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Effect of Taurine on the antimicrobial efficiency of Gentamicin

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ABSTRACT

Context: Gentamicin is mainly used in severe infections caused by gram-negatives. However toxicity including nephrotoxicity and ototoxicity is one of the most important complications of its treatment. The production of free radicals seems to be involved in gentamicin toxicity mechanism. Taurine, a major intracellular free β-amino acid, is known to be an endogenous antioxidant. So potentially the co-therapy of taurine and gentamicin would reduce the adverse effects of the antibiotic. ***Objectives:*** In this study, we wished to know the effect of taurine on the antibiotic capacity of gentamicin. ***Methods:*** strainsof *P. aeruginosa*, *E. coli, S. aureus* and *S. epidermidis* were used as test organisms. Minimum inhibitory concentrations of gentamicin in the presence and absence of taurine at quantities from 40 to 2 mg/L were determined using macro-dilution method. ***Results:*** MICs were determined in the various concentrations of taurine for bacterial indicators. The MIC values of gentamicin for *P. aeruginosa, S. aureus* and *E. coli* remained unchanged in the values of 2.5, 5 and 20 µg/ml respectively in the absence and presences of different concentrations of taurine. The bactericidal activity of gentamicin against *S. epidermidis* was increased by addition of taurine in the concentrations higher than 6 mg/L. ***Conclusion:*** According to our study the antibacterial activity of gentamicin against the indicator microorganisms were not interfere with taurine at selected concentrations. Further in vivo studies are needed to establish if a combination of gentamicin and taurine would have the same effect.

Introduction

Aminoglycosid antibiotics including gentamicin are used mainly in severe infections caused by gramnegatives especially pseudomonas, enterobacter, serratia, proteus, acinetobacter, and klebsiella and they produce synergistic bactericidal effects against enterococci, streptococci, and staphylococci.[1,2] The major complications of gentamicin treatment are nephrotoxicity and irreversible ototoxicity.[3] However, the exact mechanisms leading to gentamicin induced cell injury and cell death are unknown at present. Present evidences support the concept that reactive oxygen metabolites including free radical species are important mediators of gentamicin nephrotoxicity and outotoxicity.[4-8]

Several free radicals are produced in the body as byproducts of normal metabolism and also upon exposure to radiation and various environmental pollutants. They are highly reactive, causing damage to cellular components and leading to a variety of diseases. These free radicals are also known as reactive oxygen species (ROS) and include super oxide (O_2^-), hydroxyl radical (OH^-) and hydrogen peroxide (H_2O_2). They contribute towards cytotoxicity, morphological and metabolic changes, changes in the CNS, and increased muscle proteolysis.[9] To prevent injury from oxidative stress, aerobic organisms have evolved a system of chemical and enzymatic antioxidants.

Among the antioxidant enzymes are superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT). SOD catalyzes the dismutation of the superoxide radical anion to hydrogen peroxide and oxygen. CAT and GPx convert H_2O_2 to H_2O.[10]

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Antioxidants play an important role in health maintenance. Significant increase in lipid peroxidation and reduction of antioxidant enzymes after the treatment of gentamicin indicated the generation of free radicals and the involvement of oxidative stress to nephrotoxicity[11-13] and ototoxicity[14-16] caused by gentamicin treatment. Later in vivo experiments confirmed that several radical scavengers may attenuate aminoglycoside-induced ototoxicity and nephrotoxicity.[17-25]
Taurine (2-aminoethanesulfonic acid), a sulphur-containing amino acid, is found naturally in food, especially in seafood and meat (figure 1). It is a conditionally essential amino acid that is present at millimolar concentrations in many animal tissues, especially nervous tissue, retina and neutrophils.[9,26-30]

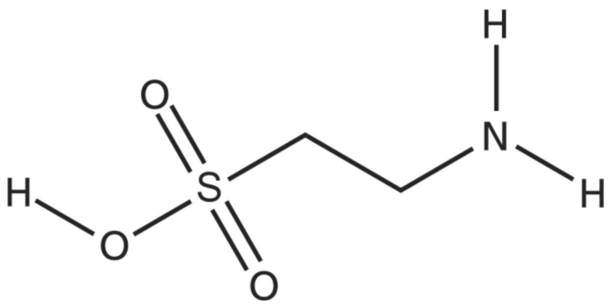

Figure 1. Taurine structure.

