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Tinnitus Control by Dopamine Agonist Pramipexole in Presbycusis Patients: A Randomized, Placebo-Controlled, Double-Blind Study

István Sziklai, MD, PhD, DSc; Judit Szilvássy, MD, PhD; Zoltán Szilvássy, MD, PhD, DSc

Objectives/Hypothesis: Since the concept of tinnitus dopaminergic pathway emerged, studies have been proposed to investigate if dopaminergic agents influence tinnitus. We hypothesized that pramipexole, an agonist on D2/D3 receptors, may antagonize tinnitus in the presbycusis patients (in the frequency range of 250 to 8,000 Hz) in a dose schedule accepted for the treatment of Parkinson's disease in elderly people.

Study Design: We designed a randomized, prospective, placebo-controlled and double-blind trial.

Methods: Forty presbycusis patients aged 50 years or older with subjective tinnitus were randomized to two groups (20 patients in both). Patients in the drug group took pramipexole over a period of 4 weeks according to a treatment schedule as follows: week 1, 0.088 mg t.i.d.; week 2, 0.18 mg t.i.d.; week 3, 0.7 mg t.i.d.; week 4, 0.18 mg t.i.d. over 3 days and 0.088 mg t.i.d. the rest of the week. Patients in the second group received placebo. Determination of subjective grading of tinnitus perception, the tinnitus handicap inventory (THI) questionnaire and electrocochleography (ECOG) examinations served as the end points. Subjective audiometry was used to produce secondary data. A significant improvement in tinnitus annoyance is found in the group treated with pramipexole versus placebo with respect to inhibition of tinnitus and a decrease of tinnitus loudness greater than 30 dB. However, neither ECOG nor subjective pure-tone threshold audiometry revealed any change in hearing threshold in response to either pramipexole or placebo.

Conclusions: Pramipexole is an effective agent against subjective tinnitus associated with presbycusis at a dose schedule used for the treatment of Parkinson's disease. The drug did not change hearing threshold.

Key Words: Idiopathic tinnitus, pramipexole, electrocochleography (ECOG), tinnitus handicap inventory (THI).

Level of Evidence: 1b.

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INTRODUCTION

By definition, tinnitus is perception of sound in the absence of acoustic stimulation. The prevalence of the disorder was estimated between 10% and 15% of the entire adult population a few decades ago,[1] and it seems to have doubled since then.[2] Although most people with tinnitus are not significantly disturbed by this abnormal sensation, the experience of living with a continuous unavoidable sound is debilitating in 0.5% to 2% of the tinnitus population, i.e., between 1.4 and 5 million people worldwide.[3] Probably reflecting the limited treatment options currently available, according to the results of a recent U.S. survey, 94% of subjects with chronic subjective idiopathic tinnitus (CSIT) did not receive any treatment.[4]

Several pathophysiologic mechanisms have been proposed for tinnitus. Multiple lines of evidence suggest that loss of inhibition in the central nervous system may underlie many aspects of auditory dysfunction including tinnitus. Tinnitus has long been recognized to be accompanied by hearing loss. Their prevalence increases with age. In advanced age, several central nervous system disorders occur simultanously underpinned by diverse biochemical abnormalities. A decreased production/release of acetylcholine has been proposed to underlie Alzheimer's disease. Similarly, dopamine deficiency is the major pathogenic factor in the development of Parkinson's syndrome. In connection with tinnitus, the concept of the tinnitus dopaminergic pathway has opened new horizons for the ear disease management as proposed by Lopez-Gonzalez et al.[5] The concept derives from the observations that tinnitus perception is processed in the prefrontal, primary temporal, and temporoparietal associative areas, as well as in the limbic system that overlaps cerebral dopaminergic projections. It is well known that dopaminergic pathways can successfully be modulated by agonists and antagonists. Some of these drugs can reduce the perception of tinnitus.[5]

Dopamine has been shown to be present in the first synapse of the auditory pathway modulating all processes responsible for sound perception. Dopamine influences afferent neurotransmission between the cochlea and the auditory pathway passing through the limbic system.[6] Thus, we examined in a randomized, prospective, placebo-controlled, and double-blind study, whether pramipexole, a dopamine receptor agonist, influenced tinnitus associated with presbycusis at a dose

From the Departments of Oto-Rhino-Laryngology and Head and Neck Surgery (I.S., J.S.); and Pharmacology and Pharmacotherapy (Z.S.), University of Debrecen, Debrecen, Hungary.

