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The effect of lycopene on the ototoxicity induced by cisplatin*

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Background/aim: To determine the efficacy of lycopene, which is considered an antioxidant agent, in decreasing the cochlear damage induced by cisplatin.

Materials and methods: A total of 38 rats were randomized into 4 groups: control, cisplatin, cisplatin + lycopene, and lycopene-treated groups. In all groups, the distortion-product otoacoustic emission measurements were performed on days 0, 1, 2, and 5.

Results: There were no significant differences between the control and lycopene groups at any frequencies. In the cisplatin group, the statistically significant differences were found in the measurements taken between day 0 and day 5 at all frequencies and between days 1 and 5 and days 2 and 5 at some frequencies (P < 0.05). In the cisplatin + lycopene group, a statistically significant difference was found at some frequencies between the measurements taken on days 0 and 5, days 1 and 5, and days 2 and 5 (P < 0.05). Contrary to the results found in the cisplatin group, hearing ability in the lycopene-treated group was observed as being preserved at low frequencies in the measurements taken on days 0 and 5 and days 2 and 5.

Conclusion: The data of this study suggest that lycopene can prevent the development of ototoxicity induced by cisplatin, especially at low frequencies. Studies on this issue with longer durations and different dose ranges may contribute to the identification of potentially prophylactic effects of lycopene against cisplatin ototoxicity at higher frequencies, as well.

Key words: Lycopene, cisplatin, otoacoustic emission, ototoxicity

1. Introduction

Ototoxicity is a widespread term for describing the damage occurring on the cochlea and vestibular organs by various therapeutic agents and/or chemicals. The ototoxic effect of cisplatin is characterized by bilateral, progressive, and irreversible sensorineural hearing loss. Cisplatin demonstrates an ototoxic effect on outer hair cells progressively from the base to the apex of cochlea. It causes ototoxicity by consuming antioxidant enzymes. Many types of protective agents have been used to decrease this damage, and investigations into this issue are still continuing (1–6).

Lycopene is an antioxidant agent that is found in tomatoes and tomato-based products (7). Lycopene has a red pigment and belongs to the carotenoid family. It protects cells from the damage induced by free radicals. In addition, it strengthens intercellular bonds and accelerates the development of cellular metabolism. The effectiveness of fat-soluble lycopene increases in tissues and organs rich in fat. Its antioxidant effect has been demonstrated in skin, which is quite rich in fat content. It was also reported that the oxidative damages resulting from diabetes mellitus were ameliorated with the administration of lycopene (8). It also has a cholesterol-decreasing effect. Lycopene provides prophylaxis against some cancer types (breast, uterus, liver, and prostate), Alzheimer disease, and cardiovascular diseases and also slows down the aging process with its antioxidant effects (9–11). The main dietary sources of lycopene (at least 85%) are tomatoes and tomato products; the remainder is obtained from apricot, pink grapefruit, guava, watermelon, and papaya (12).

In this study, we aimed to determine the efficacy of lycopene, which is considered to be an antioxidant agent, in decreasing ototoxic damage induced by cisplatin.

2. Materials and methods

2.1. Study design

The present study was performed according to the approved Industrial Animal Care and Use Committee guidelines

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any loss. However, on the sixth day, 9 rats died because of the potentially prophylactic effects of different antioxidant agents, e.g., erdosteine, aminoguanidine, and caffeic acid, on cisplatin toxicity; consequently, the measurements were terminated because of scarcity of experimental animals.

3.1. Control group
DPOAE measurements were performed on days 0, 1, 2, and 5, and a statistically significant difference did not exist at frequencies of 2003–10,078 Hz (P > 0.05) (Figure).

3.2. Cisplatin group
No statistically significant difference was found between DPOAE measurements performed on days 0 and 1, days 0 and 2, or days 1 and 2. However, statistically significant differences were found between measurements taken on days 0 and 5 at all frequencies; between days 1 and 5 in measurements performed at the frequencies of 3175, 3996, 5039, 6351, 8003, and 10,078 Hz; and between days 2 and 5 in measurements performed at the frequencies of 2003, 3175, 3996, 5039, 6351, 8003, and 10,078 Hz (P < 0.05) (Figure).

3.3. Cisplatin + lycopene group
In DPOAE measurements, no statistically significant difference was found between the measurements of days 0 and 1, days 0 and 2, or days 1 and 2. Statistically significant differences were found between the measurements performed on days 0 and 5 at the frequencies of 3175, 3996, 5039, 6351, 8003, and 10,078 Hz; between the measurements of days 1 and 5 at frequencies of 3175, 3996, 5039, 6351, 8003, and 10,078 Hz; and between the measurements taken on days 2 and 5 at frequencies of 3996, 5039, 6351, 8003, and 10,078 Hz (P < 0.05). Contrary to the cisplatin group, in the cisplatin + lycopene group, the hearing ability was observed as being preserved in the measurements of days 0 and 5 at frequencies of 2003 Hz and 2519 Hz and the measurements of days 2 and 5 at frequencies of 2003 Hz and 3175 Hz (Figure).

