ORIGINAL ARTICLE

Combined Effects of Low-Dose Kanamycin and Noise Exposure on Auditory Brainstem Response and Cochlear Microphonic Potential in Guinea Pigs

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ABSTRACT

Objectives: Aminoglycoside-induced ototoxicity is a well-recognized adverse effect that commonly presents as sensorineural hearing loss. This study investigated hearing damage by administering two doses of Kanamycin, with or without concurrent noise exposure. Auditory function was assessed using auditory brainstem response and cochlear microphonic potential.

Materials & Methods: Guinea pigs were divided into six groups: Control, Noise exposure, Kanamycin 300 mg/kg alone (low dose), Kanamycin 300 mg/kg + Noise, Kanamycin 500 mg/kg alone (high dose), and Kanamycin 500 mg/kg + Noise. Auditory threshold shifts were evaluated using click and pure tones at 4, 6, 8, 12, and 16 kHz. The cochlear microphonic amplitude was measured before and after intervention in the study groups. The latency and amplitude of waves I and III were analyzed in the groups without sensorineural hearing loss.

Results: Auditory threshold shifts were significantly greater in the low-dose Kanamycin + noise group compared to both the low-dose Kanamycin alone and the noise-only groups across all stimuli ($p < 0.05$). In contrast, the high-dose Kanamycin alone and the high-dose Kanamycin + noise groups exhibited similar thresholds. They demonstrated significantly higher thresholds than the noise-only group ($p < 0.05$). Furthermore, no significant difference in the cochlear microphonic amplitude was found among the study groups.

Conclusion: Kanamycin at low doses is not inherently ototoxic; however, when combined with noise exposure, it produces a synergistic effect resulting in severe hearing loss. In this model of auditory damage, cochlear microphonic measurements are less informative than auditory brainstem response testing, providing a more reliable assessment of both peripheral and central auditory pathway function.

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Introduction

Aminoglycosides are broad-spectrum antibiotics used to treat gram-negative bacterial and mycobacterial infections, such as tuberculosis (1). Ototoxicity is one of the common side effects associated with the systemic use of aminoglycosides, yet its global prevalence remains inadequately documented (2). Aminoglycoside-induced ototoxicity is dose-dependent and manifests as cochleotoxicity and vestibulotoxicity. Cochleotoxicity, affecting the

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auditory system and leading to sensorineural hearing loss (SNHL), is more prevalent with certain aminoglycosides, such as Kanamycin and Amikacin. In contrast, vestibulotoxicity is more common with Streptomycin and Gentamicin (3). The main mechanism of cochleotoxicity has been only partially understood. These drugs have cationic and hydrophilic properties and accumulate in the endolymphatic space after crossing the blood–labyrinthine barrier. The entry of these drugs into hair cells occurs mainly through mechano-electrical transduction (MET) channels and membrane receptor-dependent endocytosis (4). Aminoglycosides, once inside the cytoplasm, attach to mitochondrial ribosomes and disrupt protein synthesis. This disruption leads to the excessive generation of reactive oxygen species (ROS). Elevated ROS levels contribute to oxidative stress and induce irreversible degeneration of hair cells, particularly the outer hair cells (OHCs)(3).

Kanamycin, like other aminoglycosides, can induce severe cochlear damage and significant hearing loss when administered at high doses (3). At lower doses, it is generally considered less hazardous; however, prolonged exposure to Kanamycin may lead to cochlear synaptopathy (5). Evidence indicates that low doses of Kanamycin, when administered in combination with loop diuretics such as Furosemide or Ethacrynic acid, can lead to severe cochlear hair cell damage and result in irreversible SNHL (6, 7). Animal studies have demonstrated that simultaneous administration of Kanamycin at a non-toxic dose, together with noise exposure, can produce SNHL, with the extent of injury showing a nonlinear relationship (8, 9). However, the combined administration of two ototoxic agents, such as noise and aminoglycosides, does not always result in potentiated auditory damage (9). It may provide relative protection of the auditory system, depending on factors such as animal model selection, age, genetic background, and the time interval between noise exposure and drug administration (4, 9, 10). The most common pattern of this synergistic effect is simultaneous exposure to noise and Kanamycin. In contrast, in the patterns with noise presented before or after drug administration, even at a non-damaging intensity level, the potentiated hearing damage is completely dependent on the time interval between the two interventions (4). The possible mechanism underlying this synergistic effect for auditory damage is the disruption of the redox balance within hair cells. Exposure to intense noise not only causes structural damage but also induces metabolic changes, such as elevated intracellular calcium levels and increased ROS production (4, 9). It may also facilitate drug entry into hair cells by increasing the open probability of MET channels in inner hair cells (IHCs) (11) and by upregulating P2X2 channel expression at the apical surface of OHCs (12). Aminoglycosides, once inside hair cells, enhance the production of free radicals, and as a result, the combination of these two conditions can lead to exacerbated hair cell death.

