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Issues, indications, and controversies regarding intratympanic steroid perfusion

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Abstract

Purpose of Review—Office based Intratympanic inner ear steroid perfusion treatment (ITPs) for Meniere's disease, autoimmune inner ear disease and sudden sensorineural hearing loss has been expanding over the past 10-15 years, yet remains controversial. The purpose of this review is to examine the current literature of basic science and human studies of ITPs treatment.

Current Findings—Animal studies exist regarding the delivery, distribution, biochemical and microbiological changes in the inner ear post ITPs. However, few clinical studies exist of ITPs treatment in sudden sensorineural hearing loss and even less in treating Meniere's disease. There are no consistent studies regarding drug delivery methods, type and concentration of steroids. Moreover, there are no studies comparing ITPs results to the natural history of Meniere's disease.

Summary—ITPs has impacted otology and neurotology practice due to increased utilization. A sound understanding of the basic science and clinical studies is needed to establish long term efficacy of ITPs in controlling hearing loss in Meniere's disease by comparison to its natural history, as well as, potential application to other pathologies.

Keywords

Intratympanic perfusion; Meniere's disease; Sudden sensorineural hearing loss; Dexamethasone perfusion

Introduction

From a historical point of view to the best of knowledge, clinical use of intratympanic perfusion with steroids (ITPs) began when Sakata et al[1] and, ten years later, Shea et al[2] used it for Meniere's disease and tinnitus patients and, independently, reported clinical benefit to their patients with no adverse reactions to the treatment. These were retrospective cohort studies that did not include control subjects, but nonetheless showed "clinical improvement" by those days' measures. The quotation from Sakata's paper[1], "*….It was concluded from these results that the first choice of therapy for patients with Meniere disease who should resist to all conservative therapies should be the middle ear steroid infusion therapy at the out-patient clinic, and the second choice would be the inner ear anesthetic therapy, and that both therapies*

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were worth while experimenting before considering surgical treatment" continues to be a guiding principle until present time.

Since then, basic science and clinical studies of intratympanic perfusion with steroids (ITPs) have been published. For the purpose of this review, a MEDLINE search of the English language literature of human and animal studies from 2005 -2008 was performed using the key words "intratympanic and Meniere's or sudden hearing loss", "intratympanic and Meniere's or sudden hearing loss", and "steroids and inner ear". We also included other studies prior to 2006 due to their contribution to the subject. A total of 40 studies were found and reviewed with focus on description of steroids dose and delivery technique, clear description of pharmacokinetics/molecular/histological results (animal studies), reported hearing recovery and vertigo control results, and adverse outcome of the treatment. There were few review articles on the subject concluding that there is no convincing evidence of using ITPs[3-5]. The majority of non review studies were focused on ITPs in sudden hearing loss[6-15] and less so in Meniere's disease[16-18]. The following sections describe the general and specific aspects of these studies in Meniere's and sudden hearing loss. The authors views are presented, taking into consideration their respective research and clinical experiences.

Meniere's disease

There is one prospective placebo controlled study[19] and a few retrospective studies[16-18] supporting the use of ITPs in Meniere's disease. The placebo controlled study used Dexamethasone 4mg/ml for five consecutive days and followed up patients for 2 years. The study reported substantial control of vertigo in 82% of treated patients' vs 57% in placebo group. There was an additional 29% in the placebo group that showed moderated improvement of vertigo. The failure rates in the treated and placebo groups were 0% and 14% respectively. The study reported "subjective" improvement of hearing (35%), tinnitus (48%) and aural fullness (48%). The strength of this study is in the randomization and the relatively long-term follow up of patients. The relative weakness lies in the absence of a rational for choosing Dexamethasone over methylprednisolone and of using Dexamethasone 4mg/ml, particularly that ITPs primary advantage over oral is to deliver the highest dose of medicine to the inner ear. Furthermore, a similar randomized study[20] using Dexamethasone showed no benefit over placebo. One of the two retrospective studies[18] suggested that ITPs has beneficial effect on hearing loss in Meniere's disease, however it did not address vertigo control. The most recent retrospective study[16] used Dexamethasone 12mg/ml and followed patients for 2 years. Most patients (70%) needed one to three injections. The study reported 91% 'acceptable" vertigo control based on patients "not requesting" further ablative surgery. The study did not address hearing, tinnitus or aural fullness results. The study used Kaplan-Meier "survival" curve to measure the outcome of "time to next event" as opposed to vertigo control relative to either prior treatments or to a control group. Although the authors justified the use of "survival" analysis, commonly used in prospective studies, they indicated that there is a bias using retrospective data for the analysis. The strength of these retrospective studies lies in the relatively large number of patients and long follow up period. The weakness lies in the absence of a rational of choosing Dexamethasone over methylprednisolone and of using a larger dose (12mg/ml) than other studies, clear indication for repeated injections, and absent control group or taking into account the natural history of Meniere's disease. Furthermore, the criterion used for measuring outcome is based on patients not requesting ablative surgery. This is a rather arbitrary choice and may be influenced, at least partly, by talking about surgery[21]. One of the authors of the current review (Hamid MA) notes that the results of vertigo control in the above study are similar to those presented in 2006[22] using Dexamethasone 24mg/ml (95% control over 7 years follow up period). It is to be noted that Dexamethasone 24mg/ml is no longer available and has to be compounded. While there are supportive studies to the use of ITPs in Meniere's disease, there are few controlled studies to determine the efficacy of the treatment.

