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Protective effects of famotidine and vitamin C against radiation induced cellular damage in mouse spermatogenesis process

M. Mahdavi[1] and H. Mozdarani[2*]

[1]Department of Radiology, School of Paramedical Sciences, Shiraz University of Medical Sciences, Shiraz, Iran

[2]Department of Medical Genetics, School of Medical Sciences, Tarbiat Modares University, Tehran, Iran

Background: Radioprotective effect of famotidine was previously shown on radiation induced micronuclei and chromosomal aberrations in human peripheral lymphocytes and mouse bone marrow cells; however, its radioprotective property has never been studied in mouse spermatogenesis. It was also shown that vitamin C as an antioxidant also exert its radioprotective effect on many biological systems, but in some studies no protective effect is reported. ***Materials and Methods:*** Mice were injected by small and nontoxic amount of vitamin C and famotidine (3 and 2µg) inter-testicular 2 hours before irradiating by gamma ray. 29 days after irradiation, mice were sacrificed and testes were removed, weighed and either fixed for histological study or homogenized in 1.5 mL de-ionized water and 0.5 mL SDS solution. Sperm head count was done under a light microscope. Survival fractions were calculated and plotted as a function of dose of gamma rays. ***Results:*** The sperm head count in groups treated with vitamin C and famotidine before gamma irradiation show significant increase compared to groups only irradiated by gamma rays ($p<0.01$). Values of calculated dose reduction factor (DRF) are 2 and 2.68 for vitamin C and famotidine respectively. Both vitamin C and famotidine could reduce radiation induced pathological alterations in seminiferous tubules. ***Conclusion:*** These results suggest that vitamin C and famotidine have radioprotective property and could reduce cytotoxic effect of radiation in mouse spermatogenesis, one of the most radiosensitive biological systems. The possible mechanism of protection by famotidine and vitamin C might be radical scavenging. The radioprotection index for famotidine was found to be more than vitamin C.
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Keywords: *Radioprotection, gamma-rays, mouse spermatogenesis, vitamin C, famotidine.*

INTRODUCTION

Deleterious effects of radiation on biological systems have been shown in different ways. Therefore, various strategies have been developed to protect biological systems by means of chemical protection through interfering in the process of radiation damage. Since introduction of cystein as a radioprotector in 1949 [(1)], various types of natural and synthetic chemicals were tested for their radioprotective propertieson various biological systems by the use of different end points [(2)].

It was previously shown that H_2 receptor antagonists such as cimetidine and famotidine exert radioprotective effects on radiation induced micronuclei and chromosomal aberrations in human peripheral blood lymphocytes and mouse bone marrow cells [(3-5)]. Famotidine also was found to be a potent drug for reducing radiation induced apoptosis [(6, 7)]. But its radioprotective capacity has not been shown in mouse spermatogenesis, one of the most radiation sensitive biological systems.

Vitamin C as an antioxidant has shown radioprotective effect on different mammalian organs against internal or external low LET radiation with wide range of DRF (1.2 - 2.3) [(1, 8-12)]. It was also shown that vitamin C is capable of reducing paternal and maternal transgenerational genome instability [(13, 14)]. But some reports indicate that the capacity of vitamin C to reduce harmful effects of radiation is inconclusive [(15-17)], therefore further studies are needed.

It is well characterized that differentiating spermatogonia (A1, A2, Intermediate

Corresponding author:
Prof. Hossein Mozdarani,
Department of Medical Genetics, School of Medical Sciences, Tarbiat Modares University, Tehran, Iran.
Fax: *+98 21 88006544*
E-mail: *mozdarah@modares.ac.ir*

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and B) are the most sensitive cells in the mouse testis whereas; the stem and postgonial cells are relatively radioresistant [18-21]. When mouse testes are irradiated with X- rays or radionuclides, the initial damage to the spermatogonia results in reduced testicular sperm head population after the time necessary for spermatogonia to become spermatid [22, 23]. This time is about 4-5 weeks in mice. Spermatogenesis process in man is very similar to mouse [24-26]; although, spermatogonia has been shown to be more sensitive in man than mouse [24]. Therefore the result of the experimental model in mouse could be extended to man.

