Experimental Study / Deneysel Çalışma

Ototoxic effect of topical rifamycin SV applied in the middle ear of rats

Sıçan orta kulağına uygulanan topikal rifamisin SV'nin ototoksik etkisi

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ABSTRACT

Objectives: In this study, we aimed to evaluate the ototoxic effect of topical rifamycin SV in the middle ear in a rat model.

Materials and Methods: A total of 24 20-week-old adult female and eight 4-6-week-old weaned (young, post-suckling period) Wistar albino rats were used. Adult rats were separated into four groups: Group 1 (adult rifamycin), group 2 (weaner rifamycin), group 3 (gentamicin; positive control), and group 4 (saline; negative control). Before medication administration, an auditory brainstem response (ABR) test was performed on each animal under general anesthesia. Tympanic membranes of the animals were perforated, and the medications were administered to the middle ear for 10 days. Three weeks after treatment, ABR tests were repeated and pre- and post-treatment ABR threshold measurements were compared.

Results: Although the mean pre- and post-treatment ABR threshold values did not significantly differ among groups 1, 2, and 4 ($p>0.05$), the mean post-treatment ABR threshold values were significantly higher in group 3 compared to baseline ($p<0.05$).

Conclusion: Based on ABR measurements, the topical use of rifamycin SV, a broad-spectrum semi-synthetic antibiotic in the middle ear, does not cause hearing loss in adult or weaner rats.

Keywords: Auditory brainstem response; inner ear; ototoxicity; rifamycin SV.

ÖZ

Amaç: Bu çalışmada bir sıçan modelinde topikal rifamisin SV'nin orta kulakta ototoksik etkisi araştırıldı.

Gereç ve Yöntemler: Toplamda 24 adet, 20 haftalık erişkin dişi ve sekiz adet 4-6 haftalık (sütten kesilmiş yavru) Wistar albino sıçan kullanıldı. Erişkin sıçanlar dört gruba ayrıldı; Grup 1 (erişkin rifamisin), grup 2 (yavru rifamisin), grup 3 (gentamisin; pozitif kontrol), grup 4 (salin, negatif kontrol). İlaç uygulaması öncesinde her sıçana genel anestezi altında işitsel beyinsapı yanıtı (ABR) testi uygulandı. Hayvanların timpan membranları perfore edilerek, orta kulağa 10 gün boyunca ilaçlar uygulandı. Tedaviden üç hafta sonra ABR testleri tekrar edildi ve tedavi öncesi ve sonrası ABR eşik ölçümleri karşılaştırıldı.

Bulgular: Tedavi öncesi ve tedavi sonrası ortalama ABR eşik değerleri grup 1, grup 2 ve grup 4'te istatistiksel olarak anlamlı farklılık göstermez iken ($p>0.05$), grup 3'te tedavi sonrası ortalama ABR eşik değerleri, başlangıca kıyasla, anlamlı düzeyde daha yüksekti ($p<0.05$).

Sonuç: İşitsel beyinsapı yanıtı ölçümlerine dayanarak, geniş spektrumlu yarı sentetik bir antibiyotik olan rifamisin SV'nin orta kulakta topikal kullanımı, erişkin veya yavru sıçanlarda işitme kaybına neden olmamaktadır.

Anahtar Sözcükler: İşitsel beyinsapı yanıtı; iç kulak; ototoksisite; rifamisin SV.

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Ototoxicity is a pathological condition caused by specific drugs and chemicals that presents with injury of the cochlea and/or vestibule, as well as symptoms of hearing loss and disequilibrium.[1,2] Numerous interventional and medical procedures have been defined for the treatment of ear infections.[3] Topical treatments have a large number of potential advantages compared to systemic treatments. For example, they reach higher concentrations in the area of infection due to pharmacological solubility, have not intestinal absorption, and the liver does not influence tissue concentration since they bypass the systemic circulation and access infected organs.[4] Despite such advantages, topical treatments of ear conditions can enter the middle ear, reach the inner ear through the round window membrane (or other anatomical connections such as the annular ligament of stapes or micro fractures in the otic capsule), and cause toxic effects in cochlear or vestibular organs.[5]

