The effects of alprazolam on tinnitus: A cross-over randomized clinical trial

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Summary

Background: Tinnitus remains a phenomenon with an unknown pathophysiology and for which few therapeuti- c measures are available. To date there has been insufficient evidence to support the use of alprazolam in the treatment of tinnitus. We sought to evaluate the efficacy of alprazolam for relief of tinnitus.

Material/Methods: Thirty-six tinnitus sufferers participated in this cross-over, randomized, triple-blind, placebo-con- trolled trial. Inclusion criteria included patients between ages 21 and 65, with a complaint of non-pulsatile tinnitus of more than 1 year duration. Patients with depressive or anxiety disorders were excluded, as were those using hearing aids. Participants received alprazolam 1.5 mg daily versus placebo in each period. Primary outcome variables included the Tinnitus Handicap Inventory (THI), a Visual Analog Scale (VAS), and tinnitus loudness.

Results: Thirty patients completed the study. The average age of patients was 47.58±7.65 years. Alprazolam in comparison with placebo did not result in statistically significantly greater relief in THI score and tinnitus loudness. There was a significant improvement in VAS score in the alprazolam group compared with the placebo group (p<0.001).

Conclusions: These results suggest that although alprazolam did not improve the THI score or sensation level of loudness significantly, it has a desirable effect on VAS. Further work is needed to determine the beneficial effects of alprazolam in distressed or depressed patients.

key words: tinnitus • alprazolam • cross-over studies

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BACKGROUND

Tinnitus has been defined as 'the perception of a sound that results exclusively from activity within the nervous system without any corresponding mechanical, vibratory activity within the cochlea' [1]. Tinnitus affects about 10–15% of the adult population [2]. Ten percent of tinnitus sufferers experience severity of symptoms sufficient to impact quality of life significantly [3], including sleep disturbance, work impairment and psychiatric distress [4].

Efforts to treat tinnitus have met with limited success. Nonpharmacologic and surgical therapeutic approaches have been used in selected cases. These procedures have not been shown to be more than marginally effective [5]. There are no drugs approved by the US Food and Drug Administration for the treatment of tinnitus [6]. There is good evidence from animal studies that after administration of salicylates to rats, the enzyme glutamic acid decarboxylase (the rate-limiting enzyme in the formation of the inhibitory neurotransmitter GABA), is up-regulated, while GABA$_A$ receptor affinity in the auditory midbrain decreases [7]. Anxiolytics (such as benzodiazepines) confer some symptomatic relief from tinnitus. The most likely explanation is that patients’ tolerance of tinnitus improves by treating the depression [8].

There is insufficient evidence to support the use of alprazolam in the treatment of tinnitus. The Johnson trial is the only study to date assessing the role of alprazolam [9]. This study showed that 76% of those taking alprazolam reported reduction of their tinnitus, whereas only 5% of the placebo group reported a similar effect [10]. The study had several biases: dose adjustment was used only in the active group, patient blinding may have been compromised, and tinnitus impact was not measured.

Using a cross-over trial, we planned a triple-blind (investigators, patients and statisticians) study and measured several variables related to tinnitus impact. We hypothesized that the alprazolam would (1) decrease the perceived tinnitus loudness, (2) decrease participants’ disability associated with their tinnitus, (3) alprazolam’s effect on tinnitus and tinnitus-related disability would occur independently of participants’ history of depressive or anxiety disorders, and (4) any tinnitus-related improvements would occur independent of changes in depressive or anxious symptomatology.

MATERIAL AND METHODS

Study design

This was a cross-over, triple-blind, randomized, placebo-controlled study in patients with non-pulsatile tinnitus. The primary objective was to evaluate the efficacy of alprazolam on tinnitus compared with placebo. Concomitant treatments for tinnitus were excluded. The study protocol was reviewed and approved by the Guilan University Medical Science (GUMS) Institutional Review Board. Patients consented to participate on the basis of written information.