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Send correspondence to Dr. István Sziklai, Department of Oto-Rhino-Laryngology and Head and Neck Surgery, University of Debrecen, H-4032 Debrecen, Nagyerdei krt. 98, Hungary. E-mail: isziklai@dote.hu

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TABLE I.
Participant Inclusion and Exclusion Criteria.

Inclusion Criteria	Exclusion Criteria
Age at least 50 years	Meniere's disease
Tinnitus experienced continuously with a history of longer than one year	Impaired renal function
Tinnitus Handicap Inventory score values >10	Impaired hepatic function
Bilateral sensorineural hearing loss	Regular intake of sedative hypnotics
Disease that prohibits the use of pramipexole	Conductive hearing loss

schedule used for controlling Parkinson's disease in Hungary.

MATERIALS AND METHODS

The study was designed to examine the effect of pramipexole (Mirapexin, Boehringer Ingelheim, Ingelheim, Germany), a dopamine receptor agonist at a selected dose schedule used for the treatment of Parkinson's disease on tinnitus in elderly patients with presbycusis.

Patient Enrollment

The study was reviewed and approved by both the local Clinical Research Ethics Review Board of the University of Debrecen, Hungary (DELEBC 36/08 ORL), and the Hungarian National Regulatory Authority of Pharmaceutical Research (OGYI 336/08 RD). Participants were recruited through regional advertising during the period of March through August 2008. Forty-nine patients were enrolled in the study, and 40 of them completed the whole protocol. The applicants were screened using preestablished inclusion and exclusion criteria (Table I). They were selected for their ability to perform a phychophysical loudness matching procedure by means of using narrow band noise stimuli. Conventional audiometric evaluation always preceded study enrollment.

Groups

Recruitment and enrollment of the individuals with presbycusis were continued until 20 of them were assigned to a group being treated with pramipexole at a predesigned dose schedule. Another group of 20 volunteers were given matching placebo tablets manufactured by the Wagner Pharma (Budapest, Hungary).

Audiologic Assessment: Pure-Tone Audiometry

A conventional pure-tone audiometry test was performed in a double-walled, soundproof booth for each patient according to suggestion by Kapkin et al.[7] In brief, testing commenced in the patient's better ear or the right ear, by default, if the patient had symmetrical hearing. Audiometric testing included air and bone conduction threshold at octave steps between frequencies 125 to 8,000 Hz. For air and bone conduction threshold, the Telephonics (Farmingdale, NY) TDH-39 earphone and Radioear B-71 bone vibrator (Interacoustics, Assens, Denmark) were used, respectively. For threshold determination, stimuli were given by means of the ascending method, and the bracketing technique was used. The threshold value was defined as the lowest stimulus intensity detected by the patient in at least three trials. Masking was applied when a difference of >20 dB hearing level (HL) was found between the ears at any frequency of interest. Compliance and middle ear pressure were also measured via GSI Tympstar Middle Ear Analyzer (Viasys Neurocare, Madison, WI).

