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Experimental Study

ENT Updates 2016;6(3):110–115
doi:10.2399/jmu.2016003009

The effect of coenzyme Q10 on cisplatin-induced ototoxicity in rats

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Abstract

Objective: To determine the efficacy of systemic administration of coenzyme Q10 at low and high doses on cisplatin-induced ototoxicity in rats.

Methods: Our study was performed with 40 Sprague-Dawley rats. They were divided randomly into five groups: Cis, Cis+Q10$_{30}$, Cis+Q10$_{10}$, Q10, and control. Cis (n=8) group was administered cisplatin [a single intraperitoneal (i.p.) injection of 14 mg/kg], Cis+Q10$_{30}$ (n=8) group was administered cisplatin (a single i.p. injection of 14 mg/kg) and coenzyme Q10 (30 mg/kg/day, i.p.) for 3 days, Cis+Q10$_{10}$ (n=8) group was given cisplatin (a single dose of 14 mg/kg/day, i.p.) and coenzyme Q10 (10 mg/kg/day, i.p.) for 3 days, Q10 (n=8) group was administered coenzyme Q10 (10 mg/kg/day, i.p.) for 3 days and Group C (n=8) (control group) was administered saline solution (1 mL/day, i.p.) once daily for 3 days. Pretreatment and posttreatment hearing levels were evaluated with distortion product otoacoustic emissions (DPOAEs).

Results: There was no statistically significant difference in the results of measurements of 4004, 4358, 4761 and 5188 Hz at end of the study in comparison to baseline ($p>0.05$). On the other hand, there was a significant difference at the measurements of 5652, 6165, 7336 and 7996 Hz (p=0.002, p=0.037, p=0.001, p=0.001, respectively). The rate of change at 5652 Hz revealed that Cis group was different from Cis+Q10$_{10}$, control and Q10 groups ($p<0.01$); measurements at 6165 Hz revealed that change at Cis group was significantly different from control and Q10 groups ($p<0.01$, $p<0.05$). Final measurements of decrease in Cis group at 7336 and 7996 Hz were significantly different from baseline ($p<0.05$; $p<0.01$).

Conclusion: The high-dose coenzyme Q10 showed a protective effect on hearing in cisplatin-induced ototoxicity while low-dose coenzyme Q10 protected hearing at low frequencies but did not show protective effect at high frequencies.

Keywords: Ototoxicity, cisplatin, coenzyme Q10, rats.

Özet: Koenzim Q10'un ratlarda sıçanlarda sisplatinin neden olduğu ototoksisiteye etkisi

Amaç: Sıçanlarda düşük ve yüksek dozlarda koenzim Q10'un sistemik uygulamasının sisplatinin neden olduğu ototoksisite üzerine etkinliğini belirlemek.

Yöntem: Çalışmamız 40 Sprague-Dawley sıçanla gerçekleştirildi. Sıçanlar randomize şekilde beş gruba ayrıldı: Cis, Cis+Q10$_{30}$, Cis+Q10$_{10}$, Q10, kontrol. Cis (n=8) grubuna tek bir 14 mg/kg dozda intraperitoneal (i.p.) yolla sisplatin enjekte edildi. Cis+Q10$_{30}$ (n=8) grubuna tek bir 14 mg/kg dozda i.p. sisplatin ve 3 gün boyunca günde 30 mg/kg dozda koenzim Q10 i.p. enjekte edildi. Cis+Q10$_{10}$ (n=8) grubuna tek bir 14 mg/kg dozda i.p. sisplatin ve 3 gün boyunca günde 10 mg/kg dozda koenzim Q10 i.p. enjekte edildi. Q10 (n=8) grubuna 3 gün boyunca günde 10 mg/kg dozda koenzim Q10 i.p. enjekte edildi. Kontrol grubuna (Grup C) (n=8) 3 gün boyunca günde 1 mL dozda i.p. salin enjekte edildi. Tedavi öncesi ve sonrası işitme düzeyleri distorsiyon ürünü otoakustik emisyonlarla (DPOAE) değerlendirildi.

