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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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(2012 / A - 08). A total of 38 Wistar albino rats weighing between 150 and 200 g were used. During the study, the animals were kept in automatically regulated chambers under light and dark conditions, each lasting for 12 h a day, at an ambient temperature of 22 ± 2 °C and 45%–50% humidity. All rats were fed standard pellets, and every day they were given fresh tap water. After anesthetizing the animals with 50 mg/kg intramuscular (i.m.) ketamine and 5 mg/kg i.m. xylazine, they were brought into special silent cabins for the application of subsequent procedures.

Otoacoustic emission measurements were used to evaluate the hearing functions of all animals. In otoacoustic emission measurements, distortion-product otoacoustic emission test (DPOAE) values were used.

Rats were randomly divided into 4 groups. The control group consisted of 7 rats, which received physiologic saline at daily doses of 5 mL intraperitoneally (i.p.) between days 0 and 5. The cisplatin group comprised 12 rats that received cisplatin i.p. at daily doses of 8 mg/kg between days zero and 2. The cisplatin + lycopene group included 12 rats that received cisplatin (8 mg/kg i.p. daily between days 0 and 2) plus lycopene (5 mg/kg i.p. daily between days 0 and 5). The lycopene group contained 7 rats, which received lycopene (5 mg/kg i.p. daily). In all groups, DPOAE measurements were performed on days 0, 1, 2, and 5.

2.2. Otoacoustic emission measurements

The study included rats with normal DPOAE values. For DPOAE test 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.

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 were observed in hearing loss and cochlear damage by using systemic vitamin E administration (1,13). In similar studies, the potentially prophylactic effects of different antioxidant agents, e.g., erdosteine, aminoguanidine, and caffeic acid, were demonstrated (3–5).

The antioxidant effect of the carotenoid family is a result of their extended tetraterpene chemical configuration,

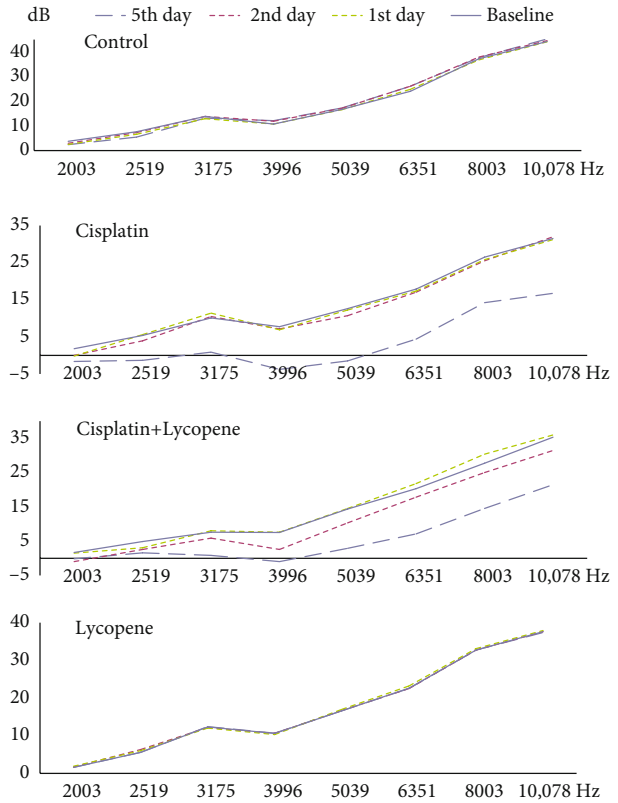

Figure. Variations in amplitudes of distortion products otoacoustic emissions with frequency for different time points in the study groups.

