Effects of anesthetic drugs on otoacoustic emissions: Experimental study

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Abstract
Aim: Otoacoustic emission measurements are generally performed under sedation for children and experimental animals. In the literature it is stated that due to systemic effects of medications used with the aim of sedation, there are variations in cochlear perfusion and as a result, otoacoustic emission (OAE) measurements are affected. Our study aims to investigate this interaction.

Material and Methods: The study was completed using 15 healthy adult Wistar Albino rats. The rats were divided into three groups based on anesthetic agent used; group midazolam (M), group ketamine (K) and group dexmedetomidine (D). After OAE measurements were performed in Groups M and D, noradrenalin was administered, OAE measurements were repeated and these were defined as group MN and Group DN. During the study, the hemodynamic data and OAE measurement results were recorded. Results were assessed for statistical significance.

Results: The mean arterial pressure in Group M and Group D was 66±16 mmHg, while in Group K, Group DN and Group MN it was 134±16. The mean HR in Group M and Group D was 196±20 beats/min, while in Group K, Group DN and Group MN it was 170±40 beats/min. In Group M and D, there was a correlation with mean arterial pressure only at 2 and 4 kHz, while in the noradrenalin group there was a direct correlation identified for mean arterial pressure only at 6 kHz.

Discussion: Though it is frequently emphasized in the literature that in addition to direct pharmacological effects of anesthetic agents, they may affect OAE results due to hemodynamic changes, in our study we conclude there is no significant interaction in clinical terms.

Keywords: Sedation; otoacoustic emission measurements; cochlear hypoperfusion.

INTRODUCTION
Otoacoustic emissions (OAE) are mild intensity acoustic energy emissions sourced in the cochlear identified in humans and animals in the external ear canal. When any sound sourced in the cochlear is recorded in the outer ear OAE responses occur. OAEs are defined in two groups as spontaneous and evoked (1). Spontaneous otoacoustic emissions (SOAE) are tonal, low level narrow band signals due to the cochlear, forming without any external acoustic stimuli. Evoked otoacoustic emissions (EOAE) are divided into three groups as stimulus frequency (SFOAE), transient evoked (TEOAE) and distortion product otoacoustic emissions (DPOAE). The DPOAE technical procedures are more complex than the TEOAE (2-3). In addition to OAEs being objective and non-invasive, they can be performed in a short duration, which has increased their use in audiology. To perform an ideal OAE measurement, firstly a normal external ear canal and membrane anatomy is necessary. Before measurement, otoscopic examination should exclude pathologies that may develop linked to obstructive lesions of the external ear canal and middle ear pathologies (4). OAEs are affected by many external factors; leading these interactions are the working mechanism of the middle ear structures and especially facial muscle movements of the tested individual. The precondition for objective assessment of the cochlear system is that emission from the cochlea reaches the microphone located in the external ear canal without
encountering any interactions. Any disruption occurring in the middle ear will affect the passage of the external stimulus to the cochlea and the returning response from the cochlea. Additionally, movement of muscle structures in the facial region negatively affect the sensitivity of the microphone located in the external ear canal and increase the noise level affecting the sensitivity of measurements (5). As a result, to remove these types of factors when performing hearing tests, the patient or subject is administered anesthesia.

In DPOAE measurements, the anesthetic agents used for sedation may cause unwanted side effects. The majority of medications used for anesthesia create hemodynamic changes characterized by heart rate (HR) and systemic arterial pressure (SAP) falls (5). In the literature there are different opinions about the effects on the cochlear system, with the general belief that cochlea hypoperfusion develops secondary to SAP reduction and as a result OAEs are affected (5). There is no study clearly revealing the effect of these medications on OAE results among previous studies in the literature. In our study we aimed to reveal whether otoacoustic emissions in adult rat groups were affected by hemodynamic changes caused by anesthetic medications. With this aim, our subjects were administered anesthesia using medications with known hypotensive effects, and after OAE measurements, the same subjects were administered noradrenalin and measurements were repeated. The correlations with the results were assessed.

MATERIAL and METHODS

Our study protocol was approved by local animal ethics committee of the university and was compatible with the Guide for the Care and Use of Laboratory Animals prepared by the National Academy of Sciences (Institute of Laboratory Animal Resources, 1996). The study was performed in accordance with regulation number 5199 about the Protection of Animals and the Ministry of Agriculture and Rural Affairs' Protection of Experimental Animals Used for Experimental and Other Scientific Purposes, and Foundation, Operation, Supervision, Procedures and Principles of Experimental Animal Production Locations and Laboratories performing Experiments.