Based on this review, most animal studies have evaluated the synergistic effect of ototoxic agents on auditory function using changes in auditory brainstem response (ABR) thresholds (4, 13) and the amplitude of otoacoustic emissions (14). However, this research found no evidence reporting the measurement of the cochlear microphonic (CM) potential in the context of Kanamycin combined with noise exposure. Since the CM is an electrical response less affected by acoustic noise and middle ear pathologies (15), this study employed both ABR testing and CM recording to investigate and compare the effects of noise and Kanamycin on the auditory system.

Materials & Methods

Thirty-three healthy male albino guinea pigs weighing 250-350 g were used to establish the SNHL model. The animals were assigned to six experimental groups: A noise-only group (n = 4), two Kanamycin-only groups (n = 4 per dose), two Kanamycin-plus-noise groups (n = 7 per dose), and a control group (n = 7). The Kanamycin-only and Kanamycin-plus-noise groups received intraperitoneal injections of Kanamycin sulfate (Sigma-Aldrich, St. Louis, MO, USA) at either 300 mg/kg (low dose) or 500 mg/kg (high dose) daily for 12 days, followed immediately by exposure to an acoustic environment (10). No evidence of middle ear infection was observed in any of the animals examined by otoscopy. Two animals receiving a high dose of Kanamycin died during the study.

A continuous pure tone at 4 kHz, 120 dB SPL, was delivered for 5 hours per day over 7 consecutive days in an acoustic chamber (60 × 80 × 100 cm) constructed of glass and galvanized iron. Noise was generated using sound stimulus generator software (Benaphone Electronic Company, Iran) and delivered through a loudspeaker equipped with a power amplifier. The speaker was centrally positioned within the chamber, and each guinea pig was housed in an individual box with a grid ceiling, placed on a table directly beneath the speaker. Prior to exposure, sound intensity was calibrated using a sound level meter (SLM; B&K, model 2243, Denmark). The distance between the animals' heads and the speaker was approximately 10 cm, and throughout the noise exposure period, guinea pigs had unrestricted access to food and water (16).

ABR recording

ABR threshold was determined using a Bio-logic auditory evoked potentials device (GN Otometrics, Denmark). Subdermal needle electrodes were positioned at the vertex (non-inverting), below the right ear pinna (inverting), and below the left ear (ground). Electrode impedance was maintained below 5 kΩ at each site and below 2 kΩ between electrodes. Prior to ABR recording, animals were anesthetized via intraperitoneal injection with a mixture of Ketamine 10% (50 mg/kg; Alfasan, Netherlands) and Xylazine 2% (5 mg/kg; RooyanDarou, Iran). Body temperature was kept at approximately 37 ± 0.5°C using a heating pad. Acoustic stimuli included click (100 ms) and tone bursts at 4, 6, 8, 12, and 16 kHz, each with a duration of 2 ms (1-ms rise/fall). Stimuli were delivered via a loudspeaker positioned 5 cm from the right ear, at a repetition rate of 21.1 per second with alternating polarity. ABR waveforms were derived from the average of 1500 responses, each processed through a band-pass filter (100–1500 Hz) within a 10.6 ms time window. Stimuli were initially presented at 80 dB SPL to elicit ABR waveforms to determine the hearing threshold, particularly the second positive peak (wave III). The intensity was then reduced in 10 dB steps, followed by 5 dB steps near threshold, until wave III was no longer visible. The threshold was defined as the lowest intensity at which wave III remained observable, stable, and reproducible. Two key parameters were measured at 80, 70, 60, and 50 dB SPL for each stimulus to analyze ABR waves: The latencies of waves I and III and their amplitudes. The wave's amplitude was determined by measuring the voltage difference between the peak and the subsequent trough of each wave. Latency time was defined as the time interval between the onset of the auditory stimulus and the peak of waves I and III (17).