Sudden Sensorineural Hearing Loss (SSNHL)

As mentioned above, there are more studies using ITPs in the treatment of SSNHL than in Meniere's disease. This is mainly because it was/is customary to treat SSNHL with systemic steroids and therefore, it was a natural progression to start injecting steroids directly into the ear. A meta-analysis study[23] in 2007 concluded that there is no difference between systemic steroids and "other active treatment". Two recent (2008) studies[6;8] showed different outcome of ITPs. The first is a prospective open label study[6] that compared systemic steroids and ITPs + systemic steroids and showed 73% and 70 % recovery, respectively, and concluded that there is no benefit from adding ITPs. However, in an earlier (2007) study[24] by the same authors, they reported that ITPs salvaged hearing in 40% of patients when given within 1-2 wks after failure of systemic steroids. This study showed declining rate of recovery when ITPs was delayed; 30% after one month and 15 % after two months. The second is a multicenter, double-blinded, placebo-controlled, randomized study[8] designed to compare hearing recovery from 3 groups; high dose systemic steroids and Dexamethasone ITPs, systemic placebo and ITPs, and systemic steroids and placebo ITPs (saline). The authors concluded that patients treated with combination therapy had higher likelihood of recovery than patients given systemic steroids only ($p<0.5$). The strength of this study lies in the randomization and "combined placebo treatment" although there was no placebo only arm. Three other studies[25-27] showed benefit from ITPs after failure of systemic steroids. Two retrospective non randomized studies[10;12] used different types of steroids; methylprednisolone and Dexamethasone 24mg/ml showed different rates of improvement; 67% with methylprednisolone[10] and 39% with Dexamethasone[12].

The data discussed above reflects significant variability in the outcome of ITPs in Meniere's disease and sudden hearing loss. The data from 2000-2006[28] showed similar pattern of variability. There are several reasons why the data on ITPs are variable. First, the dose and the type of steroids used show a wide variation. Steroid doses ranged considerably from 4 mg/ml to 24 mg/ml (Dexamethasone) or 40 mg/ml methylprednisolone). While the advantage of intratympanic perfusion is to deliver a higher concentration to the inner ear, it appears for most studies that the dose was dependent on what was available in the market instead of the maximum Dexamethasone dose of 24 mg/ml. The most common type of steroid used has been methylprednisolone, based on an animal study that favored methylprednisolone relative to Dexamethasone because it yielded "higher concentrations" in the endolymph after intratympanic injections[29]. Although this animal study provided relevant information regarding the pharmacokinetics of different steroids, re-interpretation of the results show that Dexamethasone is more efficacious. The study clearly showed that absorption, allowing for sampling effects[30], of Dexamethasone into the stria and surrounding tissues was more rapid, in contrast to methylprednisolone, which remained in the endolymph longer than Dexamethasone by a factor of 4 to 6 hours. It is known that steroids act intracellularly within the stria and surrounding tissues after being passively or actively endocytosed. Hence, the higher rate of endocytosis, the greater intracellular efficacy. Thus, the presence of high methylprednisolone concentrations in the endolymph reflects an inverse relationship with its intracellular incorporation and efficacy, making Dexamethasone more efficacious for intratympanic perfusions. Unfortunately, Dexamethasone 24 mg/ml was removed from the market in the late 2000 and can now only be produced as a compound.