Psychoacoustic Matching of Loudness and Pitch (Tinnitometry)

Frequency and loudness matching of tinnitus were carried out in each patient prior to and after treatment. In determining the pitch match frequency of tinnitus, the two-alternative forced-choice method was used. In this method, the contralateral ear was chosen to present sounds for comparison. After the intensity setting for two tones had been roughly established, a pair of tones such as 1.000-Hz and 2.000-Hz tones were presented in an alternating manner, and the patient was asked to select the one more like tinnitus. After a decision had been reached, a new pair of tones was presented for a new comparison, one of which had been judged to be more like the tinnitus. This was continued across the frequency range until the patient selected the tinnitus frequency. The exact matching was reached by identifying the tones at the narrowest noticeable frequency intervals. Octave confusion was ruled out by presenting a tone at the frequency matched by the patient and another tone one octave above it. For loudness matching, a tone was presented at the frequency matched by increasing intensity in 1- to 2-dB steps from below the threshold until the threshold was reached. Once the threshold had been established, the tone intensity was increased in 1-dB steps until its loudness seemed to the patient equal to that of the tinnitus experienced. Loudness of tinnitus was expressed in dB HL. Each test was repeated twice for the test reliability.[7]

Electrocochleography (ECOG) Recording

ECOG was performed with TIPtrodes (gold foil-wrapped polyurethane-foam eartips) that act as both inverting electrode and the stimulus delivery device. This type of electrode is noninvasive, with the least discomfort to the patient. The reference electrode was placed on the forehead. The ground electrode was placed on the contralateral mastoid. Interelectrode impedances (at 30 Hz) were typically 20 to 40 kOhm (active-ground) and 0.5 to 2 kOhm (reference-ground).

Acoustic stimulations were alternating polarity clicks (0.1 ms rectangular pulse) and rectilinear condensation and rarefaction tone-bursts with center frequences of 1, 2, 4 kHz (rise-fall of 0.5 ms and a plateau of 8 ms). A Nicolet Pathfinder (Nicolet Biomedical Inc., Madison, WI) was used as a sound-generating apparatus, and a Nicolet tubal insert earphone was coupled to the ear by a foam tip. The repetition rate was 11.1/s. The intensity of the acoustic stimuli was expressed in decibels at 95 dB nHL. Responses were amplified and summated using a Nicolet Pathfinder with a bandpass of 3-1.5 kHz with a symmetrical 6 dB/octave rejection slope. The averages of 300 responses were obtained with an artificial-reject algorithm. To obtain summed condensation-rarefaction responses, the averages at each polarity were obtained separately and then averaged off line.

The compound action potential (AP) was measured from the alternating polarity click response as the difference between the prestimulus baseline and the maximum negative deflection.

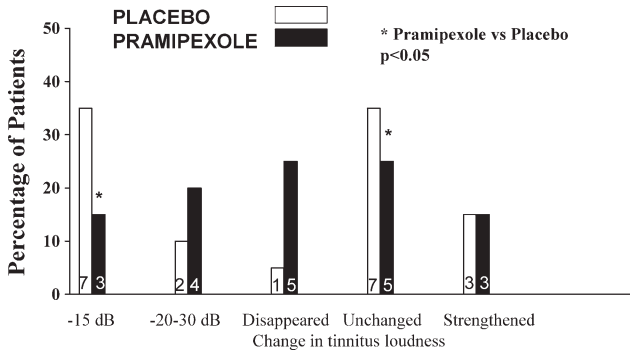

Fig. 1. The effect of pramipexole on tinnitus loudness compared with placebo. Subgroups were formed according to a significant decrease in tinnitus loudness of <15 dB, of 15 to 30 dB, complete cessation of tinnitus, or the patient experienced his/her tinnitus unchanged or even worsened. The negative dB values indicate the measure of decrease in tinnitus loudness. The number of patients providing corresponding data are indicated within or above the columns.

Similarly, the summating potential (SP) was measured from the prestimulus baseline to the knee on the leading edge of the AP.

The summating potential/action potential (SP/AP) ratios were measured at an intensity of 95 dB and then the patients of the pramipexole-treated group and of the placebo-controlled group were compared.