Although the vestibulotoxic effects of aminoglycosides (particularly streptomycin and gentamicin) are used to treat Meniere's disease, ototoxicity is generally an unwanted side effect and a medicolegal problem in the topical treatment of ear diseases.[6,7] Another issue is that side effects resembling ototoxicity may occur through the use of otic drops in pediatric cases, which can be safely used in adults for the treatment of chronic otitis media. For example, in the United States, while ofloxacin ear drops can be used in tympanostomy tube otorrhea starting from age one, its use has been approved in children older than 12 for the treatment of chronic otitis media.[8]

Rifamycin SV, an antibiotic used for the topical treatment of ear infections, is a member of the ansamycine antibiotic family. It is semi-synthetic and has bactericidal effects on Gram-positive and Gram-negative microorganisms, such as *Staphylococcus aureus*, and is produced from natural rifamycin B made from *Amycolatopsis mediterranei*. Rifamycin affects nucleic acid metabolism through DNA-dependent RNA polymerase inhibition.[9] Because the absorption of rifamycin SV from the gastrointestinal channel is weak, it is applied parenterally by injection to the target tissue or by topical application.[10]

To the best of our knowledge, there has been no study on the ototoxic effects of rifamycin SV in topical applications. Thus, we used the auditory brainstem response (ABR) test to determine if the application of rifamycin SV to the middle ear of rats had any ototoxic effects.

MATERIALS AND METHODS

Design and study groups

This study was conducted at Adnan Menderes University (Aydın, Turkey) laboratory animal research facility of the Faculty of Medicine after approval was obtained from the university's animal experiments local ethics board (file number: 64583101/2015/079). The study was conducted in accordance with the principles of the Declaration of Helsinki. A total of 24 20-week-old adult female Wistar albino rats weighing 200-220 g and eight 4-6-week-old weaned Wistar albino rats weighing 110-130 g were used in our study. During the study, the room temperature was kept standard (20±2 °C) in an environment of 12 h light/12 h dark, and the rats were fed with pellet feed and allowed free access to water and feed. Adult rats were grouped randomly and all of the rats were grouped in equal numbers as follows:

Group 1: Adult rifamycin (n=8)

Group 2: Weaner rifamycin (n=8)

Group 3: Gentamicin (40 mg/mL) (positive control) (n=8)

Group 4: Saline (negative control) (n=8)

All of the rats used in the study were anesthetized with a combination of 50 mg/kg ketamine hydrochloride (Ketalar, Eczacibaşı, İstanbul, Turkey) and xylazine 7.5 mg/kg (Rompun, Bayer, Healthcare AG, Leverkusen, Germany) administered intraperitoneally. The external auditory canal and tympanic membranes were examined with otoendoscopy. None of the rats had external or middle ear pathology. Auditory brainstem response measurements of the right ears were obtained. Under otomicroscopic inspection, the right tympanic membrane inferior quadrant was carefully perforated using a micro ear pick. Gelfoam was placed on the perforation site corresponding to the round window. Following the surgical procedure, test solutions were applied to the right ears of the rats transcanal

at a dose of 0.1 mL (two drops) two times a day for 10 days following the studies of Sagit et al.[11] and Öztürkcan et al.[12] Tympanic membrane perforations were checked every other day with otoendoscopy. After the 10th day, perforations were found to persist. At this time, the final medication was applied and the treatment was terminated. Three weeks after the treatment ended, the same general anesthesia method was applied to the control rats. Their right ears were examined by microscopic inspection, debris was cleaned, and perforations were found to have closed in all of the groups. No residual perforation was found and control ABR tests were performed.

Auditory brainstem response technique

The ABR test was performed on the right ear under general anesthesia, and recordings were acquired in a quiet room from a single channel using the Interacoustics EP25 evoked potential system (ver. 3.00, Assens, Denmark) and subdermal needle electrodes. The noninverting (active) electrode was placed at the vertex, in the midline of the scalp, and the inverting (reference) electrode was placed in the mastoid area of the tested ear. The ground electrode was inserted in the back of the rat. An E-ARTONE™ 3A (3M Company, Auditory Systems Repair, Indianapolis, USA) insert earphone was used. The ABR test was performed with a 2,000-click stimulus within a range of 100-4,000 Hz at a stimulus rate of 30.0 pps at rarefaction polarity. The measurement was conducted by lowering the sound level by 20 dB decrements, starting from 90 dB. Repeatability was confirmed and the thresholds were determined by testing twice. ABR threshold was defined as the minimum intensity at which Wave V could be identified. Pre and post-treatment ABR results were compared.

