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Comparative Vestibulotoxicity of Different Aminoglycosides in the Guinea Pigs

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The histopathological alterations in the vestibule due to aminoglycosides are well defined. Although there are reports comparing the vestibulotoxic effects of the many aminoglycosides, this is the first study to compare the effects of the most commonly used aminoglycosides i.e., streptomycin, gentamicin, amikacin and netilmicin administered both transtympanically and systemically. The transtympanic and systemic administration of each aminoglycoside caused similar histopathological alterations in the vestibule. The most severe degeneration in the cristae ampullaris, utriculus and sacculus was observed after streptomycine administration. The severity of the vestibular damage in terms of magnitude was in the order of streptomycine, gentamicin, amikacin, and netilmicin.

Key Words: Vestibulotoxicity, aminoglycosides, streptomycin, gentamicin, amikacin, netilmicin

INTRODUCTION

Ototoxicity refers to medication-caused auditory and/or vestibular system dysfunction that results in hearing loss or dysequilibrium. Although aminoglycosides are a group of antibiotics that cause ototoxicity, they are still frequently used because of their effectiveness and low cost.[1] Aminoglycosides have variable cochleotoxicity and vestibulotoxicity. Vestibular ototoxicity is defined as a chemical substance that has a destructive or damaging effect on the structure and function of the labyrinthine hair cells and their connections through the eighth nerve to the central nervous system. The damage can vary from being minimal to the complete loss of vestibular function.[1,2] It may present early with positional nystagmus. If severe, vestibular toxicity can lead to dysequilibrium and oscillopsia.

Histopathological alterations in the vestibule due to aminoglycosides are well known but there are a few studies that have compared the toxic effects of more than two aminoglycosides administered both systemically and transtympanically. To the best of the authors'knowledge, this is the first experimental study to compare the most commonly used aminoglycosides, streptomycin, gentamicin, amikacin and netilmicin, when used transtympanically and systemically.

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MATERIALS AND METHODS

This study used 45 pigmented guinea pigs, weighing 267 - 430 g. The guinea pigs were divided into 10 groups. In the first 5 groups, drug administration was performed via the peritoneal route (systemic) for 7 consecutive days. Two mililitres of a saline solution, 125 mg/kg sterptomycin, 50 mg/kg gentamicin, 150 mg/kg amikacin and 37.5 mg/kg netilmicin were administered bid in Groups 1, 2, 3, 4, and 5 respectively. The chosen doses were 10 - 20 times higher than the recommended human dosage. In the second five groups, the aminoglycosides were administered at 0.25 ml/kg in a 4% saline solution (40 mg/ml) via the transtympanic route through the right external meatus for 7 consecutive days: saline for Group 6 (opposite ears of Group 7, 8, 9, 10), streptomycin for Group 7, gentamicin for Group 8, amikacin for Group 9 and netilmicin for Group 10. The guinea

pigs were anesthetized with the intraperitoneal 3 mg/kg diazepam and 100 mg/kg ketaminhydrochloride doses 72 hours after the last aminoglycoside dose. They were then injected with glutaraldehyde 3% via the intracardiac route and then decapitated. After the temporal bones were removed within 5 minutes after decapitation, fixed in buffered formaldehyde 10% and stored at 4℃ for 24 hours. The specimens were placed in a 10% etilen diamine tetra acetic acid (EDTA) solution and stored at 4℃ for 10 days to allow for decalcification. The cochleo- vestibuler systems of the guinea pigs were removed, dehydrated, embedded in paraphine and serially cut at a 5μm thickness. Ten histological sections were examined for each end organ. Hematoxylin and eosin staining for the optical microscopic examinations was performed.

Two independent pathologists who were blinded to which group the specimens originated from, examined the specimens. The hydropic and vacuolar degeneration as well as the loss of hair cells in the utriculus, sacculus and semicircular canals were noted. The mentioned parameters were scored as follows:

Absence of hydropic and vacuolar degeneration and a loss of hair cells: 0

Mild changes: 1

Moderate changes: 2

Severe changes: 3

Very severe changes: 4

In this scoring system, the cell counts in different ten high power fields were recorded, a 0-24% decrease compared to controls was scored as 1, 25-49% as 2, 50-74% as 3, more than 74 as 4.

The Mann-Whitney U test was used to evaluate the data.