Bulgular: Başlangıca göre çalışma sonunda 4004, 4358, 4761 ve 5188 Hz'deki ölçüm sonuçlarında istatistiksel açıdan anlamlı herhangi bir değişiklik yoktu ($p>0.05$). Diğer taraftan 5652, 6165, 7336 ve 7996 Hz'deki ölçümlerde anlamlı bir farklılık vardı (sırasıyla p=0.002, p=0.037, p=0.001 ve p=0.001). Ayrıca 5652 Hz'deki değişimin hızı Cis grubunun Cis+Q10$_{10}$, kontrol ve Q10 gruplarından farklı olduğunu ortaya koydu ($p<0.01$). Yine 6165 Hz'deki ölçümler Cis grubundaki değişimin kontrol ve Q10 gruplarından anlamlı derecede farklı olduğunu gösterdi ($p<0.01$, $p<0.05$). Cis grubunda 7336, 7996 Hz'deki azalmanın nihai ölçümleri başlangıçtaki ölçümlerden anlamlı derecede farklıydı ($p<0.05$, $p<0.01$).

Sonuç: Yüksek dozda koenzim Q10 sisplatinin neden olduğu ototoksisitede işitme duyusunu koruyucu etki gösterirken düşük doz koenzim Q10 düşük frekansları işitme duyusunu korumuş, yüksek frekanstaki sesleri işitme duyusunu koruyucu etki göstermemiştir.

Anahtar sözcükler: Ototoksisite, sisplatin, koenzim Q10, sıçanlar.

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Received: August 3, 2016; **Accepted:** October 12, 2016

Online available at:
www.entupdates.org
doi:10.2399/jmu.2016003009
QR code:

Cisplatin (cis-diamminedichloroplatinum II, CDDP), a potent alkylating chemotherapeutic agent, is widely used in the treatment of several cancers despite of multiple side effects, including nephrotoxicity and ototoxicity.[1,2] Cisplatin may cause bilateral, progressive, irreversible high frequency sensorineural hearing loss with tinnitus.[3–6] Even though the potential mechanism of cisplatin ototoxicity is not fully understood, it may cause cell death by the production of reactive oxygen species (ROS). Several clinical and experimental studies demonstrated that multiple areas of the cochlea such as outer hair cells particularly at the basal turn, spiral ganglion cells, and stria vascularis can be damaged after cisplatin treatment; thereby leading to hearing loss. The outer hair cells in the basal turn of the cochlea are initially affected, then the apical turn, and finally the inner hair cells are affected. The formation of free radicals is believed to decrease intracellular glutathione levels and impair the activities of antioxidant enzyme activities. The derangement in antioxidant mechanism may lead to an increase in lipid peroxidation and cause apoptosis of hair and support cells, stria vascularis, and cochlear nerves.[7]

Coenzyme Q10 (CoQ10) terclatrate (Q-Ter) is a moving electron carrier in the mitochondrial electron transport chain and a major source of ATP. Ubiquinone is reduced by the respiratory chain to its active ubiquinol form, an effective antioxidant which prevents lipid peroxidation and mitochondrial damage.[8]

Based on this mechanism, several antioxidants have been reported in the literature;[9–12] however, none of the medicinal products with protective effects against cisplatin ototoxicity has been approved by the FDA. Therefore, the aim of this study is to determine the protective effect of CoQ10 on cisplatin-induced ototoxicity in rats.

Materials and Methods

International Review Board approval was taken from Animal Research Ethics Committee. This study was performed at the Experimental Animal Research Laboratory.

Our study has been performed with a total of 80 ears of 40 male Sprague-Dawley albino rats. Weights of the rats ranged from 200±20 g. Rats were accommodated in an environment under 12 hours light and 12 hours dark where the background noise level was below 50 dB, temperature was 21 °C, and the rats could get free food and water.

In all groups, Sprague-Dawley albino rats were anesthetized by ketamine hydrochloride (JHP Pharmaceuticals, Parsippany, NJ, USA) (0.45 mg/kg) and xylazine (Bayer, Leverkusen, Germany) (5 mg/kg).