Statistical analysis

The mean ± standard deviation, and lowest and highest mean values were used in the descriptive statistics. The Kolmogorov Simirnov test was used to measure the distribution of variables, the Kruskal-Wallis and Mann-Whitney U tests were used to analyze the quantitative data, and the Wilcoxon test was used to analyze repeated measures. An IBM SPSS version 22.0 (IBM Corp., Armonk, NY, USA) program was used for the analyses.

Table 1. Auditory brainstem response findings before and after treatment in all of the groups

	Group 1			Group 2			Group 3			Group 4			
ABR thresholds	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	*p*
Before treatment	17.5±4.6	20	10.0-20.0	15.0±5.3	15	10.0-20.0	17.5±4.6	20	10.0-20.0	13.8±5.2	10	10.0-20.0	0.335‡
After treatment	18.8±3.5*	20	10.0-20.0	16.3±5.2*	20	10.0-20.0	48.8±12.5	50	30.0-70.0	15.0±5.3*	15	10.0-20.0	0.000‡
Difference	1.3±3.5*	0	0.0-10.0	1.3±3.5*	0	0.0-10.0	31.3±12.5	30	10.0-50.0	1.3±3.5*	0	0.0-10.0	0.000‡
p		0.317†			0.317†			0.011†			0.317†		

SD: Standard deviation; Min: Minimum; Max: Maximum; ‡ Kruskal-Wallis (Mann-Whitney U test); † Wilcoxon test; * Difference with grup 3 $p<0.05$.

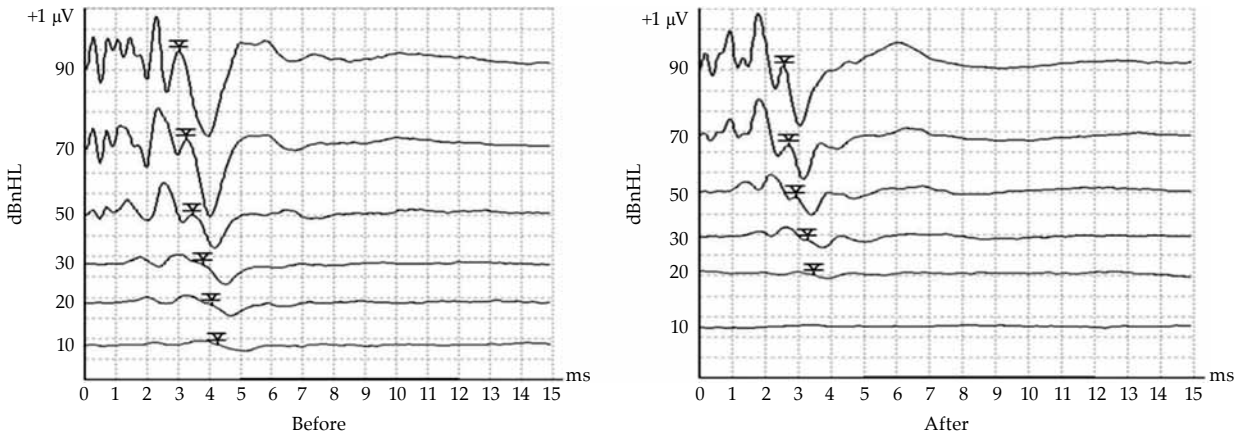

Figure 1. *The auditory brainstem response threshold of an adult rat from group 1 is shown before and after the test.*
dBnHL: Decibels normalized hearing level.