Patients were recruited through the Department of Otolaryngology at Amiralmomenin Hospital, GUMS, from November 2006 to April 2008. Sixty-two patients were considered for participation in this study. Inclusion criteria were patients 21–65 years old having a history of tinnitus of more than 12 months prior to entry. Exclusion criteria were Menière’s disease, vestibular schwannoma, otosclerosis, hearing aid use, temporal lobe tumor, depression, anxiety, and inability to tolerate minimal effective dose of alprazolam (0.5 mg bid). The initial assessment included a history and physical examination, an audiogram, and a psychiatric assessment. Patients completed a demographic questionnaire. Audiometric testing included a baseline assessment of hearing sensitivity in both ears. Depressive and anxiety symptoms were assessed using the Beck Depression Inventory (BDI) and Hamilton Rating Scale for Anxiety (HRS-A), with cutoff points 16 and 14, respectively. The Structured Clinical Interview for DSM-IV-TR was administered by a psychiatrist to determine the presence of psychiatric disorders. After initial assessment, 44 patients were eligible for inclusion in this study and were enrolled in the placebo lead-in phase. In this phase, patients were given a placebo (chlordiazepoxide 5 mg, bid, 10 days), which lead to drowsiness in some cases. This phase was used to familiarize patients with the study procedures and to minimize the effect of any pre-existing treatment for tinnitus. Thirty-six cooperative patients were selected and randomized using fixed-block randomization into 2 groups: A and B. Randomization was done in blocks of 8 subjects in a 1 group A to 1 group B ratio (Figure 1).
Participants received alprazolam (Xanax, Pharmacia NV/SA, Puurs, Belgium) or active placebo (Chlorpheniramine Maleate, Mehr Darou, Tehran) treatment. The active placebo simulated the side-effect of the active treatment (drowsiness). It is popularly believed that mild induced sedation does not relieve tinnitus but deceives patients more effectively than an inert placebo. These drugs were prepared by the Amiralmomenin Hospital Pharmacy and placed into similar gelatinous capsules (Alprazolam 0.5 mg or Chlorpheniramine Maleate 4 mg). Drugs were labeled by study subject number according to the randomization schedule. The key to the randomization was held by the pharmacy, and randomization was broken only for potential adverse events. To avoid significant side effects, patients were placed on an escalating dosage scale. The medication was begun at 1 capsule each evening for 2 weeks, then 1 capsule bid for the third and fourth weeks, and 1 capsule tid for the fifth to eighth weeks. After completion of the eighth week of treatment, tapering was begun at the ninth week as follows: 1 capsule bid for 3 days, then decreased to 1 capsule daily for 3 days. All patients were given the same dosing schedule for blinding purposes. If full dose treatment could not be tolerated due to over-sedation, the patient received 1 capsule bid during the fifth to eighth weeks. Participants received no drug on the last day of the ninth week and through the tenth week (washout period). The washout period was at least 15 times as long as the biologic half-life of the alprazolam (11 to 15 hours). Period 2 covered the first day of the 11th week to the last day of the 19th week.

The primary outcome variables were the sensation of tinnitus as measured on the Tinnitus Handicap Inventory (THI) and a Visual Analog Scale (VAS), and tinnitus loudness.

THI is a 25-item scale and consists of 3 group items: functional, emotional and catastrophic [11]. We used the Persian version of THI, validated by Afshin Majd S, et al. [12]. They showed a robust internal consistency reliability (Cronbach’s alpha =0.94), comparable to those of the original version. Subjects were asked to complete the corresponding questionnaire at each clinic visit.

VAS measurements were obtained in standard fashion as defined by the consensus conference of IVth International Tinnitus Seminar, Bordeaux, 1991. VAS was used where 0 represented “no tinnitus” and 100 represented “the worst imaginable tinnitus”. This procedure was done with paper and pencil.