Mammals are able to endogenously synthesize taurine, but some species such as humans are more dependent on dietary sources of taurine.[31] It is not incorporated into proteins, but is found free in many tissues. Taurine is involved in a number of physiological processes including bile acid conjugation,[32-33] (osmoregulation, detoxification of xenobiotics, cell membrane stabilization (2001), modulation of cellular calcium flux, and modulation of neuronal excitability.[34-35] Low levels of taurine have been associated with retinal degeneration,[36] growth retardation, and cardiomyopathy (2001). Taurine has been used clinically in the treatment of cardiovascular diseases,[37-38] hypercholesterolemia, seizure disorders,[39] ocular disorders, diabetes,[40-42] Alzheimer’s disease,[43-44] hepatic disorders,[26] cystic fibrosis,[45] acetaminophen toxicity,[46] and alcoholism.[47] Taurine is reported to exhibit direct anti-oxidant properties by lowering ROS and/or as an indirect antioxidant by preventing changes in membrane permeability due to oxidant injury.[48]
Taurine has been recognized as an antioxidant long time ago, scavenging both ROS and nitrogeneous radicals.[26]
In view of the importance of gentamicin in treatment of a wide variety of systemic infections, several researches focused on the possibility of lowering its toxicities. In this regard, various studies have been investigated the mitigating effect of antioxidants, such as D-methionine,[21] aspirin,[32] vitamins E & C,[49] N-acetylcysteine,[50] deferoxamine and 2,3-dihydroxybenzoate[51] on gentamicin-induced ototoxicity or nephrotoxity.
As we mentioned above, taurine can act as an antioxidant so potentially it could prevent the development of gentamicin-induced toxicities. But first of all it should be determined if or whether cotreatment of taurine and gentamicine is compatible with gentamicin's antibacterial activity or not. The purpose of this study was to ascertain the interaction of taurine on the antibiotic capacity of the aminoglycosides.

Materials and methods

Bacteria

The microorganisms used in this study included *Staphylococcus aureus* ATCC 29737, *Pseudomonas aeruginosa* ATCC 9027, *Staphylococcus epidermidis* ATCC 12228, and *Escherichia coli* ATCC 8739all were stocks of the Department of Pharmaceutical and Food Control, School of Pharmacy, Tabriz University of Medical Sciences.

Antibiotic and Taurine

Gentamicin sulfate (Merck, Germany) and taurine (Aviforme, UK) were provided as pure powders of stated potency and stored at 4°C.

Media and Buffers

The bacterial culture media included Soybean-Casein Digest Broth medium (SCDB) purchased from Merck Co. (Germany). For preparing buffer (buffer NO. 3) 16.73 g of dibasic potassium phosphate and 0.523 g of monobasic potassium phosphate dissolved in 1000 ml of distilled water and its pH was adjusted with 18N phosphoric acid or 10 N potassium hydroxide to 8.0 ± 0.1.

Gentamicin and Taurine stock solution

To prepare a stock solution, 1000 mg of gentamicin sulfate powder were accurately weighed and dissolved in the 1000 ml of buffer NO.3, stored in refrigerator. To prepare a stock solution, 800 mg of taurine powder were accurately weighed and dissolved in the 1000 ml of sterile distilled water, stored in refrigerator**.**

Inoculum preparation

Inocula were obtained from an overnight agar culture of the test organisms. Inoculum for the MIC test was prepared by transferring at least one to two well-isolated colonies of the same morphology from an agar plate culture into a tube containing 4 ml of Soybean-Casein Digest Broth. The broth culture was incubated for 24 h at 35º C. The turbidity of the actively growing broth culture was adjusted with sterile broth on a spectrophotometer set at a wavelength of 580 nm to achieve a turbidity equivalent to a 0.5 McFarland standard. This results in a suspension containing approximately 1 to 2 x 10^8 CFU/ml.

Minimum inhibitory concentrations (MICs)

Standard antibiotic solutions were prepared in sterile buffer No.3 for using at the same day. MICs were determined using broth macro-dilution MIC method; twofold serial dilutions of gentamicin yielding the concentrations of 40-0.156 mg/L were prepared in 4-ml volumes in the absence or presence of taurine (extending from 40-2 mg/L, a few concentrations more and less than it's serum concentrations: 22-8 mg/L). Bacterial inocula (100 µl) were transferred to the tubes; accordingly all tubes were incubated for 24 h ± 1 h at 35 ° C, finally turbidity of the cultures was assessed visually by comparison to uninoculated controls. The MIC was recorded as the lowest concentration of antibiotic at which visible growth was inhibited as detected by the unaided eye. All experiments were performed in independent triplicate occasions.

Results

To demonstrate if the in vitro activity of gentamicin could be affected by the concentration of dissolved taurine in the broth media, MICs were determined in the absence and presence of various concentrations of taurine in growth media for bacterial indicators.

First of all, potential antibacterial activity of taurine powder against the selected strains was evaluated. To this end susceptibility testing of our indicator bacteria for taurine were performed with diminution of taurine in broth. Based on the results taurine didn't show any antibacterial activity against all four strains.

