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Topical Administration of Caroverine in Somatic Tinnitus Treatment: Proof-of-Concept Study

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Abstract: This prospective study, which conformed with good clinical practice (GCP-conform), tested the concept that the topical transtympanic administration of the quinoxaline derivative Caroverine promises a new approach to the treatment of tinnitus. The rationale for the study is the hypothesis that tinnitus reflects sequelae of auditory neurotoxicity that can prevented and repaired by the neuroprotective and neuroregenerative activities of quinoxaline derivatives exhibited in previous preclinical tests. In a representative patient cohort, the probability of a long-lasting tinnitolytic effect of lipophilic eardrops containing 1% Caroverine as their active ingredient gained in significance, crossing from low-intensity levels to high-intensity levels of individual tinnitus sensations. These results encouraged us to design consequential GCP-conform phase 2 and phase 3 studies.

Key Words: auditory neurotoxicity; Caroverine; eardrops; tinnitus; treatment

Tinnitus, the perception of sound in the absence of real sound stimulation, handicaps millions of people in the world. However, as the underlying reason for this symptom is not clearly identified, a generally accepted causal treatment does not exist yet. Local and general circulatory disturbances, metabolic disorders, inflammatory reactions (mainly of viral etiology), noise and head traumas, and aging processes are singled out as triggering this auditory impairment.

Considering the discussed multifactorial etiology of the symptom, Ehrenberger and Felix [1] interpreted the origin of tinnitus as evidence for a final common pathway of cochlear injury. In the mammalian (including the human) cochlea, the excitatory amino acid glutamate mediates neurotransmission between inner hair cells and afferent neurons [2–4]. Under different pathological conditions, the physiological transmitter glutamate exerts a uniform neurotoxic action [5,6], and reactive oxygen species are incriminated as the main mediator of tissue damage [7,8]. This appropriate model of glutamatergic otoneurotoxicity promises to make a crucial contribution to our understanding of the origin of a variety of inner-ear diseases characterized by tinnitus with or without concomitant hearing loss.

In the cochlea of guinea pigs, quinoxaline derivatives prevent these pathological conditions and trigger dendritic and synaptic repair mechanisms of glutamatergic units [9,10]. On the basis of these preclinical findings, we hypothesized that the clinical administration of quinoxaline derivatives would protect the human cochlea from neurotoxic attacks and stimulate intracochlear repair mechanisms necessary for the successful treatment of tinnitus.

To test this hypothesis, we initiated a study program using the quinoxaline derivative Caroverine as a specific test substance. Caroverine was chosen because it is the only quinoxaline derivative successfully proved in preclinical phase 1 trials [11], is clinically available, and therefore is free for clinical test programs [12].

Homeostasis of the fluid compartments of the inner ear depends on blood-labyrinth barrier function. This active process crucially influences the transport of drugs from the blood into the inner-ear fluids. Metabolic imbalances may affect the blood-labyrinth barrier and hence systemic drug delivery into the inner ear [13]. For this reason, local transtympanic administrations are increasingly preferred [14]. In this study, we describe first clinical results of Caroverine in tinnitus treatment using a nonsurgical, transtympanic approach to the tinnitus generators.

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STUDY DESIGN AND METHODS

Good Clinical Practice

According to the guidelines of the Center for Drug Evaluation and Research (CDER) of the U.S. Food and Drug Administration (FDA), at the end of the preclinical phase 1 trial program, an early "proof-of-concept" study is highly desirable for developing an understanding of the therapeutic potential of an agent in humans. Consideration should be given to the more modest goal of determining whether the pharmacological effect predicted from the preclinical development is present. Controlled trials in small patient cohorts are recommended. Only in subsequent phase 2 studies is the use of placebo arms desirable, for several reasons.

The European Federation for Pharmaceutical Sciences reconfirmed in 1999 the recommendations of the FDA and emphasized that proof-of-concept trials represent the most important decision point for gaining time and value in fast-track, informative drug development. On the basis of the foregoing considerations and the results of the phase 1 studies, we designed this proof-of-concept study.

Our goal was to prove the fitness of the predictive model in that the local administration of Caroverine attenuates the activity of cochlear tinnitus generators. The study was performed according to the Declaration of Helsinki on Biomedical Research (Summerset West amendment), and was approved by the ethics commission of the Medical University of Vienna.

