The Effect of Alprazolam on Acoustic Stapedius Reflex Thresholds in Healthy Volunteers

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Abstract Alprazolam, a widely used drug, has widespread, nonspecific depressant effects on the central nervous system, similar to other benzodiazepines. This inhibitor effect may cause changes in reflex thresholds by affecting the acoustic stapedial reflex (ASR) arc. This study was performed on 31 healthy volunteers. Initially, the basal ASR thresholds were measured and measured again 2 h after oral intake of 1 mg of alprazolam; by measuring the reflex thresholds once again the mean values of thresholds before and after the drug were compared. Only the left ipsilateral and contralateral 2,000 Hz increases were significantly different. The left ipsilateral and contralateral 500, 1000, and 4000 Hz, and the right ipsilateral and contralateral 500, 1000, 2000, and 4000 Hz measurements showed no differences. Although an increase in ART thresholds was generally observed after the intake of alprazolam, it was not significant. Its use in healthy adults does not statistically produce an additional risk of acoustic trauma at most of the frequencies, but its use with the agents potentiating the effect of alprazolam may increase this risk.

Keywords Acoustic stapedius reflex · Alprazolam · Acoustic trauma · Anxiety

Introduction

Acoustic stapedial reflex (ASR) is a reflex that protects the inner ear from high sounds. Different neurotransmitters serve in this reflex arc and provide proper functioning of the reflex. Agents that have nonspecific stimulant or depressant effects on the central nervous system can affect this reflex, thus it may not perform its function.

Benzodiazepines that are defined as minor tranquilizers, especially alprazolam, are commonly used antidepressants, and anxiolytic and hypnotic agents in clinical practice. However some adverse effects and addiction may develop with the use of these drugs. Side effects such as lethargy and drowsiness emerging the following day, amnesia, muscle weakness, headache, vertigo, hypotension, rash, visual impairment, libido change, and urinary retention may be observed when these drugs are used.

There are a limited number of studies regarding how antidepressant and anxiolytic agents affect the reactions of the organism to light, sound, and tactile stimuli [1–6]. On the other hand, in the literature review, no studies regarding the effects of these drugs on the ASR were encountered. As already known, the acoustic reflex is a mechanism that prevents the inner ear from violent sound stimuli. In case of attenuation or dysfunction of this mechanism, the risk of injury of the sensorineural units of the inner ear increases, transient or permanent hearing loss may develop.

This study aimed to evaluate the effects of alprazolam, which is an antidepressant and anxiolytic and hypnotic agent, on the ASR.

Materials and Methods

This study was performed in 31 healthy volunteers aged between 18 and 50 years, as part of the study criteria. The

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individuals were informed about the study and the study drug and the individuals who approved to participate in the study were included. The human research ethics committee approval of Kocaeli University (KOU IAEK, number: 2010/37 (4/3), date: 09.02.2010) and informed consent of all patients were obtained.

The medical records of all volunteers regarding their psychiatric and ear-throat-nose status were recorded and physical examinations were conducted. The individuals who did not have hearing loss, tympanic membrane perforation, chronic otitis media, 5th and 7th cranial nerve problems, drug addiction, severe psychosis, pregnancy or breast-feeding were included the study.

In all individuals, the thresholds of hearing were determined with pure tone audiometry and tympanometry, and acoustic reflex measurements (ART) were carried out with impedancemetry in Audiometry Unite. The pure tone audiometry was completed with AC 40 (Interacoustic, Assens, Denmark), and the ART were completed with AZ 26 impedance audiometer (Interacoustic, Assens, Denmark). The tone of the probe was 226 Hz. The hearing threshold higher than 20 dB in audiometry between 250 and 4,000 Hz was determined as the exclusion criteria. A 1 mg tablet of alprazolam was administered orally to the individuals and a period of 2 h was allowed to produce the maximum effect. At the end of 2 h, by performing the ART test on all individuals again, ART thresholds at frequencies of 500, 1000, 2000, and 4000 Hz with ipsilateral and contralateral stimulus before and after the drug were determined and recorded. The same audiologist performed all tests. The volunteers to whom the drug was administered were provided rest under observation under hospital conditions and they were warned not to drive for 12 h. One volunteer was excluded from the study, as he was unwilling to attend the second measurement; the data of the remaining 30 individuals were analyzed by paired *T* test. All analyses were performed by Statistical Package for the Social Sciences (Chicago, IL), version 20.0. A *p* value <0.05 was accepted as statistically significant. During the analysis, the mean values of ipsilateral and contralateral ART thresholds at 500, 1000, 2000, and 4000 Hz were recorded for all individuals, and these mean values were compared with the values before and after the drug for all frequencies.