An assessment of tinnitus in the affected ear(s) was performed by matching reported tinnitus to externally presented sounds. The matching was done using a 2-sample forced-choice method to determine the frequency and intensity level after characterizing the type of tinnitus sound. Tinnitus was measured in dBA hearing level and was converted to dBA sensation level by subtracting the patient’s hearing threshold at the tinnitus apparent frequency (measured at 1/24 octaves) from the measured intensity level (measured in 1-db steps) of the tinnitus. In patients with bilateral tinnitus, the worse ear was selected as the involved ear.

**Statistical analysis**

The power of study was estimated from the previous, double-blind study [9]. We estimated that recruitment of 30 cases would provide 90% power to detect a significant difference between the effects of treatment on tinnitus loudness at a significance of p<0.05 [13]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [14]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [15]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [16]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [17]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [18]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [19]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [20]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [21]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [22]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [23]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [24]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [25]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [26]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [27]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [28]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [29]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [30]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [31]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [32]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [33]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [34]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [35]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [36]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [37]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [38]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [39]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [40]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [41]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [42]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [43]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [44]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [45]. The same number permits detection of significant difference between 2 treatments at a significance of p<0.05 [46].
RESULTS

Sixty-two patients were screened, and a total of 36 patients were enrolled. The mean age of the subjects was 47.58±7.65 years (range, 32–62 yr). Twenty-four (66.67%) patients were men, and 12 (33.33%) were women. Thirteen (36.11%) patients reported bilateral tinnitus. The mean duration of tinnitus was 63.44±85.55 months before enrollment. There were no significant differences in the mean age, bilateral or unilateral tinnitus. Six patients withdrew from the study (Figure 1). The dose of alprazolam was decreased to bid in 1 subject.

Characteristics of the demographic variables are presented in Table 1. The mean of pure tone audiometry (PTA) in the involved ear(s) was 20±18.5 dB and the mean speech discrimination score was 94.6±6.3 percent (Figure 2). The median frequency of tinnitus matching was 4712.1±1898.7 Hz and the tinnitus intensity was matched at 8.6±4.9 dB Sensation Level (Table 2). Mean frequency of tinnitus in cases with high frequency (N=26) and flat (N=9) hearing loss was 4640.5 (±1539.7) Hz and 4187 (±2181) Hz, respectively. Comparisons between the change of THI, VAS, loudness and tinnitus frequency, and hearing loss were carried out using Spearman rank correlation. None of these comparisons showed any significant correlation (Table 2).

No abnormality was found in the psychiatric questionnaire used. BDI and HRS-A scores in our participants were 7±5.2 and 2.5±1.8, respectively. There was no psychiatric diagnosis in participants.

Outcomes

Outcomes were measured in 30 patients (Table 1). There was no significant correlation between loudness and VAS, but there was a significant correlation between loudness and THI scores ($r^2=0.176, P<0.02$).

Table 2. Results of response to treatment with alprazolam on outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Effect</th>
<th>95% CI of the difference</th>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>THI*</td>
<td>Period</td>
<td>–10.5–1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Group</td>
<td>–4.4–7.9</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>–15.2–3.9</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>VAS**</td>
<td>Period</td>
<td>–12.4–9.0</td>
<td>NS</td>
</tr>
<tr>
<td>Group</td>
<td>–10.4–10.7</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>11.4–27.1</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Loudness***</td>
<td>Period</td>
<td>–2.6–1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Group</td>
<td>–3.4–0.2</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>–1.6–2.1</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

* The paired t-test for period and treatment effects and t- test for group effect.
** The Sign test for period and treatment effects and Mann-Whitney U test for group effect.
*** Reported as Sensation Level (dB). The paired t-test for period and treatment effects and t- test for group effect.
THI scores were calculated pre- and post-treatment for periods 1 and 2 (Figure 3). We did not observe a substantial change with treatment. Post hoc analysis of subscales of THI in the 2 groups showed a 2.4 decrease in the alprazolam group and a 0.4 increase in the placebo group on the catastrophic subscale (Figure 4). The difference was significant (P<0.007).

