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Effect of cimetidine and famotidine on survival of lethally gamma irradiated mice

H. Mozdarani[1]*, M. Salimi[1], M. Froughizadeh[2]

[1] Department of Medical Genetics, School of Medical Sciences, Tarbiat Modares University, Tehran, Iran
[2] Novin Medical Radiation Institute, Tehran, Iran

Background: Currently available radioprotectors are poorly tolerated in man and the general use of aminothiols is compromised by their side effects. This study was carried out to test and compare the radioprotective potential of cimetidine and famotidine against lethally gamma irradiated NMRI mice. ***Materials and Methods:*** Adult male NMRI mice in groups of 10 were exposed to various doses of gamma rays at a dose rate of 93.3 cGy generated from a Co-60 source. Mortality was examined daily for 30 days after irradiation. Various doses of gamma rays were used to calculate $LD_{50/30}$. Different doses of cimetidine and famotidine were used in combination with 8 Gy gamma rays to find out the optimum protecting concentration of either drug. Finally the optimum protecting concentration of either drug was used in combination with various doses of gamma rays. Each experiment was repeated for three times. ***Results:*** Results show that mean $LD_{50/30}$ for radiation alone was found to be 723.7 cGy. When using different doses of cimetidine in combination with 801 cGy gamma rays, the dose of 15 mg/kg cimetidine produced optimum protection, while optimum dose of famotidine was found to be 10 mg/kg. However, $LD_{50/30}$ obtained with optimum dose of either cimetidine or famotidine led to a DRF of 1.11 and 1.05 respectively. ***Conclusion:*** Cimetidine compared to famotidine was found to be more protective against mortality induced by radiation in mice. This effect of cimetidine might be due to its immunomodulatory role and thus protecting bone marrow and lymphoid tissue injuries following whole body gamma irradiation. **Iran. J. Radiat. Res., 2008; 5 (4): 187-194**

Keywords: *Radiation lethality, radioprotection, cimetidine, famotidine, $LD_{50/30}$, DRF.*

INTRODUCTION

There has been a major progress in the area of radioprotective agents since the early 1980s in terms of biological and mechanistic evaluation of the large number of naturally occurring or synthesized compounds. This information led to the development of a new generation of derivative compounds. The development of radio protective agents has been the subject of intense research in view of their potential utility in radiation environments like accidental exposure, tumor radiotherapy, space exploration, and even in a nuclear battlefield [1]. The sensitivity of whole-body irradiated animals to ionizing- radiation in terms of bone marrow death has also been shown to fluctuate due to physiological conditions and the administration of various kinds of drugs.

All organ systems are potentially vulnerable to radiation-induced injury, but the hemopoietic and lymphoid systems are especially sensitive. Whole body exposure to doses of 200-1000 cGy is sufficient to produce a severe peripheral blood pancytopenia which results from depletion of the highly sensitive hemopoetic stem and progenitor cells. This leads to infection, hemorrhage, anemia and ultimately death within 30 days [2]. Survival in this hemopoetic system dose range can be increased by agents that simulate the function and recovery of the hemopoetic system.

The search for chemical agents which protect against tissue damage caused by exposure to ionizing radiation has led to the identification of thiol (sulfhydryl) compounds with marked activity in experimental models [3].

**Corresponding author:*
Dr. Hossein Mozdarani, Department of Medical Genetics, School of Medical Sciences, Tarbiat Modares University, P.O.Box: 14115-111, Tehran, Iran.
Fax: *+98 21 88006544*
E-mail: *mozdarah@modares.ac.ir*

Sulfhydryl compounds and chemicals that increase protein SH or nonprotein SH are strong radioprotectors because of their radical scavenging effects [1]. However, these are effective only before or during irradiation and sometimes have heavy side effects so that the use of the most promising agent WR 2721 (S-2-(3-aminopropylamino)-ethylphosphorothioic acid), has become limited by its poor clinical tolerance [4, 5]. Other compounds of synthetic and natural origin like- antioxidants, sulfhydryl compounds, cytoprotective agents, metalloelemnents, immunomodulators, lipopolysaccharides and prostaglandins, vitamins and DNA binding ligands have been tested by *in vivo* and *in vitro* models with little success [6].

