

Intratympanic Drug Therapy with Steroids for Tinnitus Control: A Preliminary Report

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Abstract: Intratympanic drug therapy (ITDT) is a surgical technique of instilling medication into the middle ear to perfuse the inner ear in treating hearing loss, tinnitus, vertigo, and ear blockage, alone or in combination, in patients with a predominantly inner-ear site of lesion. This preliminary report of ITDT focuses on attempts at tinnitus control (TC). Between November 1997 and February 1999, 10 patients with severe tinnitus were treated with steroid medication and were last seen in February 2000. TC was established in 7 of these 10 patients (70%). The clinical diagnosis of a predominantly cochlear-type tinnitus was established in each patient by a correlation of the clinical history with a medical-audiological tinnitus patient protocol that included cochleovestibular testing. An additional single patient with sudden hearing loss experienced no hearing improvement on ITDT steroid therapy. Vertigo as an associated complaint was reported by 6 of 10 patients with subjective idiopathic tinnitus. Significant control of the associated vertigo complaint was reported by 5 of 10 patients. Duration of tinnitus relief in 7 of 10 patients was hours in 1 of the 7; days in another of the 7; and 1 year or more in 5 of the 7. One of the seven patients reported TC 3 months after the procedure. Complications included tympanic membrane perforation that persisted for more than 6 months in two patients and an increase in the complaint of ear blockage and tinnitus intensity in one patient. In our preliminary study, ITDT with steroid has resulted in both short- and long-term tinnitus relief in 7 of 10 patients (70%) identified to have a predominantly cochlear-type tinnitus.

Keywords: catheter pump; intratympanic drug therapy; medical-audiologic tinnitus patient protocol; microdosage; steroid; steroid resistance; steroid toxicity

Although no cure currently is available for the symptom of tinnitus, protocols for attempting to establish an accurate diagnosis of the symptom of tinnitus and for providing tinnitus control (TC; i.e., relief) are available. One such relief system is intratympanic drug therapy (ITDT), reported since 1982 by Sakata et al. [1-5].

In 1982, Sakata et al. [1] reported for the first time the results of a steroid-targeting therapy for a cochlear-type tinnitus using intratympanic dexamethasone infu-

sion, with an overall effective rate of 71% in 1,214 patients with 1,466 affected ears. Our preliminary report outlines our initial clinical experience with ITDT using steroid medication, which was introduced into the treatment protocol of the tinnitus clinic of the Health Sciences Center at Brooklyn, State University of New York (HSCB-SUNY) in 1997 [6]. Our goals have been to achieve TC (i.e., to provide relief, maintain hearing, and provide neuroprotection). Our ITDT protocol differentiates between clinical application (i.e., patient care) and clinical research.

Clinically, two stages of treatment are planned and offered to each patient. Stage I is an office procedure using the technique of Sakata et al. [1,5]. The goal in stage I has been to test the efficacy of an office-based surgical technique for achieving TC in a predominantly cochlear-type tinnitus. Stage II is an operating room

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procedure wherein a catheter is inserted into the round window niche to permit microdosage delivery of a drug selected for perfusion of the inner ear. The pump provides a calculated constant delivery of an anesthetic (lidocaine), an antiinflammatory (steroid), or an aminoglycoside drug (gentamicin-streptomycin) in the attempt to achieve tinnitus relief. Stage II is reserved for patients in whom stage I treatment either fails or provides an inadequate degree of tinnitus relief.

ITDT for attempting control of hearing loss, tinnitus, vertigo, and ear blockage, either alone or in combination, in patients having a predominantly inner-ear site of lesion is not new. The surgical technique has been applied for Ménière's disease to control vertigo, in attempts to restore hearing for sudden hearing loss syndrome, and in attempts to control a cochlear-type tinnitus. Three classes of drugs have been selected for ITDT of inner ear complaints: anesthetic agents (i.e., lidocaine), ototoxic drugs, and steroids. Recently, a new class of drugs, called *neuroprotective drugs*, has been introduced and focuses on calpain antagonists for in vivo inner-ear perfusion experiments in animals [6].

