# Intratympanic Dexamethasone Treatment for Control of Subjective Idiopathic Tinnitus: Our Clinical Experience

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> **Abstract:** In this report, we summarize our clinical experience with intratympanic dexamethasone treatment (IDT) for control of tinnitus. From March 2000 through February 2001, we observed 54 patients (23 women, 31 men; mean age, 49.6  $\pm$  7.2 years; range, 24–71 years) suffering from subjective idiopathic tinnitus (SIT). After common audiological tests had been performed, all patients underwent specific topodiagnostic tests to verify the cochlear SIT genesis. The 50 subjects with positive results from a furosemide test and negative results from caraverine and carbamazepine tests were selected for the IDT, consisting of transtympanic perfusion of 4 mg dexamethasone to the round window via the middle ear. The treatment was repeated three times daily for 3 consecutive months. Its short-term effects were evaluated 2 weeks after the last perfusion. In 17 of 50 of these patients (34%), the SIT disappeared; 20 of the 50 (40%) reported a significant decrease of the symptom; and the remaining 13 of the 50 (26%) did not experience any improvement. Therefore, we believe that IDT represents an effective drug delivery system for SIT control, as long as the condition arises from inner ear disorders only and treatment occurs within 3 months of symptom onset.

Key Words: drug delivery system; inner ear; tinnitus; transtympanic perfusion technique

Subjective idiopathic tinnitus (SIT) might be defined as a noise or ringing in the ears, audible to the patient only and with uncertain pathogenesis. Frequently, it arises from a dyssynchrony between neuronal firing and the regular activity of the auditory nervous system, but its origin could also be connected with cochlear latency disorders, cytoneural synapse dysfunctions and, sometimes, central nervous system diseases.

A useful method for determining the source of SIT consists of pharmacological topodiagnosis, based on assessment of the responses reported by patients to specific drug administration. Treatment may be based not only on systemic pharmachological administration. Some authors have proposed local administration of drugs for tinnitus relief [1,2]. Once the common audiological tests and the pharmacological topodiagnostic examinations have verified the pathogenesis of cochlear SIT, it is possible to perform intratympanic dexamethasone treatment (IDT), as described by Sakata et al. [3–6], to act more directly on the peripheral pathogenetic mechanisms. This therapeutic modality entails introducing 2 or 4 mg dexamethasone directly into the tympanic cavity through a fine-needle syringe entered into the tympanic membrane, so that the drug can reach the round window and, hence, the inner ear [7,8].

It is assumed that the medicine, absorbed by the labyrinth, may offer improved metabolic outcomes and have sedative and especially edema-relieving effects on auditory hair cells, eliminating the abnormal excitation state that could cause SIT [3,4,9–12].

To estimate the effectiveness of the described treatment in SIT control, we tested subjects suffering from

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unilateral tinnitus with meaningful signs of cochlear involvement. This report describes the results of our clinical experience.

#### MATERIAL AND METHODS

From March 2000 through February 2001, we observed 54 patients (23 women, 31 men; mean age, 49.6  $\pm$  7.2 years; range, 24–71 years) who reported the presence of a unilateral tinnitus that occurred in a 1-month to 2-year variable period. After an accurate anamnesis, all patients underwent common audiological tests, including pure-tone audiometry, tympanometry with acoustic reflex threshold research, tinnitus matching, masking Feldmann test, and analysis of auditory evoked potentials. Clear identification of SIT's origin was not possible in any cases. Therefore, to obtain this information, we performed three pharmacological tests.

#### **Furosemide Test**

The furosemide test was described by Risey et al. [13] in 1995. Furosemide is a drastic diuretic acting on the ionic exchanges in the Henle's loop. This drug is supposed to produce beneficial effects on cochlear nervous potentials. Thus, a positive response to furosemide administration indicates a cochlear SIT genesis. The test is performed by giving a patient 500 mg furosemide slowly IV in 500 ml of physiological solution. The main side effects of the drug are hypotension, drowsiness, and vertigo.

## **Caraverine Test**

The caraverine test was proposed by Denk et al. [14] in 1997. Caraverine is a papaverine-like drug that acts on cytoneural synapses as a specific glutamate antagonist. A positive response to the test shows that the SIT comes from a synaptic dysfunction. Instead of caraverine, magnesium sulfate can also be used [14]. It is assumed that magnesium sulfate acts as a potent glutamate antagonist, the main side effect of which is only a moderate vertigo. The test consists of the administration of two caraverine ampules in 250 ml of physiological solution. The main side effects of this drug are vertigo, confusion, headache, and nausea.

