

## Review Article

## Intratympanic steroid injection for inner ear disease

Yi-Chen Pai<sup>a</sup>, Chia-Fone Lee<sup>a,b,\*</sup><sup>a</sup> Department of Otolaryngology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan<sup>b</sup> Department of Medicine, Tzu Chi University, Hualien, Taiwan

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## ABSTRACT

Many inner ear diseases are not adequately treated by systemic delivery of medication. The blood–cochlear barrier limits the concentration and size of molecules that leave the circulation and access the inner ear. This paper reviews the updated status of intratympanic steroid injections (ITS) for the treatment of inner ear disease. ITS is a nonaggressive procedure in which high concentrations of medication reach the cochlea and systemic side effects are minimized. In addition, this procedure is effective for cochleovestibular symptoms caused by various inner ear diseases including noise-induced hearing loss, idiopathic sudden sensorineural hearing loss, Ménière's disease, and autoimmune inner ear disease. Although the effect of ITS on noise-induced hearing loss is inconclusive, there is a possibility that its indications could be extended, with a new horizon for pharmacological, neurotrophin, gene, and cell-based therapy.

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## 1. Introduction

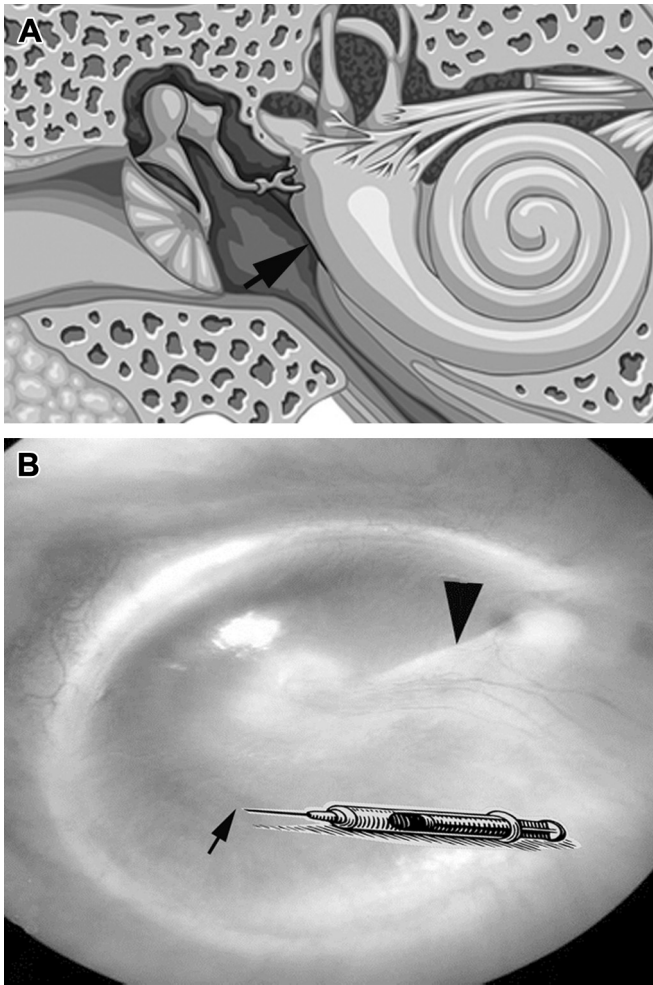
The inner ear is unique for drug delivery [1]. Drug access is limited by the blood–cochlear barrier, which is anatomically and functionally similar to the blood–brain barrier [2,3]. The small size and relative inaccessibility of the cochlea in humans present additional challenges in drug delivery to the inner ear [4]. The cochlea is surrounded by hard bone and is approximately 2 mm in diameter at the entrance. In addition, the organ of Corti within the cochlea is very sensitive to shear stress, mechanical and chemical damage. Since the cochlea contains only about 80  $\mu$ L of fluid, it is susceptible to very small changes in fluid volume [4]. Therefore, a delicate approach is required to avoid damage from drug delivery [1].

Therapeutic management of inner ear disease is undergoing a paradigm shift [5]. Initial treatments for inner ear disease including aminoglycosides for bilateral Ménière's disease and steroids for sudden sensorineural hearing loss (SSNHL) are delivered systemically. Systemic delivery of medication has various drawbacks, such as variable access to the inner ear due to the blood–cochlea barrier and potential systemic side effects. Side effects of systemic