The study was performed on 15 healthy adult Wistar Albino rats. The rats weighed from 200-230 g and were aged from 9-10 months. They were housed in an environment of rats during the experiment is between 37.5 and 39.0 degrees centigrade, there is no effect on OAEs, so oral temperatures of subjects were set to between 37.5 and 39.0 degrees (6). Distortion product otoacoustic emissions were measured using a GSI Audera® device with newborn probe. After placing the head of the animal in horizontal position, a tympanometry rubber probe was inserted with appropriate size for the external ear canal and measurements were made. After observing that the probe marker and stimulating wave form were in appropriate configuration and the device was in appropriate measurement position, measurements began. Distortion product otoemissions (2f1-f2 cubic distortion product components) were measured with the GSI Audera® device in general diagnostic mode. The ratio between f2 and f1 frequencies (f2/f1) was held to 1.22. The stimulating intensity was taken as L1 for f1 frequency and L2 for f2 frequency and L1-L2 was set to 10 dB SPL (L1=65, L2=55). The results are given as geometric mean of primary tones (f1 and f2). Otoacoustic emissions were stimulated using two different speakers for two different stimuli (f1 and f2) in the outer ear canal. DPOAEs were measured with a microphone in the external ear canal with 2f1-f2 frequency and recorded at the geometric means of f1 and f2 of 3000, 4008, 5004, 6000, 6999, 8004, 9012, 10008, 11004 and 12000 Hz. The test duration was nearly 30 s. DPOAE amplitudes with values 3 dB above the noise threshold were accepted as significant. Measurements were performed in a room with noise levels not exceeding 45 dB. Evaluation of DPOAE result is based on the obtained 2f1-f2 cubic distortion produced from the geometric means of f1 and f2, in other words, the signal to noise ratio formed at 3000, 4008, 5004, 6000, 6999, 8004, 9012, 10008, 11004 and 12000 Hz frequency bands. In our study separate means were obtained for these ratios in each rat and statistical analysis was performed.

All subjects were administered xylazine 10 mg/kg intraperitoneal (i.p.) (Rompun®) anesthesia and then had non-invasive peripheral O₂ saturation (SpO₂), peak heart rate (PHR), and non-invasive arterial pressure (AP) monitoring in the femoral artery (Nihon Kohden Corporation, BSM-2353 NT, Japan). Mean arterial pressure (MAP), SpO₂, and PHR values were recorded. The depth of anesthesia, righting reflex, and chin and muscle tonus were assessed. Group D were administered dexmedetomidine 50 µg/kg (Precedex®, Abbott Lab., North Chicago USA), Group M were administered midazolam 5 mg/kg (Dormicum®, Roche, 5 mg ml⁻¹, Fontenay-sous-Bois, France) and Group K were administered ketamine 90 mg/kg (Ketalar 50 mg/mL; Pfizer, Zentiva, Lüleburgaz, Turkey) and left for sufficient sedation to form. After the waiting period (5-10 min) DPOAE measurements were performed in both ears separately and the results were recorded (1st measurement). After completing the first measurements, in the same session Group M and Group D were administered low dose inotrope (steradine 3 µg/kg) intraperitoneal and DPOAE measurements were repeated.
Hemodynamic data and DPOAE measurement results were recorded for Group MN and Group DN. At the end of the experiment, subjects had no procedure applied and were returned to the research center officials.

Statistical analysis was carried out using the Statistical Package for the Social Sciences version 13.0 software for Windows (SPSS Inc., Chicago, IL, USA). All quantitative variables were estimated using measures of central location (i.e. mean and median) and measures of dispersion (i.e. standard deviation (SD)). Data normality was checked using the Kolmogorov–Smirnov test of normality.

RESULTS

In Group M and Group D the mean arterial pressure was observed as 66±16 mmHg, while in Group K, Group DN and Group MN it was observed as 134±16 mmHg (p≤0.05) (Table 1).

In Group M and Group D the mean PHR was 196±20 beats/min, while in Group K, Group DN and Group MN it was observed as 170±40 (p≤0.05) (Table 1).

Though there was a statistical difference in mean arterial pressure between Group M and Group K, there was no correlation observed between the hemodynamic differences and OAE results (p≤ 0.05).