CM recording

The CM is a receptor potential that generates with hair cells. This potential was recorded using the same electrode arrangement as for ABR responses, with the Bio-logic auditory evoked potentials device (GN Otometrics, Denmark). In the same session, following ABR recording, CM responses were obtained using click and tone bursts at 4, 6, and 8 kHz, (1-ms rise/fall) presented at an intensity of 80 dB, with a stimulation rate of 7.1/s, 1000 sweeps, a band-pass filter of 100–1500 Hz, and a time window of 5.33 ms with 1 ms prestimulation period. To ensure the validity of the CM response and distinguish it from phase-locking artifacts, recordings were performed using condensation, rarefaction, and alternating polarity modes. The CM wave reversed with changes in polarity and was eliminated in the alternating polarity recording (18). To determine the amplitude, responses recorded during the condensation and rarefaction phases were subtracted to enhance CM activity and reduce the contribution of waves I and III. The amplitude was measured from the largest peak to the subsequent trough (19).

Histological examination

The animals were euthanized at the end of the experiment under deep anesthesia induced by Ketamine and Xylazine to assess tissue response. The right temporal bone was promptly excised, and the cochlea was exposed. A formalin solution 10% was infused into the perilymphatic space via the round and oval windows, followed by incubation in the same fixative for 24 hours. Subsequently, the cochlea was decalcified in 10% Ethylenediaminetetraacetic acid (EDTA) for four days at 4°C.

Following decalcification, the cochlear tissue was dehydrated through a graded ethanol series and cleared with Xylene. Paraffin embedding was then performed, and the tissue was sectioned at a thickness of 5 µm using a microtome. Sections were mounted on saline-coated slides. The mid-turn region of the cochlea (approximately 1.5 turns from the apex) was stained with Hematoxylin and Eosin (H&E) and prepared for microscopic analysis(16). Morphological changes were examined using a light microscope (LABOMED, USA).

Statistical analysis

Data were described using the mean ± standard deviation. Threshold shifts for each stimulus were calculated as the difference between the thresholds measured before and after the experiment. Data normality was assessed using the Shapiro–Wilk test, followed by one-way ANOVA analysis to compare these shifts across groups. The average amplitude and latency of waves I and III at four stimulus intensities (80, 70, 60, and 50 dB SPL) were calculated and analyzed using paired t-tests, under the assumption of paired measurements within each of the three groups without SNHL (K300 mg/kg alone, Noise-only, and Control groups). To compare the amplitude of the CM wave, repeated-measures ANOVA, one-way ANCOVA, and paired t-tests were performed, provided the assumptions were satisfied, and the data were approximately normally distributed. A P-value of less than 0.05 was considered statistically significant. All analyses were performed using SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA).

Results

Table 1 shows comparisons of auditory threshold shifts among the study groups for various stimuli. Significant differences were statistically observed between the groups of K500, K500+N, K300+N, and the groups of K300, Noise, and Control (all of P-values <0.05) using the Tukey test of pairwise comparisons. No statistically significant differences were found among the three groups: K500, K500+N, and K300+N. The K300, Control, and Noise groups exhibited similar threshold shifts across all stimuli. However, each of these groups showed statistically significant differences when compared with the K300+N group ($P < 0.05$; Figure 1-A). The auditory threshold shifts across all stimuli were comparable between the K500 and K500+N groups. Both groups exhibited significantly greater threshold shifts when compared with the Control and Noise groups ($P < 0.05$; Figure 1-B).

Table 1. Comparison of auditory threshold shifts among study groups

Group	Click	4 KHz	6 KHz	8 KHz	12 KHz	16 KHz
K300	10.00 (4.08)	3.75 (4.78)	5.00 (2.08)	10.00 (4.08)	3.75 (2.50)	5.00 (4.08)
K300+N	37.14 (13.18)	45.71(7.31)	49.28 (8.86)	37.14 (13.18)	45.00 (9.57)	50.71(10.96)
K500	47.50 (9.57)	48.75 (7.50)	48.75 (2.50)	47.50 (9.57)	38.75 (2.50)	46.25 (6.29)
K500+N	43.57 (8.99)	44.28 (11.70)	50.00 (11.18)	43.57 (8.99)	46.42 (5.56)	48.57 (3.77)
Noise	15.00 (10.80)	13.75 (9.46)	10.00 (7.07)	15.00 (10.80)	16.25 (4.78)	5.00 (4.08)
Control	5.71(6.07)	3.57 (3.77)	4.28 (3.25)	5.71(6.07)	2.85 (3.93)	3.57 (3.77)
P-value*	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

