INTRODUCTION

Fungal external ear canal infections are commonly known as Candida albicans; fungal pathogens causing this condition are Candida species and Aspergillus species (1, 2). Most patients diagnosed with otomycosis can be treated successfully with topical antifungals, especially if uncomplicated cases. Topical treatment involves determination of fungal growth by culture and combined with topical antifungal drugs (3, 4). The main advantages of topical antifungal drugs include a high concentration at the affected site and decreased systemic side effects. Status of the tympanic membrane is very important in the selection of local antifungal treatment.

Potential ototoxicity of some antifungal solutions has been investigated in many studies (5, 6, 12). In these animal studies, gentamicin, tobramycin, actinomycin, and boric acid in alcohol has shown significant evidence whereas ciclopirox, miconazole, terbinafine, clotrimazole, nystatin, boric acid in distilled water and Castellani solution demonstrated no evidence of ototoxicity. In a recent study, ciclopirox cream showed toxic effect on rats (13). Oxiconazole, an imidazole derivate and acid boric in alcohol solutions are frequently used agents in otomycosis, but little is known about possible ototoxicity. The purpose of the study was to determine the ototoxic effects of the oxiconazole and boric acid in alcohol solutions together have not been previously reported in the English literature. In the current study, we aimed to evaluate the possible effects of oxiconazole and boric acid in alcohol solutions to the cochlear outer cell function of rats by measuring distortion product otoacoustic emission (DPOAE) amplitudes.

MATERIALS AND METHODS

The study was performed after approval from the Committee of Ethics of The Faculty of Veterinary Medicine, Aydin University, Turkey. Fifty, 5-wk-old male Wistar albino rats (weighing 230 to 260 g) were divided into 5 groups of consisting 10 animals each. The animals were anesthetized by 5 mg/kg xylazine (Romberg; Bayer Ltd, Leverkusen, Germany) and 80 mg/kg ketamine (Ketalar; Eczacibasi, Istanbul, Turkey) administered via intraperitoneal injection before surgical procedure and measurements of ototoxic acoustic emission. The ear canals and the tympanic membranes of the animals were examined and retracted tympanic membranes were partially perforated and a very small piece of gel foam inserted middle ear under an operating microscope. After the surgical procedure, the baseline DPOAE measurements of the right ears were done by using Echopod (Easytech Ltd, Letchworth, UK). All of the hearing tests performed in a quiet room. Primary tones were given into the sealed external ear canals through an earphone with a 20 dB SPL input (Leek Acoustics, LTD, UK). The levels of 1,121 Hz of 80 dB SPL 70 dB SPL with the 0.01% ratio of 1.20 dB then amplitudes of the DPOAE signal was analyzed. During this fifteen days, the rats in Group I received 0.1 ml of oxiconazole solution (0.1%, Oncador, Turkey) in ears (Sabia Ilaq, Istanbul, Turkey). Group II received four percent boric acid solution in alcohol drops, group III and IV received gentamycin (40 mg/ml) and saline solution, respectively. Group V received no medication. Each solutions used were given twice a day.

RESULTS

All of the rats completed the study. None of them showed signs of infection. In the examination of the tympanic membranes it was observed that the perforations became wider in some of the rats during the post-treatment period. Also we observed a transient vestibular imbalance nearly between 6th and 10th days in the animals of different groups. By the effect of ototoxic parameters, the apparatus was measured by DPOAE values at 2000, 2900, 4000, 6000, 8000 Hz. Pre-treatment and post-treatment measurements were performed with an interval of 15 days. Table 1 summarizes the DPOAE results before and after the treatment.

In the statistical analysis using the Kruskal-Wallis test, there was no significant difference between the all groups’ pre-treatment DPOAE data. When we compared post-treatment values from all groups, we found a statistically significant difference (p<0.0001). In all groups except gentamycin group, the differences between pre-treatment and post-treatment values for all frequencies were not statistically significant difference. However, group III which received gentamycin showed significant deterioration of the DPOAE amplitudes (p<0.0001).

In the light of these results, oxiconazole and boric acid in alcohol solutions are appeared to be safe in rat ears.

Table 1. Means and standard deviation of DPOAE values for 2000, 2900, 4000, 6000 and 8000 Hz frequencies before and after drug administration in the right ears of rats (n=70/group).

<table>
<thead>
<tr>
<th>Group</th>
<th>DPOAE (dB SPL)</th>
<th>Mean±SD</th>
<th>Post-treatment</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (Oxiconazole)</td>
<td>2000</td>
<td>20.4±3.2</td>
<td>20.4±3.2</td>
<td>20.4±3.2</td>
</tr>
<tr>
<td>II (Boric acid)</td>
<td>2000</td>
<td>20.4±3.2</td>
<td>20.4±3.2</td>
<td>20.4±3.2</td>
</tr>
<tr>
<td>III (Gentamycin)</td>
<td>2000</td>
<td>20.4±3.2</td>
<td>20.4±3.2</td>
<td>20.4±3.2</td>
</tr>
<tr>
<td>IV (Control)</td>
<td>2000</td>
<td>20.4±3.2</td>
<td>20.4±3.2</td>
<td>20.4±3.2</td>
</tr>
<tr>
<td>V (Saline)</td>
<td>2000</td>
<td>20.4±3.2</td>
<td>20.4±3.2</td>
<td>20.4±3.2</td>
</tr>
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</table>

DISCUSSION

Topical use of drugs is more effective than systemic use in external ears. They can reach the ears with tympanic membrane intact, and provide therapeutic concentrations (3, 14). Food and Drug Administration did not approve any topical used preparation for otomycosis to date (15). In the study of Kritikos et al., hair cells and supporting cells of the organ of Corti may temporarily or permanently damage (6). In this study we preferred DPOAE which is a noninvasive tool to determine the outer cell functions of the cochlea and so the DPOAE amplitudes can be employed in this study.

Oxicnozale and boric acid in alcohol solutions have been widely used in the treatment of otomycosis by otorlaryngologists. Oxiconazole is a broad spectrum imidazole derivate antifungal drug against dermatophytes, yeasts, fungi, molds and mixed infections due to fungi and gram-positive bacteria (16). Imidazole derivatives involve the extraprotoplasmic biosynthesis which is critical for cellular membrane integrity of fungi (6). Boric acid solutions can be prepared with alcoholic or distilled water. These solutions have antifungal and also affects both in external and middle ear infections (12).

There are many animal studies investigated the ototoxic potentials of antifungal agents. In his study in guinea pigs Tom reported that topical use of clotrimazole, miconazole, nystatin and tobramycin had ototoxic effects (6). Baylanpiek et al showed topical ciclosporin solution and Serin et al showed Burrow solution had no effect to the inner ear of guinea pigs (8, 17). In a different study, Giakali et al, reported that Castellani solution in external ears compromised middle ears by using DPOAE to measure hearing (9).

We could find only one study about oxiconazole’s ototoxic potentials. Kritikos et al (12) found that oxiconazole could affect the inner ear (13). They compared the pretreatment and post-treatment hearing levels with ABR. This result about oxiconazole is opposite to the

EFFECTS OF OXICONAZOLE AND BORIC ACID IN ALCOHOL SOLUTIONS TO THE INNER EAR

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REFERENCES