To test the opinion in the literature that systemic blood pressure variations affect OAE results, after measurements in the midazolam and dexmedetomidine groups, noradrenalin was administered and the later measurements were compared with previous results (Figure 1-2). There were significant differences between the measurements (p=0.001). When measurements are classified within themselves, Groups M and D are accepted as hypotensive, while Groups K, MN and DN are the normotensive group. In the hypotensive group, a correlation was only observed with mean arterial pressure at 3 and 4 kHz (Figures 3-4), while in the normotensive group a direct correlation with mean arterial pressure was only identified at 6 kHz (Figure 5) (p<0.05).

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<th>Table 1. Intraoperative measurements</th>
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<td><strong>PHR</strong></td>
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PHR: Peak heart rate  MAP: Mean arterial pressure
DISCUSSION

OAEs are defined in two groups as spontaneous otoacoustic emissions (SOAE) and evoked otoacoustic emission (EOAE) (1). SOAE are tonal, low level narrow band signals due to the cochlear, forming without any external acoustic stimuli. EOAE comprise three types of stimulus frequency (SFOAE), transient evoked (TEOAE) and distortion product otoacoustic emissions (DPOAE). The DPOAE is a non-invasive, rapid and cheap measurement method to assess presynaptic hearing function (7). The most important point during otoacoustic emission measurement is silence. This is not a problem for adult patients, but this element is a problem for some newborns and infants. As a result, the environment should not be noisy and the individual assessed should not move. To prevent interaction of the assessed individual with the environment and to reduce movement, anesthetic agents may be used sometimes (5). For reliable measurement results, the anesthetic agents used should not have any effect on OAE results (5).

Many drugs used for treatment or study are known to have temporary or permanent effects on the hearing system (8). Some of these form ototoxic effects, while some form temporary functional loss. In the literature, though the effect mechanism of anesthetic agents on the hearing system is not clear; it is known they may cause clinical temporary functional losses (5). There are a limited number of studies performed with the aim of identifying the effects of anesthetic agents on OAEs. The majority of this research is limited to animal experiments. Some studies on animals and humans have stated that anesthetic agents (propofol, ketamine, thiopental, midazolam, sevoflurane and isoflurane) affect OAE measurements due to changes caused to systemic blood pressure or via direct effects on the cochlear system (7,9).

As it is predicted that systemic blood pressure changes will affect cerebral perfusion pressure like cochlear perfusion pressure, it is expected that anesthetic agents with known hypotensive effects will affect cochlear perfusion. As a result, it is expected that cochlear functions will be affected. In fact, the general literature information is such. Preliminary studies have shown that cochlear function is worse with systemic hypotension and these changes are related to variations in both cochlear blood flow and to systemic blood pressure (10). A study by Kettembeil et al. stated the DPOAE in chickens was related to the level of general anesthesia administered (11). Patients with cardiopulmonary bypass are observed to have hearing loss at high frequencies and this loss is associated with hypoperfusion forming as a result of long-term extracorporeal circulation (13).

Harel et al. identified that anesthesia with ketamine (15 mg/kg) and intraperitoneal barbiturates (60 mg/kg) in chinchillas reduced cochlear afferent activity causing an increase in DPOAE amplitudes (12). In our study in spite of the PHR and MAP increases in the group administered ketamine, there were no significant changes observed in OAE. Groups given sedation with midazolam and
dexmedetomidine had noradrenalin administered in the same session to investigate this hypothesis, with an increase in systemic arterial pressure induced and measurements repeated. However, in spite of significant differences in mean arterial pressure in all subjects, significant differences were only identified at high frequencies and only at two levels and two measurements in OAE results.

In hypoperfusion situations external hair cell groups are first affected and the result of this interaction appears as temporary hearing loss at high frequencies (3, 4, 5, 10, 11, 12, 13 thousand kHz). The hearing loss at high frequency observed in patients with extracorporeal circulation after coronary bypass surgery is explained by this mechanism (9). Thus, the data in the literature comply with results obtained in our study. However, as the variations occurring do not affect speaking frequencies, it is not clinically significant. Consequently, for research with study aims investigating high frequency injury, care should be taken that the anesthetic agents used not affect high frequencies as they may lead to erroneous results.

With physiology not fully explained in the hearing system, the effects of anesthetic agents on the middle ear are still controversial with system assessment into the effect on OAE measurements still debatable. Though it is frequently emphasized that anesthetic agents affect OAE results, in our study we observed a variation only at high frequencies. This variation does not represent clinical significance, but is important for experimental studies. Though certain variations were identified in measurements, we believe there is a need for new studies to enlighten this interaction supported by histopathologic data.

**Competing interests:** The authors declare that they have no competing interest.

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