RESULTS

No histopathological alterations were found in the control groups (Group 1 and 6) (Fig. 1A). In the systemic streptomycin group (Group 2), moderate to severe degenerative alterations were observed in the epithelium of the crista ampullaris, utriculus and sacculus. Pathological alterations in the epithelium of the crista ampullaris due to transtympanic streptomycine were shown in Fig. 1B. Similar findings were also noted in the systemic streptomycin group (Group 7) ($p>0.05$). In group 3 (systemic gentamicin group) and group 8 (topical gentamicin group) milder degenerative alterations were observed when compared to the streptomycin groups ($p<0.05$). Fig. 1C, 1D, and 1E show the histopathological alterations in the crista ampullaris due to systemic gentamicine, systemic amikacin and transtympanic netilmicin, respectively. The degenerative alterations due to the systemic administration of gentamicin, amikacin and netilmicin were milder than that of the systemic streptomycine group ($p<0.05$). This study found that the histological damage scores of the guinea pigs administered transtympanic aminoglycosides were similar to those of the systemically administered ones ($p>0.05$). The comparative mean scores of the degenerative alterations and statistical evaluations of these scores are shown in Fig. 2 and Table 1, respectively. No middle ear inflammation were observed in the transtympanic injection animals. No damage score higher than 3 was detected in any of the guinea pigs.

Table 1. Statistical Evaluation of the Histological Damage Scores of Different Groups

Compared groups (Systemic administration)					
Streptomycin Gentamicin	Streptomycin Amikacin	Streptomycin Netilmicin	Gentamicin Amikacin	Gentamicin Netilmicin	Amikacin Netilmicin
$p<0.05$	$p<0.05$	$p<0.05$	$p<0.05$	$p<0.05$	$p>0.05$
Compared groups (Transtympanic administration)					
Streptomycin Gentamicin	Streptomycin Amikacin	Streptomycin Netilmicin	Gentamicin Amikacin	Gentamicin Netilmicin	Amikacin Netilmicin
$p<0.05$	$p<0.05$	$p<0.05$	$p<0.05$	$p<0.05$	$p>0.05$

