

Can aspirin protect or at least attenuate gentamicin ototoxicity in humans?

To the Editor

We read the article by Behnoud et al¹ with great interest and concentration, and appreciate the work of these researchers from our brotherly country Iran. After going through the article, we would like to make the following comments.

First, the authors did not mention the exact time period of their study, only writing between 2007 and 2008. Second, the authors did not indicate the upper age limit of their patients, which is very important here, as after 65 years presbycusis occurs, but it can occur at a very early age due to hereditary predisposition,² which itself can give the false interpretation of pure tone audiometry (PTA). Also, advancing age is positively related to decreased renal function. As aminoglycoside clearance is directly proportional to the creatinine clearance, it is necessary to carry out a renal function test before instituting gentamicin therapy to avoid toxicity, and for patients between 40-60 years, the Cockcroft-Gault formula would give better prediction values.^{3,4} Third, they stated the trial was double blind, however, they did not include a statement to indicate that the drugs being used were not known by both the researchers and the patients, so their study would be better classified as a single blind rather than double blind. Fourth, the authors did not include the sociodemographic characteristics in the results or in table format, to indicate the total number of patients from each gender. Fifth, the authors carried out 2 tests before patients received therapy, however, they did not include the speech discrimination scores in the results. Sixth, the incidence of ototoxicity is partly genetically determined, having been linked to point mutations in mitochondrial DNA or a mitochondrial 12S rRNA A827G mutation, and occurs in 1-5% of the population receiving gentamicin for more than 5 days.^{3,5} Also gentamicin, streptomycin, and tobramycin are primarily vestibulotoxic. They selectively destroy type 1 hair cells of cristae ampullaris but, administered in large doses, can also damage the cochlea.² As the sample size was only 60 patients, and considering varied pharmacogenetics among individuals, it would be impossible to apply these results to the general population, and large multicenter trials should be carried out before these results could be applied to a larger population. Seventh, aspirin can synergistically enhance gentamicin toxicity. Aspirin itself is a hair cell toxin particularly affecting higher frequencies.² It also reduces prostaglandins in the kidneys, which may decrease renal blood flow to the

kidneys,⁶ and as gentamicin is excreted by glomerular filtration through the kidneys, aspirin can indirectly enhance gentamicin levels and precipitate toxicity. In addition, gentamicin causes nephrotoxicity in 5-25% of patients,³ and as the authors have also included a cephalosporin in their treatment regimen, which itself is nephrotoxic,⁷ a triple nephrotoxic regimen is not a prudent act. Considering the additional toxicities of aspirin and the availability of other antibiotics with wide therapeutic windows, we recommend that gentamicin should be reserved for serious conditions only. Lastly, the type of infection encountered in the study was not included, and the results may give the impression of researcher bias. We look forward to the positive response of our senior colleagues.

Muhammad Naeem, Nasir A. Rahimnajiad
Dow University of Health Sciences
Karachi
Pakistan

Reply from the Author

We would like to thank our colleagues for their interest in our article, and clarify the points raised.

First, it is not important to specify the days or months for this study, as our patients were admitted throughout the year and the study took the entire year. Second, the lower limit of patients' ages, which is important when using these drugs, was mentioned in the methods section. We did not include the upper limit as none of our patients were over 60 years old. Additionally, the patients in the control group were similar with respect to gender and age. The differences in age and gender were not statistically significant between the 2 study groups. As the patients were randomly divided into 2 groups, we felt the effects of any difference in factors such as pharmacogenetics and sociodemographics were minimal. Third, the trial was double blind, as aspirin and placebo were given to all patients by a nurse, and both the researcher and the audiologist were unaware of the situation. Fourth, we agree with your comments regarding the absence of demographic characteristics in tabular format, however, we thought the number of tables would then be excessive, and none of the referees asked about these factors. Fifth, the aim of this study was to evaluate the hearing threshold after therapy; therefore, the PTA was sufficient for follow up. Sixth, at least 96 different agents have potential ototoxic side effects, among these, aminoglycosides are perhaps the most common offending agents. Risk factors for aminoglycoside-induced hearing loss have been established and include: presence of renal disease, longer duration therapy, increased serum levels, advanced age,

and concomitant administration of other ototoxic drugs, particularly the loop diuretics.⁸ Our patients did not have any of these conditions. Additionally, gentamicin is used often with other antibacterials (for example, the penicillins group), especially in systemic infections due to gram-negative organisms.⁹ Furthermore, aspirin-induced hearing loss is dose-dependent and reversible (toxic dose = 6-8 g/day), while our patients received aspirin 1.5 g/day. Finally, as you are aware, aspirin has very important antioxidant effects, and has been used as a therapeutic agent in different fields, including the prevention of gentamicin-induced hearing loss.^{10,11} We recently received communication from Professor Jochen Schacht from the University of Michigan indicating an interest in lowering the dose of aspirin required to attenuate aminoglycoside ototoxicity.

Fatholah Behnoud

*Department of Ear, Nose, and Throat
Medical School, Hamadan University of Medical Sciences
Hamadan
Iran*

References

1. Behnoud F, Davoudpur K, Goodarzi MT. Can aspirin protect or at least attenuate gentamicin ototoxicity in humans? *Saudi Med J* 2009; 30: 1165-1169.
2. Dhingra PL, editor. Hearing loss. In: Diseases of Ear, Nose and Throat. 4th ed. India: Elsevier; 2007. p. 30-40.
3. Chambers HF. Aminoglycosides and Spectinomycin. In: Katzung BG, editor. Basic and Clinical Pharmacology. 10th ed. Singapore: McGraw Hill; 2007. p. 755-770.
4. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16: 31-41.
5. Fischel-Ghodsian N. Genetic factors in aminoglycosides toxicity. *Pharmacogenomics* 2005; 6: 27-36. Review.
6. Dunn MJ, Scharschmidt L, Zambraski E. Mechanisms of the nephrotoxicity of non-steroidal anti-inflammatory drugs. *Arch Toxicol Suppl* 1984; 7: 328-337.
7. Chambers HF. Beta lactams and other cell wall and membrane-active antibiotics. In: Katzung BG, editor. Basic and Clinical Pharmacology. 10th ed. Singapore: McGraw Hill; 2007. p. 738.
8. Arts HA. Sensorineural Hearing Loss: evaluation and management in adults. In: Cummings CW, editor. Otolaryngology Head and Neck Surgery. 4th ed. Philadelphia (PA): Elsevier; 2005. p. 3540.
9. Sweetman SC. Martindale: The complete drug reference. 35th ed. London (UK): Pharmaceutical Press; 2007. p. 253.
10. Chen Y, Huang WG, Zha DJ, Qiu JH, Wang JL, Sha SH, et al. Aspirin attenuates gentamicin ototoxicity: from the laboratory to the clinic. *Hear Res* 2007; 226: 178-182.
11. Sha SH, Qiu JH, Schacht J. Aspirin to prevent gentamicin-induced hearing loss. *N Engl J Med* 2006; 354: 1856-1857.

Supplements

- * Supplements will be considered for work including proceedings of conferences or subject matter covering an important topic
- * Material can be in the form of original work or abstracts.
- * Material in supplements will be for the purpose of teaching rather than research.
- * The Guest Editor will ensure that the financial cost of production of the supplement is covered.
- * Supplements will be distributed with the regular issue of the journal but further copies can be ordered upon request.
- * Material will be made available on Saudi Medical Journal website