Effect of Parenteral Aminoglycoside Administration on Dark Cells in the Crista Ampullaris

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Objective: To observe the early and late effects of the parenteral administration of aminoglycosides on the dark cells of ampullae in the inner ear.

Study Design: Comparative study of the histopathologic characteristic of human temporal bones.

Subjects and Methods: Sixty-three temporal bones from 44 subjects (age range, 16-81 years) were examined by light microscopy. Three groups of temporal bones were selected for this study: group 1, 30 “normal” temporal bones from 22 subjects (mean age, 59 years; age range, 25-81 years) with no history or histopathologic findings of otologic disease or ototoxic drug use; group 2, 14 temporal bones from patients who received aminoglycoside treatment within 2 weeks before death; and group 3, 19 temporal bones from patients who received aminoglycoside treatment between 2 weeks and 6 months before death.

Results: The mean ± SD number of dark cells in group 1 was 15.0 ± 2.47; in group 2, it was 17.3 ± 1.93 in the subjects who received gentamicin sulfate and 15.0 ± 3.08 in those who received kanamycin sulfate and tobramycin; in group 3, it was 14.6 ± 1.67 in the subjects who received gentamicin and 15.2 ± 2.31 in those who received kanamycin and tobramycin. The overall difference between the 3 groups was not statistically significant (P = .07). The cytologic characteristics of dark cells were similar in all 3 groups. The number of dark cells showed a decline with increasing age in group 1.

Conclusions: The result of this study suggests that the treatment period was probably too short to destroy the dark cells. Therefore, long-term aminoglycoside therapy may be necessary to get a more permanent result.

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THE VESTIBULAR effects of aminoglycosides are well known. These antibiotics have been used parenterally or topically to treat patients with Ménière disease. Clinical studies have shown that aminoglycoside therapy can eliminate vertigo attacks in patients with Ménière disease. This treatment method is based on postulated effects on the dark cells of the vestibular labyrinth. Animal experiments have demonstrated that aminoglycosides can cause damage to dark cells and vestibular hair cells. A few human temporal bone studies have investigated the vestibular effects of aminoglycosides, however, to our knowledge, the effects of these drugs on dark cells have not been investigated in human temporal bones. The purpose of this study was to observe the early and late effects of the use of parenteral gentamicin sulfate or other aminoglycosides (kanamycin sulfate or tobramycin) on dark cells of the ampulla in the inner ear.

METHODS

A total of 63 temporal bones from 44 subjects who ranged in age from 16 to 81 years were included in this study. The temporal bones were obtained from the collection at the University of Minnesota, Minneapolis.

Three groups of temporal bones were selected for this study: group 1 comprised 30 “normal” temporal bones from 22 subjects (mean age, 59 years; age range, 25-81 years) with no history or histopathologic findings of otologic disease or ototoxic drug use; group 2 comprised 14 temporal bones from patients who had received aminoglycoside treatment within 2 weeks before death; and group 3 comprised 19 temporal bones from patients who had received aminoglycoside treatment from 2 weeks to 6 months before death. The temporal bones from groups 2 and 3 were subdivided into groups according to the ototoxic effects of aminoglycoside therapy (vestibulotoxic and cochleotoxic): 9 temporal bones were from 6 subjects (mean age, 27 years; age range, 17-68 years) in group 2 and 12 temporal bones were from 8 subjects in group 3 who had received parenteral gentamicin treatment in therapeu-
In some ears, the dark cells had swollen cytoplasm and characteristics of dark cells were similar in all 3 groups. This was not statistically significant (15.2±2.31 in those who had received kanamycin and tobramycin; and in group 3, it was 15.0±3.08 in those who had received gentamicin and 14.6±1.67 in those who had received kanamycin and tobramycin; and in group 2, it was 17.3±1.93 in the subjects who had received gentamicin). The mean±SD number of dark cells in group 1 was 15.0±2.47; in group 2 and 7 temporal bones were from 4 subjects in group 3 who had received parenteral injections of kanamycin (500 mg 2 or 3 times per day) or tobramycin (80 mg 2 or 3 times per day) in therapeutic doses for at least 10 days. In the groups 2 and 3, the temporal bones were excluded if the patients had other otologic disease or histopathologic findings of otologic disease or a history of other ototoxic drug use. All temporal bones were examined by light microscopy, and their findings were compared.