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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References

1. Teranishi MA, Nakashima T. Effects of trolox, locally applied on round windows, on cisplatin-induced ototoxicity in guinea pigs. Int J Pediatr Otorhinolaryngol 2003; 67: 133–139.
2. Rybak LP, Whitworth C, Somani S. Application of antioxidants and other agents to prevent cisplatin ototoxicity. Laryngoscope 1999; 109: 1740–1744.
3. Kizilay A, Kalcioglu MT, Ozerol E, Iraz M, Gulec M, Akyol O, Ozturan O. Caffeic acid phenethyl ester ameliorated ototoxicity induced by cisplatin in rats. J Chemother 2004; 16: 381–387.
4. Iraz M, Kalcioglu MT, Kizilay A, Karatas E. Aminoguanidine prevent ototoxicity induced by cisplatin in rats. Ann Clin Lab Sci 2005; 35: 329–335.
5. Kalcioglu MT, Kizilay A, Gulec M, Karatas E, Iraz M, Akyol O, Egri M, Ozturan O. Protective effect of erdosteine against ototoxicity induced by cisplatin in rats. Eur Arch Otorhinolaryngol 2005; 262: 856–863.

6. Şanlı A, Aydın S, Sarısoy ZA, Paksoy M, Ayduran E, Çelebi Erdivanlı Ö. The protective effect of dexamethasone and lactate against cisplatin-induced ototoxicity. Turk J Med Sci 2011; 41: 467–474.

7. Giovannucci E. Tomatoes, tomato-based products, lycopene and cancer: review of the epidemiologic literature. J Natl Cancer Inst 1999; 91: 317–331.

8. Aydın M, Çelik S. Effect of lycopene on plasma glucose, insulin levels, oxidative stress, and body weights of streptozotocin-induced diabetic rats. Turk J Med Sci 2012; 42 (Suppl. 2): 1406–1413.

9. Mashima R, Witting PK, Stocker R. Oxidants and antioxidants in atherosclerosis. Curr Opin Lipidol 2001; 12: 411–418.

10. Boileau TW, Clinton SK, Zaripheh S, Monaco MH, Donovan SM, Erdman JW Jr. Testosterone and food restriction modulate hepatic lycopene isomer concentrations in male F344 rats. J Nutr 2001; 131: 1746–1752.

11. Rousseau EJ, Davison AJ, Dunn B. Protection by beta-carotene and related compounds against oxygen-mediated cytotoxicity and genotoxicity: implications for carcinogenesis and anticarcinogenesis. Free Radic Biol Med 1992; 13: 407–433.

12. Nguyen ML, Schwartz SJ. Lycopene: chemical and biological properties. Food Technol 1999; 53: 38–45.

13. Kalkanis JG, Whitworth C, Rybak LP. Vitamin E reduces cisplatin ototoxicity. Laryngoscope 2004; 114: 538–542.

14. Bramley PM. Is lycopene beneficial to human health? Phytochemistry 2000; 54: 233–236.

15. Khachik F, Carvalho L, Bernstein PS, Muir GJ, Zhao DY, Katz NB. Chemistry, distribution and metabolism of tomato carotenoids and their impact on human health. Exp Biol Med (Maywood) 2002; 227: 845–851.

16. Gupta SK, Trivedi D, Srivastava S, Joshi S, Halder N, Verma SD. Lycopene attenuates oxidative stress induced experimental cataract development: an in vitro and in vivo study. Nutrition 2003; 19: 794–799.

17. Breinholt V, Lauridsen ST, Daneshvar B, Jakobsen J. Dose-response effects of lycopene on selected drug-metabolizing and antioxidant enzymes in the rat. Cancer Lett 2000; 154: 201–210.

18. Cadenas E, Packer L. Handbook of Antioxidants. New York, NY, USA: Marcel Dekker Inc.; 1996.

19. Sarkar PD, Gupta T, Sahu A. Comparative analysis of lycopene in oxidative stress. J Assoc Physicians India 2012; 60: 17–19.

20. Yilmaz S, Atessahin A, Sahna E, Karahan I, Ozer S. Protective effect of lycopene on Adriamycin-induced cardiotoxicity and nephrotoxicity. Toxicology 2006; 218: 164–171.

21. Karahan İ, Ateşşahin A, Yilmaz S, Çeribaşı AO, Sakin F. Protective effect of lycopene on gentamicin-induced oxidative stress and nephrotoxicity in rats. Toxicology 2005; 215: 198–204.

22. Ateşşahin A, Yilmaz S, Karahan İ, Çeribaşı AO, Karaoğlu A. Effects of lycopene against cisplatin-induced nephrotoxicity and oxidative stress in rats. Toxicology 2005; 212: 116–123.