In this paper the influence of vitamin C and famotidine on the radiation response of mouse spermatogenesis process is examined.

MATERIALS AND METHODS

Animals: Male Balb/c mice aged 9 weeks and weighting about 26 g was purchased from Pasteur Institute (Tehran, Iran). They were kept in the university animal house at 22 ± 1 ℃ and a light: dark cycle of 14: 12 hours, fed with standard mouse pellet and water *ad libitum*. This study was approved by the ethical committee of Tarbiat Modares University, Tehran, Iran, and Institutional Animal Care and Use was followed.

Irradiation: Mice were irradiated whole body with various doses (50, 75, 100 and 150 cGy) of gamma-rays generated from a radiotherapy cobalt-60 source (Theratron II, 780 C, Canata, ON, Canada) at a dose rate of 76.66 cGy/min, with source sample distance (SSD) =82 cm, field size: 20×20 cm and at room temperature (23 ± 2 ºC). Optimal sacrifice day was found by sperm head count at various time intervals (27-29, 34, 35 days) for animals irradiated with 100 cGy gamma rays. The day 29 was chosen for sacrifice day because minimum sperm head count was observed in this day.

Drug treatment: To determine non toxic level of vitamin C and famotidine in mouse testis, mice were etherized and the vitamin C (Baker Co; England) dissolved in 1 µL normal saline was injected with various doses (0.75 to 6 µg) intra-testicular with Hamilton micro-syringe. The same procedure was applied for famotidine (Glob Organics Ltd; India) with doses of 0.25 to 2 µg. After 29 days, mice were sacrificed and testes were removed and homogenized in 1.5 ml deionized water and 0.5 ml SDS solution (Sigma, USA) (7.5% concentration of sodium dedecyle sulfate could separate sperm and spermatid head). Testicular sperm heads were counted using hemocytometer under a light microscope (×400), sperm head survival were compared with control testes. A nontoxic level of vitamin C, 3 µg and famotidine 2 µg was selected for radioprotective studies.

Two hours before irradiation with 50, 75, 100 and 150 cGy gamma radiation, mice were injected by 3 µg vitamin C and 2 µg famotidine intra-testicular. 29 days after irradiation mice were sacrificed and sperm head count was performed as described above. Survival fraction is calculated then survival curve is plotted for each group and compared with control groups based on sperm head count. Dose reduction factor (DRF) at 37% survival, is calculated based on the ratio of absorbed doses with and without vitamin C and famotidine at a given sperm head survival.

Histopathological analysis: Similar groups of animals were treated with radiation in the presence or absence of famotidine and vitamin C for histopathological analysis. Testes were surgically removed and weighed, then fixed in Bouin's fixative, dehydrated and embedded in paraffin. Five-µm serial sections were prepared from each testis. Slides were prepared by routine procedure and stained in hematoxilin and eosin (H&E). Histological alterations in the testicular architecture were observed in the seminiferous tubules. For the measurement of weight index, weight of both the testes

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from each animal was recorded. In each experiment six animals were used.

Statistical analysis: Data were statistically analyzed by SPSS software (version 16) using student's *t-test* and analysis of variance. Mean ± SD was calculated for each value. P value less than 0.05 was considered as significant level.

RESULTS

Figure 1 shows the chemotoxicity of vitamin C alone injected intra-testicular .No chemotoxicity is observed when up to 3 µg of the vitamin C. Similar observation was made for famotidine but the none toxic value for famotidine was found to be 2 µg (results not shown).