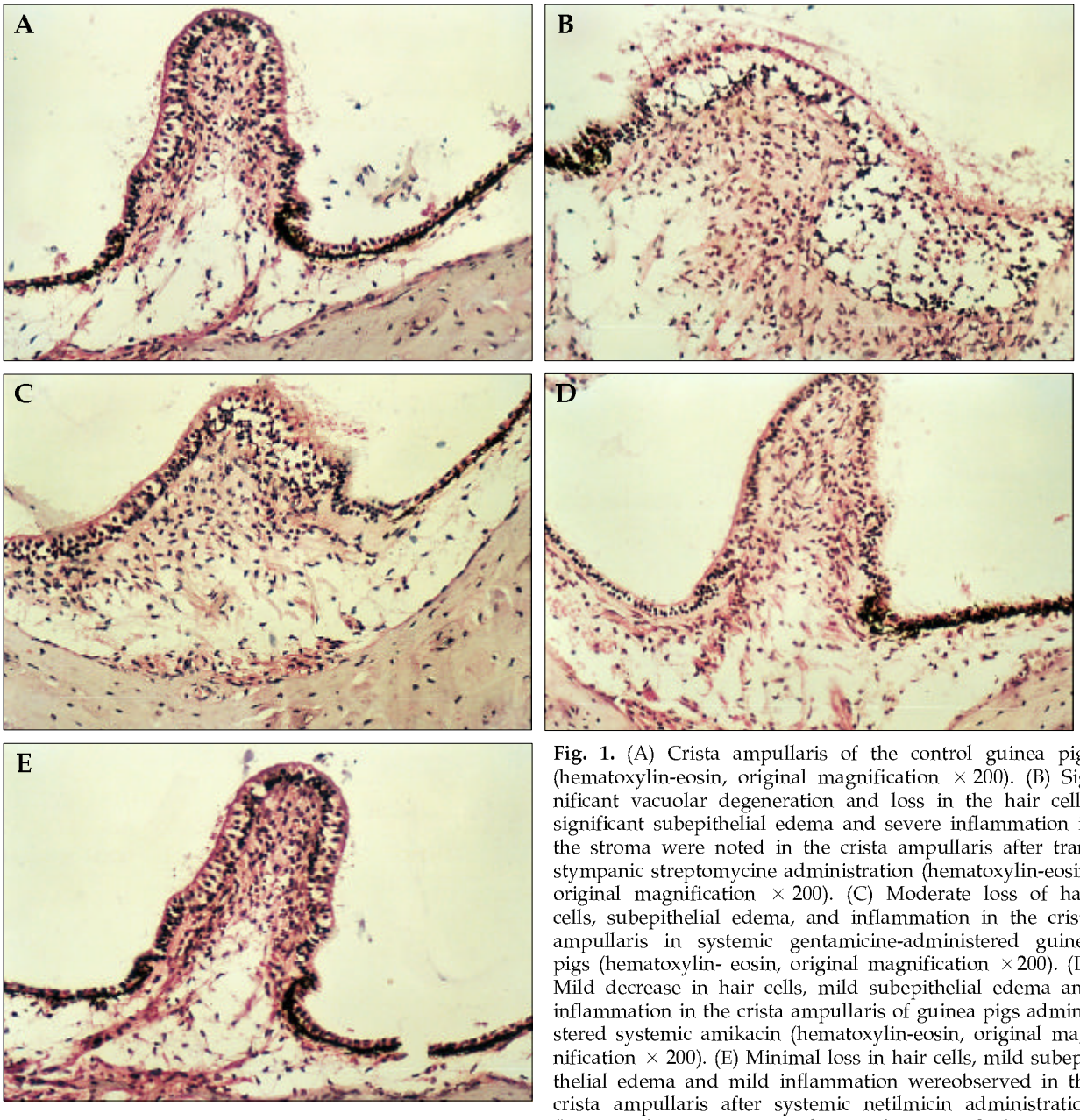

Fig. 1. (A) Crista ampullaris of the control guinea pigs (hematoxylin-eosin, original magnification × 200). (B) Significant vacuolar degeneration and loss in the hair cells, significant subepithelial edema and severe inflammation in the stroma were noted in the crista ampullaris after transtympanic streptomycine administration (hematoxylin-eosin, original magnification × 200). (C) Moderate loss of hair cells, subepithelial edema, and inflammation in the crista ampullaris in systemic gentamicine-administered guinea pigs (hematoxylin- eosin, original magnification ×200). (D) Mild decrease in hair cells, mild subepithelial edema and inflammation in the crista ampullaris of guinea pigs administered systemic amikacin (hematoxylin-eosin, original magnification × 200). (E) Minimal loss in hair cells, mild subepithelial edema and mild inflammation wereobserved in the crista ampullaris after systemic netilmicin administration (hematoxylin- eosin, original magnification ×200).

DISCUSSION

Aminoglycoside antibiotics are the first ototoxic agents to highlight the problem of drug-induced hearing and vestibular loss. However, the problem is significant as they are still widely used to treat serious gram-negative infections. Among them, streptomycin and gentamicin are primarily vestibulotoxic, whereas amikacin, neomycin, dihydrostreptomycin, and kanamycin are primarily cochleotoxic. Less is known regarding the netilmicin ototoxicity but its ototoxic potential appears to be low.

With vestibular toxicity, the initial and most extensive hair cell damage occurs in the apex of the cristae and the striolar regions of the maculae.

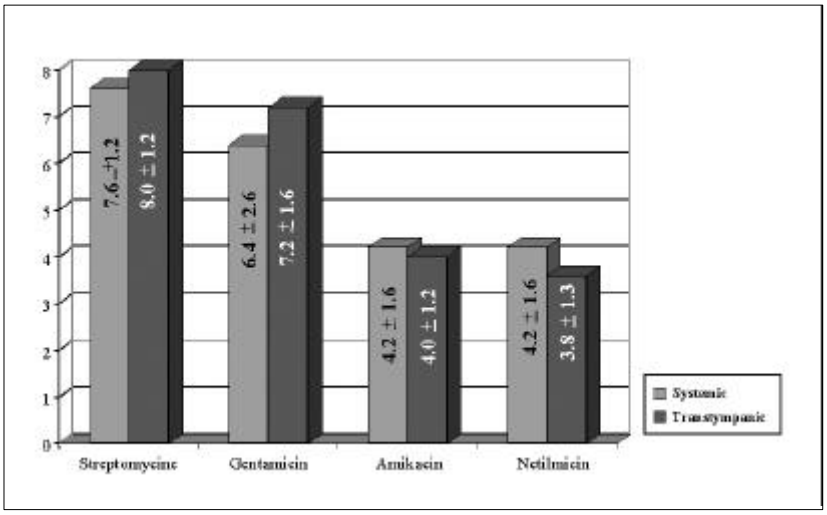

Fig. 2. Mean of the sum of histological scores and the standard deviations of each utriculus, sacculus and semicircular canals of the guinea pigs given different aminoglycosides via systemic or transtympanic route.