The patients were requested to complete a tinnitus handicap questionnaire form before and after the treatment.[8]

Study Design

The sudy was carried out in a randomized, prospective, placebo-controlled, and double-blind fashion with 40 presbycusis patients suffering from subjective tinnitus with age 50 years and older. They were randomized to two groups consisting of 20 volunteers in each. For allocation of the participants, a computer-generated list of random numbers was used to identify patients as to whether they received the placebo or active drug. The pramipexole and the placebo were administered in capsule form and identical in appearance. They were prepacked in bottles and consecutively numbered for each patient according to the randomization schedule. Each volunteer was assigned an order number and received the capsules in the corresponding prepacked bottle. Both the voluteers and the physicians allocated to the study groups were kept blinded throughout the study. Similarly, outcome assessors and data analysis also were kept blinded to the allocation. Patients in the pramipexole group were given the drug over a period of 4 weeks according to the following treatment schedule: week 1, 0.088 mg t.i.d.; week 2, 0.18 mg t.i.d.; week 3, 0.7 mg t.i.d.; week 4, 0.18 mg t.i.d. over 3 days and 0.088 mg t.i.d. the rest of this week. This treatment schedule was identical to that suggested for the treatment of Parkinson's disease in the first four-week period of Mirapexin therapy in Hungary. Presbycusis patients in the second group were given a placebo. Determination of subjective grading of tinnitus perception (including frquency and intensity assessments) was performed by completion of the use of the tinnitus handicap inventory (THI) questionnaire. This score value with results from objective and subjective audiometric evaluations were referred to as the end points of the study.

Statistical Analysis

For nonparametric measures, the Mann-Whitney U test was used. For parametric evaluations, ANOVA was used followed by a modified t test according to Bonferroni's method.[9] Changes were considered significant at $P \leq .05$.

RESULTS

Patient Dropout

Sixty-one volunteers were initially recruited into the study with 32 males and 29 females, but only 40 of them completed the protocol. The average age of the participants completing the study was 61 ± 7.6 years. The reasons for failure to complete the study were as follows: dizziness attributed to pramipexole/placebo (3 patients), noncomplience with study instructions (12 patients), accidental intake of sedatives (4 patients), allergic reactions to pramipexole/placebo (2 patients). Variations in psychoacoustic performance reflected in within-session loudness-match did not exceed 4 dB standard deviation during the study.

Pramipexole at the dose administered did not produce any significant change in electrocardiogram (ECG) or routine laboratory chemistry such as serum electrolytes, transaminases creatinine, urea, blood glucose, and hematology tests. The placebo also was without effect. No change in blood pressure was seen over the study period.

Tinnitometry: Interindividual Responses to Drug or Placebo

As shown in Fig. 1, the nonresponder ratio was 25% in the pramipexol-treated group. Conversely, 45% of the patients receiving placebo exhibited an improvement in tinnitus loudness by results from the THI scores. However, in the post hoc analysis of results according to the degree of changes in tinnitus, 5 of 20 volunteers disclosed complete inhibition of the formerly experienced tinnitus in the pramipexole group. This is shown by results from the subjective audiometric studies and the THI scores (the latter means a zero score value in each case). Pramipexole attained a significant improvement of tinnitus in 35% of patients (7 of 20) by both tests (THI and tinnitus match) in addition to the complete tinnitus cessation in 5 patients (Figs. 2 and 3).

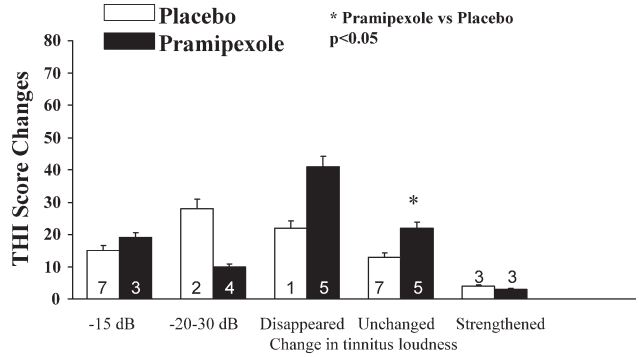

Fig. 2. The effect of pramipexole on tinnitus handicap inventory (THI) scores in the function of tinnitus loudness change compared with placebo. Subgroups were formed according to a significant decrease in tinnitus loudness; if the tinnitus decrease fell into a range <15 dB, of 15 to 30 dB, complete cessation of tinnitus, or the patient experienced his/her tinnitus unchanged or even worsened. The negative dB values indicate the measure of decrease in tinnitus loudness. The figure shows changes in THI scores. The results are means ± standard deviation. The number of patients providing corresponding data are indicated within or above the columns.