N: Noise, K: Kanamycin
*: Using one –way ANOVA

Table 2. Comparison of latency (ms) and amplitude (μV) of waves I and III in groups with threshold shifts less than 30 dB SPL.

Variable	Wave I amplitude			Wave III amplitude			Wave I latency			Wave III latency		
	Before	After	P-value*	Before	After	P-value*	Before	After	P-value*	Before	After	P-value*
						Click						
K300	4.71(0.14)	4.90(0.97)	0.79	5.81(0.64)	6.17(1.29)	0.67	1.57(0.03)	1.59(0.07)	0.57	2.75(0.05)	2.78(0.20)	0.88
Noise	2.14(1.33)	2.45(0.92)	0.47	4.58(1.33)	4.82(0.98)	0.37	1.61(0.13)	1.66(0.14)	0.08	2.55(0.16)	2.44(0.08)	0.23
Control	4.08(0.79)	3.88(0.79)	0.33	5.54(1.92)	5.72(1.74)	0.22	1.63(0.07)	1.61(0.07)	0.48	2.86(0.10)	2.88(0.12)	0.07
						4 KHz						
K300	2.06(0.62)	2.04(0.56)	0.70	2.22(0.16)	2.14(0.35)	0.66	2.06(0.07)	2.13(0.02)	0.11	3.22(0.11)	3.25(0.18)	0.69
Noise	1.10(0.15)	1.10(0.18)	0.86	1.63(0.55)	1.69(0.44)	0.58	2.19(0.05)	2.19(0.04)	0.98	3.55(0.29)	3.40(0.12)	0.45
Control	1.27(0.60)	1.33(0.54)	0.36	1.67(0.63)	1.74(0.63)	0.38	2.19(0.03)	2.14(0.02)	0.34	3.54(0.08)	3.56(0.05)	0.99
						6 KHz						
K300	2.17(1.01)	2.18(1.01)	0.28	2.23(1.00)	2.25(1.01)	0.64	1.98(1.02)	2.01(0.11)	0.25	3.09(0.12)	3.11(0.13)	0.13
Noise	1.66(0.61)	1.63(0.29)	0.86	3.18(1.03)	2.56(0.67)	0.67	2.09(0.01)	2.09(0.02)	1.00	3.24(0.18)	3.31(0.24)	0.33
Control	2.00(0.56)	2.04(0.61)	0.83	2.94(0.72)	3.06(0.65)	0.57	2.15(0.09)	2.11(0.04)	0.39	3.50(0.15)	3.49(0.15)	0.39
						8KHz						
K300	2.69(0.15)	2.27(0.28)	0.13	3.58(0.03)	3.35(1.40)	0.88	1.96(0.03)	2.03(0.10)	0.39	3.19(0.09)	3.37(0.25)	0.34
Noise	2.04(0.90)	2.45(0.60)	0.42	1.92(0.76)	2.06(0.15)	0.75	1.91(0.14)	1.90(0.15)	0.42	3.00(0.03)	2.86(0.23)	0.50
Control	2.11(0.45)	2.13(0.46)	0.78	2.88(1.22)	2.92(1.20)	0.69	2.07(0.08)	2.04(0.03)	0.33	3.52(0.18)	3.46(0.17)	0.17
						12KHz						
K300	2.89(0.11)	2.69(0.75)	0.48	5.25(1.34)	5.50(1.26)	0.54	1.50(0.15)	1.57(0.23)	0.09	2.75(0.31)	2.76(0.32)	0.17
Noise	3.20(0.48)	3.25(0.34)	0.66	5.20(0.96)	5.20(0.95)	0.90	1.74(0.11)	1.69(0.01)	0.45	3.24(0.12)	3.21(0.08)	0.17
Control	3.00(0.97)	2.85(0.78)	0.46	4.45(1.88)	4.33(1.78)	0.43	1.67(0.13)	1.63(0.08)	0.40	3.12(0.18)	3.10(0.16)	0.24
						16 KHz						
K300	3.25(0.13)	2.74(0.63)	0.36	4.50(0.27)	4.28(0.26)	0.37	1.54(0.09)	1.44(0.22)	0.32	2.88(0.11)	2.92(0.17)	0.43
Noise	2.99(0.60)	3.00(0.61)	0.72	4.47(0.52)	4.61(1.07)	0.67	1.54(0.09)	1.56(0.15)	0.74	2.75(0.10)	2.80(0.16)	0.32
Control	2.60(0.77)	2.65(0.76)	0.21	4.48(1.65)	4.49(1.58)	0.49	1.63(0.08)	1.59(0.08)	0.88	3.09(0.13)	3.08(0.10)	0.82