Historically, ITDT control of tinnitus and vertigo in Ménière's disease with the anesthetic agent lidocaine was reported by Barany (1935) [7], Lempert (1946) [8], Kroath (1960) [9], Gejrot (1963) [10], Ristow (1968) [11], and Sakata et al. (1982) [1]. Ototoxic drug use for vertigo control attempts in Ménière's disease were reported with streptomycin by Fowler (1948) [12], Schuknecht (1957) [13], Graham et al. (1984) [14], and Bagger-Sjovack et al. (1990) [15]. Steroid use for vertigo control in Ménière's disease was reported by Sakata (1982) [1], Shea and Ge (1996) [16], and Silverstein et al. (1996) [17,18]. For tinnitus associated with Ménière's disease, results with gentamicin have been reported by Hoffer et al. (1998) [19]. TC for a predominantly cochlear-type tinnitus has been reported with the anesthetic agent lidocaine by Coles et al. (1992) [20] and with steroids by Sakata et al. (1996) [5], Silverstein et al. (1996) [17], Shulman (1998) [6], Seidman (1998) [21], Hicks (1998) [22], and Parnes et al. (1998) [23]. Neuroprotective drug protocols focusing on the calpain antagonist Leupeptine in in vivo animal experimentation have been reported by Shulman (1997) [24], Salvi et al. (1998) [25], and Stracher (1997) [26].

This preliminary report includes a description of the ITDT method used with steroid treatment and the both short- and long-term tinnitus relief results in 10 patients with a severe, disabling, primarily cochlear-type tinnitus. Treatment was followed up for more than 1 year in an attempt to establish short- and long-term benefits of ITDT with steroids. Clinical issues of patient selection, classification and standardization of terminology, and fundamentals of steroid action are discussed.

METHODS

Patient Selection

Tinnitus patient selection for ITDT with steroids was limited to patients with a clinical history of subjective idiopathic, severe, disabling tinnitus predominantly of a cochlear type and of at least 1–3 years' duration. The clinical diagnosis of a predominantly cochlear-type tinnitus was established for each patient with a medical-audiological tinnitus patient protocol (MATPP) that included cochleovestibular testing [27–29].

A stable personality with control of the affect component was identified and confirmed by psychiatric evaluation when indicated. Each patient was given the option of instrumentation or medication prior to surgery [30]. Treatment of factors identified in the clinical history or neurootological evaluation was carried out in an attempt to achieve TC prior to surgery. No tinnitus relief had been reported by patients selected for ITDT with either medication or instrumentation (or both). The ear selected exhibited the greater loss of hearing and greater intensity of tinnitus. Associated complaints of ear blockage or vertigo (or both) and a positive test finding of a reduced vestibular response or a positive result on the Fukuda stepping test reinforced the selection of the ear chosen for ITDT.

The ITDT technique with steroids was recommended for 11 patients (9 male and 2 female, aged 38–80 years (mean age, 62). Ten patients had the indication of subjective idiopathic, severe, disabling tinnitus of the cochlear type. One patient had a sudden hearing loss syndrome for which ITDT was recommended in an attempt to improve hearing. ITDT was repeated once in three tinnitus patients. One patient had an initial and repeat office procedure with instillation of steroid therapy (stage I) followed by catheter pump placement under anesthesia (stage II). A total of 15 ears were treated in 11 patients (Table 1). The steroids selected were dexamethasone, 8 mg/ml (n = 4), and hydrocortisone (Solu-Cortef), 100 mg/ml (n = 6). No significant difference

Table 1. Results of Intratympanic Drug Therapy with Steroids to Achieve Tinnitus Control

	Number
Total patients	11
Sudden hearing loss patients	1
Tinnitus patients	10
Repeat procedures	3
Catheter pump procedure	1
Total ear procedures	15
Tinnitus patients in whom tinnitus control was achieved	7 (70%)

for either steroid has been observed qualitatively in either the degree or duration of tinnitus relief.

A tinnitus evaluation was completed by the audiologist for each patient. Cochleovestibular correlates were interpreted clinically as consistent with a primarily cochlear-type tinnitus. All patients revealed a mild to moderate degree of sensorineural hearing loss, primarily cochlear in location. Six of the 10 tinnitus patients reported an associated complaint of vertigo. Ear blockage was present in the chosen ear in all tinnitus patients selected for ITDT to attempt TC with steroids.

Technique

Initial physical examination of the ear, nose, and throat identified presence or absence of disease of the head and neck, with particular attention to the absence of inflammatory disease. Patients were examined in a reclining position under the microscope. The external ear canal was cleaned, and the tympanic membrane was anesthetized with local topical 2% phenol anesthesia.

Dexamethasone, 8 mg/ml, was introduced initially via a myringotomy into the selected ear in three patients. Solu-Cortef, 100 mg/ml, was injected as the steroid of choice via a puncture of the tympanic membrane in seven other patients. The tympanic membrane was punctured at the site of phenol anesthesia. Puncture was performed in the posteroinferior quadrant overlying the round window niche and the anteroinferior quadrant. The syringe containing 1 ml of either dexamethasone or Solu-Cortef was attached to a No. 19 spinal needle. Instillation of 0.5–0.8 ml of steroid was made into the middle ear. The head of the patient was positioned with the chin supported by a towel roll to allow maximum contact of the drug with the round window membrane. Patients were kept at rest at the described position for 1 hour. The infusion was repeated three times at 1-week intervals, such that a total of three doses were applied. A second steroid course of ITDT was employed in three patients 6 months after the first treatment. In one patient 2 months after the initial course of dexamethasone treatment, the catheter pump was inserted and kept in place for 2 weeks.