#### **Carbamazepine Test**

The carbamazepine test is based on experimental studies performed by Shulman et al. [15] regarding a central SIT treatment involving carbamazepine. Carbamazepine is an antiepileptic drug effective on neural membranes. Thus, a positive carbamazepine test response

indicates that the SIT has a central genesis. It is useful to administer 400 milligrams of the drug orally once daily. Its main side effects are vertigo, confusion, ataxia, and intestinal disorders.

At present, it is not possible to assert that the pharmacological tests exactly define the origin of SIT. As a matter of fact, it is not unusual to find a combination of positive and negative responses to the same test performed at different times in the same patient. These data testify to the complexity of SIT's pathogenesis. However, use of the pharmacological tests should be considered in the treatment-planning phase, because they allow identification of the effectiveness of specific drugs in comparison with others.

To determine whether the SIT has been changed by the acute drug administration, we usually estimate the loudness visual analog scale and modification of the masking curve, the loudness discomfort level, residual inhibition, and the masking "mixing point" [15]. Drug administration should be performed on consecutive days according to a well-defined model.

The furosemide test must be performed on the first day. If results are positive, we verify the peripheral SIT's source, and then we can carry out the caraverine test to recognize the presence of a synaptic dysfunction. If, instead, the result is negative, the SIT most likely has a central origin, in which case we perform the carbamazepine test, which may confirm the central involvement.

Fifty subjects of the group tested positive to the furosemide test and negative to the others, demonstrating in this way the SIT's cochlear origin. Once the SIT's peripheral source was verified, we started performing the IDT. The intratympanic injection of 4 mg dexamethasone was administered with patients in the supine position, using a tuberculin syringe (27-gauge needle) entered into the tympanic membrane just behind the umbo. The drug reached the tympanic cavity so as to be absorbed through the round window by the inner ear. Before the procedure, subjects were asked to try to hold their posture steady and to avoid swallowing during the injection and for approximately 15 minutes thereafter to prevent the escape of dexamethasone through the eustachian tube. The perfusion was repeated three times monthly at an interval of 1 week for 3 consecutive months. At the end of each month of treatment, patients took a week off before starting the next month.

A 10-grade scale for the evaluation of SIT improvement was applied using a decimal visual analog scale. The severity of tinnitus at the time of discharge was reported by patients who made a comparison with their pretherapy report of tinnitus severity. According to Sakata et al. [3–6,16], the efficacy of IDT was classified as "complete resolution" for grade 0 (100% decrease); "good decrease" for grade 2 (80% decrease); "unsatisfactory" for grades 3–6 (40–70% decrease); and "no improvement" for grades 7–10 (decrease of less than 30%).

Short-term overall effects of the treatment on tinnitus were evaluated 2 weeks after the last perfusion. A reevaluation of visual analog scale grades was performed 6 weeks after the short-term effects quantification (2 months after the last treatment).

#### RESULTS

At the end of treatment, the short-term effects could be summarized as follows: complete resolution of the tinnitus symptom in 17 of 50 patients (34%); good decrease of the symptom in 20 of 50 patients (40%); and unsatisfactory or no improvement in the remaining 13 of 50 patients (26%).

Six weeks after this evaluation, the effects were calculated in the 37 patients who recorded either complete resolution or good decrease of the symptom. In these patients, SIT remained completely absent in only 5 (13.5%). In the others, IDT could be classified as having accomplished a good decrease of the symptom in 29 (78.3%), whereas in 3, SIT returned to pre-IDT levels.

One-year follow-up was possible for 18 patients. Of this group, 5 recorded unsatisfactory results or no improvement (27.7%) at short-term follow-up. After 1 year, for the remaining two patients, SIT had completely disappeared, whereas in two, it returned at pre-IDT levels. In the other nine, the effect of IDT on SIT was still classified as a good decrease, and these patients were satisfied.

The only side effects that we observed during inner ear drug delivery were pain at the moment of tympanic puncture and temporary vertigo immediately after the injection. The temporary vertigo is probably caused by caloric stimulation. This effect could be avoided by infusing the drug solution at body temperature [17].

## CONCLUSIONS

The drug reached the tympanic cavity. It has been claimed that when dexamethasone remains in the tympanic cavity, it could be absorbed through the round window to carry out its favorable effects [18–20]. It is not yet well-known how dexamethasone modulates inner ear fluids [21]. The effects may be due to modification of electrical activity of auditory hair cells [18] or, more generally, to the mechanisms generating endocochlear potentials, such as intermediate cells in stria vascularis, as hypothesized by Takeuchi et al. [22]. It appears that IDT provides a useful control of SIT in a meaningful percentage of patients without inducing

remarkable local or systemic effects. Clearly, the treatment effectiveness increases when pharmacological therapy is performed within 3 months of SIT onset and in the absence of dysmetabolic disorders. We believe that IDT represents an effective therapeutic option for SIT due to cochlear disorders and not modifiable by medical treatment alone.

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