*: Using paired t test
N:Noise, K: Kanamycin

The SNHL model was identified in the K500, K500+N, and K300+N groups. The maximum threshold shift observed in the K300, Noise, and Control groups was approximately 30 dB SPL, whereas in the SNHL groups it ranged from 55 to 65 dB SPL. In the k300+N group, ABR analysis revealed an absence of wave III responses at low intensities (Figure 1-C). These findings align with histological evidence showing the destruction of the organ of Corti (Figure 1-D). In the K300 and Noise groups, the amplitude and latency of waves I and III did not differ significantly from those of the Control group (P-values for all stimuli > 0.05; Table 2).

In the CM assessment, the CM amplitude at 4 kHz was significantly greater than for other stimuli ($P < 0.05$). As the frequency increased, the CM amplitude decreased; thus, a statistically significant difference was observed in the repeated-measures analysis, and this trend was also observed after the intervention ($P < 0.05$ for both). No statistically significant difference was found in CM amplitude before and after Kanamycin treatment (P-values for all stimuli > 0.05; Figure 2-A & B). However, a reduction in CM amplitude was noted in the high-dose Kanamycin groups, although the response was not completely abolished (Figure 2-C & D). The CM amplitude after the intervention, controlling for baseline values, was compared among the study groups using ANCOVA. This analysis was not significant for any of the stimuli (Table 3).

Discussion

In the present study, the combination of low-dose Kanamycin and noise exposure produced a synergistic effect, leading to significant SNHL. In contrast, high-dose Kanamycin, with or without concurrent noise, caused substantial hearing loss, with no significant difference between the two conditions. The animals treated with either low-dose Kanamycin alone or noise exposure alone did not develop SNHL. Consistent with previous reports, the synergistic interaction between noise and Kanamycin was evident at low doses(4, 8, 9). At high doses of Kanamycin, a ceiling effect occurred, and noise had no potentiated effect on auditory damage.

Table 3. Comparison of cochlear microphonic (CM) amplitude after kanamycin treatment among study groups.

Group	Click	4 KHz	6 KHz	8 KHz
K300	0.77(0.45)	1.10 (0.88)	0.72 (0.25)	0.64 (0.30)
K300+N	0.65 (0.34)	1.00 (0.67)	0.67 (0.32)	0.42 (0.25)
K500	0.43 (0.14)	0.69 (0.01)	0.36 (0.18)	0.25 (0.17)
K500+N	0.48 (0.33)	0.70 (0.49)	0.46 (0.38)	0.35 (0.17)
Noise	0.47 (0.07)	0.62 (0.08)	0.51(0.11)	0.36 (0.16)
Control	0.58 (0.27)	0.84 (0.45)	0.60 (0.30)	0.46 (0.15)
P-value*	0.28	0.54	0.11	0.20