RESULTS

All of the animals completed the study in good health. In all four groups, the mean pre-treatment hearing thresholds were not significantly ($p>0.05$) different. In group 3, the mean posttreatment hearing thresholds were significantly ($p<0.05$) higher than those in groups 1, 2, and 4, although the threshold did not significantly differ among these three groups or compared to the pre-treatment threshold ($p>0.05$ for both comparisons) (Table 1). In group 3, the mean post-treatment hearing thresholds significantly ($p<0.05$) increased compared to pre-treatment (Table 1). In groups 1, 2, and 4, the changes in pre- and post-treatment hearing thresholds did not significantly ($p>0.05$) differ (Table 1). In group 3, the increase in mean hearing thresholds was significantly ($p<0.05$) higher compared to that in groups 1, 2, and 4 (Table 1).

Examples of pre- and post-treatment ABR recordings in group 1 (adult rifamycin), group 2 (weaner rifamycin), and group 3 (gentamicin) are shown in Figures 1-3, respectively. The graphic shows before and after treatment median ABR thresholds in all groups (Figure 4).

DISCUSSION

In addition to reaching high concentrations in target tissue, topical antibiotic drops used in ear infections have advantages of causing relatively harmless side effects such as local irritation and allergy compared to side effects that may develop during systemic antibiotic use (e.g., diarrhea, nausea, vomiting, rash, abdominal ache, headache, seizures, Steven's-Johnson syndrome, aplastic anemia, and death.[4] On the other hand, the potential of topical ear drops to cause ototoxicity by passing through the

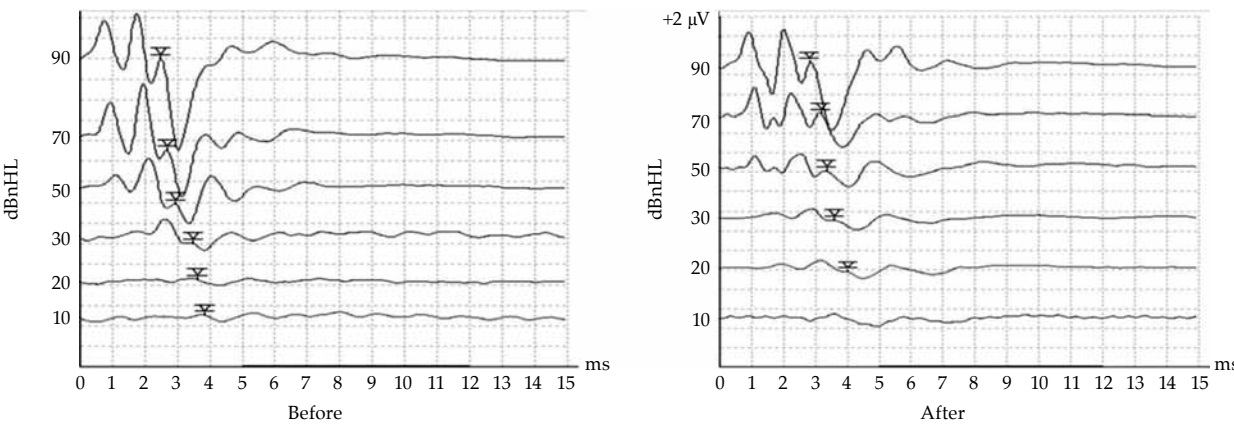

Figure 2. *The auditory brainstem response threshold of a weaned rat from Group 2 is shown before and after the test.*
dBnHL: Decibels normalized hearing level.