medications are affected by a range of pharmacokinetic factors that influence the concentration of the drug in the inner ear, such as varying volume of distribution in the body, variability in the ability of different medications to cross the blood–labyrinth barrier, and different routes of excretion [6]. Extensive experience with intratympanic (IT) injection of gentamicin in Ménière's disease opened a door to inner ear therapy [7]. Basic and clinical research on IT administration of drugs for inner ear disease has increased significantly [8]. Oral steroids have been at the forefront for many inner ear diseases [9,10]. However, glucocorticoid and mineralocorticoid receptors in the inner ear were discovered recently. Steroids may affect the electrolyte and fluid balance of the inner ear, and the endocochlear potential [11,12]. The primary concern in usage of systemic steroids has been potential side effects [5], ranging from minor to potentially life-threatening. Systemic steroid therapy has been associated with hyperglycemia, hypertension, hypokalemia, peptic ulcer, osteoporosis, immune suppression, adrenal suppression [13], and serious organ damage [5]. These side effects often lead to a change in medication or a switch to a less efficacious alternative. The clinical drive for safe and effective medications for inner ear disorders has resulted in the development of techniques for local drug delivery [5,14]. Strategies in IT delivery of drugs into the inner ear for local absorption include injection, perfusion, hydrogel vehicles, nanoparticle carriers, and microcatheter systems. This review provides information on the current status of IT therapy (Fig. 1).

\* Corresponding author. Department of Otolaryngology, Buddhist Tzu Chi General Hospital, 707, Section 3, Chung-Yang Road, Hualien, Taiwan. Tel.: +886 3 8561825; fax: +886 3 8560977.

E-mail address: [e430013@yahoo.com.tw](mailto:e430013@yahoo.com.tw) (C.-F. Lee).



**Fig. 1.** (A) Large arrow shows the round window membrane from Lee et al and Copyright 201x, Slideworld. Reprinted with permission. (B) Intratympanic steroid injection procedure. Injections are performed using an office microscope with the patient (left ear) lying down. A small needle (e.g., no. 22 spinal puncture needle) and syringe are used and the needle (small arrow) is passed through the tympanic membrane so that the needle tip is near the round window membrane. The arrowhead indicates the malleus.

## 2. IT steroid injection application in inner ear disease

### 2.1. IT steroids for noise-induced hearing loss

Noise-induced hearing loss (NIHL) is thought to be due to mechanical and metabolic damage [15,16]. Mechanical damage includes trauma to the stereocilia, reticular lamina, hair cell membranes, and the organ of Corti [17–20]. In a guinea pig experiment, damage occurred in the region 8.74–14.44 mm from the apex [21]. Takemura et al speculated that focal damage in the 9–14 mm region was caused primarily by direct mechanical damage to the cells of the organ of Corti, and secondarily by cell death in border regions [21]. Previous studies revealed that NIHL might involve hypoxia and formation of free radicals. Hypoxia in NIHL may reduce blood flow and finally lead to reduction in the hearing threshold [22]. Ischemia may induce reactive oxygen species and glutamate excitotoxicity, and activate the cell death pathway [23,24]. In addition, NIHL induces excitotoxicity and the formation of nitric oxide by converting free radicals to much more active and destructive species [21]. Excitotoxicity is triggered by  $Ca^{2+}$  entry leading to influx of ions and water. The cascades triggered by  $Ca^{2+}$  include activation of free radicals, protease, and endonuclease [25].

The effectiveness of steroids in reducing NIHL is not conclusive [1]. In guinea pigs, infusion of dexamethasone resulted in a dose-dependent reduction in loss of outer hair cells, and attenuation of the auditory brainstem response shift 7 days after noise exposure [21]. A direct infusion of methylprednisolone into the cochlea for 7 days after exposure of guinea pigs to impulse noise reduced hair cell loss, and promoted the recovery of temporary hearing shifts [26], but not permanent hearing loss. These findings suggest that IT steroids may be an alternative for patients with significant side effects from systemic therapy [1].

### 2.2. IT steroids for Ménière's disease

Itoh and Sakata reported improvement in 80% of patients with vertigo who received IT steroid injections [27]. In a randomized case-controlled clinical trial, IT dexamethasone demonstrated a statistically significant difference in complete vertigo control for Ménière's disease compared with a placebo [28]. Boleas-Aguirre et al showed that vertigo was significantly improved with intermittent IT steroids for as long as 2 years in 91% of patients [29]. In addition, Ménière's disease-associated symptoms can be treated with IT steroids [30].

### 2.3. IT steroids for idiopathic SSNHL

Sudden hearing loss is characterized by abrupt loss of hearing, which is typically unilateral [12]. Up to 65% of patients experience spontaneous recovery [31], usually within 2 weeks after the hearing loss. The chance of recovery decreases the longer the time between onset and first treatment. Proposed treatments include vasodilators, steroids, antiviral agents, hyperbaric oxygen, and plasmapheresis [12]. Infusion of rheological agents (e.g., dextran and pentoxifylline) is the standard treatment used in some countries [9,10]. Wilson et al reported that systemic steroids were beneficial in patients with moderate to severe hearing loss [32]. However, 30–50% of patients did not respond to high-dosage oral or intravenous steroid therapy, and IT steroid injections were proposed as rescue therapy for those refractory cases [33–36]. IT dexamethasone injections improved hearing in 39% of patient with a pure tone average (PTA) improvement of 12 dB, versus 10% and 10 dB in the control group [36]. Plaza and Herráiz demonstrated that 55% of patients had improvement after IT steroid injections with a mean PTA improvement of 33 dB, versus 0% and 12 dB, respectively, in those patients who refused therapy [37]. In diabetic patients, IT steroid injections significantly improved hearing in 70% of patients with a mean PTA improvement of 41 dB, versus 67% and 25 dB, respectively, in patients who received intravenous dexamethasone [38]. Therefore, some authors promote IT steroids as the first-line therapy for all idiopathic SSNHL [33–39].