***:** Using one –way ANCOVA
K:kanamycin, N:Noise

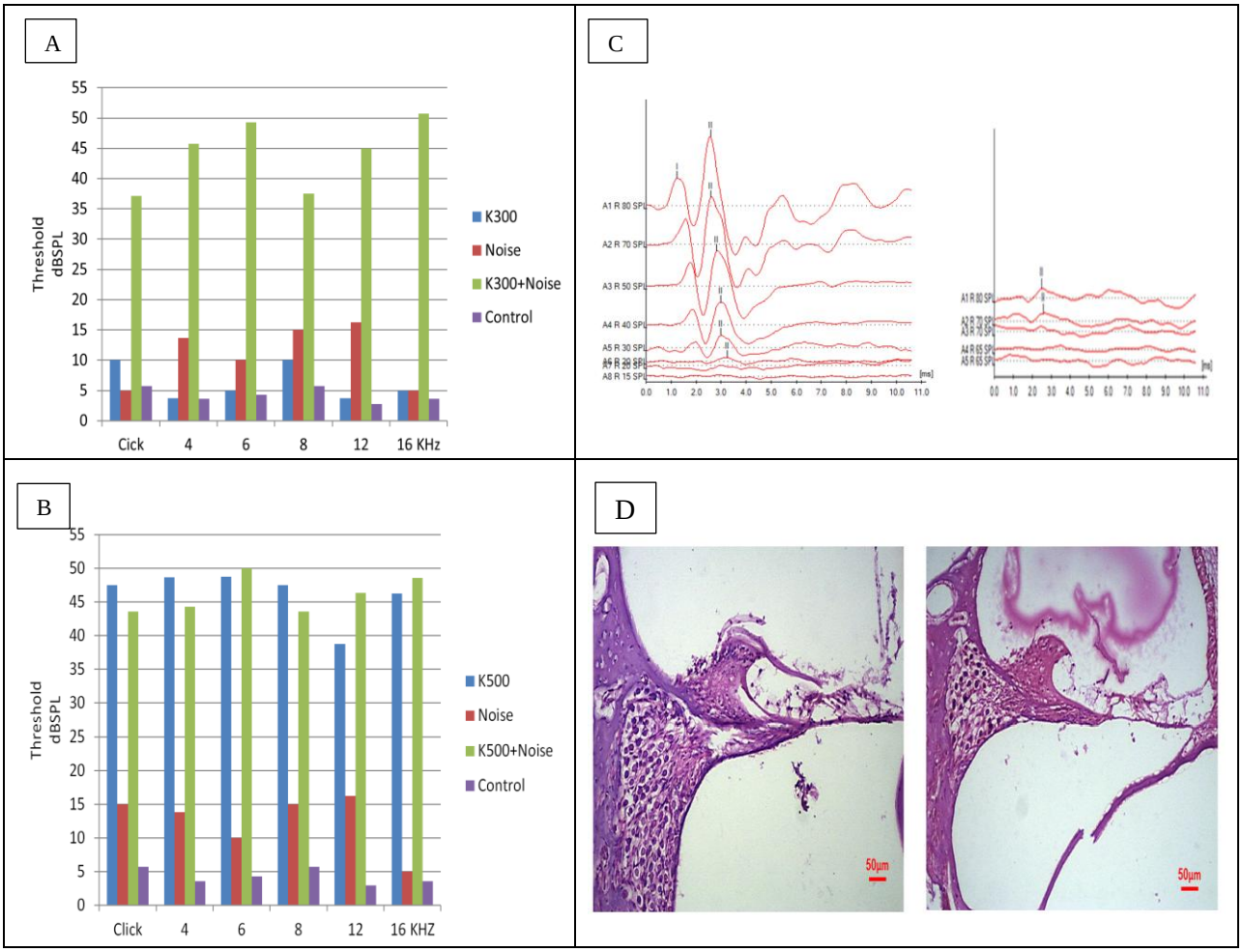

Figure 1. Auditory threshold based on acoustic stimuli among study groups. A: Threshold shift in low-dose kanamycin, B: Threshold shift in high-dose kanamycin, C: left; Click-ABR before hearing loss, right; Click-ABR after hearing loss, D: left; Healthy the organ of Corti, right; Damaged the organ of Corti.

Ototoxic aminoglycosides primarily affect the sensory epithelium of the cochlea, particularly the hair cells [3]. One of the earliest pathological changes involves alterations in ribbon synapses, which are typically detectable within the first week following drug administration. Low doses of these agents may induce cochlear synaptopathy [6]. An observed feature of synaptopathy is a reduction in wave I amplitude at suprathreshold intensities [21]. However, in this study, this finding was not present in the group that received low-dose Kanamycin alone.

One known mechanism of aminoglycoside-induced hearing loss is the accumulation of the drug within the mitochondria of hair cells, leading to the release of pro-apoptotic factors and oxidative enzymes into the cytoplasm, which ultimately results in cell death [22]. In addition to damaging the sensory epithelium, aminoglycosides, such as Kanamycin, may also affect other auditory structures, including spiral ganglion neurons and auditory efferent pathways [23].