Results

The mean age of the individuals involving the study was 23.9 years; 13 of the individuals were female and 17 individuals were male. One volunteer who was unwilling to participate in the second measurement was excluded from the study and a total of 30 patients were evaluated. Any

adverse effects from alprazolam were not observed in the patients.

ASR measurements were not obtained in six patients at the ipsilateral 500 Hz; in 13 patients at the ipsilateral 4,000 Hz; in 1 patient at the contralateral 500 Hz; in 2 patients at the contralateral 1,000 Hz; in 2 patients at the contralateral 2,000 Hz; in 2 patients at the contralateral 4,000 Hz in the left ear; and in 16 patients at the ipsilateral 4,000 Hz in the right ear. The numbers of volunteers for whom the measurements were collected and the mean values of the ipsilateral and contralateral ART thresholds of all individuals at frequencies of 500, 1000, 2000, and 4000 Hz before and after drug administration are shown in Table 1. When the pre-drug administration measurements and post-drug administration measurements are compared, ART thresholds in left ears showed an increase of 2.4, 1.5, and 2.4 dB, at the ipsilateral 500, 1000, and 2000 Hz, retrospectively, and 0.6, 2.5, 3.7, and 3.8 dB, at the contralateral 500, 1000, 2000, and 4000 Hz, retrospectively. The alterations in the thresholds are given in Table 2, and the thresholds are in Fig. 1. The mean values of the ipsilateral 4,000 Hz showed no difference. When the pre-drug administration measurements and post-drug administration measurements of the mean ART thresholds in the right ears showed an increase of 1.4 dB at the ipsilateral 4,000 Hz, and 1.2, 1.0, 1.2, and 1.9 dB, and at the contralateral 500, 1000, 2000, and 4000 Hz, respectively. The alterations in the thresholds are given in Table 2, and the thresholds are in Fig. 2. In the right ear, differing from the other measurements, there were slightly increase of 0.4, and 0.3 dB in the mean thresholds at the ipsilateral 1000, and 2000 Hz before and after alprazolam, while there was a decrease of 1 dB in the mean thresholds at the ipsilateral 500 Hz. Although there was an increase in both the ipsilateral and contralateral mean reflex thresholds in both ears in after drug measurements when compared with the before drug measurements, these increases were not found to be very pronounced.

When these increases and decreases of the acoustic stapedius reflex thresholds were compared statistically, only the left ipsilateral and contralateral 2,000 Hz were slightly significantly different (*p* = 0.042 for LI 2,000 Hz, and *p* = 0.019 for LC 2,000 Hz). The other fourteen comparisons showed no differences.

Discussion

ASR is an autonomic reflex that protects the inner ear from high noise and sounds. It is reported that, in addition to its protective function, it has the duty of selecting the frequency during hearing [7]. The neuronal pathway for the reflex is the cochlea, 8th nerve, ventral cochlear nucleus,

Table 1 The mean ART thresholds according to the frequencies (Hz) before and after alprazolam administration, and the number of the volunteers for whom the measurements were collected (n)

	LI 500	LI 1000	LI 2000	LI 4000	LC 500	LC 1000	LC 2000	LC 4000	RI 500	RI 1000	RI 2000	RI 4000	RC 500	RC 1000	RC 2000	RC 4000
Volunteers (n)	24	30	30	17	29	28	28	28	30	30	30	14	30	30	30	30
Thresholds; Before	90.1	89.3	88.2	91.2	94.6	87.3	88.7	92.2	93.6	93.8	92.3	91.9	96.6	88.7	90.8	95.3
Thresholds; After	92.5	90.8	90.7	91.2	95.2	89.8	92.5	96.0	92.3	93.3	92.0	93.2	97.8	89.7	92.0	97.2

LI left ipsilateral, LC left contralateral, RI right ipsilateral, RC right contralateral

Table 2 The alterations in the pre-drug and post-drug administration measurements of the mean ART thresholds in the right and left ears

	LI 500	LI 1000	LI 2000	LI 4000	LC 500	LC 1000	LC 2000	LC 4000	RI 500	RI 1000	RI 2000	RI 4000	RC 500	RC 1000	RC 2000	RC 4000
The alteration before and after drug	+2,4	+1,5	+2,4	0	+0,6	+2,5	+3,7	+3,8	−1	+0,4	+0,3	+1,4	+1,2	+1,0	+1,2	+1,9

LI left ipsilateral, LC left contralateral, RI right ipsilateral, RC right contralateral

Fig. 1 The pre and post drug main acoustic stapedius reflex thresholds in the left ears (LI left ipsilateral, LC left contralateral)

superior olivary complex, facial motor nucleus, and the stapedial branch of the 7th nerve.

