International Tinnitus Journal, Vol. 10, No. 1, 91–93 (2004)

Tinnitus: Pharmacological Topodiagnosis

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Abstract: The difficulty of accurately localizing the source of subjective tinnitus is well-known. Anamnesis and traditional audiological tests can often suggest a source if its origin as peripheral or merely central (or both). Therefore, several authors, such as Risey, Denk, and Shulman, recently proposed identifying the source of subjective tinnitus through the evaluation of the responses reported by patients to adequate pharmacological treatments. Our study presents a useful plan to perform tinnitus topodiagnosis, which consists of specific audiological tests evaluating the characteristics of symptoms (annoyance, pitch, loudness, hyperacusis) and of several pharmacological tests carried out through the administration of particular drugs, the pharmacodynamic mechanisms and meaningful side effects of which are described. On the basis of pharmacological effects on tinnitometry, some drugs will be combined.

Key Words: hyperacusis; tinnitometry; tinnitus

One of the most interesting subjects still able to generate lively discussions among audiologists regards the possibility of performing an accurate topodiagnosis of subjective idiopathic tinnitus (SIT) [1]. Even though unknown or multifactorial etiopathogenesis and variable clinical features of this symptom render the localization of its source very difficult, several researchers continue seeking some kind of test that may suggest whether the SIT has a cochlear genesis, is due to a cytoneural synapse dysfunction, or is produced by a central nervous system disease. At any rate, SIT often arises from a dyssynchrony between the neuronal firing and the regular activity of the auditory nervous system.

METHODS

Audiological Evaluation

Undoubtedly, any attempt to pick out the source of SIT should be supported by the results of a series of specific audiological tests evaluating the main features of the disorder as reported by affected patients (e.g., annoyance, pitch, loudness, hyperacusis). Therefore, after performance of audiological tests, such as pure-tone audiometry, tympanometry, and acoustic reflex threshold research, and auditory evoked potentials, it is necessary to begin the quantification of annoyance, which is executed through self-administered questionnaires (both reactive and cognitive) and decimal visual analog scales.

Then, we suggest the assessment of the SIT's pitch, perception of which is thought to be coded both by the place of stimulation and by the rate of temporal activity. The "pitch-matching adaptive method" consists of presenting a pure tone to a patient's unaffected ear and asking whether the tinnitus pitch is higher or lower. Depending on the patient's answer, the next stimulus presentation will bracket the tinnitus pitch. When the patient reports a binaural tinnitus, pitch will be matched for each ear individually.

At the third stimulus, assessing the loudness of the SIT is important because the changes of this feature could correspond to changes in the number of nerve fibers involved or in the temporal firing patterns within or across neurons. SIT loudness may be measured easily by adjusting the level of a pure tone (identified through pitch-matching procedures) so that it has roughly

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This manuscript was presented at the Third Tinnitus Meeting, Saint Peter Ording, Germany, February 16, 2001.

the same loudness as that of the tinnitus. Finally, as is well-known, the dysfunctions causing the SIT could have any effect on the loudness perception, leading to a reduced uncomfortable loudness level and hence to the hyperacusis.

Hyperacusis in persons with normal or elevated hearing thresholds can be defined as an unusual intolerance to the loudness of ordinary environmental sounds. It is usually accompanied by tinnitus [2]. The values of two mean parameters, according to the method presented by Goldstein and Shulman [3], allow us to verify a hyperacusis condition: the *loudness discomfort level* (LDL), obtained by instructing affected patients to indicate when the sound delivered from the audiometer through the earphone becomes uncomfortable to the ear, and the *dynamic range*, obtained by calculating the difference between the pure-tone threshold and the LDL for each of the discrete frequencies. When the LDL is 90 dB or less at two or more frequencies or the dynamic range is 55 dB or less at any frequency, a patient will be considered affected by hyperacusis.

We also consider the monaural masking test posited by Feldmann [4], a very powerful tool in the physical investigation of SIT. The Feldmann masking curves are established using narrow-band and white noises administered to the affected ear. An affected patient will indicate when the sound administered is masking the SIT. A comparison of the pure-tone audiometric curve of the affected ear with the masking curve permits the recognition of different types of curves: type 1, convergence; type 2, divergence; type 3, congruence; type 4, distance; and type 5, persistence.