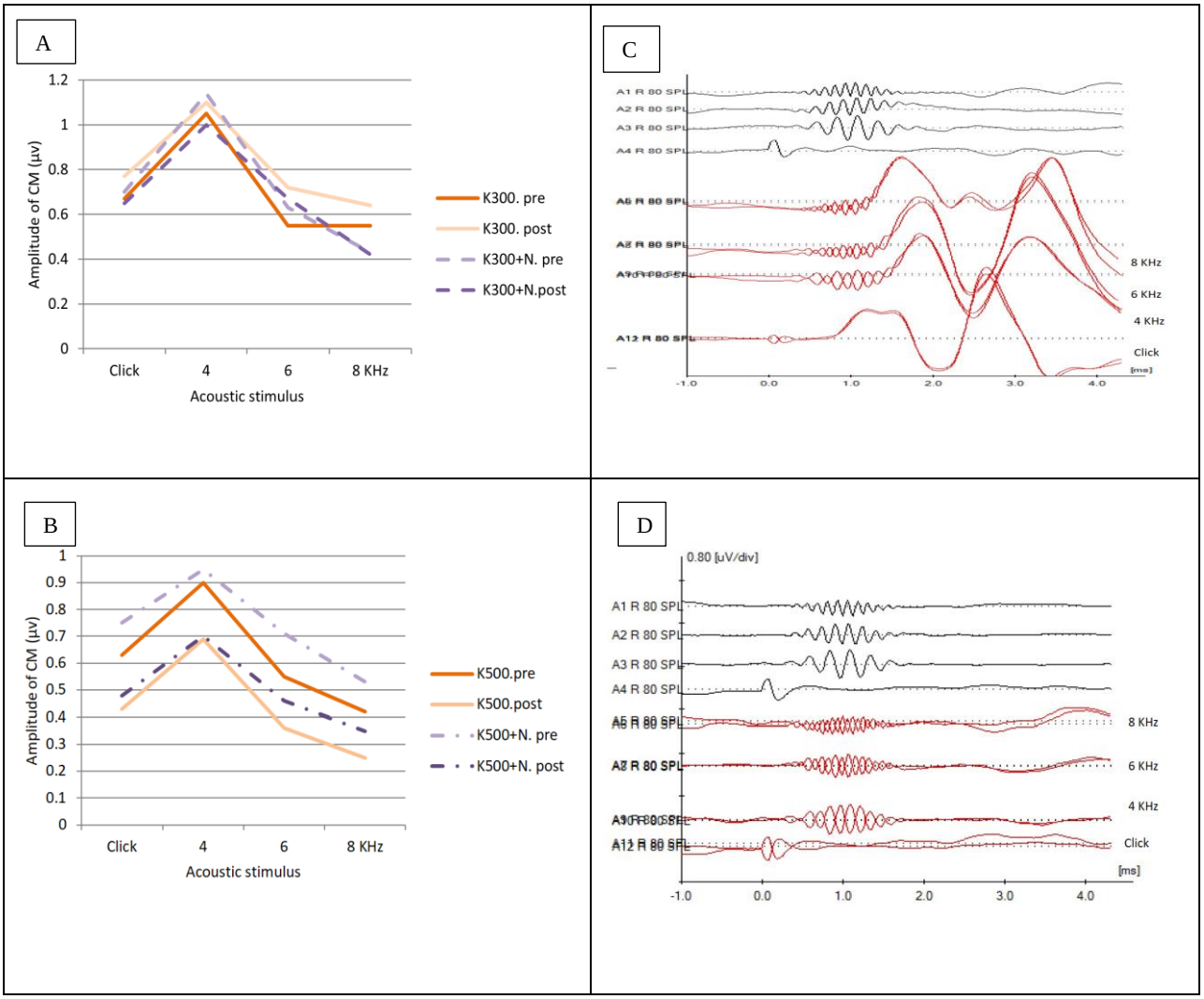

Figure 2. The amplitude of CM before and after kanamycin treatment.A: Comparison of CM amplitude in low-dose kanamycin, B: Comparison of CM amplitude in high-dose kanamycin, C: Recording of CM with acoustic stimuli before treatment, D: CM response after high dose of kanamycin treatment in click, 4, 6, 8 KHz.