Results

Outcome determinations were based on comparison of initial and follow-up completed tinnitus questionnaires, a tinnitus handicap inventory, tinnitus stress test, depression questionnaire, and clinical follow-up. The patients were seen for follow-up at weekly intervals for 6 weeks. Thereafter, monthly visits were made to identify the presence or absence of a latency or additive (positive or negative) effect of the steroid therapy on TC and

to check the status of the tympanic membrane. After 6 months, patients were seen every 4 months. Screening audiograms were obtained prior to ITDT and at 3, 6, and 12 months.

A total of 15 ITDT procedures with steroids were performed in 11 ears, 10 of which were affected by subjective idiopathic, severe, disabling tinnitus of the cochlear type, and 1 of which had experienced a sudden hearing loss. TC was achieved in 7 of the 10 ears that began with severe, disabling tinnitus (70%) (see Table 1). Tinnitus relief lasted hours in one patient, days in another, 6 months or longer in five patients, and 1 year or longer in five patients. An intermittent latency period greater than 3 months prior to a report of tinnitus relief was experienced by one patient.

Among the patients undergoing a stage I procedure, ear blockage increased with an increase of tinnitus intensity in 1 patient; a perforated tympanic membrane was present for more than 6 months in 2 patients; transient vertigo (lasting seconds) after instillation of steroids was experienced by all 10 patients; and 5 patients suffered transient discomfort of the operated ear for minutes after puncture; but no hearing loss occurred. In the single ear treated for sudden hearing loss of 4 weeks' duration, no hearing improvement was noted. A catheter pump was used in one of the tinnitus-affected ears that had been "dead" for more than 3 years, which then experienced a dramatic return of sound perception of 2–3 days' duration. Tinnitus relief of 10 days' duration, marked by reduction in the frequency and intensity of the tinnitus, was noted in the ear with the catheter pump.

All patients have been followed to date for more than 18 months. Five of seven patients continue to report "significant" tinnitus improvement (i.e., relief or control).

Criteria for Success

For tinnitus, the first criterion for success is to do no harm. The technique of ITDT with steroids has as its goal a significant reduction in the tinnitus intensity index (TII) to 3 or less, on a scale of 0–7, where 0 is no tinnitus and 7 is maximal intensity [31]. The relief should be considered by the patient to be mild or moderate to maximum relief (i.e., absence of tinnitus). An accompanying improvement in affect lasting longer than 3 months is desired (i.e., reduction or elimination of anxiety, depression, negative emotion, fear). Associated complaints of ear blockage, hearing loss, or vertigo, when present, should be relieved. Audiometric testing should be unchanged, and the patient should report no subjective increased loss of hearing.

Success has been measured by the TII and the outcome determinations as described earlier. In addition,

patients were asked to identify their degree of tinnitus relief by establishing a percentage of improvement based on a comparison of the tinnitus before and after treatment. If the tinnitus was eliminated, the patient reported 100% improvement. If no change was evident, the patient reported 0% improvement. In the five patients with tinnitus relief in excess of 1.5 years, the patients reported a range of tinnitus relief of 35–95% (mean, 60%). The improvement was in the sensory and the affect components of tinnitus.

DISCUSSION

A significant degree of tinnitus relief has been obtained using Sakata's technique of ITDT in both the short and long term. The key to achieving the degree of reported efficacy for TC is considered to be the establishment of an accurate tinnitus diagnosis (i.e., clinical identification of a cochlear-type tinnitus) [27–30].

In general, the use of ITDT for attempting TC raises significant issues for professionals. Such issues include the patient selection method, drug delivery systems, and criteria for success of TC. Neuroprotection (i.e., understanding the basic scientific mechanisms involved in ITDT and its application for inner ear complaints, especially tinnitus) is another issue of concern to professionals using ITDT [6,24–26]. In addition, professionals must have an understanding of steroid therapy (i.e., of glucocorticoid receptor distribution in the inner ear, steroid resistance and toxicity, and the relationship of stress to steroid toxicity [31]). Finally, combined drug therapy is an issue in the use of ITDT for TC [24,30].