Once having identified the masking noise, we can know whether the SIT has a high or a low chance of vanishing by observing the time during which it remains inaudible after a particular acoustic stimulation. In the procedure, the masking noise is administered to the affected ear for more than 1 minute. Another meaningful audiological test is the mixing-point research. The *mixing point*, according to Jastreboff and Hazell [5], is defined as the level of "partial masking" evident when tinnitus changes in loudness or annoyance. Comparison with the hearing threshold may predict the range of effectiveness of eventual sound therapies.

Pharmacological Topodiagnosis

At the conclusion of the aforementioned audiological tests, the pharmacological localization of the SIT's origin may be performed. At present, four fundamental pharmacological tests are available: the furosemide, caroverine (Calmaverine), amantadine, and carbamazepine tests.

Furosemide Test

The furosemide test was described by Risey et al. [6] in 1995 and by Risey and Guth in 2000 [7]. Furosemide is a drastic diuretic acting on the ionic exchanges in 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 intravenously in 500 ml of a physiological solution. The main side effects of the drug are hypotension, drowsiness, and vertigo.

Caroverine Test

The caroverine test was proposed by Denk et al. [8] in 1997. Caroverine 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 originates from a synaptic dysfunction. Instead of caroverine, magnesium sulfate can also be used [9]. Magnesium sulfate is assumed to act as a potent glutamate antagonist, the main side effect of which is simply a moderate vertigo. The test consists of the administration of two caroverine ampules in 250 ml of a physiological solution. The drug's main side effects are vertigo, confusion, headache, and nausea.

Amantadine Test

Amantadine is a nonselective glutamate and N-methyl-D-aspartate inhibitor. A positive response to this test confirms a previous caroverine test and provides the chance for a prolonged treatment based on amantadine administration [10]. A dose of 100 mg of the drug should be given to an affected patient orally twice daily. The agent's main side effects are insomnia, confusion, and tremors.

Carbamazepine Test

The carbamazepine test is based on experimental studies performed by Shulman et al. [11] regarding the central SIT treatment using this drug. Carbamazepine is an antiepileptic drug effective on neural membranes. Thus, a positive carbamazepine test response indicates a central genesis of SIT. A useful course is to administer 400 mg of the drug orally once daily. Its main side effects are vertigo, confusion, ataxia, and intestinal disorders.

CONCLUSIONS

At the moment, we cannot assert definitely that the pharmacological tests exactly define the source of SIT. As a matter of fact, finding a combination of positive and negative responses is not unusual. These data testify to the complexity of SIT's etiopathogenesis. However, these pharmacological tests should be considered

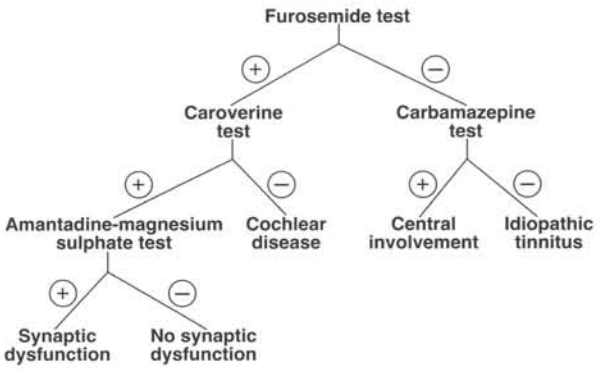

Figure 1. Pharmacological topodiagnosis model.

in the treatment-planning phase, because they allow the 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 subjective analog scale, the modification of the masking curve, the modification of LDL, the modification of residual inhibition, and the modification of the masking mixing point. Administration of the drugs should occur in subsequent days according to a well-defined model (Fig. 1).

The furosemide test must be performed on the first day. If results are positive, we verify the source of peripheral SIT; hence, we can carry out the caroverine test to verify the presence of a synaptic dysfunction. If, instead, results are negative, the SIT probably has a central origin. Therefore, we perform the carbamazepine test, which may confirm the central involvement. If the caroverine test results are positive, a further useful investigation can be obtained from the amantadine–magnesium sulfate test. Naturally, on the basis of pharmacological effects of the aforementioned parameters, drugs will be combined with surgical therapies if necessary.

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