The second reason of ITPs outcome variability is due to the method of delivery of steroids into the middle ear. Several methods are available which include direct intratympanic perfusion into the middle ear and, microcatheters or microwicks which are placed against the round window. The most common used method worldwide is the direct perfusion into the middle ear. Although ITPs should be a straight forward procedure, there is some degree of variability in how it is done. Some inject directly using single puncture of the TM while others use two

punctures to "vent out" the middle ear space. Some fill in the middle ear space every 10 minutes while others do not. Unfortunately, there is no general consensus but it is reasonable that the physician should insure that there is enough medicine in the middle ear, with or without venting, for 30 min after the injection. The 30 minutes was arbitrary however, a recent study[31] showed that it is an optimal time for diffusion through the round window membrane. Recent studies of the anatomy of the round window and of post injection concentration gradients in the scala tympani showed both immunological aspects[32] and intrinsic gradient characteristics[33] that influence drug delivery methods to the inner ear. These findings will ultimately influence future methods of optimal drug delivery to the inner ear.

The third reason for ITPs outcome variability is the disease stage at the time of the perfusion treatment. Most of the studies referenced above agree that early treatments associated with a better outcome although in clinical practice patients are seldom seen at the early stages of Meniere's or, to a lesser extent, of SSNHL. Physiologically and pathologically it makes sense that perfusion should be performed at an early stage of the disease before, supposedly, the ear has not undergone permanent damage. The pathology of Ménière's disease, sudden hearing loss and immune inner ear diseases is frequently "idiopathic". Immune-mediated inner ear disease is similar to Ménière's, but has a more rapid course affecting both ears[34]. Recent data support an ionic imbalance of the endolymph as the final common pathway in steroid-responsive autoimmune mouse hearing loss, suggesting that steroids improve and restore normal stria vascularis function[35]. Dexamethasone was shown to increase the expression of active and passive Na/K channels[36] and of active water channels (aquaporins)[37;38] in the endolymph surrounding tissues.

Movement of steroids into the inner ear

The round window membrane is the major entry site for intratympanic drugs into the inner ear scala tympani[39]. This is a semi-permeable membrane that is lined on the middle ear side with cuboidal epithelial cells joined by tight junctions and lined on the inner ear side with mesothelial cells that often are intermittent[40]. Between these lining layers are loosely organized collagen and elastic fibers, fibrocytes and fibroblasts, occasional blood vessels, and nerve fibers. The lack of an organized epithelial barrier on the scala tympani side means the fibrous layer is bathed in perilymph. Although tight junctions join epithelial cells on the middle ear side, molecules as large as 1 μm can pass through this layer into the inner ear either intercellularly or transcellularly via pinocytosis. Thus, the round window membrane provides little impediment to the movement of most drugs or other molecules into the inner ear. Although the human round window membrane (60-70 μm) is thicker than most experimental rodents (10-15 μm), they are essentially similar in the fact the only real barrier is the single layer of epithelial cells on the middle ear side. Thus, interspecies differences in transport are due mainly to the time it takes to move through the fibrous layer. While this minimal anatomical barrier appears to offer little protection of the inner ear, a recent study in monkeys suggest mucous glands around the round window and extensive inflammatory cell populations within the round window vessels provide a basic immunological defense to the cochlea[32]. The glands secrete macromolecules that form a physical barrier to trap pathogens and other toxic agents, which are then degraded and phagocytosed by the immune cells. This mucous membrane over the round window has been discussed as a barrier to intratympanic drug movement into the cochlea[40].

Where do drugs go in the ear?

Steroids injected into the middle ear reach the scala tympani within minutes[41] and quickly reach scala vestibuli through the spiral ligament laterally and/or Rosenthal's canal medially[33;42]. Actual measurement and modeling of drug entry and dispersion suggests a

concentration gradient exists from base to apex, but sufficient amounts can reach the apical regions[33;43;44]. Factors controlling this apical ward movement will include the molecular weight, charge, concentration and amount injected, round window characteristics (fibrosis, inflammation) that impact the amount getting through, length of cochlea, any intrinsic perilymph flow patterns, speed of absorption into tissues at the base, etc. Delivering Dexamethasone within slow release gels will provide slower release and therefore prolonged delivery at the round window[45]. The communication routes between scala tympani and the organ of Corti and spiral ganglion assure that hair cells and nerve cells will rapidly be exposed to drugs delivered through the round window. Presence of drug within the scala media demonstrates transport into the endolymphatic spaces as well[46].