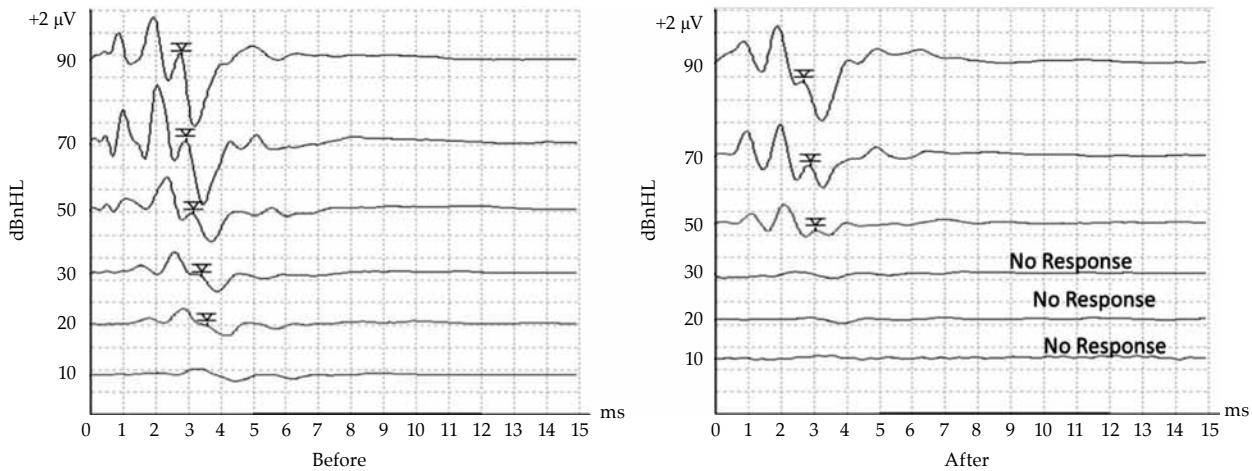

Figure 3. *The auditory brainstem response threshold of an adult rat from group 3 is shown both before and after the test.* *dBnHL: Decibels normalized hearing level.*

round window membrane to the inner ear is an undesired side effect.[13] Animal models have been used to explore whether systemic and topical uses of a variety of antimycotics, antiseptic, and antibiotic drugs have ototoxic effects.

Several topical agents have been explored in previous reports, including the topical use of antimycotics such as clotrimazole, miconazole, nystatin, tolnaftate, and terbinafine, which did not show ototoxic effects, and gentian violet which does have this effect.[11,14] While the application of antiseptics chlorhexidine and alcohol (70%) to the middle ear showed vestibulotoxic and cochleotoxic effects in rats, they were not observed in povidone-iodine, and the results obtained from the control agent, saline, were similar.[15] While ototoxic effects were observed for Burow's solution (aluminum acetate of approximately 13% with a pH of 3.7), ear drops containing acetic acid and boric acid solutions prepared with 70% alcohol, they were not observed for boric acid solutions prepared with distilled water.[12,16,17] In addition, although ototoxic effects were observed during the topical application of antibiotics such as aminoglycosids,[18] chloramphenicol,[19] polymyxin B,[20] vancomycin,[21] and daptomycine,[22] they were not observed for the topical application of antibiotics such as ciprofloxacin,[23] ofloxacin,[24] mupirocine,[21] and vasocidine.[25]

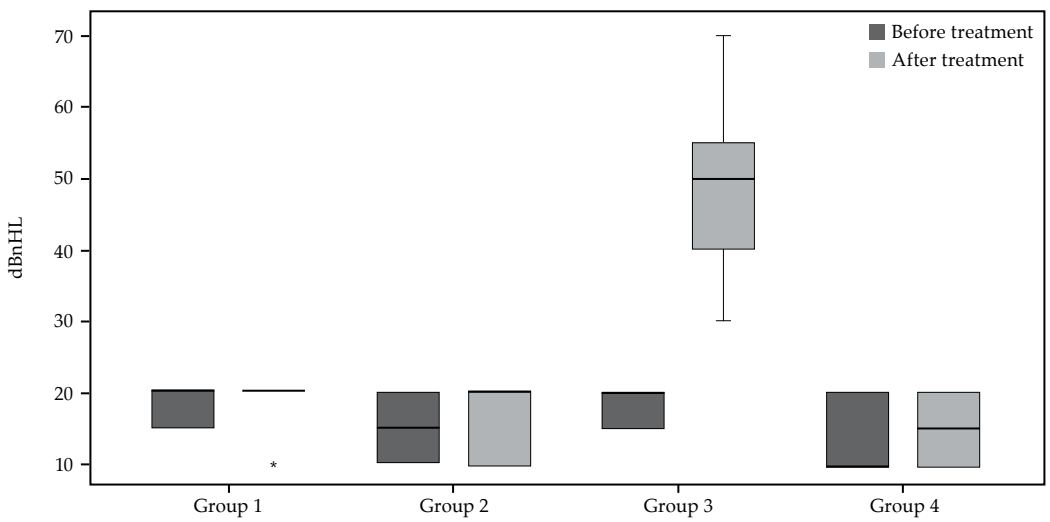

Figure 4. *The graphic shows median auditory brainstem response thresholds for click stimulus before and after treatment in all of the groups.* *dBnHL: Decibels normalized hearing level.*