Patient Selection via the MATPP

Patient selection for ITDT was reserved for tinnitus patients in whom a clinical diagnosis of subjective, idiopathic, severe, disabling tinnitus of predominantly a cochlear type had been established. The duration of the severe, disabling tinnitus prior to recommendation of ITDT was at least 1 year. Basic scientific reports suggest that the window for effective ITDT treatment is initiation within weeks of tinnitus onset [32]. A trial of instrumentation, either alone or in combination with medication, prior to use of ITDT has been recommended. The goal was to do no harm, provide TC or tinnitus relief, maintain hearing, and provide neuroprotection for function of the inner ear [24].

Medical-audiological protocols are recommended to provide a clinical tinnitus diagnosis based on a correlation of the clinical history with cochleovestibular correlates of inner ear function. The MATPP includes an electrodiagnostic battery of cochleovestibular tests highlighted by site of lesion impedance audiometry,

electrical and air conduction high-frequency audiometry, auditory brainstem responses (ABR) for short latency responses, otoacoustic emissions, volume discomfort levels, Feldmann masking curves, vestibular testing using the rotary chair, pursuit tracking systems, and electronystagmographic recording, Romberg test, the Fukuda stepping test, and assessment of the presence or absence of abnormal extraocular eye movements [27]. The clinical diagnosis of a predominantly cochlear-type tinnitus is established in a manner identical to that which is taught in neurotology for identification of a predominantly cochlear-type sensorineural hearing loss or peripheral vertigo. Complaints associated with tinnitus, particularly ear blockage or vertigo, are significant for selection of the ear for ITDT. The electrophysiologic cochleovestibular test results are correlated with the clinical history and the neurotological examination.

It is recommended that the ear selected for ITDT be the ear with the greater intensity of tinnitus and poorer hearing. The presence of ear blockage, with or without a finding of reduced vestibular response in the blocked ear, has been found to be associated in this series with an increased success rate of ITDT for TC. In this series, significant relief of associated complaints of ear blockage and vertigo have been reported by patients with and without reported tinnitus relief.

The clinical diagnosis of a secondary endolymphatic hydrops (SEH) was established in the ear selected for ITDT in 5 of 10 patients. All five patients were in the group that reported positive TC. This suggests that patient selection for ITDT can be further increased by the identification of an SEH. Furthermore, the medical significance of the tinnitus for such patients may be a gradual progressive sensorineural hearing loss, the underlying mechanisms of which may be an SEH [29].

In five of the seven patients who reported long-term tinnitus relief, all presented a clinical history of 1–3 years of severe, disabling tinnitus; cochleovestibular findings of a Feldmann masking curve (FMC) of I, III, or IV; a reduced vestibular response with vestibular testing; and an associated complaint of ear blockage. Five of the seven patients with tinnitus relief in excess of 1 year had an FMC of I or III (three of seven with a type I FMC and two of seven with a type III FMC) (Table 2). An FMC of IV was seen in one of seven and an FMC of V in another of seven patients with significant TC. To summarize, significant TC was reported by 5 of 10 patients identified to have a type I or III FMC. Of the additional two successes reported, one in a patient with a type V FMC and one in a patient with a type IV FMC, the patient with FMC V achieved relief of the shortest duration and had a profound sensorineural hearing loss. The patient with FMC IV had the shortest duration of severe, disabling tinnitus (i.e., 1 year).

Table 2. Type of Feldmann Masking Curve in Patients in whom Tinnitus Control Was Achieved After Intratympanic Drug Therapy with Steroids

Feldmann Masking Curve Type	No. of Patients (N = 10)
I	3
II	2
III	1
IV	1

These outcomes suggest that the cochleovestibular correlates FMC I, III, and possibly IV, a reduced vestibular response with vestibular testing, and the duration of severe, disabling tinnitus all are positive factors that, in this series, may have contributed significantly to the positive long-term (>1 year) tinnitus relief (see Table 2).

The MATPP has identified two findings that are considered significant for patient selection and that may have increased the incidence of tinnitus relief with ITDT in this series—specifically, the type of FMC and a reduced vestibular response in the ear to be treated, as established by caloric or rotary-chair vestibular testing. The presence or absence of vertigo and ear blockage and the vestibular test result should be relied on to support the selection of an ear for surgery.

Correlation of Duration of Severe, Disabling Tinnitus and Duration of Tinnitus Relief

The tinnitus duration prior to ITDT ranged in this series from 1 to 40 years. Of the successful group of patients, the most significant duration and degree of tinnitus relief was reported in patients with an average tinnitus duration of 3 years. The shortest duration of severe, disabling tinnitus of the cochlear type was 1 year. The duration of tinnitus relief in five of seven patients currently is in excess of 1 year. The five patients experiencing successful TC reported tinnitus of between 1 and 3 years' duration. Two of the seven patients who reported the shortest duration of relief (described as hours or days) reported tinnitus to have been present in excess of 7 years (one in excess of 40 years and the other in excess of 7 years).