All temporal bones had been removed from the subjects at autopsy less than 24 hours after death and fixed in formalin solution. Each bone was decalcified, embedded in celloidin, and serially sectioned in the horizontal plane at a thickness of 20 µm. Every 10th section was stained with hematoxylin-eosin and mounted on a glass slide for light microscopy assessment. Histologic sections in which the crista of any semicircular canal was cut close to perpendicular to its axis were selected for study. The dark cells can be distinguished from the other cells by the position of their nuclei high and close to the endolymphatic space and by the melanin particles seen in the connective tissue just underneath them. All dark cells within 100 µm of the space and by the melanin particles in the connective tissue just beneath them.

For statistical analysis, 1-way analysis of variance was used to compare the numbers counted in the 3 groups. Linear regression analysis was performed to evaluate the effects of age on the number of dark cells in normal temporal bones.

RESULTS

In the lateral or posterior semicircular canal, the crista was cut perpendicular to its axis (Figure 1). The mean±5D number of dark cells in group 1 was 15.0±2.47; in group 2, it was 17.3±1.93 in the subjects who had received gentamicin and 15.0±3.08 in those who had received kanamycin and tobramycin; and in group 3, it was 14.6±1.67 in those who had received gentamicin and 15.2±2.31 in those who had received kanamycin and tobramycin. The overall difference between the 3 groups was not statistically significant (P=.07). The cytologic characteristics of dark cells were similar in all 3 groups. In some ears, the dark cells had swollen cytoplasm and nuclei, but these changes were not significant between groups. The number of dark cells showed a decline with increasing age in the normal control group (Figure 2).

COMMENT

It has been reported that the structure and distribution of dark cells are the same in all 3 semicircular canals. Horizontal sections of the crista of the semicircular canal are cut tangential to its surface so that the cytoarchitecture of the dark cells in the crista is quite difficult to evaluate. For this reason, in our study we evaluated the dark cells in the crista of the lateral or posterior semicircular canals (depending on which crista was sectioned more closely perpendicular to its axis).

Dark cells show several enzyme activities and are involved in the regulation of endolymph. Aminoglycosides have been successfully used for the treatment of Ménière disease. Parenteral or topical use of gentamicin or other aminoglycosides has also been advocated as a treatment option in Ménière disease. Animal experiments have demonstrated damage to the vestibular dark cells from the ototoxic effects of aminoglycosides. Streptomycin damaged the dark cells before affecting other cells. It has been suggested that the primary injury was to the secretory tissues and that the loss of vestibular hair cells was due to the disturbance of the microhomeostasis of the vestibular system. Other observations have established that streptomycin primarily affects the vestibular sensory cells. The use of lower dosages and fewer injections of streptomycin to control vertigo attacks has been advocated, especially in patients with bilateral disease. However, after a 5- or 15-day period of parenteral gentamicin treatment, dark cells still possessed ion-fluid regulation of the endolymph and Na+, K+, adenosine triphosphatase activity was retained on the basolateral folded plasma membranes of the cells. Yoshihara et al also suggested that melanin possesses a protective function against ototoxic drugs in the inner ear. Konishi and Mori have indicated that the Na+,...
K+ concentrations of the endolymph were not altered in kanamycin-treated animals. In our study, we evaluated the toxic effects of gentamicin and other aminoglycosides on the dark cells of the vestibule in a very select group of patients. We observed that the number and appearance of dark cells were similar in normal temporal bones and in temporal bones from patients with clinical histories of aminoglycoside use.

Ototoxic drugs have been used to treat Ménière disease for many years. Although the mechanisms of the drugs are not clear, vestibular hair cell damage can play the primary role in the treatment of the disease. We are aware that the number of the patients is small. This study was limited as to the dosage, frequency, and duration of aminoglycoside therapy, because the material of the study was archival human temporal bones. Therefore, it is likely that the treatment period may have been too short to destroy the dark cells. The therapeutic dosage and frequency should be taken into further consideration. To conclude, the long-term administration of these drugs at high dosages and frequencies may be necessary to obtain a permanent result.

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REFERENCES