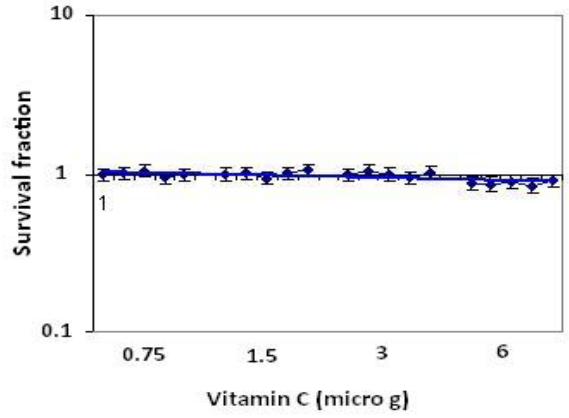


Figure 1. Sperm head survival as a function of vitamin C dose, injected intra-testicular. Five independent data point is related to each dose of vitamin C (0.75, 1.5, 3 and 6 µg). Maximum nontoxic amount of vitamin C was found to be 3 µg.

Figure 2 shows weight of both testes (right and left) of studied mice in gram with standard deviation. One way analysis of variance showed no significant difference between the weight of famotidine or vitamin C treated mice compared to controls ($p>0.05$). There was a significant difference between the weight of testis in irradiated mice 29 days after irradiation compared to normal controls ($P<0.05$), however, neither famtidine nor vitamin C could improve the weight of irradiated testis ($p>0.05$). Histological examination of seminiferous tubules of irradiated mice with 100 and 150 cGy showed significant pathological alterations in the form of intertubular edema and hemorrhage in intertubular space, distortion of cellular arrangement, shrinkage of tubules, cellular vacuolization, lower rate of differentiating cells toward tubules' centre and low mitotic index when compared with non-irradiated mice (figure 3 A and B). As seen in figure 3, treatment of mice 2 hours prior to irradiation with vitamin C (C and D) and famotidine (E and F) could effectively reduce pathological and histological alterations in seminiferous tubules after irradiation.

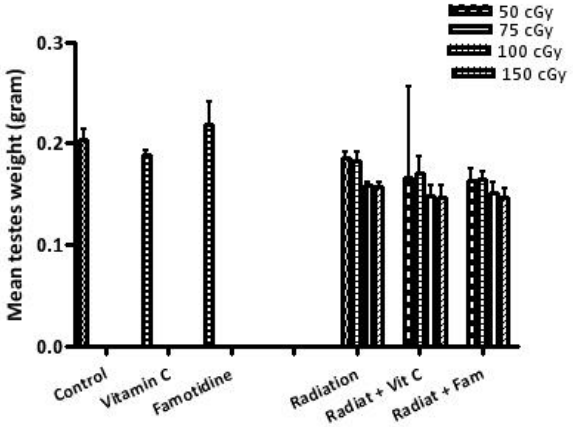


Figure 2. Testes weight of mice in all study groups, controls, and irradiated with various doses of gamma rays in the absence or presence of vitamin C and famotidine. Values are mean weight of both testes of mice obtained from 6 mice. Error bars indicate standard deviation of mean values.

The surviving fraction of sperm head as a function of absorbed gamma dose shows exponential dose response curve. By using non linear regression exponential function of data, D_0 value for spermatogonia types A, In and B is estimated to be 95.17 cGy with gamma ray (figure 4). Squared multiple correlation coefficient (R^2) is calculated to be 0.978. These cells require 28-30 days to produce late spermatid and spermatozoa.

The analysis was repeated for groups treated with vitamin C and famotidine. The mean lethal dose at 37% survival of spermatogonia when vitamin C and famotidine were preinjected are 191.04 cGy and 255.44 cGy respectively (R^2 = 0.9858 for vitamin C and R^2= 0.9943 for famotidine) (figure 4).

The corresponding DRF at 37%

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survival, being the ratio of absorbed doses with and without vitamin C and famotidine at a given sperm head survival, is 2 and 2.68 respectively. The DRF greater than 1.2 is considered as good radioprotection.

DISCUSSION

Effects of Famotidine

The photomicrographs shown in figure 3 (E and F) suggest that gamma- irradiation may cause significant injury in the structure of mouse spermatogenic epithelium and marked pathological alterations in seminiferous tubules. Injury degree correlates with dose of radiation. These findings are in agreement with the earlier reports which documented similar types of testicular injuries in irradiated mice [27-29].