Experimental design

Sprague-Dawley rats (n=40) were randomly divided into following groups: (i) Cis, (ii) Cis+Q10$_{30}$, (iii) Cis+Q10$_{10}$, (iv) Q10 and (iv) control. Cis (n=8) group was administered cisplatin [a single intraperitoneal (i.p.) injection of 14 mg/kg], Cis+Q10$_{30}$ (n = 8) group was administered cisplatin (a single i.p. injection of 14 mg/kg) and coenzyme Q10 (30 mg/kg/day, i.p.) for 3 days, Cis+Q10$_{10}$ (n=8) group was given cisplatin (a single dose of 14 mg/kg/day, i.p.) and coenzyme Q10 (10 mg/kg/day, i.p.) for 3 days, Q10 (n=8) group was administered coenzyme Q10 (10 mg/kg/day, i.p.) for 3 days and Group C (n=8) (control group) was administered saline solution (1 mL/day, i.p) once daily for 3 days. 3 rats at Cis group and another 3 at Cis+Q10$_{30}$ group died so 34 rats were able to complete the study.

The DPOAE recordings

All rats underwent the distortion product otoacoustic emission (DPOAE) measurements on days 0 and 4. Otomicroscopic examinations of all of the ears of the rats were performed before DPOAE examination, and rats with middle ear pathologies were excluded. "ILO Cochlear Emission Analyzer" (Otodynamics, London, UK) was used for the measurement of the DPOAEs. Distortion product grams (DPgram) were measured at 80 dB (L1=L2). Two different frequencies (f1 and f2) that might be the most powerful responses were organized as f2/f1=1.22. DPgram measurements were performed and noted at 1001, 1501, 2002, 3003, 4004, 4358, 4761, 5188, 5652, 6165, 6726, 7336 and 7996 Hz frequencies. The noise levels for both DPgram and I/O functions were measured at frequencies 50 Hz above the DPOAE frequencies. During measurements at 2f1-f2 frequency, the OAEs ?3 dB above the noise intensity were considered positive. Emission values were under the noise threshold at 1001, 1501, 2002, and 3003 Hz and above it at the other frequencies. Therefore, statistical analyses were applied to the results obtained at 4004, 4358, 4761, 5188, 5652, 6165, 6726, 7336 and 7996 Hz.

Statistical analysis

An intra- and intergroup comparisons of measurements that were taken before and after experiment were performed. In order to evaluate the results of the study, IBM SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. Descriptive statistics were presented as means and standard deviations. Kolmogorov-Smirnov test demonstrated that values were not normally distributed. Therefore, intergroup comparisons were per-

Table 1. Pretreatment and posttreatment evaluations of 5652 Hz DPOAEs measurements in the groups.

	Baseline measurement	Final measurement	Baseline-final difference
5652 Hz	**Mean±SD (median)**	**Mean±SD (median)**	**p‡**
Cis	32.43±8.82 (32.45)	20.48±5.41 (21.6)	**0.005***
Cis+Q10$_{30}$	38.98±6.57 (38.8)	32.18±13.82 (37.55)	**0.093**
Cis+Q10$_{10}$	29.17±7.63 (28.1)	29.58±8.24 (29)	**0.796**
Q10	40.41±5.54 (41.95)	38.38±8.91 (38.7)	**0.589**
C	40.41±5.54 (41.95)	40.74±13.76 (43.3)	**0.767**
p†	**0.001***	**0.001***	

*p<0.1. †Kruskal-Wallis test, ‡Wilcoxon signed ranks test. **C:** control, **Cis:** cisplatin, **Q10:** coenzyme Q10, **SD:** standard deviation.

Table 2. Pretreatment and posttreatment evaluations of 6165 Hz DPOAEs measurements in the groups.

	Baseline measurement	Final measurement	Baseline-final difference
6165 Hz	**Mean±SD (median)**	**Mean±SD (median)**	**p‡**
Cis	32.91±4.72 (33.2)	21.68±6.78 (22.35)	**0.005***
Cis+Q10$_{30}$	35.53±6.55 (34)	30.32±13.32 (32.7)	**0.333**
Cis+Q10$_{10}$	32.86±6.1 (32.5)	27.76±8.01 (29.5)	**0.066**
Q10	39.47±5.3 (40.45)	35.66±8.8 (36.1)	**0.179**
C	39.47±5.3 (40.45)	38.35±8.85 (40.9)	**0.575**
p†	**0.002***	**0.001***	

*p<0.01. †Kruskal-Wallis test, ‡Wilcoxon signed ranks test. **C:** control, **Cis:** cisplatin, **Q10:** coenzyme Q10, **SD:** standard deviation.

formed using Kruskal-Wallis test, and the Mann-Whitney U test was used in order to determine from which group the difference arose. The Wilcoxon signed-ranks test was applied for intra-group comparisons. All results were evaluated at 95% confidence interval, and a p value of less than 0.05 was considered statistically significant.

