must be considered the first and foremost obstacle for a more widespread use of the i.t. treatment concept. To date, all i.t. treatments are used off-label, relying on empirical experience rather than on licensed pharmaceutical compounds that have been specifically developed, comprehensively tested, and licensed for inner-ear therapy. Most of the studies carried out so far also suffer from important shortcomings such as a lack of statistical power, double-blinding or placebo control: The absence of the latter is of particular importance given that tinnitus treatments may elicit substantial placebo responses.[59]

Still, important groundwork has been done. The numerous lidocaine experiments have proved that tinnitus can indeed be modulated pharmacologically, although the mechanism of action through which tinnitus suppression is achieved still remains a mystery.[60] The quest for the discovery of effective and safe therapeutic molecules is continuing, and with the ongoing increase in scientific tinnitus research, and a growing involvement of the pharmaceutical industry, it seems highly likely that i.t. therapy for tinnitus will come of age in the not-too-distant future.

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