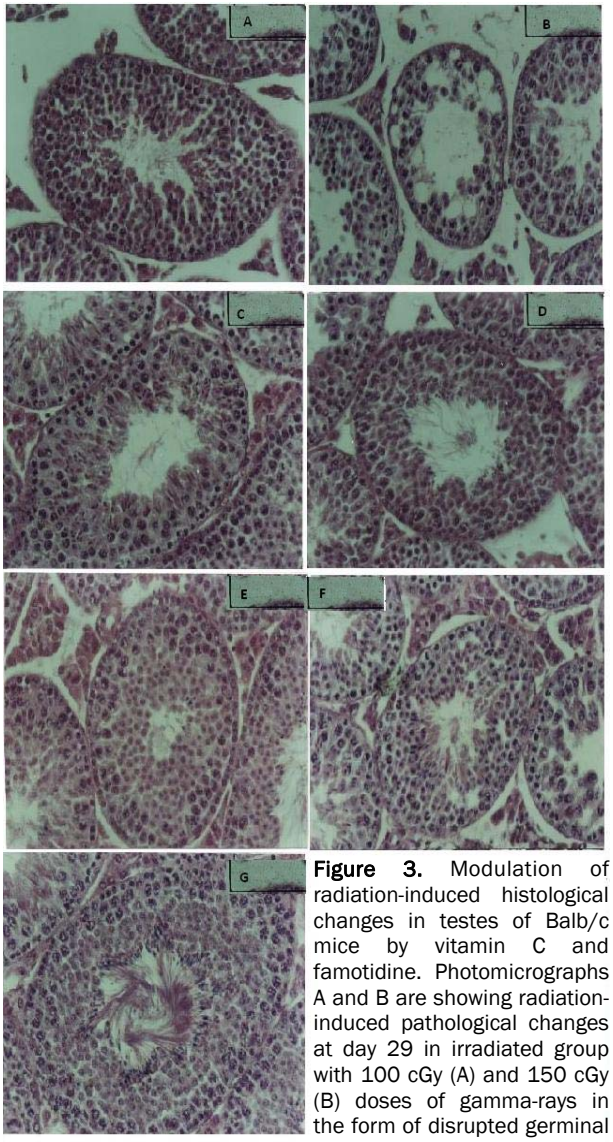


Figure 3. Modulation of radiation-induced histological changes in testes of Balb/c mice by vitamin C and famotidine. Photomicrographs A and B are showing radiation-induced pathological changes at day 29 in irradiated group with 100 cGy (A) and 150 cGy (B) doses of gamma-rays in the form of disrupted germinal epithelium, empty tubule, intertubular oedema, and intraepithelium vacuolation with depleted germ cells population. Photomicrographs C and D are showing vitamin C and photomicrographs E and F are showing famotidine treated mice before irradiation with 100 and 150 cGy respectively, with better testicular architecture and almost normal at day 29 of experiment. Photomicrograph G is showing normal architecture of testis. Magnification of photomicrographs ×400.

Gamma radiation exert its harmful effects through the generation of free radicals such as hydroxyl, superoxide and peroxyl which react with macro-molecules such as DNA, proteins and lipids in cell membrane. These free radicals known as reactive oxygen species (ROS) could damage radiosensitive cells such as spermatogonia by disturbing normal metabolism, proliferation and differentiation, which may lead to mutagenesis, apoptosis and necrosis [30]. It was previously shown that AET (Aminoethylisothiouronium), one of the aminothiols, effectively reduced radiation effects on mouse spermatogonia [22]. The DRF of 3.4 is reported for low LET ionizing radiation for AET [22]. The same biological model and data acquisition is used in our study.