VAS values decreased 20.83 units in the alprazolam group and decreased 1.5 units in the placebo group. The difference between the 2 groups was statistically significant (P<0.001).

We calculated period, group and treatment effects for each outcome and observed a significant difference in VAS scores with alprazolam (Table 2).

Because subscales of THI didn’t have normal distribution, the correlation between subscales of THI and VAS scores was examined using Spearman rank correlation (Table 3). There were no significant correlations between the pre-treatment scores, but there was a significant correlation between THI, subscales (functional and emotional), and VAS scores after treatment.

Tinnitus loudness decreased 0.1 dB in the alprazolam group but no change in loudness was observed in the placebo group. The difference was not statistically significant.

**DISCUSSION**

Benzodiazepines have anxiolytic, hypnotic, and anticonvulsant properties. Alprazolam, as one of this group of drugs, might decrease the discomfort related to tinnitus by interacting with GABA receptors.

This study had a 16.6% dropout rate, suggesting overall good toleration of alprazolam. Although there is a proposal to limit clinical use of the drug due to its highly addictive nature, tapering and discontinuing its use was successful in all of our participants.

Further evidence shows the aggravation of anxiety by tinnitus and vice versa [14], and as tinnitus severity and psychosocial disability is significantly higher in depressed patients than non-depressed ones [15], we excluded both the anxious and depressed patient groups from the study.

Objective measurement of the level of tinnitus is not available; however tinnitus matching can provide a better estimate of the perceived loudness of the tinnitus. In addition to loudness, we used the THI and VAS as measures of the treatment effect of alprazolam. In our study alprazolam generally showed no improvement compared to the placebo, and there was only a slight improvement of VAS (P<0.001), but not loudness or THI score, with alprazolam. This is in contrast with Johnson’s study of loudness [10]. It could be postulated that THI may not be sensitive or responsive enough to detect a measurable improvement in tinnitus level. We observed that the total score of THI was not high and this low handicap score may cause a floor effect that can obscure the effect of treatment on post-intervention THI. Perhaps the exclusion of depressed and anxious patients is the reason for the lack of significant changes in THI scores with treatment. In post hoc analysis, finding significant benefits of alprazolam in the catastrophic subscale of the THI allowed us to speculate that alprazolam may have some effects on different subscales of THI. It should be noted that THI subscales had wide 95% confidence intervals due to small sample size, enough to warrant testing in future studies.

In the present trial, loudness correlated only modestly with THI score (r²=0.176). This finding supports the belief that measuring the changes of tinnitus sensation before and after treatment tells us nothing about its impact on the patient’s psychosocial situation. No study of treatment has shown that reductions in loudness are correlated with reductions in impact [16].

Indeed, we considered that intervention moved the total scores of THI and VAS towards each other. This means that post-treatment, patients were reporting levels of disability more related to their tinnitus perception levels.

Some findings suggest that the best outcome in depression and anxiety results from combining medications and...
psychotherapy (often cognitive behavioral therapy) [17]. Therefore, we cannot rule out the possibility that alprazol- 
am may be effective in subjects who suffer from depressive or anxiety disorders.

Another issue is the duration of the tinnitus. In a report by She and colleagues, who treated patients with intratympan- 
ic steroid injection, tinnitus duration was the most impor-
tant factor impacting the efficacy of treatment [18]. In the 
present trial, the mean of tinnitus duration of our partic-
ipants was 63 months. Because of the size of the samples, 
we could not analyze the effect of tinnitus duration on pa-

tients’ responses. We believe it may be worthwhile to con-
duct a trial with a larger sample group.

CONCLUSIONS

Although we found some improvement of VAS, there is no 
evidence to support the overall superiority of alprazolam 
versus placebo in the treatment of tinnitus. It remains to 
be proven that alprazolam is useful in ameliorating tinni-
tus in patients with comorbid mood or anxiety disorders.

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