Alternative ways effective for the protection include the transplantation of bone marrow cells and the administration of immunomodulators [7, 8]. Immunomodulators are usually less toxic and are effective even after irradiation; therefore, they may be available for people accidentally exposed to large doses. A wide variety of agents as well as immunomudelators, both naturally occurring and synthetic show promise in this regard as potential adjuncts to therapeutic and radioprotector regimens. Cimetidine, an antagonist of histamine type II receptors, usually used for peptic ulcer treatment, have shown to play a role in immune system by anti-suppressor cell activity [9, 10] and also when used with radiation effectively helped recovery of lymphohematopoetic system [11]. At cellular level it was effective against the clastogenic effects of gamma rays [12] and low doses of neutrons [13]. Famotidine, on the other hand, another compound in the class of histamine H_2 receptor antagonists but not an immunomudelator, has shown to greatly reduce micronuclei formation in mouse bone marrow cells [14, 15], initial DNA damage in mouse leukocytes [16], and apoptosis in leukocytes [17] following gamma irradiation. In the present study we used cimetidine and famotidine to test their ability for protection of bone marrow death following lethal doses of gamma rays.

MATERIALS AND METHODS

Animals and chemicals

Six to eight weeks old male NMRI mice were purchased from Razi Institute, Karaj. Mice were housed in polypropylene boxes, in a controlled environment (temperature 23 ± 2 °C and 12 hr dark and light cycle) with standard laboratory diet and water *ad libitum* in the animal house of the Novin Medical Radiation institution for two weeks before being used for experiments. After treatments mice were kept at similar condition for 30 days.

Cimetidine and famotidine (Guden Ritcher, Hungary) provided by Chemidarou Co. in Tehran, were diluted in physiologic serum and intra-peritoneal injected (i.p) at different concentrations 1 hour prior to irradiation, to allow enough time for accumulation in bone marrow.

The study groups were consisted of 8 groups as follows:

1- Control, untreated; 2, Cimetidine control with the highest selected dose (30 mg/kg); 3, Famotidine control with the highest selected dose (10 mg/kg); 4, Radiation alone with various doses (528 cGy-801 cGy); 5, Radiation (801 cGy)+various doses of cimetidine (10 mg/kg-30 mg/kg); 6, Radiation (801 cGy)+ various doses of famotidine (0.62 mg/kg-10 mg/kg); 7, Cimetidine (15 mg/kg)+various doses of radiation (590 cGy-1032 cGy); 8, Famotidine (10 mg/kg)+various doses of radiation (590 cGy-1032 cGy). For each dose in each experiment 10 mice were used. Experiments with radiation alone were repeated four times, the rest were performed in triplicate experiments. This study was approved by the Ethical Committee of the Novin Medical Radiation Institute and all animals were treated according to the regulations.

Gamma irradiation and examination of mortality

Irradiation was carried out using a cobalt-60 radiotherapy unit (Theratron II, 780C, Canada). Groups of mice were irradiated in a perforated plexiglass chamber (25×25 cm)

with various doses of radiation with a source to sample distance (SSD) of 82.5 cm at room temperature (24 ± 2°C). Dosimetry was performed with a Farmer dosimeter (Victorean). Dose rate at this condition was 93.3 cGy/min.

Mortality was examined daily for 30 days after irradiation. Ten mice were used for each group of experiments. Various doses of gamma rays (590 cGy-1032 cGy) were used to calculate $LD_{50/30}$. Various doses of cimetidine (10, 15, 20, 25 and 30 mg/kg) and famotidine (0.62, 1.25, 2.5, 5 and 10 mg/kg) were used in combination with 801 cGy gamma rays to find out the best protecting concentration of either drug. Finally the best protecting concentration of either drug was used in combination with various doses of gamma rays. Each experiment was repeated for three times.