The low sperm count 29 days after gamma irradiation which is best indicated by D_0 of cells (95.17 cGy) (figure 4) might be due to insult of free radicals to DNA which cause mitotic and apoptotic death in differentiating spermatogonia (Intermediate, B) which take 28-30 days to differentiate to mature spermatozoa. These cells are highly sensitive and can not proliferate after low dose of gamma radiation (50-100 cGy) [18, 21]. On the other hand, intra-testicular injection of famotidine led to increase in D_0 to 255.44 cGy (figure 4) indicating that famotidine might preserve cell proliferation by scavenging free radicals as seen in histological sections (figure 3). It was previously shown that famotidine as a H_2 receptor antagonist with reaction rate constant of 1.7×10^{10} $mol^{-1}.s^{-1}$, could scavenge $OH^{\cdot}$, HOCl and NH_2Cl radicals more effective than well known hydroxyl scavenger,

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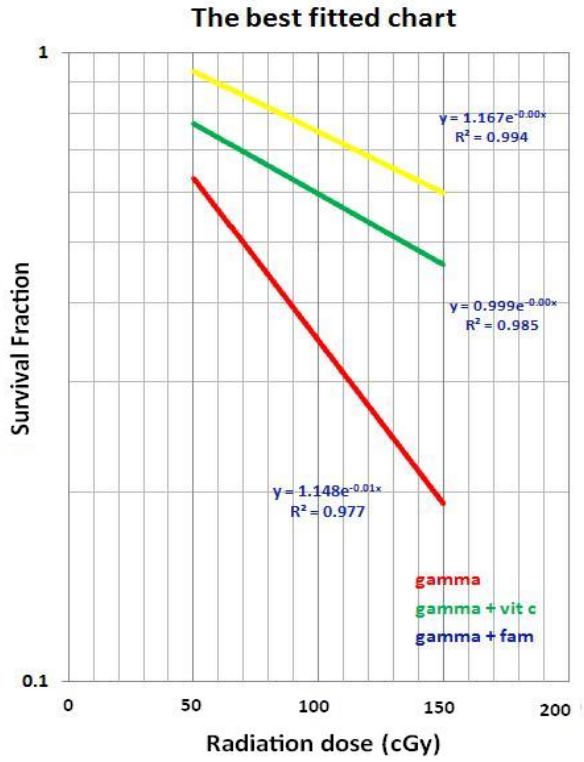


Figure 4. Sperm head survival as a function of various doses of gamma-rays alone or in the presence of famotidine (2 µg) and vitamin C (3 µg). Each data point is obtained from 6 mice.

manitol (1.7×10^9 $mol^{-1}.s^{-1}$) and glucose (1×10^9 mol^{-1} s^{-1}) [31, 32], thus this ability introduces famotidine as a potential radioprotector against gamma radiation. On the other hand, an ideal radioprotector should have the abilities to scavenge free radicals and oxidative damage and facilitate DNA repair [33]. The effect seen in this study is compatible with previous *in vivo* study with famotidine which effectively mitigate gamma induced micronuclei in mouse [5, 34]. In addition, famotidine is shown to reduce clastogenic effects of gamma ray against chromosomal aberration formation both *in vitro* and *in vivo* [34-36]. These radioprotective effects of famotidine are attributed to its radical scavenging properties.

All of these evidences indicate that famotidine may mitigate the harmful effects of radiation on spermatogonia by its radical scavenging and antioxidant specification. Famotidine ameliorated cytotoxic effect of gamma radiation on spermatogonia and this finding is supported by remarkable increase in mean sperm count in mice treated by famotidine in compare with mice only irradiated by gamma radiation ($p< 0.01$) 28-30 days post irradiation which is necessary for spermatogonia to differentiate into spermatozoa. Modulation of cytotoxic effect of gamma rays on seminiferous tubules by famotidine might be indicative of this observation (figure 3 E and F). The DRF calculated for famotidine is 2.68 which is considered to be an appropriate radioprotector for spermatogenesis process against radiation.

Effects of vitamin C

Results shown in figures 3 (C and D) and 4 clearly show that vitamin C effectively reduced radiation cytotoxicity in male germ cells. Many investigators showed that vitamin C exert its radioprotective effects on *in vitro* systems [9, 37-39]. It was previously shown by micronucleus test and metaphase analysis that ascorbic acid alone or in presence of vitamin E could decrease clastogenic effect of X and gamma rays in mouse bone marrow cells *in vivo* [40, 41]. In addition it was shown that vitamin C could effectively reduce paternal and maternal transgenerational genomic instability to preimplantation embryos [13, 14]. Also it was shown that vitamin C could have a slight radioprotective effect on sister chromatid exchange in radiosensitized murine cells *in vivo* [42].