The first synaptic area of the cochlear nerve is in the brainstem. Although it is stated that different neurotransmitters such as aspartate, glutamate, acetylcholine, and noradrenalin provide transmission in this synapses, there is no certain evidence of this [1]. Similarly, the same neurotransmitters were also found in the efferent nucleus of ART. The neurotransmitter in the motor end plate is acetylcholine. Because of this neuroanatomical structure of the reflex arc, the agents that have sedative or depressant effects on the central nervous system may affect this reflex [1].

The stapes muscle contracts bilaterally with the ASR and results in a change of acoustic admittance. The sound energy transmitted to the cochlea is decreased with the

increase in admittance. Generally this reflex is produced above 80 or 90 dB in humans. With this test, the auditory nerve and the auditory function of the brainstem could be tested in a non-invasive manner.

Alprazolam is the most frequently used benzodiazepine in the treatment of panic disorder and anxiety, and also one of the most misused benzodiazepine. Alprazolam, like other benzodiazepines, binds to specific sites on the GABA_A gamma-amino-butyric acid receptor, which is the most prolific inhibitory receptor within the brain [8]. After oral administration of alprazolam, peak plasma concentrations are reached within 0.7–1.8 h after intake [9]. In the current study, ART thresholds were evaluated again 2 h after oral intake.

Alprazolam in doses of 0.5 mg and higher impairs a variety of cognitive and psychomotor skills [10]. In

Fig. 2 The pre and post drug main acoustic stapedius reflex thresholds in the right ears (*RI* right ipsilateral, *RC* right contralateral)

general, it has a safety profile and a well-established utility, but it may cause non-specific depression of the central nervous system.

When the results of the current study were examined, it can be considered that alprazolam after the first use increased ART thresholds and left the cochlea slightly unprotected against sudden sounds, although not statistically significant except two values. On the other hand, it can be concluded that it does not affect ART. It can be said that alprazolam does not damage the acoustic reflex at most frequencies in healthy adults who have no additional psychiatric disorders, and it does not introduce an additional risk of acoustic trauma and hearing loss to the patients.

Different from the others, it was found that there was a statistically significant increase in ART thresholds after drug administration at the ipsilateral and contralateral 2,000 Hz in left ear. However, there was no statistically significant difference in these increases. While the p value for left ipsilateral 2,000 Hz was 0.042, this value was 0.019 for left contralateral 2,000 Hz.

A potential limitation of the present study might be that the effect was assessed only after a single dose administration of alprazolam. The effects of benzodiazepines can be changed with chronic use [10].

In addition, the performance of healthy subjects may be different from performance of anxiety patients. The fact that the volunteers did not use alprazolam previously may also affect the results. When these factors were considered, different results could be obtained in a study conducted with clinical cases.

Another confounder of the current study is the observed anxiety in the volunteers prior to the test. Anxiety produced in the volunteers during the first measurements may cause ART thresholds to response differently. Anxiety may have a partial depressant role on the central reflexes or a

stimulant role on some reflexes due to the general alertness [11]. Upon evaluation of the effect of anxiety on light reflex, it is established that there is a tendency of attenuation of the light reflex due to the decrease in parasympathetic activity, while there was an increase in sympathetic activity [12]. In previous study, it was demonstrated that while ART thresholds in anxiety situations decrease in disfluent speakers, it remain stable or shows a slight increase in fluent speakers [11]. The effect of anxiety on ART thresholds in normal volunteers may increase, similar to the fluent speakers, and perhaps may cause a decrease similar to the disfluent speakers. The alprazolam that was administered in order to observe its effect may have caused normalization of the reflexes or different responses by decreasing anxiety. In such a study evaluation of the patients, at first measurements with a momentary anxiety assessment scale would be better. Further studies would enlighten this prediction.

Conclusion

The effects of benzodiazepines, like alprazolam, on all reflexes are important for patients, as they are widely used drugs. For otolaryngologists, it would be useful to consider its effects on ART. In the current study, an increase in ART thresholds after alprazolam use was generally observed, although it is not statistically clear. The use of this drug in combination with the agents increasing the effects of benzodiazepines, such as alcohol or with other agents that may increase the ART threshold, may make patients prone to inner ear injury after high sounds by increasing ART thresholds. Similarly, the patients' use of benzodiazepines, like alprazolam due to different reasons, who had increased reflex thresholds in middle and inner ear diseases, may

increase the possible risk of sound damage. In addition, when analyzed from a different viewpoint, it can be assumed that in general, at most of the frequencies, alprazolam does not statistically change ART thresholds and thus the use of alprazolam in healthy adults would not produce an additional risk of cochlear acoustic damage. The studies investigating the effect of alprazolam on ART in a patient population other than healthy volunteers or evaluating the neuroanatomical structure of ART at the molecular level would facilitate access to different knowledge on this subject.

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Conflict of interest None.

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