Correlation of Age and Duration of Tinnitus

The age of the patients ranged from 38 to 80 years (mean, 62 years). The success rate was marked in patients with a duration of severe, disabling tinnitus averaging 1–3 years. The factors of age and duration of tinnitus may be significant in successfully identifying patients who may benefit from ITDT for TC.

Failures

In this series, ITDT for tinnitus relief failed in three patients. The FMC was type III in one of these patients and type I in the remaining two patients. One FMC type I patient was 80 years of age and had suffered severe, disabling tinnitus for more than 40 years and chronic inflammatory middle-ear disease for more than 20 years. Failure in this patient is hypothesized to be due to failure of the medication to reach the inner ear owing to fibrosis or scar formation in the round window niche. The remaining FMC I and FMC III patients were examined with single-photon emission computed tomography (SPECT) of the brain. Significantly, both revealed marked abnormalities consistent with a clinical diagnosis of a predominantly central-type tinnitus.

This experience with brain SPECT, which identified significant central-type tinnitus in two patients in whom ITDT failed, suggests that prior to any ITDT, brain SPECT should be considered to increase the accuracy of diagnosis of the clinical type of tinnitus. The use of brain SPECT, by accurately identifying a primarily central-type tinnitus, may increase the rate of success of inner-ear perfusion techniques for TC.

Previous reports of ITDT failure owing to obstruction in the round window niche support rejection of patients so affected for the Sakata technique of ITDT for attempting tinnitus relief. The three failed treatments in our series include the oldest patient (age 80 years), who had tinnitus of more than 30 years' duration and a long history of chronic inflammatory ear disease, and two patients whose tinnitus was identified by brain SPECT to be a predominantly central type.

Drug Delivery Systems

Specification of the techniques for perfusing the inner ear is recommended in clinical reports of ITDT attempting TC. The techniques and results reported by Sakata et al. [1] since 1982 and the results reported in our series support attempting TC as a staged approach for a predominantly cochlear-type tinnitus. Stage I is an office-based procedure using the Sakata technique and is followed by stage II, which involves a catheter pump delivery system for microdosage drug delivery, if TC is inadequate or no improvement occurs with stage I treatment.

Techniques currently available for introduction of medication into the inner ear include the Sakata technique of direct introduction of medication into the middle ear [1–5], placement of Gelfoam into the round window niche via a tympanostomy opening, and the use of a microcatheter pump arrangement to access the round window niche [33]. Silverstein [34] has identi-

fied a delivery system called the *Microwick*TM (Micro-medics Inc., Eagan, MN). This wick is inserted through the tympanic membrane via a vent tube into the round window niche. The advantage is that once the wick is inserted, the patient can self-administer ear drops into the ear canal. It is hypothesized that the ear drops are absorbed by the wick and transported to the round window membrane and inner-ear fluids.

It is recommended that terminology for ITDT drug delivery systems be standardized. The terminology recommended by Arenberg (personal communication, 1999) is logical: intratympanic drug therapy (ID), which is equivalent to the technique as described by Sakata; intra-ear drug therapy (IE or "bull's-eye"); and intrascalar catheter pump drug therapy (IS), which is invasive.

Variations in the volume of the middle ear, type of anesthesia for the tympanic membrane, and role of otic endoscopes for examination of the middle ear are considered significant in the performance technique for ITDT and the results obtained. *Acute delivery* is a term used to denote delivery of drugs over a few days. *Chronic delivery* describes drug delivery over a period of 2 weeks or longer.

Clinical and basic scientific investigations should attempt to identify factors that may influence the chances of achieving positive control of inner-ear complaints. Specific questions that should be addressed include the following: What is the effective amount of drug that must be placed into the middle ear? What is the significance of the status of the middle-ear mucosa and, in particular, the round window niche? Do the differences in results reported for TC reflect levels of susceptibility of the patient to the drug action? Is the drug active at a cellular or a subcellular level? What is the influence of the drug in question on cochlear blood flow and TC?

The results with ITDT for control of inner-ear complaints, as described by Sakata [1], is supported by this series as a surgical technique that can result in long-term tinnitus relief in a significant number of tinnitus patients in whom a predominantly cochlear-type tinnitus has been diagnosed. The long-term results are the basis for recommending this technique as a first-line office-based procedure prior to attempting other perfusion techniques of the inner ear.