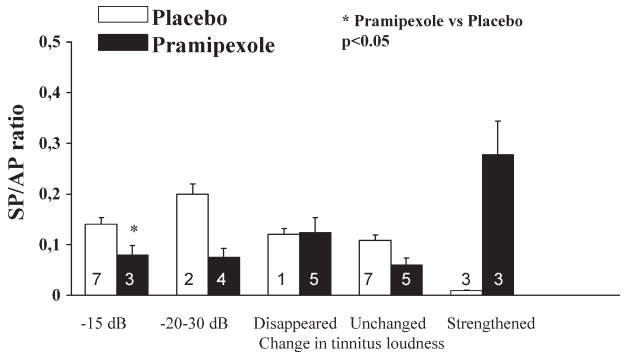

Fig. 3. The effect of pramipexole on summating potential/action potential (SP/AP) ratio in the function of tinnitus loudness change compared with placebo. Subgroups were formed according to a significant decrease in tinnitus loudness of <15 dB, of 15 to 30 dB, complete cessation of tinnitus, or the patient experienced his/her tinnitus unchanged or even worsened. The negative dB values indicate the measure of decrease in tinnitus loudness. The data show changes in SP/AP ratio in response to pramipexole versus placebo with reference to the subgroups defined. The results are means ± standard deviation. The number of patients providing corresponding data are indicated within or above the columns. *Significant difference between pramipexole and placebo in parametric or score data at $P \leq .05$.

Only 1 of 20 patients exhibited cessation of tinnitus in the placebo group (Fig. 3). Regarding the age dependence of the response to either the drug studied or placebo, there were no significant differences between results obtained with volunteers of 50 to 60 or 60 to 70 years. This possibly can be attributed to the low number of patients (Table II). Notwithstanding, the THI score value did not increase in any of the volunteers irrespective of the groups studied.

ECOG and Hearing Thresholds

Pure-tone threshold change was not detected during the treatment in any groups. Electrocochleography did not show correlations of SP/AP change to subjective THI score or tinnitus match changes (Fig. 1).

DISCUSSION

The results presented here show that pramipexole, a dopamine D2/D3 agonist[10] improves tinnitus annoyance. This drug has originally been registered for the treatment of Parkinson's disease. The anti-Parkinson dose schedule of pramipexole was followed in this study with the aim of improving tinnitus.

The beneficial effect of pramipexol was reflected in psychoacoustic measures but not by electrocochleography. Moreover, neither pramipexole nor placebo produces any effect on presbycusis, the secondary end point of the study. To the best of our knowledge, no studies have been dedicated to examine the effect of pramipexole on tinnitus associated with presbycusis. The results that an anti-Parkinson drug produces a beneficial effect on psychoacoustic measures of tinnitus in presbycusis patients is a novel finding of the study.

The idea that dopaminergic drugs may be beneficial for tinnitus derives from the tinnitus dopaminergic pathway hypothesis.[6] This relies on studies on the perception of tinnitus examined by imaging techiques such as positron emission tomography (PET) and photon emission tomography (SPECT). These identified the temporal, frontal, and parietal lobes with the amygdala and hippocampus as tinnitus perception areas.[11,12] These areas, where tinnitus is perceived, are the same where the major dopaminergic inhibitory projections are present. These are the prefrontal area, temporal primary area, temporo-parietal associative areas, and the limbic system.[13,14] These molecular imaging studies explored a correlation between aging, a decrease in dopamine receptor density in the prefrontal area and the limbic system, and the onset of tinnitus in elderly people.[6,15] As far as the therapeutic implications are concerned, the dopamine concept of tinnitus perception opened new possibilities for dopamine supplementation and/or dopamine receptor modulators in the treatment of tinnitus. This is underpinned by a proven deficiency in various dopamine-related inhibitory central nervous system pathways in advanced age closely related to a decrease in D2/D3 receptor density and function.[5] However, it has not yet been defined as to whether dopamine receptor agonists or antagonists might be of benefit for patients with or at risk of tinnitus. The latter is further colored by the fact that pramipexole, an agent known to predominantly act on D3 receptors, may induce dopamine receptor heterodimerization that may result in a mixed dopamine receptor agonist effect.[16]