Selection of Patients

The selected patients had experienced decompensated tinnitus as a leading symptom. In contrast to manifest neuropsychiatric, cardiovascular, and metabolic disorders, concomitant cochlear and vestibular disorders were no reason for exclusion. Between February 2002 and March 2003, we included a total of 77 patients in this study.

Diagnostic Procedure

After all patients' histories were recorded, patients received an adequate audiometric, vestibular, and radiological examination. The audiometric test battery included pure-tone audiometry (complete with air and bone conduction threshold at 250–8,000 Hz), tympanometry, reflex audiometry, and the registration of transient evoked otoacoustic emissions. To exclude retrocochlear processes, we recorded auditory brainstem responses and magnetic resonance imaging of the peripheral auditory system. We performed vestibular assessment with the help of electronystagmographic records of spontaneous and caloric nystagmus.

The specific effect of Caroverine on tinnitus sensations was controlled correlating the pre- and posttherapeutic results of a subjective rating test: The patients' scores scaled introspectively—in a range from 0 (no tinnitus) to 10 (raging tinnitus)—the severity of their actual tinnitus sensation [15,16]. A reduction of a minimum of 2 points in the 0–10 numerical rating scale was registered as therapeutic success. Additionally, after therapy, we questioned the patients' subjective reflection of the tinnitus-related condition: whether much better, better, worse, or unchanged.

Therapeutic Procedure

We treated all patients according to a standardized procedure for an exclusive, topical application of the quinoxaline derivative Caroverine (Phafag AG, Schaanwald, Liechtenstein) in the external auditory canal of the tinnitus-affected ear. For this study, the administered form consisted of a solution containing 1% of the active ingredient, locally dripped twice daily on a cotton strip that was in contact with the eardrum. The molecular basic configuration of Caroverine we used promised lipophilic properties necessary for a self-regulating penetration of Caroverine through membranes.

Criteria for Stopping Individual Caroverine Application

The study design provided that this therapeutic procedure be stopped under the following conditions: unexpected and intolerable local and general side effects; total compensation of the tinnitus within the first 2 weeks after the beginning of the therapy; and after 2 weeks of consequent drug administration, irrespective of its therapeutic effect. An external monitoring company (MEDICOMP Corp.) performed the analysis of individual patient data listings and of the demographic and anamnestic characteristics.

RESULTS

Of the 77 patients treated, 44 (57.1%) were men and 33 (42.9%) were women. Their ages ranged from 16 to 82 years (mean, 47.6; median, 49.5). In 49 patients, tinnitus was found as an isolated auditory symptom (idiopathic tinnitus; noise-induced tinnitus). In 28 patients, tinnitus was part of defined complexes of otological symptoms (sudden hearing loss, Ménière's disease).

Overall, we registered a treatment success in 57% of the patients (44 of 77). On average, the rating improved by 3.4 points (median, 3.5; maximum, 7.5; minimum, 0; standard deviation, 2.23). The relationship between the results of the individual tinnitus scaling before and