The catheter pump system has been selected as the stage II procedure for tinnitus patients in whom a predominantly cochlear-type tinnitus has been diagnosed but who have had no response or varying degrees of relief from stage I treatment but desire more. Steroids have been selected for their neuroprotective action as the initial drug class of choice for attempting tinnitus relief via ITDT. The pump affords the practitioner the ability to develop pharmacotherapeutic curves for treat-

ment that deliver a microdosage of the drugs in question [18]. The ability of the catheter pump system to deliver a concentration of drug lower than that delivered by ITDT to achieve effective control of vertigo in patients with Ménière's disease is considered significant for future TC delivery systems. The pump may provide bypass of systemic barriers by delivery of medication directly into the inner ear; its use also may avoid side effects related to high drug dosages that are otherwise prescribed to reach effective levels of activity within the inner ear.

The cornerstone for patient selection for ITDT is a clinical history of tinnitus of the severe, disabling type. A correlation of cochleovestibular test results with the clinical history is considered to be significant (as revealed in this series) for achieving long-term tinnitus relief with ITDT. It is anticipated that, in the future, specialized drug delivery systems will be introduced to attempt treatment for inner-ear complaints, especially tinnitus. This will require a collaboration of otologists, audiologists, engineers, and clinicians.

The currently evolving international clinical experience with perfusion of the inner ear should lead to the establishment of standardized protocols and principles for drug delivery for each drug delivery system and each inner-ear complaint that is being treated. Drug distribution in the inner-ear fluids of perilymph and endolymph in tinnitus patients may differ from that of normal individuals.

Both normal and abnormal labyrinthine blood-barrier function must be considered in basic scientific terms of as well as in terms of the pharmacology applied [35–37]. First, what is the nature of the barriers controlling entry of material and drugs into the inner ear, brain, and cerebrospinal fluid (CSF)? Second, how do the pharmacological properties of drugs influence their entry into the inner ear, brain, and CSF in terms of normal blood labyrinthine and blood-brain barrier function and endolymph, perilymph, and CSF physiology? Third, what is the role of the perilymph or endolymph and CSF circulation in distributing the drugs placed into the middle ear for perfusion of the inner ear? Fourth, how does the pathological alteration of the labyrinthine blood barrier influence entry of the drug selected for attempting control of such inner-ear complaints as hearing loss, tinnitus, vertigo, and ear blockage, either alone or in combination?

Criteria for Success

The criteria for success of ITDT include differentiating between the sensory and affect components of the symptom of tinnitus. For the sensory components, TII is used [30]. In the current series, all patients had a tin-

nitus level of 6–7 prior to ITDT. Relief was considered to have been achieved for the tinnitus sensory component if the intensity level was 3 or less and was maintained for longer than a 3-month period and if the patient reported the degree of TC to be in excess of 35–50% (a result of comparing preoperative and postoperative values). TC in this study averaged 60%. Two patients reported 90–95% tinnitus relief; three patients reported 35%; one patient reported 50%; and one patient reported 10%. The duration of tinnitus relief in excess of 18 months is considered significant in our series. Outcome questionnaires were completed both at the onset and on completion of drug delivery and have been repeated at 1, 3, and 6 months and again at 1 year.

Neuroprotection

The term *neuroprotection* refers to processes that protect neuronal function from injury or that improve such function after injury [24–26]. The chief etiologies of neuronal injury are ischemia, trauma, hemorrhage, and neurodegenerative disease. Neuroprotective drug therapies for central nervous system etiologies of ischemia, hemorrhage, and trauma are hypothesized to have innovative applications for control of the symptom of tinnitus, particularly of the severe, disabling type [24]. Drugs that provide neuroprotection are considered to be applicable for treatment of inner-ear complaints, particularly hearing loss, tinnitus, vertigo, and ear blockage, either alone or in combination. Pharmacological agents considered to be neuroprotective have been identified and include calcium channel blockers, free radical scavengers, corticosteroids, antagonists of glutamate at *N*-methyl-D-aspartate (NMDA) and non-NMDA receptors, in various thrombolytic agents. Such neuroprotective drug therapies using ITDT are being considered for attempts of TC and for the prevention and short- and long-term treatment of inner-ear complaints. The calpain antagonist Leupeptine has demonstrated neuroprotection from noise trauma in the chinchilla [6,25]. Neuroprotective drug therapy directed to interruption of the calpain protease final common pathway for cell destruction with calpain antagonists may be of value for achieving tinnitus relief [6,24,26].