### 2.4. IT steroids for autoimmune inner ear disease

Autoimmune inner ear disease results in hearing loss when immune regulation is compromised [1,40]. The results of treatment with high-dose systemic steroids and local IT steroid delivery are not conclusive [41,42]. Swan et al proposed local drug delivery to correct autoimmune inner ear disease [1]. Ryan et al suggested treatment with high-dose prednisolone, with methotrexate added for relapses [43].

## 3. Potential drawbacks of IT steroid injections

IT drug delivery for inner ear disorders alleviates some of the problems associated with systemic drug delivery. In recent years, IT steroid delivery has become routine for inner ear disease. However,

the clinician should be aware of some potential drawbacks, for example, anatomic barriers to absorption at the round window membrane, loss of drug down to the Eustachian tube, and the varying pharmacokinetic profiles of medications currently used for IT delivery [5]. The round window membrane is the primary transfer site for IT therapy. In one study, about one-third of temporal bones (i.e., the round window membrane) were obstructed by a pseudo membrane, fibrous tissue, or a fat plug [44]. Loss of medication via the Eustachian tube is another anatomic consideration that may affect the efficacy of IT steroid injection. Results of animal studies suggest potential ototoxicity of direct steroid application [45]. Persistent tympanic perforation, short-duration vertigo, tinnitus, and otitis media were reported after perfusion of high concentrations of steroids [46], but the incidence was very low in clinical applications.

#### 4. The finite element method to predict drug concentrations in the cochlea with IT injections

One contributing factor in the variation in drug delivery is the absence of reliable data on the pharmacokinetics of drugs delivered into the inner ear [47]. In humans, direct measurements of time-dependent alterations of drug concentrations in the inner ear are almost impossible. Therefore, computer simulation is a valuable tool for estimating drug concentrations in the inner ear [48]. Simulations have been used to interpret published data on gentamicin and corticosteroid perilymph concentrations in the chinchilla and guinea pig cochlea [49,50]. An established one-dimensional simulation model (Washington University Cochlear Fluid Simulator, FluidSim <http://oto.wustl.edu/cochlea/model.htm> [48]) has provided a good presentation of the longitudinal distribution of drugs. Plontke et al developed a more advanced three-dimensional simulation model to assist in both drug and drug delivery system design [47]. This method can assist in understanding the existence of substantial drug gradients across the scalae in the basal turn of the cochlea. In addition, the development of a rationale-based local drug delivery system to the inner ear and its successful establishment in clinical practice can be accelerated [47].

#### 5. Conclusion and future directions

IT drug delivery for the treatment of inner ear disease can maximize drug concentrations in the cochlea and minimize systemic dissemination. This method is relatively safe with minimal risks. There are many methods that can deliver drugs to the cochlea using the route of the middle ear including passive and active drug delivery systems [1]. Passive methods include biodegradable polymers, hydrogel-based systems, and nanoparticles. Active methods use a variety of components and devices including microcatheters, microwicks, and osmotic pumps. Future perspectives may extend the indications for IT steroid injections and offer a new horizon for pharmacological, neurotrophin, gene, and cell-based therapy. Patients with inner ear disease can look forward to improvement in quality of life and relief of cochlea-vestibular symptoms as the development of IT delivery progresses.

Hu and Parens conducted a literature review of some clinical trials investigating IT steroid therapy for inner ear disorders [51]. They found that there are no good studies on IT steroid that meet the criteria of comparability, internal validity, and external validity. First, the data are heterogenous with respect to steroid doses, treatment protocols, previous treatments, and definitions of disease and improvement. Second, Ménière's disease and SSNHL have a natural history of spontaneous resolution. Third, there is a lack of placebo controls in many studies. Fourth, the sample sizes for the studies are small. In the future, studies should be randomized and

**Table 1**

Results obtained using intratympanic steroid injection for inner ear disease [8].

Disease	Author(s), year	Patients, n	Improvement (patient, %)	Improvement (dB or %)
Sudden sensorineural hearing loss	Parnes et al 1999 [34]	13	46	62 dB
	Ho et al 2004 [35]	15	53	28 dB
	Fitzgerald et al 2007 [52]	21	67	26.6 dB
Ménière's disease	Battaglia et al 2008 [53]	120	70	31 dB
	Ito and Sakata 1991 [27]	61	78	—
	Silverstein et al 1998 [30]	17	NS	NS
	Garduño-Anaya et al 2005 [28]	22	82	10%

dB = decibels; NS = not statistically significant.

controlled to eliminate selection bias and the placebo effect. The application of IT steroid injection for treatment of inner ear disease is shown in Table 1 [8].

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