The Role of Aspirin as Otoprotective Agent in Patients Receiving Amikacin Therapy

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Abstract

Objective: To investigate and prove that aspirin protects, or at least attenuates amikacin ototoxicity in humans.

Method: This study was conducted in 60 patients that completed all
requirements .The patients were divided into two groups:

- Control group: receive placebo treatment.
- Drug–treated group: They receive aspirin coated tablets (1.5gm/ day), 500mg 8 hourly.

Both groups had similar aspects regarding the gender, age and weight. The duration of therapy was 7 days and dosage of amikacin was 1gm/day (500mg 12 hourly).

Results: Comparison of Audiometry test in Ear/Nose/Throat (E.N.T.) Department (Pure Tone Audiometry) at 1000 Hertz (Hz), 2000 Hz, 4000 Hz, and 8000 Hz showed significant differences between mean Audiometry at 250Hz was significantly different only at 8th and 15th day while at the frequency of 500Hz the difference was significant at the 15thday only.

Conclusion: In present study, we had shown that aspirin can protect the patients who are receiving amikacin therapy from it' s ototoxicity.

Key words: Aspirin , amikacin , Pure Tone Audiometry, and ototoxicity.

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Introduction

Aminoglycosides are used for treating gram–negative bacterial infections.[1, 2] These drugs may be the most commonly used antibiotics world wide, especially in developing countries.[3] Although these drugs are extremely efficacious, they can result in ototoxicity. [1, 2] The incidence of cochlear-ototoxicity has been reported [2] in up to 33% of patients, while the balance apparatus may be affected in approximately 15%.[1] The incidence of side effects may be higher in developing countries because the drug serum levels in patients are not routinely obtained for adjustment of dosing, to avoid levels that may be associated with a higher risk of ototoxicity. [1,3] The biochemical mechanisms leading to aminoglycosides ototoxicity are not fully understood,[4]but several evidences suggest that damage may result from the formation of reactive oxygen species that overwhelm the cellular antioxidant defense systems of the inner ear. [4, 5] The resulting cellular imbalance causes apoptotic or necrotic cell death. [6, 7]In fact, the use of amino glycosides leads to chromatin condensation, DNA fragmentation and consequently leads to cell death. [4]Several agents have been shown to reduce ototoxicity mostly focusing on antioxidant therapy, [8, 9, and 10] for example, aspirin, [1, 3, and 11] sodium thiosulfate, glutathione, [6, 12] and melatonin. [13] The aim of this study is to evaluate the effectiveness of aspirin coated tablet as an otoprotective agent against amikacin ototoxicity. Actually, it is well known that aspirin has several potential benefits in different fields of medicine. This drug is relatively safe, easily available and cheap.

Method:

Sixty patients above 18years old who were scheduled for treatment with amikacin and patients were excluded if they had a preexisting hearing loss or systemic disease and if they were pregnant. The patients were divided into 2 groups, the experimental and the control group that were similar with respect to gender, [3] age and weight .The treatment group received 1.5gm/day (500mg 8 hourly) aspirin and the control group received placebo treatment similar to the other group. The duration of therapy was 7 days and the dosage of amikacin was 1gm/day (500mg 12 hourly).At the beginning of the study, the hearing threshold of all patients was determined by audiometry, then they retested 8 and 15 days later. All patients were examined for any hearing defect including middle ear damage, and if there was a problem that case would be excluded. Selection of all patients for the 2 groups was based on what part of body had been infected, (e.g. orthopedic, head and neck infection or burn). All patients in 2 groups received a second drug (keflin 1 gm 6 hourly, a second generation of cephalosporin). Initially, a complete clinical examination and then audiometry was performed for all cases and controls. Statistical analysis: paired t-test was used to compare differences in means for continuous variables. A $p < 0.05$ was used as a significant level.

Results:

The mean results for E.N.T study (hearing defect) in the 2 patients groups were comparable at the beginning of the study except in 2, 4, and 8 kilohertz (kHz) frequencies that the threshold of audiometry in aspirin

was a little higher than the placebo group. The event was random, and no selection had been carried out. At different periods of time (the beginning, 8th and 15th day) in the placebo group, audiometry test was measured on different frequencies (figure.1).

Comparison of audiometry at 1000 Hz, 2000Hz, 4000Hz and 8000Hz showed significant differences between mean of audiometry at the beginning, 8th and 15th day(for 1000 Hz p=0.03, 2000 Hz p=0.003, 4000Hz p=0.001,and 8000 Hz p=0.001.The threshold of audiometry at 250Hz,was significantly different only at 8th and 15th day(p=0.004),also at frequency of 500Hz the difference between the beginning with 15th day and 8th day with 15th day were significant (p=0.001) figure 2 shows the results of audiometry test in the aspirin group. According to the results, there were significant differences in 4000Hz and 8000 Hz at 3 settings of audiometry test (figure 2). The comparison between measured means of audiometry threshold in control group shows significant difference between them at the beginning,8th, and 15th day, except for the first and 8th days at 2 frequencies of 250 and 500 Hz. Also in the control group, 11cases of patients showed changes equal to 15db or more in there hearing threshold in 4000Hz and 6 in 8000Hz had this value while in the aspirin group, there was only one case in each above mentioned frequency.