Steroid Therapy, Glucocorticoid Receptors, and Steroid Resistance

Neuroprotective agents influence underlying processes of apoptosis, necrosis, and the etiologies of ischemia, trauma, hemorrhage and neurodegenerative disease. Cellular and neuronal death are manifested in interference in function [24,26]. Steroids are considered to be

neuroprotective agents and are classified into three main groups: (1) glucocorticoids, (2) mineralocorticoids, and (3) androgenic steroids.

Steroid activity exerts both positive and negative effects, all of which are related to the glucocorticoid receptor (GR). The sensitivity of patients to the action of the steroid hormones can result from either a deficiency in the number of receptors and target cells or from an alteration in the receptor itself.

Adrenal steroids (corticosteroids) are hormones that act via intracellular receptors that mediate slow genomic actions. Adrenal steroids are classified as either type I or type II receptors [38,39].

The GR has both peripheral and central binding sites. Peripheral sites are demonstrated clinically by parapsychological processes (e.g., inflammation that manifests as asthma, rheumatoid arthritis, osteoarthritis). The central site is composed of adrenocorticotrophic hormone products.

Glucocorticoid hormones have been reported to suppress the systemic inflammatory response by mechanisms involving cytokines. Other mechanisms involve inhibition of inflammatory enzymes (e.g., nitric oxide synthase, platelet-activating factor II, angiotensin-converting enzymes, adhesion molecules) [40,41]. GRs, located intracellularly, bind to the glucocorticoid hormones. The binding of these hormones to the receptors in the target tissue provides control of protein synthesis via gene expression. The hypothalamic-pituitary-adrenal axis provides a feedback system for regulating cellular expression of the GRs. Glucocorticoid hormones act on specific systems of the body (e.g., brain, immune system, gastrointestinal system) [42].

The inner ear has been known to respond to systemic delivery of steroids. The clinical success of our evolving experience with steroids for ITDT is limited by what is known and not known about steroid receptors and their interaction with other neurotransmitter systems and, specifically, the influence of stress. The systemic response of patients with inner-ear complaints to glucocorticoid hormones suggests a distribution network within the inner ear that is responsible for the positive effects of such hormones [43,44]. GRs have been identified in the lateral wall of the cochlea [45,46]. In addition, the enzyme Na,K-ATPase, which is involved in the production and regulation of the endocochlear potential and regulation of fluid-ion content and is present in the lateral wall of the cochlea [47,48], interacts with the GRs. Reports of this interaction indicate that both receptors are significant for water-ion regulation and normal function of the inner ear [49,50]. A correlation has been identified between serum concentration of glucocorticoids and the amount of Na,K-ATPase in the inner ear [51,52].

It has been speculated that glucocorticoids have an effect on the permeability of the round window membrane. However, inner-ear studies in rat otitis media could not detect any effect on the regulation of GRs and Na,K-ATPase in the inner ear [53].

Steroid hormone function results from binding of steroids to their respective intracellular receptors, which act as transcription factors and regulate gene expression [54,55]. Steroids that alter neuronal excitability at the cell surface by interaction with specific neurotransmitter receptors have been designated as *neuroactive steroids* [56–58]. *Neurosteroids* are a variety of neuroactive steroids formed within the brain from cholesterol, without the aid of peripheral sources [59]. The original term *neuroactive steroids* has been challenged by identification of steroid hormones that modulate various neurotransmitter receptors allosterically and by genomic effects that modulate the gamma-aminobutyric acid receptor: That is, effects are not incited solely by specific interactions with neurotransmitter receptors.

A disturbance in homeostasis of neuroactive steroids may be a risk factor for the development of neuropsychiatric illnesses. Antidepressants may, in part, be effective by influencing the equilibrium of neuroactive steroids [60,61]. The explanation for potential success of a neuropsychopharmacological drug treatment may lie in intracellular cross-talk between genomic and non-genomic steroid effects and the influence of the drug on stress, depression, neuroprotection, and other behavioral functions and dementias [62].

The issues of steroid resistance and steroid toxicity are considered significant in the interpretation of results of ITDT treatment for cochleovestibular complaints, particularly tinnitus. Glucocorticoid resistance has been demonstrated clinically by the finding of adrenocorticotrophic hormone insufficiency by an alteration in receptor concentration in patients with the acquired immunodeficiency syndrome. What is the significance of this concept in relation to negative results reported with ITDT with steroids? The distribution of GRs in the cochlea may be related to the specificity of action of dexamethasone or methylprednisolone. The ITDT administration of steroids for perfusion of the inner ear avoids potentially dangerous complications that result from prolonged corticosteroid therapy. Such complications include growth retardation, osteoporosis, surgical collapse, behavioral change (highlighted by depression), and even death. Intermittent corticosteroid therapy revealed impairment of the functional capacity of the hypothalamic-pituitary component of the hypothalamic-pituitary-adrenal axis [63].