Current evidence strongly suggests that pathologic changes in peripheral and central auditory pathways contribute to the onset and persistance of tinnitus. Deficiency in central inhibition principally of dopaminergic nature has been demonstrated in experimental animals due to aging[17] or acoustic trauma.[18] This prompted clinical studies with dopaminergic agonists[2] or dopamine precursors[19] on tinnitus. Nevertheless, either study produced essentially negative results, i.e., no significant effect was seen on the variables investigated. Somewhat more positive results were obtained with sulpiride, a dopamine receptor antagonist with patients with an age ranging from 53 to 84 years,[5] a population similar to that present in our work.

Probably the most important result of our work is that the significantly increased number of elderly patients got rid of their tinnitus in response to pramipexole compared with the placebo group possibly independent of presbycusis. The low number of patients who were able to complete the study along with an additional high interindividual variability in the response to either drug or placebo render the results rather preliminary. Dose-response relationship cannot be examined due to ethical reasons. Another factor that may also be considered a limiting one is the lack of follow-up results. A tendency to reexperience tinnitus was seen in patients after cessation of daily pramipexol intake. The low post-study compliance of the patients reduced the follow-up data to a level that does not permit making any conclusion pertaining to the follow-up period.

TABLE II.
Age-Dependence of Pramipexole Effects on Tinnitus Indicated by Summating Potential/Action Potential (SP/AP) Ratio and Tinnitus Handicap Inventory (THI) Score.

	Pramipexole			Placebo		
Tinnitus Loudness Match	Case No.	SP/AP	Score	Case No.	SP/AP	Score
Patients aged 50 to 60 years						
15 dB or smaller decrease in tinnitus loudness	1	0.06↑	32i	2	0.1↓	16i
					0.14↓	0o
20 to 30 dB decrease in tinnitus loudness	3	0.06↑	18i	0	—	—
		0.2↑	10i			
		0.07↓	6i			
Disappeared	2	0.23↑	36i	1	0.12↓	22i
		0.16↑	48i			
Unchanged	2	0.23↑	16i	3	0.12↑	32i
		0.01↑	0o		0.18↑	10i
					0.11↑	2i
Strengthened	2	0.00	4i	2	0.00	4i
		0.02	1i		0.01	2i
Patients aged 60 to 70 years						
15 dB or smaller decrease in tinnitus loudness	1	0.08↑	0o	4	0.23↑	24i
					0.00	28i
					0.05↑	2i
					0.03↓	2i
20 to 30 dB decrease in tinnitus loudness	1	0.08↑	0o	2	0.09↓	14i
					0.41↑	42i
Disappeared	2	0.00	38i	0	—	—
		0.03↑	32i			
Unchanged	2	0.07↓	54i	2	0.00	10i
		0.00	8i		0.14↑	0o
Strengthened	1	0.43↑	4i	1	0.01↑	4i
Patients aged >70 years						
15 dB or smaller decrease in tinnitus loudness	1	0.11↓	6i	1	0.00	0o
20 to 30 dB decrease in tinnitus loudness	0	—	—	0	—	—
Disappeared	1	0.16↓	44i	0	—	—
Unchanged	1	0.11↑	4i	2	0.22↑	0o
					0.02↓	0o
Strengthened	0	—	—	0	—	—

↑ = Increase; ↓ = decrease; i = improved; o = unchanged.

CONCLUSIONS

In summary, the present results underlie the promise of dopamine receptor modulators in the treatment of tinnitus. A dose-finding study of crossover nature probably provides more precise information about the use of pramipexole in the treatment of tinnitus accociated with advanced age.

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