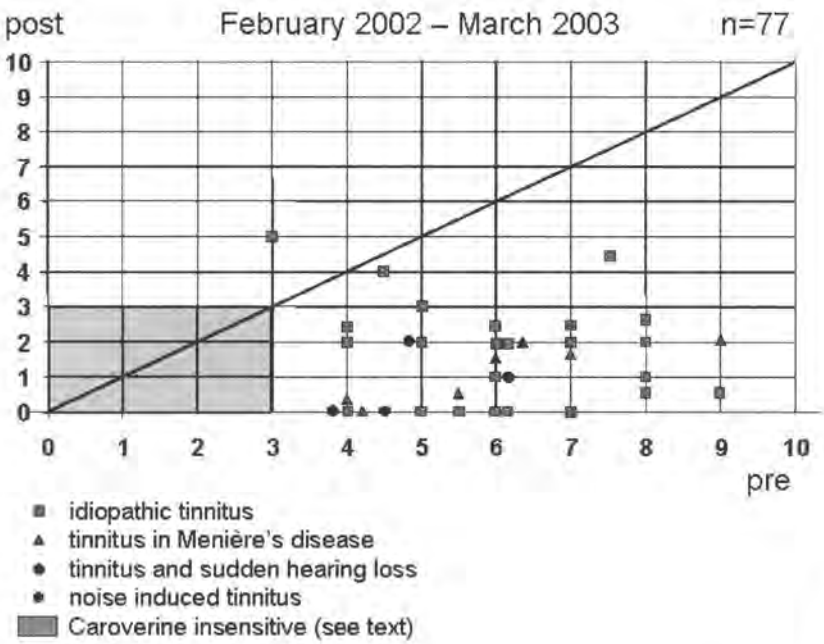

Figure 1. Correlation of individual pre- and posttherapeutic rating points reflecting the actual tinnitus sensations of 77 patients.

after the local administration of Caroverine is depicted in Figure 1. The diagram shows the positive correlation between therapeutic success rate and pretherapeutic tinnitus intensity. The majority of nonresponders were registered only in the low-intensity range.

A breakdown of the results by diagnosis (presumed cause of tinnitus) shows that the treatment was especially successful in patient with Ménière's disease and sudden hearing loss associated with tinnitus. Additionally, under the influence of Caroverine, patients showed signs of lessening of tinnitus-related symptoms in sudden hearing loss and Ménière's disease. However, these findings are not the topic of this study, which is focused exclusively on tinnitus.

For the next 3 months, the posttherapeutic course of patients' individual conditions in relation to tinnitus sensations was observed. In 51% of patients, the stable condition was rated as much better and, in a further 9%, as better. A worsening of the condition was observed in only one patient. Eighteen patients (23.4%) reported no therapy-related changes in their condition during the entire period of observation.

Passing itchiness was reported as a transient side effect during repetitive local application of Caroverine. However, in no case did therapy have to be stopped because of this temporary discomfort. No other clinically manifest adverse effects were observed.

DISCUSSION

For the first time, a noninvasive topical application determined the outcome of a trial checking the efficacy of a drug in the treatment of tinnitus. In 77 patients selected for this proof-of-concept study, Caroverine selectively reduced tinnitus sensations psychophysically scaled in a rating test. Mid- and high-intensity tinnitus was suppressed to a faint noise, whereas the drug had minimal or no distinct effect on low-intensity tinnitus. The irritating tinnitus in sudden hearing loss and Ménière's disease usually was Caroverine-sensitive, in contrast to some discrete sensations of idiopathic tinnitus, which were Caroverine-insensitive.

Both the design and the interpretation of the results of this PCG-conform study must take into account a number of obstacles that are very specific to trials of prospective tinnitolytic agents. One factor is the ubiquitous nature of the complaint. Epidemiological studies have shown that tinnitus is clearly more frequent among patients with somatization and hypochondriac disorder [17]. Second, tinnitus is often related to stress-induced malfunctions of the motor system, especially that of the masticatory system [18,19].

This frequent concurrence of tinnitus of sensorineural etiology and mental and motoric weakness prompted us to replace "objective" tinnitus-simulating ("matching") tests by the purely subjective procedure of a rating of tinnitus sensations on a visual analog scale, quantitatively reflecting loudness and annoyance of the complaint [15,16]. The described long-term effects demonstrated that the suppressive action of locally applied Caroverine on subjective tinnitus sensations is correlated with a stable amelioration of the individual condition. Accordingly, tinnitus seems to be more likely a reason for than a reaction to concomitant stress and psychopathology.

The proven impact of the quinoxaline derivative Caroverine supports the hypothesis that tinnitus is of neurotoxic origin and that a topically applied neuroprotective agent would promise a practicable approach to treating this stressful auditory discomfort. After corresponding experiments in guinea pigs [20], Caroverine was actually discussed as a potent candidate for topical transtympanic round-window drug delivery in humans [21,22]. In contrast thereto, we aimed to find a management for treating inner-ear diseases by applying appropriate eardrops to penetrate intact membranes and actively cross the space of the middle ear. The lipophilic configuration of the molecule we used offers this approach for Caroverine. Further active transport systems are being tested in ongoing clinical experiments. The hope is that the described proof will seriously gain in significance, crossing the clinical test program from proof-of-concept to final phase 3 study.

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