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Oxidative Stress of Radioiodine Treatment in Patients with Hyperthyroidism

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Aims: To investigate radiation-induced oxidative damage in erythrocytes after administration of radioiodine-131 (^{131}I) in patients with hyperthyroidism.

Materials and Methods: Twenty patients with hyperthyroidism (11 F, 9 M) treated with ^{131}I were included into the study. Blood samples were taken from patients just before, 1 hour after and 3 hours after applying radioiodine. Malondialdehyde (MDA) and levels of antioxidant enzymes such as glutathione peroxidase (GPX), superoxide dismutase (SOD) and catalase (CAT) were measured to evaluate the radiation-induced oxidative damage.

Results: We found that enzyme activities of SOD, GPX and CAT were decreased 1 hour and 3 hours after radioiodine treatment ($P < 0.05$), while MDA levels were increased 1 hour and 3 hours after the radioiodine treatment ($P < 0.05$).

Conclusions: Ionizing radiation causes harmful effects through the generation of free radicals. We found that radiation caused an oxidative damage in erythrocytes after administration of ^{131}I in patients with hyperthyroidism. In conclusion, although the population of the study was too small, these results indicate that exposure of hyperthyroid patients to ^{131}I decreased the erythrocyte antioxidant levels and increased MDA levels.

Key Words: Radioiodine treatment, hyperthyroidism, free radicals

Hipertroidide Radyoaktif İyot Tedavisinin Oksidatif Etkileri

Amaç: Hipertroidli hastalarda radioiodine-131 (^{131}I) uygulaması ile eritrositlerinde meydana gelen radyasyon kaynaklı oksidatif zararın tespiti.

Yöntem ve Gereç: 20 hipertroidi hastasına (11 kadın ve 9 erkek) ^{131}I verilmiştir. Hastaların kan örnekleri, ^{131}I verilmesinden hemen once, 1 saat ve 3 saat sonra olmak üzere üç kez alınmıştır. Radyasyon kaynaklı oksidatif zararın tespit edilmesi amacıyla, malondialdehit (MDA) ile glutatyon peroksidaz (GPX), süperoksit dismutaz (SOD) ve katalaz (CAT) gibi antioksidan enzimlerin seviyeleri tespit edilmiştir.

Bulgular: SOD, GPX ve CAT enzimlerinin aktivitelerinin I-131 verilmesinden 1 ve 3 saat sonra azaldığı ($P < 0.05$), MDA seviyesinin ise radyoaktif iyot alımından 1 ve 3 saat sonra arttığı tespit edilmiştir ($P < 0.05$). Hipertroidli hastaların ^{131}I ışınımına maruz bırakılmaları eritrosit antioksidan seviyelerini azaltırken, MDA seviyelerini yükselttiği tespit edilmiştir.

Sonuç: İyonize radyasyonun serbest radikallerin jenerasyonu yoluyla zararlı etkileri olduğu bilinmektedir. Hipertroidli hastalarda ^{131}I alımı ile eritrositler üzerinde oksidatif zararlar oluştuğunu tespit ettik.

Anahtar Sözcükler: Radyoaktif İyot Tedavisi, Hipertroidizm, Serbest Radikaller

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Introduction

Radioiodine-131 (^{131}I) has been used in therapy for more than six decades (1) and has proved clinically efficient, safe and cost-effective in comparison with other therapeutic alternatives (2). ^{131}I has been used as a first-line therapy for hyperthyroidism especially in elderly patients (3). In recent years, the use of ^{131}I among young patients has also increased.

It is known that the biological targets of radiation are the living cells. Radiation produces lethal effects on cells, particularly during division, and delays the onset of mitosis. Eventually, cell death or the loss of reproductive capacity occurs. Radiation

directly affects the DNA molecule of the cell nucleus and results in chromosomal abnormalities. Indirect effects of radiation occur via free radicals, which are highly reactive. Free radicals are oxygen metabolites that cause damage by oxidizing and reducing structures in the local environment. The production of free radicals is mainly the result of water radiolysis. The key reactive species are superoxide radical (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radical (OH^-) (4). Ionizing radiation produces the first two as immediate agents of cellular damage by lipid peroxidation of the membrane phospholipids (5,6). Hydroxyl radicals are generated by ionizing radiation either directly by oxidation of water or indirectly by the formation of secondary reactive oxygen species (ROS) (7).

Cells develop a defense mechanism against ROS by the antioxidant system, which includes enzymatic and non-enzymatic components (8). Low-molecular-weight antioxidant molecules such as glutathione (GSH), melatonin and various antioxidant enzymes are components of the antioxidant system. Superoxide dismutase (SOD) is the first-line of defense against oxygen-derived free radicals and catalyzes the dismutation of the superoxide anion (O_2^-) into H_2O_2. Catalase (CAT) is involved in peroxisomes in eucaryotic cells and transforms the H_2O_2 into H_2O and O_2. Glutathione peroxidase (GPX), a selenoprotein, reduces lipidic or nonlipidic hydroperoxides as well as H_2O_2 while oxidizing GSH to generate oxidized glutathione (GSSG), which is then reduced to GSH by glutathione reductase (9,10).

The process of lipid peroxidation is one of oxidative conversion of polyunsaturated fatty acids to products of native aldehydes such as malondialdehyde (MDA) and 4-hydroxynonenal by a well-studied, biologically relevant free radical reaction. MDA has been used as an index of oxidative damage (11).

The aim of this study was to investigate radiation-induced oxidative damage in erythrocytes after administration of ^{131}I in patients with hyperthyroidism.

Materials and Methods

The study was approved by the ethics committee of our hospital. MDA and antioxidant enzymes GPX, SOD, and CAT were measured to evaluate radiation-induced oxidative damage.