In the second step, the MIC values of gentamicin alone against *P. aeruginosa, S. aureus* and *E. coli* were determined that were 2.5, 5 and 20 µg/ml respectively. Furthermore the MIC values of gentamicin against *P. aeruginosa, S. aureus* and *E. coli* measured in the presence of different concentrations of taurine (40, 32, 20, 16, 8, 6 µg/ml), had no significant changes in comparison with those obtained in the absence of taurine.

Surprisingly, as it can be seen in table 1, the inhibitory activity of gentamicin against *S. epidermidis* was increased by the addition of taurine. Taurine at quantities higher than 6 mg/L amelioratedgentamicin's antibacterial activity against *S.epidermidis*. The lower concentrations of tuarine (≤ 6µg/ml) did not alter the MIC values of gentamicin against the bacterium. The results of this experiment are summarized in Table 1.

Table 1. MIC values of gentamicin ± Taurine

Concentration of taurine	MIC values of gentamicin against *S.pidermidis*(µg/ml)	MIC values of gentamicin against S.*aureus* (µg/ml)	MIC values of gentamicin against *P.aeruginosa*(µg/ml)	MIC values of gentamicin agains *E. coli* (µg/ml)
40 µg/ml	0.312	5	2.5	20
32 µg/ml	0.312	5	2.5	20
20 µg/ml	0.312	5	2.5	20
16 µg/ml	0.312	5	2.5	20
8 µg/ml	1.25	5	2.5	20
6 µg/ml	5	5	2.5	20
0 µg/ml	5	5	2.5	20

Discussion

Gentamicin has been extensively used for the prophylaxis and the treatment of severe infectious diseases. The clinical application of this antibiotic has been limited by nephrotoxicity & outotoxicity that is related in part by its enhancing effect on the production of free radicals. In order to test the hypothesis that taurine may become useful in quenching the gentamicin's side effects, at first it should be investigated whether taurine hampers gentamicin's bactericidal activity. For this reason, we have tried to evaluate the possible interactions between taurine at serum level concentrations and the antibacterial action of gentamicin.

According to our study the MIC values of gentamicin against S. *aureus, P. aeruginosa, S. epidermidis,* and *E. coli* resembled those of gentamicin plus taurine against bacterial indicators. In the present study taurine can even augment gentamicin's antibacterial activity against *S. epidermidis*. Previous studies also showed that N-chlorotaurine exhibit antibacterial, antiviral, antifungal, antiamoebic and vermicidal activity.[52-57] According to Grisham et al. NH_2Cl is responsible for N-chlorotaurine's antioxidant and bactericidal effects.[58] Taurine, or 2-aminoethanesulfonic acid, is a derivative of the Cysteine, a sulfur-containing amino acid. It appears to be one of the naturally occurring sulfonic acids. Taurine contains sulfonate group instead of carboxylic acid group but it is often called an amino acid, even it is called an amino sulfonic acid. It is of interest that sufonic acid and sulfonates has already been proven to be moderately bactericidal, viricidal and fungicidal. Sucrose octa-sulphate suspension has shown inhibitory and antibacterial activity against 85% of 128 strains of Gram-negative bacilli.[59] Poly sulfonated compounds have shown microbicidal activity against human papillomavirus (HPV).[60] It has reported that substituted 8-quinolinol sulfonic acids have antifungal activity.[61] According to Zaneveld et al**.** T-PSS (poly (sodium 4-styrenesulfonate)) gel was an effective inhibitor of the infectivity of STD-causing microbes (HIV, HSV-1, HSV-2, *C. trachsomatis* and the multiplication of *N. gonorrhea*).[62]Another study indicated that several sulfunated compounds showed antiviral activity against bovine papillomavirus type 1 (BPV-1).[60] Sulfunated Schiff bases had antibacterial activities against *E. coli, Klebsilla and S. aureus.*[63] In this study, we used pure taurine, so it may concluded that taurine's sulfonic acid moiety cause its microbicidal activity against *S. epidermidis.*

Conclusion

According to our study it was verified that Taurine alone did not produce inhibition of the microorganisms. In the same way, when gentamicin was used in combination with taurine the inhibition produced by this antibiotic was not decreased. As a result, it can be concluded that taurine does not interfere with the antibiotic capacity of Gentamicin against *S. aureus, P. aeruginosa, S. epidermidis,* and *E. coli*. Taurine can also ameliorate Gentamicin's microbicidal activity against *S. epidermidis*.

Further studies are needed to determine if a combination of gentamicin and taurine would have the same effect in vivo.

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Conflict of interest

The authors report no conflicts of interest in this work.

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