The issues of GRs in the inner ear and steroid toxicity and resistance are pertinent to a discussion of un-

derling mechanisms of failure of steroid therapy for inner-ear complaints [64–66]. With respect to GRs, Silverstein et al. [18] have reported that dexamethasone has no benefit over placebo for the treatment of hearing loss and tinnitus in a group of patients with unilateral Ménière's disease. Shirwany et al. [67] studied the effects of ITDT dexamethasone injection on cochlear blood flow. Their results suggest that ITDT steroid application is not likely to be detrimental to the inner ear. Seidman [21] have reported on the safety of steroids applied to the inner ear. They identified an increase in blood flow, which may explain the pharmacological effects of steroids on the inner ear. Parnes et al. [23] has demonstrated that levels of various steroid medications that appear in inner-ear fluids may be significantly different depending on the route of administration used [23]. The highest levels were achieved by transtympanic administration as compared to either oral or parenteral administration in the guinea pig.

Stress and Steroid Toxicity

Patients with subjective, idiopathic, severe, disabling tinnitus all are adversely influenced by stress. The symptom of tinnitus is a stressor, a perturbation in the outside world that disrupts homeostasis. The stress response is a set of neural and endocrine adaptations that help to reestablish homeostasis [31,68].

Acute stress leads to a dramatic increase in glucocorticoid production. A feedback loop has been identified between immune and endocrine function and glucocorticoids. Glucocorticoids play a significant role. Steroids are not only of different types but their underlying mechanisms of action are different, and they interact with one another.

Juhn et al. [35,69] have demonstrated good evidence to suggest that stress-related hormones such as epinephrine can alter inner-ear fluid homeostasis and auditory function.

A stress diathesis model for tinnitus in brain has been proposed [70]. In the face of preexistent stress and the presence of significant increasing cortisol levels in a given patient, the introduction of glucocorticoid into the patient's ear may additionally increase an extant elevated level of cortisol secondary to the stress syndrome, with consequent steroid toxicity.

Steroid toxicity has been reported with steroid use and is related directly to the distribution of the GRs in tissue [42]. The issues of steroid resistance and steroid toxicity are considered significant for interpreting the results of treatment for cochleovestibular complaints. The overall effect of steroids on inner-ear maladies may be counterproductive (i.e., a negative result).

Combined Therapy

Use of a combination of drugs with steroids may increase the efficacy for tinnitus relief by providing antagonist activity to the cascade of processes involved in apoptosis [29,30]. Steroids are modulators of immunological responses. Steroids in combination with other drugs may influence the pathological processes of ischemia, hemorrhage, trauma, and neurodegeneration. Such pathological processes, either alone or in combination, may result in the clinical manifestation of inner-ear complaints of hearing loss, tinnitus, vertigo, or ear blockage, either alone or in combination. In other words, a combination of therapeutic approaches is recommended, one agent of which may be a steroid, to achieve maximal efficacy of treatment, as desired for neuroprotection and treatment of a cochlear-type tinnitus.

CONCLUSIONS

ITDT is recommended as an initial office procedure prior to catheter pump insertion or another route of drug administration. The catheter pump delivery system is recommended as a second-stage approach for patients who achieve no result or minimal improvement after initial ITDT treatment. Standardization of protocols is recommended such that principles can be drafted for ITDT perfusion of the inner ear, on the basis of patient selection, drug usage, and the drug delivery system.

Significant long-term tinnitus relief was achieved in 70% of patients in this preliminary study of ITDT and steroids in 10 patients with subjective, idiopathic, severe, disabling tinnitus of a predominantly cochlear type. The key for efficacy of the ITDT technique is establishment of an accurate diagnosis of a predominantly cochlear-type tinnitus. We conclude that the Sakata technique of ITDT using corticosteroids is a satisfactory method of providing tinnitus relief in both the short and long term to patients with a predominantly cochlear-type tinnitus of the severe, disabling type.

In this series, associated complaints of ear blockage and vertigo were markedly improved, as reported by all patients with tinnitus relief as well as in those patients with no tinnitus relief. The medical significance of tinnitus may be a gradually progressive sensorineural hearing loss. The underlying mechanism may be a secondary endolymphatic hydrops.

Steroid resistance and steroid toxicity are considered significant in the evaluation of failure of ITDT and steroids in patients with subjective, idiopathic, severe, disabling tinnitus of a primarily cochlear type. Neuroprotective drug therapies are recommended alone or in combination for perfusion of the inner ear to control

inner-ear complaints of hearing loss, tinnitus, vertigo, and ear blockage, either alone or in combination.

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