The first local application of rifamycin SV, the target agent of this study, was conducted in lung caverns; several subsequent studies have shown its topical use on both animals and wounds that occurred due to human surgery and trauma.[26-29] In their study, Kaya et al.[27] reported that in the tibia defect they created in rats, rifamycin caused significant histological improvement and new bone formation in the group where a bone graft was not used compared to the control group. Iselin et al.[28] reported that topical rifamycin is useful for hand injuries, and could control infection and accelerate wound recovery. The efficiency of povidone iodine solution and the topical application of rifamycin in patients who underwent surgery for hand injury were compared based on the amount and quality of healing. In the rifamycin group, the symptoms of infection significantly decreased and the recovery was faster. In a clinical study conducted by Köşüş et al.,[29] 1,196 patients who had cesarean incisions were divided into two groups; povidone iodine was applied to patients in the first group preoperatively and postoperatively at the site of incision, while in the second group, the patients were applied rifamycin SV to subcutaneous tissue before closure of skin, in addition to application of povidone iodine. Overall, rifamycin SV applied under the skin decreased infection at the site and the cost of treatment.

Several studies have discussed the anti-inflammatory and immunomodulatory effects of rifamycin, as well as its antibacterial effects. Caruso et al.[30] injected rifamycin SV in 15 of 30 patients with rheumatoid knee synovitis, and injected saline intraarticularly to the other 15 patients. The authors found clinical success in 14 patients in the rifamycin group, whereas persistent effusion was observed in all of the patients in the saline group. In synovial fluid samples obtained before and after treatment with aspiration, a significant decrease was observed in post-treatment leukocyte number and polymorph nuclear leukocyte rate compared to pre-treatment, whereas no difference was observed in the saline group. These effects were believed to be due to the potent anti-inflammatory effects of rifamycin. Successful clinical results were also obtained for the treatment of inflammatory bowel diseases (Crohn's disease and ulcerative colitis) with oral use of rifaximine, which contains the active ingredient rifamycin.[31,32] In addition to its antibacterial effects, studies have shown that rifaximine increases expression of the pregnant X receptor in intestinal epithelial cells and antagonizes the effects of tumor necrosis factor.[33,34]

Rifamycin is a well-tolerated agent with topical uses that causes few side effects including moderate allergic skin reactions, and rarely, anaphylactic shock when applied to surgical wounds.[35,36] Although it is used as a topical drug alone or with other agents for the treatment of external otitis, suppurative otitis media, ventilation tube-induced otorrhea, and tympanoplasty, so that patients can benefit from the antibacterial and anti-inflammatory effects, its ototoxic effects in topical uses have not been reported. Several anatomic and physiological factors, including the molecular weight of the agent, influence the conductivity of the round window membrane, which is the main site for transmission of topical agents to the inner ear. It has been demonstrated in animal models that compounds with a molecular weight <1000 can be easily transported to the inner ear through active transport.[37] Similarly, this conductivity was also shown in a human model in which gentamicin applied intraoperatively (facial recess approach) to the round window was found in fluid samples within minutes.[38] Thus, the molecular weight of aminoglycoside group antibiotics (<1000) is an important factor for transport to the inner ear through the round window membrane. Because the molecular weight of rifamycin SV is 720 g/mol and its molecular weight is <1000, this drug has the potential to move through this membrane to the inner ear via active transport.[39] We did not detect rifamycin in inner ear fluid and did not perform any histopathologic evaluation. This was a weakness of this study. We presumed that even though rifamycin may pass into the inner ear there was no significant hearing loss determined.

In conclusion, in this study, we found that ABR thresholds in the speech frequencies of both pediatric and adult rats did not change after 10 days of rifamycin topical application. Although this drug appears to be safe and did not cause hearing loss in the adult or

weaned rats, additional studies including electrophysiological tests, vestibular tests, and histopathology should be performed to more definitely determine if it has any effects on the vestibular system.

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Declaration of conflicting interests

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