Nara *et al.* [8, 43] have shown that vitamin C could exert its radioprotective effect against radionuclide's such as 5-(^{125}I)-iodo-2'-deoxyuridine(^{125}IdU) and H^{131}IPDM (N,N,N'-trimethyl-N'-(2-hydroxyl-3-methyl-5-iodobenzyl)-1,3-propanediamine), but not ^{210}Po citrate. In spite of the type of biological damage usually associated with high LET radiation and auger emitters incorporated into DNA, indirect effect associated with damage by free radicals play a major role in the mechanism of action of damage caused by auger cascade [43].

The capacity of ascorbic acid to mitigate radiation damage from external radiation to

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mouse testis was examined and a DRF of 1.2 was reported [8]. This finding is consistent with our study on mouse spermatogonia, but the the DRF for ascorbic acid in our examination was higher than reported by Nara *et al.* (2.03 versus 1.2) [8]. Since free radical production is related to the dose rate and total dose, higher concentration of vitamin C may be required when radiation is delivered acutely, therefore, the higher DRF obtained in our study (figure 4) might be due to higher but not cytotoxic concentration of vitamin C (3 µg versus 1.5 µg) (figure 1) injected intra testicular. Many previous experiments on radioprotective agents revealed that the second factor to determination of DRF of radioprotective agent is appropriate time of administration of agent in tissue [2]. Since the other evidence of greater DRF in our experience is the time of administration of vitamin C to mouse testes (2 hours versus 4 hours in previous study).

It was reported that vitamin C alone (0.01 µmol, 1 µmol) did not reduce radiation induced apoptosis in human lymphoblastic cell line, when given before 3 Gy gamma irradiation, but it showed radioprotective effect only at 0.01 µmol concentration after irradiation [17]. All of these finding suggest that presence or absence of radioprotective effect of vitamin C in examinations depend on concentration of vitamin C in biological environment, time of administration, radiation dose rate and type of radiation (low or high LET). In our experiment the ascorbic acid was injected intratesticularly, so the vitamin C was present in the tissue with nontoxic and appropriate concentrations before production of free radicals by irradiation. Lipid peroxidation takes place after irradiation or free radical attack [33]. Functionally, these changes can be expressed as altered membrane fluidity and permeability, which could trigger the release of potent physiological mediators [33, 44]. Vitamin C is an antioxidant molecule and prevents lipid peroxidation in plasma and inside the cell [44, 45], so inactivation of free radicals and preserving spermatogonial cell membrane may be attributed to scavenger property of ascorbic acid which is distinct by increase in mean sperm count in group that treated with vitamin C before exposing to gamma radiation in this experiment (figure 4). It was reported that the killing of male germ cells in mice irradiated by 0.5-5 Gy gamma rays might be attributed to apoptosis. These effects were most prominent among the B spermatogonia and early pre-leptotene spermatocytes [46]. On the other hand, it was shown that vitamin C and famotidine could efficiently reduce the frequency of apoptosis in irradiated human peripheral leukocytes *in vitro* [7]. Therefore in our study the increase in sperm head count 29 days following gamma irradiation in mice treated with vitamin C and famotidine may attribute to antiapoptotic properties that were shown previously for these two agents.

The histological findings in mice treated with vitamin C in comparison with the control group suggest that vitamin C exert its radioprotective effect on spermatogonia which is the most radiation sensitive cell in seminiferous epithelium of mouse testis and take 28-30 days to convert to spermatozoa (figure 3). DRF of vitamin C is calculated 2.01 (~2) which can be considered as an appropriate radioprotector of male germ cells.

CONCLUSION

The results presented here regarding the radioprotective effects of nontoxic amount of famotidine and vitamin C against gamma ray indicate that, vitamin C and famotidine could mitigate cytotoxic effects of gamma ray on mouse spermatogonia cells. The protection of famotidine was greater than vitamin C (2.68 versus 2). The proposed mechanism of protection for famotidine might be free radical scavenging and for vitamin C might be due to its radical scavenging and antioxidant property.

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