Results

No statistically significant difference was determined among groups at baseline measurements (p>0.05). Cis group had remarkably low results at the end of the study when compared to all other groups (p<0.01). There was no significant difference at the final measurement of 4004, 4358, 4761 and 5188 Hz in comparison to baseline values (p>0.05). On the other hand, there was a significant change at final result of 5652 Hz compared to baseline (p=0.002; p<0.01). Mann-Whitney U test revealed that the change in Cis+Q10$_{10}$ (p=0.001) group had significantly higher values than control (p=0.001) and Q10 groups (p=0.003). Change at Cis+Q10$_{30}$ group was significantly higher than the control group at 5652 Hz (p=0.049; p<0.05). There was no significant difference among the changes of other groups at the end of the study in comparison to baseline (p>0.05) (Table 1).

Final measurement showed that there was a significant change in 6165 Hz compared to baseline values. Mann-Whitney U test revealed that the change in Cis group (p=0.037; p<0.05) was significantly higher than control (p=0.001) and Q10 groups (p=0.035; p<0.01; p<0.05). There was no significant difference among the changes of other groups at the end of the study in comparison to baseline (p>0.05) (Table 2).

Final measurement showed that there was a significant change in 7336 Hz compared to baseline value (p=0.001; p<0.01). Mann-Whitney U test revealed that the decrease in Cis group was higher than Cis+Q10$_{30}$, (p=0.023), Cis +Q1010 (p=0.031), control (p=0.001) and Q10 (p=0.001) groups (p<0.05; p<0.01). Cis+Q10$_{30}$ (p=0.017) and Cis+Q10$_{10}$ (p=0.011) groups had significantly higher decrease rates than control groups (p<0.05). There was no significant difference among the changes of other groups at the end of the study in comparison to baseline (p>0.05). (Table 3)

Final measurement showed that there was a significant change in 7996 Hz compared to baseline value (p=0.001; p<0.01). Mann-Whitney U test demonstrated that the decrease in Cis group was higher than Cis+Q10$_{30}$, (p=0.028), Cis+Q10$_{10}$ (p=0.006), control (p=0.001) and Q10 (p=0.001) groups (p<0.05; p<0.01). Decreases in Cis+Q10$_{30}$ and Cis +Q1010 groups were remarkably higher than control group

Table 3. Pretreatment and posttreatment evaluations of 7336 Hz DPOAEs measurements in the groups.

	Baseline measurement	Final measurement	Baseline-final difference
7336 Hz	**Mean±SD (median)**	**Mean±SD (median)**	**p‡**
Cis	34.26±6.04 (35.9)	12.75±11.37 (11.95)	**0.005***
Cis+Q10$_{30}$	39.6±3.98 (40.1)	30.43±14.77 (35.5)	**0.014****
Cis+Q10$_{10}$	37.08±10.22 (36.05)	26.36±13.24 (32.85)	**0.006***
Q10	38.71±2.58 (38.3)	34.49±10.44 (38.25)	**0.469**
C	38.71±2.58 (38.3)	37.91±5.62 (37.85)	**0.674**
p†	**0.005***	**0.001***	

*p<0.05, **p<0.01. †Kruskal-Wallis test, ‡Wilcoxon signed ranks test. **C:** control, **Cis:** cisplatin, **Q10:** coenzyme Q10, **SD:** standard deviation.

(p=0.021; p=0.014 respectively). At the end of the study, no statistically significant difference among the changes of other groups was found when compared with baseline results (p>0.05) (Table 4, Fig. 1).

Discussion

Cisplatin administration can cause hearing loss due to functional and structural changes in the cochlea. Cisplatin may reduce endocochlear potentials, and cause structural damages at several regions of cochlea; thereby, leading to hearing impairment.[4,7] Although the mechanism of cisplatin ototoxicity is not fully understood, it appears to involve the formation of ROS that trigger cell death.[4,7]

As cisplatin damages the organ of Corti, particularly the basal cochlear turn, hearing loss starts at higher frequencies, which may then progress to involve all frequencies.[2,13] In our study, hearing loss involved all frequencies in cisplatin-treated rats. Hence, we saw that single dose of cisplatin caused ototoxicity.