3.4. Lycopene group
DPOAE measurements were performed on days 0, 1, 2, and 5, and a statistically significant difference did not exist at frequencies of 2003–10,078 Hz (P > 0.05) (Figure).

4. Discussion
Cisplatin is an antineoplastic drug that is frequently used in head, neck, testicular, and ovarian malignancies. Many investigations have been performed to ensure the safe usage of this chemotherapeutic agent due to its important adverse effects, such as ototoxicity. For instance, in studies performed by Teranishi and Nakashima and by Kalkanis et al., reductions of this chemotherapeutic agent due to its important adverse effects, such as ototoxicity. For instance, in studies performed by Teranishi and Nakashima and by Kalkanis et al., reductions in DPOAE measurements, the GSI Audera DPOAE (Grason Stadler, Madison, WI, USA) device was used. The otoacoustic emission probe was placed into the external auditory canal. For accuracy, the implantation and calibration of the probe were examined using automated measurement systems before each test. The measurements were performed in a silent ambient environment with sound pressure levels not exceeding 45 dB. Primary stimuli levels were equalized at 65 dB for DPOAE measurements (L1 = L2). Two separate frequencies (f1 and f2) were set at a f2:f1 ratio equivalent to 1:22 to obtain the strongest responses. DPOAE measurements were performed at frequencies of 2003, 2519, 3175, 3996, 5039, 6351, 8003, and 10,078 Hz, and the results were recorded.

2.3. Statistical analysis
Data were analyzed using SPSS 11.0 for Windows (SPSS Inc., Chicago, IL, USA). The results for all items were expressed as mean ± SEM, assessed within 95% reliance and at a significance level of P < 0.05. Wilcoxon’s paired-t test was used to analyze the data.

3. Results
Initially, the duration of the study was planned as 10 days. The rats completed the first 5 days of the study without any loss. However, on the sixth day, 9 rats died because of enteritis, nephrotoxic effects, and weight loss possibly due to cisplatin toxicity; consequently, the measurements were terminated because of scarcity of experimental animals.
in which a total of 40 carbon units are bound end-to-end with single and double conjugated bonds. The free radical-neutralizing property of this chemical formation, with its protective effects against some cancer types, cardiac dysfunctions, and degenerative eye diseases, has been revealed in many investigations. As a result of these studies, the prominent antioxidant effect of lycopene is associated with preventing ROS damage via free radical scavenging and detoxifying lipid peroxides (14–16).

Studies performed with lycopene from the carotenoid family have demonstrated that lycopene induces decreased levels of malondialdehyde, which is the end product of fatty acid oxidation and is known to correlate with the degree of oxidative damage. However, as shown in various studies, lycopene also increases activities of endogenous antioxidants such as superoxide dismutase and glutathione peroxidase (14,17,18).

In a previous study, the antioxidant effects of synthetic and naturally occurring (i.e. found in tomatoes) forms of lycopene were compared with placebo-group patients. Decreased lipid peroxidation and oxidative stress were found in both lycopene-supplementing groups when compared with the placebo-group patients. In comparative analysis, a statistically significant difference was noted between the lycopene groups. As a result, it was suggested that dietary intake of natural lycopene is favorable against oxidative stress; however, the synthetic form is more bioavailable and more effective (19).

The protective effect of lycopene against chemotherapy agent toxicities such as cisplatin-induced nephrotoxicity, doxorubicin-induced myocardial or kidney toxicity, gentamycin-induced nephrotoxicity, and oxidative stress was shown in animal studies (20–22).

In the present study, we evaluated the protective effect of this potent antioxidant agent against ototoxicity induced by cisplatin. However, the study was terminated earlier than planned due to the loss of the majority of the rats on the sixth day, from the systemic toxicity of cisplatin. The results of the DPOAE measurements performed in cisplatin-administered rats revealed statistically significant deteriorations at all frequencies, while hearing ability was preserved at low frequencies in the cisplatin + lycopene-administered group. These data suggest that lycopene can prevent the development of ototoxicity, especially at lower frequencies. Future studies on this issue with longer durations and different dose ranges may contribute to the identification of potentially prophylactic effects of lycopene against cisplatin ototoxicity at low and higher frequencies, as well.

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