The CM, as a receptor potential, reflects the displacement of the basilar membrane containing intact hair cells. Both IHCs and OHCs contribute to the generation of this potential, although OHCs play a greater role than IHCs (18). At low frequencies, CM amplitude is stronger because a broader region of the basilar membrane and a larger number of OHCs are involved in producing the response (23). In the current study, the recorded CM was a far-field response, which naturally has a smaller amplitude than near-field recordings. Consistent with scientific evidence (15), CM amplitude decreased with increasing stimulus

frequency, with the largest amplitude observed at 4 kHz. The overall pattern of CM amplitude changes was similar before and after Kanamycin and noise treatment, indicating that hair cell damage extended across the tested frequency ranges. In pathological conditions of the cochlea, CM amplitude decreases due to a significant loss of hair cells, particularly OHCs (24). Nevertheless, this study did not observe a statistically significant reduction in CM amplitude in the SNHL groups. In practical terms, CM amplitude after high-dose Kanamycin treatment showed a decreasing trend compared to baseline, consistent with the findings of Chen et al.(25). Moreover, this decline was more pronounced than in the other groups. The trend in CM amplitude changes in the low-dose Kanamycin group with noise (synergistic effect group) was similar to that in the groups without hearing loss, and there was no statistically significant difference. The small changes in CM amplitude, especially in the synergistic effect group, despite significant hearing loss, suggest two possible hypotheses:1. The damage was greater in the IHCs than in the OHCs, 2. The CM responses from the remaining hair cells were compensatorily enhanced by altered modulation of the medial olivocochlear (MOC) bundle. Given that OHCs are more sensitive to ototoxic agents such as Kanamycin than IHCs, they are expected to undergo severe damage, according to available scientific evidence (26). Therefore, the first hypothesis can be rejected.

One of the primary targets of aminoglycosides in the cochlea is the central auditory system. Studies have shown that these drugs act on the synaptic terminals of medial olivocochlear neurons, blocking acetylcholine transmission and thereby inhibiting the efferent auditory system (21, 27). This system naturally regulates OHC function by inhibiting it, reducing mechanical responses, and increasing electrical responses (3, 28). Pedemonte's study showed that in guinea pigs exposed to noise, CM amplitude was reduced, and when the efferent system was blocked with gentamicin, the noise presented had no effect on CM amplitude for the first 10 min (27). Based on these findings, it seems that the modulatory function of the efferent system on the remaining hair cells was altered, resulting in no significant reduction in CM amplitude following hearing damage, and perhaps was a compensatory enhancement. To prove the second hypothesis, animal studies could be conducted using selective inhibition of the efferent system to evaluate OHC function in generating electrical and mechanical responses in SNHL. Seemingly, this efferent system alters its effects on hair cell function in cochlear pathology. In this type of SNHL model, interpreting the CM as an electrical response of OHCs should be approached with caution, as the expected reduction in CM amplitude requires further investigation (4).

In many experimental studies, various doses of Kanamycin have been employed to establish models of hearing loss (29, 30). The present study introduced an animal model of auditory damage in which low-dose Kanamycin was combined with noise exposure to minimize the adverse effects associated with high-dose administration. The resulting ABR threshold shifts were like those observed with high-dose Kanamycin ototoxicity.

In Conclusion

Kanamycin alone, at low doses, does not induce ototoxicity. However, when combined with noise exposure, it produces a synergistic effect that results in severe hearing loss. In this model of auditory damage, ABR testing provides a reliable measure of functional impairment, whereas CM recordings are less informative in assessing the extent of injury. These findings emphasize the need for caution when administering aminoglycosides to pediatric patients in hospital or intensive care settings, particularly in environments with prolonged and intense noise exposure.

Acknowledgment

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Authors' Contributions

Mahbobeh Oroei and Mehdi Akbari contributed to the conception, design, and statistical analysis of the study. Mahbobeh Oroei, Mehdi Akbari, and Morteza Zarrabi were involved in data collection and drafting the manuscript. Mehdi Akbari and Morteza Zarrabi supervised the study. All authors contributed to the critical revision of the manuscript and approved its final version.

Conflict of Interest

The authors declare that they have no conflicts of interest related to this study.

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