Animal studies have demonstrated that cisplatin administration may elevate the ABR thresholds. In addition, cisplatin induced ototoxicity may occur as a result of inner ear hair cell degeneration due to oxidative stress. In the literature, a variety of antioxidant agents have been suggested to prevent ototoxicity, including dexamethasone,[3] alpha-tocopherol, tiopronin,[6] sodium salicylate,[12] amifostine,[13] d-methionine,[14] vitamin E,[15] pentoxifylline,[16] neurotropines,[17] flunarizine,[18] and melatonin.[19] In cisplatin ototoxicity, the use of protective agents may prevent hearing

Table 4. Pretreatment and posttreatment evaluations of 7996 Hz DPOAEs measurements in the groups.

	Baseline measurement	Final measurement	Baseline-final difference
7996 Hz	**Mean±SD (median)**	**Mean±SD (median)**	**p‡**
Cis	36.38±6.36 (37.85)	6.82±9.48 (1.5)	**0.005***
Cis+Q10$_{30}$	40.19±5.31 (41.15)	27.82±17.61 (32)	**0.037****
Cis+Q10$_{10}$	35.02±6.11 (35.15)	24.02±15.52 (21.95)	**0.023****
Q10	39.7±3.78 (40.4)	36.58±11.77 (41.2)	**0.776**
C	39.7±3.78 (40.4)	38.44±4.2 (38.45)	**0.069**
p†	**0.026****	**0.001***	

*p<0.05, **p<0.01. †Kruskal-Wallis test, ‡Wilcoxon signed ranks test. **C:** control, **Cis:** cisplatin, **Q10:** coenzyme Q10, **SD:** standard deviation.