What do drugs do in the ear?

The two main effects of drugs in the inner ear impact immune suppression and ion homeostasis. Numerous cochlear insults induce pro-inflammatory cytokines and chemokines and production of reactive oxygen species (nitric oxide, etc.). Immune-mediated cochlear tissue destruction results from acute and chronic otitis media[47], noise[48], hydrops[49] ototoxic drugs[50], ischemia[51], meningitis[52], and systemic inflammatory disease[53]. All initiate cochlear inflammatory processes that are responsive to glucocorticoid treatments. Therefore, immunosuppression is a key factor in protecting the ear or reversing hearing loss in a variety of disorders. Intratympanic delivery of steroids show protection of the inner ear in otitis media[54], cochlear electrode implantation[55] and ototoxic drugs[50]. Many clinical studies have suggested that intratympanic steroids offer additional benefit over systemic delivery due to higher concentrations reaching the inner ear. There is now human evidence this is the case[56]. However, the measurement of drug levels in perilymph[46] or endolymph[29] does not necessarily prove functional impact if the drugs are simply increasing due to concentration gradients across the round window and are not being absorbed and utilized by cochlear tissues where they exert their action. To answer this question of steroid functional impact, we have conducted studies of cochlear gene expression following the two delivery methods. Our studies show that Dexamethasone delivered systemically suppresses some pro-inflammatory cytokine genes in the cochlear tissues, but greater numbers of genes are down regulated if the drug is delivered intratympanically (unpublished observations). Thus, the clinical observations of improved hearing recovery with intratympanic steroid delivery appear to be supported by animal studies. The added advantage is that systemic side effects from oral steroids are virtually eliminated[57].

The effects of steroids on ion homeostasis are well established in animal studies. The tightly regulated fluids in the ear require sophisticated ion transport mechanisms[58]. To date, approximately 83 different ion channel genes have been identified in mouse and human inner ear[59]. The most critical ion transport process is the maintenance of endolymph ion potentials for auditory and vestibular hair cell function. The stria vascularis pumps K^+ into the endolymph (and Na^+ out) to maintain the endolymphatic potential (EP +80 mV) critical for normal hearing. This process requires the recycling of K^+ from the base of hair cells through the lateral wall (spiral ligament) via intercellular gap junctions. Any pathologic process that interferes with this movement of K^+ or stria vascularis function will cause hearing loss. Although vestibular endolymphatic potentials are lower (+5-10 mV), the homeostasis of K^+ is equally important. Contributing to the maintenance of these endolymphatic potentials is the blood labyrinth barrier, a series of tight junctions that isolate fluid compartments for tight regulation of ion movements.

The endothelial cells lining the stria blood vessels are sealed by tight junctions, which establish the blood labyrinth barrier critical for maintenance of this endolymphatic potential. Loss of barrier integrity will equilibrate the endocochlear potential (+80 mV) to that of blood (0 mV),

leading to hearing loss. It also is now known that the cochlear lateral wall is literally a syncytium of cells interconnected by gap junctions for K^+ recycling back to the stria vascularis after hair cell transduction[58]. This syncytium includes supporting cells in the organ of Corti, fibrocytes of the spiral ligament, basal and intermediate cells of the stria vascularis, and probably stria endothelial cells, as well. Compromise of any of these K^+ recycling processes will cause hearing loss due to disruption of ion homeostatic processes. Inflammatory processes include the lateral wall fibrocytes since acute and chronic otitis media[47] and systemic endotoxin treatment[53] cause expression of NF-kB, the pro-inflammatory transcription factor. Dexamethasone also suppresses TNF-α induced nitric oxide production by spiral ligament fibrocytes, demonstrating a direct glucocorticoid effect on K^+ transport and ion homeostasis[60].

Glucocorticoids also have a significant binding affinity for the mineralocorticoid receptor[57;61]. Thus, another ion homeostatic impact of glucocorticoid treatments is induction of mineralocorticoid receptor-mediated genes. These include synthesis of Na^+,K^+-ATPase and the epithelial sodium channel, both major ion transport channels necessary for stria vascularis function. In fact, blockage of the mineralocorticoid receptor with spironolactone prevents glucocorticoid hearing recovery in autoimmune mice[57], suggesting these ion transport functions are more critical than immune suppression in hearing restoration. Also, it was shown that glucocorticoids induce transcription of these ion transport channels at the same level as the mineralocorticoid aldosterone[62], further demonstrating the impact of glucocorticoids on ion homeostasis.