Figure 1- Pure tone audiometry (PTA) threshold dB in the placebo group in different frequencies.

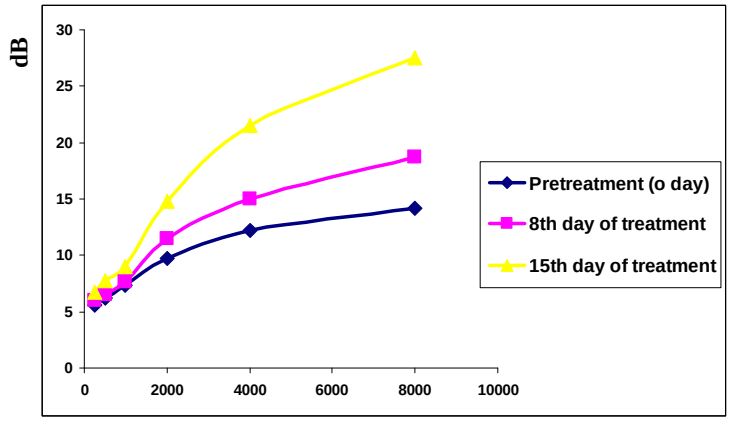
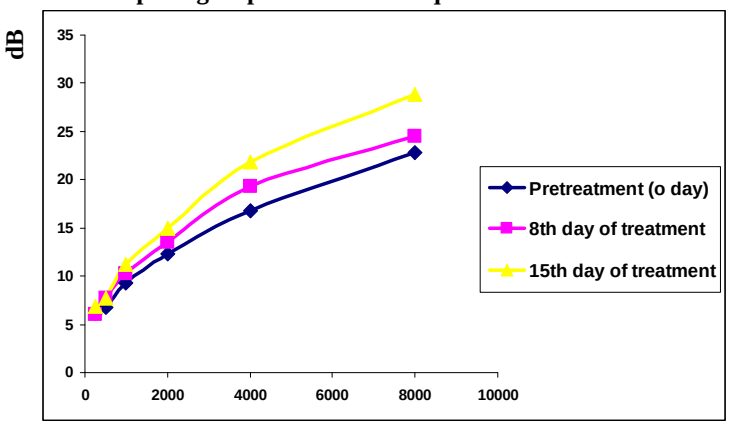


Figure 2- Pure tone audiometry (PTA) threshold dB Aspirin group in different frequencies.



Discussion:

Our study done to determine the effectiveness of aspirin as a protective agent to ear against amikacin in our patients. Significant ear protection was demonstrated in patients receiving aspirin by pre-treatment and post-treatment audiometry testing. [1, 3, 9] In control group at the 8000Hz frequency, the mean hearing threshold was14.2db on the first and 27.5db on the 15th day .In fact, this result shows that the threshold was 2-fold. In contrast, in the aspirin group at 8000Hz frequency the mean threshold was 22.8db on the first day and 28.8db on the 15th day and this means that aspirin has a protective role on hearing for amikacin ototoxicity. In this study, in accordance with previous clinical studies, threshold shift of more than 15db at 6 and 8 kHz had been chosen as the criterion for hearing loss. Aminoglycosides in general were found to displace calcium from it's binding sites resulting in limitation of calcium –dependant physiological mechanisms. In details, aminoglycosides were found to be able to block the transduction channels at the tips of sterocilia and the N-type with P/Q type channels in neurons, as well as acetylcholine-evoked K^+ currents in outer hair cells.[14] Some of the antioxidants (mannitol, glutathione and salicylate) have shown to protect against aminoglycosides ototoxicity in vivo.[9, 15] Aspirin may also provide further benefit for potentiating antimicrobial therapy. [1] A previous study [16] found that a significant hearing loss of 15db or more at 6 and 8 KHz in 13% of patients who received placebo, in contrast, only 3% of the patients that received aspirin showed evidence of hearing loss at the high frequencies .Although aspirin significantly has positive effect on amikacin ototoxicity, it does not provide complete protection. In general, none of our patients in the 2 groups complained of vertigo during period of the study. Because aminoglycosides remain in the cochlea for a long period after end of therapy, patients should be advised to avoid noisy environments for 6 months after therapy completion, because they remain more susceptible to noise-induced cochlear damage. Further works are required to clarify whether a dosage lower than that might provide protection against amikacin-induce hearing loss.

Conclusion:

In present study, we showed that aspirin can protect the ototoxic effects of amikacin in our patients, and further works are needed to clarify whether the dose lower than what used in this study might provide protection against amikacin-induced hearing loss.

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