There may be hair cell loss extending toward the periphery of the vestibular receptor, and additional damage to the otoconial membrane and the otolith structures themselves.[1,3,4]

Although there are many individual and comparative studies on the vestibultoxicity of several aminoglycosides, there are no studies comparing the vestibulotoxicity of the commonly used aminoglycosides, gentamicin, amikacin, netilmicin and streptomycin, which is administered either systemically or topically.

It is known that streptomycin preferentially affects the vestibular system rather than the auditory system. Although its use has been limited in the past due to its toxicity, its use has climbed again with the emergence of tuberculosis. Some studies reported that systemic streptomycin administration caused dose dependent necrosis in the vestibular hair cells particularly in the epithelium of the cristae ampullaris.[5,6] This study found that streptomycin is the most vestibulotoxic aminoglycoside particularly when used topically. This finding was similar to that reported by Kimura, et al.[7] However, they found that the topical use streptomycin had a slight effect on the sacculus, which contrasts with our study that found the least histological alterations in the utriculus. While the systemic administration caused a slight degeneration in the sacculus in their study, this study observed moderate to severe degeneration in utriculus, sacculus and cristae ampullaris. In this study, the cristae ampullaris was the most affected region in both the systemic and topical administration as demonstrated by Lindeman.[8] Moderate to severe degeneration was reported in experimental studies using transtympanic streptomycine in guinea pigs.[9] Wanamaker, et al.[10] reported that the vestibulotoxicity of streptomycin was similar to that of gentamicin. This study particularly emphasized the effect of streptomycin on vestibule since streptomycin is one of the therapeutic agents for Meniere disease and there is little experimental data that directly demonstrates the vestibular ototoxicity resulting from its topical use available. The main recognized ototoxic effect of gentamicin is on the vestibular system and consists of a degeneration in vestibular sensory cells with the resultant loss of function.[11,12] Kitasato, et al.[13] found mild to moderate degeneration in the cristae ampullaris and moderate to severe degeneration in the utriculus of gentamicin-treated guinea pigs. Aran, et al.[12] reported that a large proportion of hair cells missing both in ampulla and in the utricule and the sacculus appeared to be slightly affected. In this study, the cristae ampullaris, utriculus and the sacculus were equally affected. Experimental studies on transtympanic gentamicin administration in different animals demonstrated some degeneration in the vestibule.[11,14-17]

Amikacin is a derivative of kanamycin and has very little vestibular toxicity. Its adverse effects primarily involve the auditory system. However, it is considered less ototoxic than gentamicin.

Mild to moderate degeneration was observed in the vestibular system in the amikacin group and the vestibulotoxic effects of netilmicin and amikacin were similar. Wersall[18] reported no degeneration in the systemic netilmicin group but significant degeneration was noted in the amikacin group. We could not find any study comparing vestibulotoxic effects of the topical administration of netilmicin and amikacin.

Comparative studies showed that netilmicin appears to be the safest among the aminoglycosides, with the lowest incidence ototoxicity. In a comparative study investigating netilmicin and gentamicin, netilmicin caused less degenerative alterations in the vestibule than gentamicin.[19] Kitasato, et al.[13] found mild degeneration in the cristae ampullaris and utriculus with 150 mg/kg netimicin. Unlike this finding, this study found mild to moderate degeneration in the cristae ampullaris, utriculus and sacculus with 75 mg/kg netilmicin.

While the ototoxicity from intravenous aminoglycoside administration is well documented, there is considerable controversy regarding the existence and significance of ototoxicity from the topical preparations. Human studies are presently lacking, but it is likely that the aminoglycoside ear drops used in this situation can cause vestibular damage even more frequently. This study found that the pathological alterations after transtympanic administrations were similar to those of systemic administrations ($p > 0.05$), which was also reported by Igarashi, et al.[20]

In conclusion, the severity of vestibular damage was in the order of streptomycine, gentamicin, amikacin, and netilmicin. Consequently, while netilmicin and amikacin can be the treatment of choice for systemic infections due to their low vestibulotoxicitiy, significant vestibulotoxicity can be achieved in Menier's disease with transtympanic streptomycine and gentamicin.