Another ion and fluid homeostasis function of the ear potentially controlled by steroids are the aquaporin channels. Nearly all known aquaporin channels occur in the inner ear, particularly surrounding the endolymph spaces and endolymphatic sac[63;64]. These channels appear to be largely controlled by vasopressin (anti-diuretic hormone)[65] and Dexamethasone[66]. There are data to show a close relationship between aquaporin 4 and Meniere's disease[67;68]. Although other glucocorticoids have not been investigated for their effect on aquaporin control of inner ear fluid dynamics, it is interesting to speculate that Dexamethasone has dual effects in the ear through its impact on water transport and, to a lesser extent, mineralocorticoid receptors. The use of diuretics in Meniere's disease, while controversial, may have multiple effects on the inner ear. They may be effective because they suppress the NaK2Cl transporter to reduce K^+ transport into the endolymph and reverse hydrops[66], as well as opposing the vasopressin control of water balances by acting directly on aquaporin channels. Another possible mechanism is through increased aldosterone, which has positive effects on the stria vascularis, to counter act intravascular volume loss due to use of diuretics[69] Research into the control of inner ear water dynamics is crucial and hopefully will provide significant new findings in the next few years.

Thus, steroid delivery to the inner ear can have multiple functions. One can no longer ignore the potential impact of glucocorticoids on ion homeostasis functions in addition to immune suppression. These functions are quite interlinked with regard to maintenance of the endolymphatic potential in fluids around auditory and vestibular hair cells. Also, the fact these processes are capable of healing recovery from insult suggests they may be involved in those forms of hearing loss that recovery spontaneously. Therefore, assuming all steroid-responsive hearing loss is due to immune processes simply cannot be justified in light of our current understanding of other cellular and molecular processes under the control of glucocorticoids. The key issue in such treatments is to identify the pathologic process and target therapy with the most appropriate steroid, or other drug. For example, the synthetic glucocorticoid Dexamethasone has less binding affinity to the mineralocorticoid receptor than prednisone or prednisolone. Thus, it will have less impact on K^+ and Na^+ transport dysfunction, possibly explaining the questionable efficacy of Dexamethasone for certain hearing disorders.

Future directions

The effective intratympanic delivery of drugs has fostered a variety of new approaches to delivery of substances to the inner ear. Many of these hold promise for effective management of cochlear disorders. Gene delivery via the middle ear shows it is feasible to deliver the necessary genes in vehicles that will move through the round window[70;71]. Also, the intratympanic delivery of drugs, antibodies, and other antagonists show the ear can be protected from loud sound damage by JNK inhibitors[72;73] and inhibitors of calpain and lipid peroxidation[74]. Intratympanic delivery of infliximab, to bind pro-inflammatory TNF-α to reduce progressive inflammation of the inner ear[75], and gancyclovir[76] also have shown some promise for the future. A more recent ITPs using intratympanic Gadolinium[77] has been used to "visualize" the inner ear compartment in Meniere's disease and show promise in "seeing endolymphatic hydrops" as we treat these patients. The middle ear delivery of these molecules will permit better targeted interventions that will transfer more products to the inner ear than conventional systemic delivery methods. Thus, it is likely the intratympanic delivery method will increase in the future as these and other applications are developed.

Conclusion

Several animal basic science studies exist supporting positive biological effects of intratympanic steroids perfusion ITPs on inner ear functions. Few clinical studies exist of ITPs treatment in sudden sensorineural hearing loss and even less in treating Meniere's disease. There is no convincing evidence that ITPs is effective in sudden sensorineural hearing loss. There are inconsistent results of ITPs in controlling vertigo and few studies focused on hearing recovery in Meniere's disease. There are no studies comparing ITPs results to the natural history of Meniere's disease. Few randomized clinical trials exist however, long term (> 5 years) efficacy has not been established. Despite that, there is general acceptance of using ITPs in sudden hearing loss and Meniere's disease. Given the recognized difficulties in conducting randomaized controlled clinical trails, it is suggested that studies evaluating "therapeutic gain" of ITPs relative to current treatments and to the natural history of Meniere's disease[78] should be acceptable alternatives.

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