The study was carried out in the Medical Faculty of Süleyman Demirel University, Isparta, Turkey from January to April 2004. Twenty patients (11 F, 9 M) who had been treated with ^{131}I because of hyperthyroidism were included into the study. The mean age was 58 ± 9 years. Blood samples were taken from patients before, 1 hour after and 3 hours after applying 370-740 MBq ^{131}I in liquid form (Monrol, Kocaeli, Turkey).

Oxidative Stress Studies in Erythrocytes

MDA was determined by the double heating method of Draper and Hadley (12). The activities of SOD (13), GPX (14), and CAT (15) were measured by previously described methods. An autoanalyzer, Abbott Aeroset (IL, USA), was used to determine the activities of SOD and GPX, and the spectrophotometer, Shimadzu UV-1601 (Kyoto, Japan), was used to estimate MDA and CAT.

Statistical Analysis

Data were analyzed using the statistical package SPSS for Windows (Ref. 9.05, SPSS Inc., Chicago, IL, USA). Results were expressed as mean ± SD. Statistical significance was set at 0.05. Differences within the same group were tested by the repeated measures of ANOVA since all data were time-dependent.

Results

Results are tabulated in Table. The enzyme activities of SOD and CAT were decreased in samples taken 1 hour ($P = 0.013$, $P = 0.026$, respectively) and 3 hours ($P = 0.000$, $P = 0.028$, respectively) after administration of radioiodine according to before treatment values. GPX levels were decreased in samples taken 3 hours after administration of radioiodine ($P = 0.030$). MDA levels were increased in samples taken 3 hours after administration of radioiodine ($P = 0.000$).

Discussion

Ionizing radiation causes harmful effects through the generation of free radicals (16). We found that the radiation caused an oxidative damage in erythrocytes after administration of ^{131}I in patients with hyperthyroidism. The main reason for choosing erythrocytes as the model cell is the rich content of polyunsaturated lipids in erythrocyte membranes (17). Decline in the enzymatic activities of SOD, GPX and CAT

Table. Antioxidant and MDA levels (mean ± SD) before and after administration of radioiodine.

	MDA (nmol/mg Hb)	SOD (U/g Hb)	GPX (U/g Hb)	CAT (k/g Hb)
Before radioiodine	38.22 ± 7.92	1930.65 ± 693.21	79.686 ± 18.248	65.70 ± 25.31
1 hour after radioiodine	39.39 ± 16.54	1496.90 ± 182.65[a]	78.544 ± 7.283	52.84 ± 15.69[a]
3 hours after radioiodine	92.62 ± 24.36[ab]	1077.26 ± 464.72[ab]	62.253 ± 25.098[a]	52.22 ± 15.45[a]

MDA: malondialdehyde; SOD: superoxide dismutase; GPX: glutathione peroxidase; CAT: catalase.

[a] $P < 0.05$ compared to before radioiodine.

[b] $P < 0.05$ compared to 1 hour after radioiodine.

suggests that ^{131}I applications cause enzyme deficiencies, arising as a result of production of free radicals in the system. Lipid peroxide accumulation is believed to be a cause of cell membrane damage. Increased MDA level is an index of lipid peroxidation; its level increases in tissue after administration of ^{131}I. Pereira et al. (18) and Bilgihan et al. (19) found that hypothyroidism tended to diminish lipid peroxidation in lymphoid organs, and the concentration of MDA suggested an increased state in hypothyroidic cases. The suggestion was also made by Konukoğlu et al. based on the increased radical-induced lipid peroxidation in erythrocytes with elevated tissue hypoxia in hypothyroidic state (20). On the other hand, Dimitriu observed high levels of blood peroxides in both hyper- and hypothyroidism (21). Although hyper- and hypothyroidism cause elevation in MDA levels, radioactive iodine treatment led to the intensification of lipid peroxidation expressed by a significant increase in MDA values (20).

Konukoğlu et al. also reported that they did not find any correlation between administrated radioiodine dose and effects on the erythrocyte oxidant and antioxidant status (20).

Sabitha and Shyamaladevi demonstrated in their study that activities of erythrocyte SOD, CAT and GPX enzymes were significantly lower after radiotherapy than before radiotherapy (22). Our results were similar to Sabitha and Shyamaladevi's findings. This suggests that ionizing radiation causes enzyme deficiencies arising as a result of free radical production in the system. The increase in GSH levels in erythrocytes resulted from the elevated antioxidant enzyme activities (20). Lee et al. reported that SOD was an important anti-oxidant protein in the protection of yeast cells against ionizing radiation (23).

Lipid peroxide accumulation is believed to be a cause of cell membrane damage. MDA is an index of lipid peroxidation; its level increases in tissues after radiation-induced tissue injury (24). Greenstock et al. (25) and Büyükokuroğlu et al. (26) reported that ionizing radiation increased the level of MDA. In agreement with these results, we found that administration of ^{131}I increased erythrocyte MDA levels. Nikishkin et al. reported that levels of enzymatic and non-enzymatic antioxidants decrease after irradiation (27). SOD and GPX each play a role in the antioxidant defense system, but their response to radiation is unclear. Green et al. found that radiation did not significantly affect GPX activities in the long term (28), while Kaya et al. reported that GPX activities were not decreased significantly after irradiation compared with sham controls (29).

Diminished serum activities of SOD, GPX and CAT after administration of ^{131}I suggest that radiation causes enzyme deficiencies, arising as a result of production of free radicals in the system.

In conclusion, although the population of the study was too small, these results indicate that exposure of hyperthyroid patients to ^{131}I decreased the erythrocyte antioxidant levels and increased MDA levels.

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