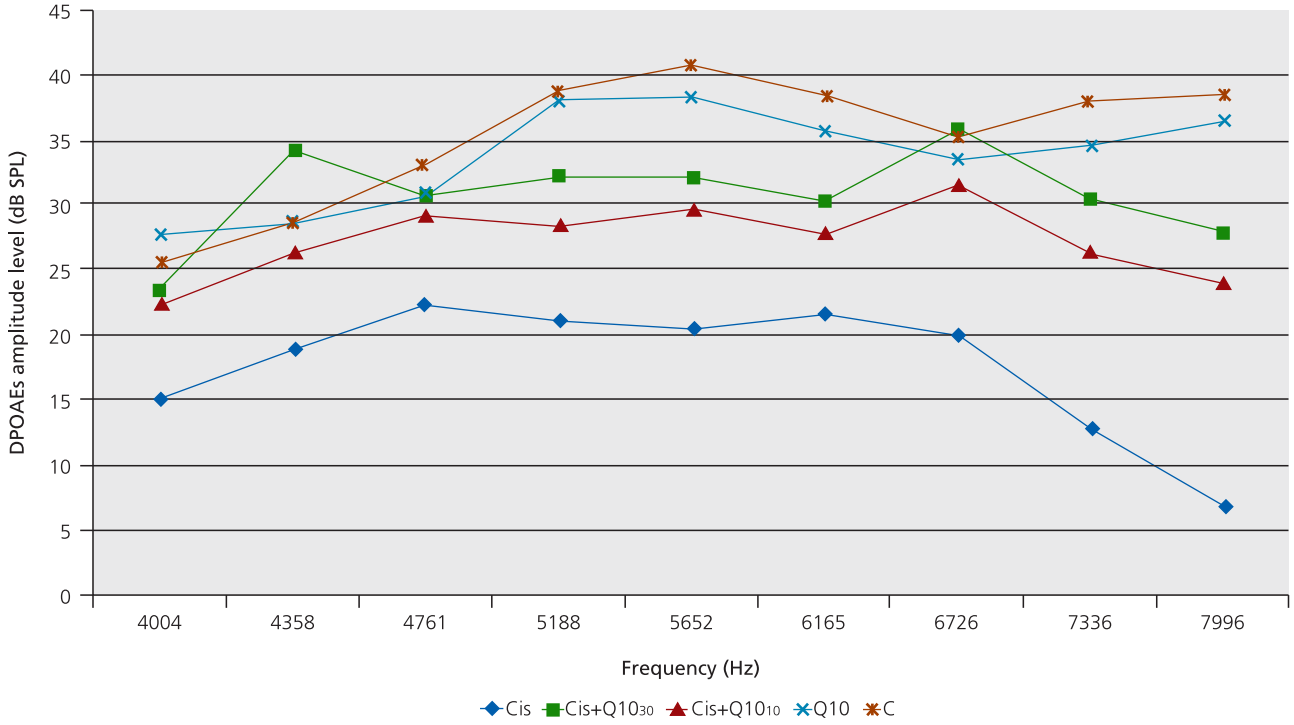

Fig. 1. Post-treatment DPOAE amplitudes (dB SPL) of the groups by frequencies. **C:** control, **Cis:** cisplatin, **Q10:** coenzyme Q10 (10 mg/kg/day), **Q10$_{10}$:** coenzyme Q10 (10 mg/kg/day), **Q10$_{30}$:** coenzyme Q10 (30 mg/kg/day).

loss and lipid peroxidation. In addition, clinical application of these protective agents may reduce or prevent the cisplatin related damage to the inner ear in patients who were administered chemotherapy for cancer without causing an alteration in antitumor effect of cisplatin.[20,21] Cisplation administration may lead to a significant elevation in superoxide dismutase, catalase activities, and malondialdehyde levels; on the other hand, cochlear GSH-peroxidase and GSH reductase activities are decreased.[2] CoQ10, with its known antioxidant properties, has been popularized recently, and has been investigated for the treatment of diseases related to oxidative stress. Within mitochondria, ubiquinone is reduced by the respiratory chain to its active ubiquinol form, which is an effective antioxidant that prevents lipid peroxidation and mitochondrial damage.[22] Some studies have demonstrated that CoQ10 is effective for the treatment of noise-induced hearing loss, presbyacusis, and sudden sensorineural hearing loss.[9,21–23]

Idebenone, a synthetic analogue of CoQ10, reduces noise-induced hearing loss. CoQ10, with its antioxidant properties, shows protective effects against gentamicin ototoxicity both in ABR as well as histopathologically.[24]

This study was designed in order to evaluate the protective role of CoQ10 based on dose. We detected that although it did not protect hearing totally, it kept it at better level. There was no difference between high and low dose.

Several recent studies have evaluated the functional changes in the cochlea in cisplatin ototoxicity. Guinea pig may be the most sensitive animal for studies of cisplatin ototoxicity; transient-evoked otoacoustic emissions (TEOAEs) and DPOAEs are sensitive techniques for assessing the functional status of the outer hair cells.[25] In this study, we particularly selected DPOAEs for the assessment of cochlear function because it is a noninvasive, objective, and highly sensitive technique for the assessment of outer hair cell function and cochlear damage. It is a useful technique for monitoring drug-induced ototoxicity. Fetoni monitored the protective effects of Q-Ter® and reported that DPOAEs represent a sensitive test for monitoring the effects of noise in preclinical conditions and under pharmacological treatment.[26]

There are several limitations in this study. As cisplatin is administered in humans for several months at intervals of 2 to 4 weeks, typically no hearing loss is induced with a single dose. However, as in previous animal studies, we evaluated the effects of a single dose of cisplatin in animals for effort- and cost-related reasons. Different cisplatin doses were used in previous studies to evaluate cisplatin ototoxicity; it was reported that no significant hearing loss occurred at doses below 14 mg/kg/day, while hearing loss could occur at doses over 14 mg/kg/day, but the mortality rate also increased.[2,13] In our study, we administered cisplatin at the dose of 14 mg/kg/day, and there was a marked impairment in the general condition of the rats.

Conclusion

Although Q10 did not protect hearing, it kept it at better levels. There was no difference in protecting function of high and low.

Conflict of Interest: No conflicts declared.

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Please cite this article as: Berkiten G, Kumral TL, Saltürk Z, Tutar B, Göker AE, Sünnetçi G, Uyar Y, Uğraş H. The effect of coenzyme Q10 on cisplatin-induced ototoxicity in rats. ENT Updates 2016;6(3):110–115.