REFERENCES

1. Roland JT Jr, Cohen NL. Vestibular and auditory ototoxicity. In: Cummings CW, Frederickson JM, Harker LA, Krause CJ, Schuller DE, Richardson MA, editors. Otolaryngology&Head and Neck Surgery. 3rd ed. St. Louis: Mosby; 1998. p.3186-97.
2. Lerner SA, Schmitt BA, Seligsoh R, Matz GJ. Comparative study of ototoxicity and nephrotoxicity in patients randomly assigned to treatment with amikacin or gentamicin. Am J Med 1986;80:98-104.
3. Baloh RW, Honrubia V, Yee RD, Hess K. Changes in the vestibulo-ocular reflex after loss of peripheral sensitivity. Ann Neurol 1984;16:222-8.
4. Black FO, Peterka RJ, Elardo SE. Vestibular reflex changes following aminoglycoside induced ototoxicity. Laryngoscope 1987;97:582-6.
5. Nakagawa T, Yamane H, Takayama M, Sunami K, Nakai Y. Dose-dependent response of vestibular hair cells of guinea pigs following streptomycin ototoxiation. Acta Otolaryngol 1998;118:530-3.
6. Tsuji K, Velazquez-Villasenor L, Rauch SD, Glynn RJ, Wall C 3rd, Merchant SN. Temporal bone studies of the human peripheral vestibular system. Aminoglycoside ototoxicity. Ann Otol Rhinol Laryngol 2000;181 Suppl: 20-5.
7. Kimura RS, Lee KS, Nye CL, Trehey JA. Effects of systemic and lateral semisircular canal administration of aminoglycosides on normal and hydropic inner ears. Acta Otolaryngol (Stockh) 1991;111:1021-30.
8. Lindeman HH. Regional differences in sensitivity of the vestibular sensory epithelia to ototoxic antibiotics. Acta Otolaryngol 1969;67:177-89.
9. Proctor LR, el-Kashef Y. The use of streptomycin to induce unilateral ablation of vestibular function in the rat: a preliminary report. Am J Otolaryngol 1989;10: 188-97.
10. Wanamaker HH, Slepecky NB, Cefaratti LK, Ogata Y. Comparison of vestibular and cochlear ototoxicity from transtympanic streptomycin administration. Am J Otol 1999;20:457-64.
11. Marais J, Rutka JA. Ototoxicity and topical eardrops. Clin Otolaryngol 1998;23:360-7.
12. Aran JM, Erre JP, Guilhaume A, Aurousseau C. The comparative ototoxicities of gentamicin, tobramycin and dibekacin in the guinea pig. Acta Otolaryngologica 1982;390 Suppl:1-30.
13. Kitasato I, Yokota M, Inouye S, Igarashi M. Comparative ototoxicity of ribostamycin, dactimicin, dibekacin, kanamycin, amikacin, tobramycin, gentamicin, sisomicin and netilmicin in the inner ear of guinea pigs. Chemotherapy 1990;36:155-68.
14. Wanamaker HH, Gruenwald L, Damm KJ, Ogata Y, Slepecky N. Dose-related vestibular and cochlear effects of transtympanic gentamicin. Am J Otol 1998;19:170-9.
15. Norris CH, Amadee RG, Risey JA, Shea JJ. Selective chemical vestibulectomy. Am J Otol 1990;11:395-400.
16. Bareggi R, Grill V, Narducci P, Zweyer M, Tesei L, Russolo M. Gentamicin ototoxicity: histological and ultrastructural alterations after transtympanic administration. Pharmacol Res 1990;22:635-44.
17. Chen JM, Kakigi A, Hirakawa H, Mount RJ, Harrison RV. Middle ear instillation of gentamicin and streptomycin in chinchillas: morphologic appraisal of selective ototoxicity. J Otolaryngol 1999;28:121-8.

18. Wersall J. The ototoxic potential of netilmicin compared with amikacin. An animal study in guinea pigs. Scand J Infect Dis 1980;23 Suppl:104-13.
19. Anniko M. Aspects on the ototoxic potential of netilmicin. Acta Otolaryngol (Stockh) 1983;96:75-89.
20. Igarashi M. Vestibular ototoxicity in primates. Audiology 1973;12:337-49.