Calculation of DRF

For assessment of DRF, optimum protecting concentration of drugs was used. The mice in control and vehicle groups were irradiated by doses in range of 528-801 cGy and in drug treated animals; the dose range was higher from 590 to 1032 cGy. To determine the protective ratio of cimetidine or famotidine against lethal doses of gamma irradiation, the DRF was calculated by dividing the $LD_{50/30}$ of control animals.

Statistical analysis

The statistical significance of the differences in survival rates compared to controls was determined according to the two-tailed chi-square test. Differences in survival time were evaluated according to a two-tailed *t*-test. Significance of any inter-group difference in the survival fraction was statistically evaluated by one way analysis of variance (ANOVA). Graphs were drawn using graphpad prizm version 4 for windows.

RESULTS

Survival of gamma irradiated animals

240 male mice were used to assess $LD_{50/30}$ following exposure of mice to various doses (528, 586, 650, 722 and 801 cGy) of gamma-irradiation. Irradiated animals were transferred to animal house and survival was monitored daily for 30 days. All experiments were repeated 4 times and the results are shown in figure 1. As seen, there is a good dose response relationship for the dose ranges used in these experiments. The mortality of 528 and 586 cGy doses did not show a significant difference with control un-irradiated mice, whereas for doses of 650, 722 and 801 cGy observed difference was statistically significant ($p<0.05$). Accordingly, doses of 801 and 722 cGy led to 20% and 55% survival respectively. Based on these observations, $LD_{50/30}$ was calculated to be 750 cGy for the animals and irradiation condition used in these experiments. The survival at 30 days of male NMRI mice irradiated over the whole body with various doses of gamma-rays is shown in figure 1.

Effect of various doses of cimetidine on whole body gamma irradiated mice

In order to determine the optimum protective dose of cimetidine, a total number of 270 male mice were used. Mice in groups of 10 were irradiated with a dose of 801 cGy in combination with a dose range of

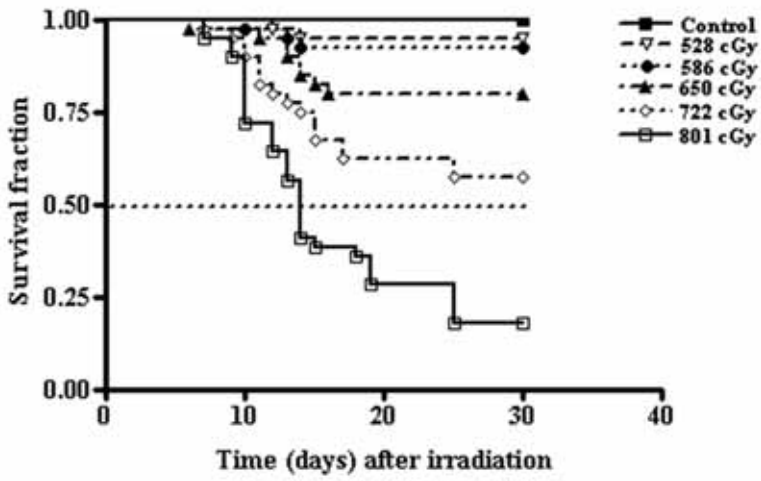

Figure 1. Survival of male NMRI mice irradiated with various doses of gamma rays at a dose rate of 93.3 cGy. Each time point indicates the results obtained with 40 mice.

cimetidine (10, 15, 20, 25, 30 mg/kg) intraperitoneal injected 1 hour before irradiation. A group of mice with only solvent injection and a group receiving the highest dose of cimetidine (30 mg/kg) were also considered as controls. Results of triplicate experiments are shown in figure 2. As seen in figure 2, the survival of only gamma irradiated mice with a dose of 801 cGy was about 5%. This survival rate was considerably increased following cimetidine treatment. Doses of 10, 15 and 20 mg/kg cimetidine led to a survival of 20, 37.5 and 25% respectively. Survival rate following treatment with doses of 20, 25 and 30 mg/kg did not show statistically significant difference with each other ($p>0.05$) whereas there was a significant difference observed for other doses of cimetidine ($p<0.05$). Based on this observation dose of 15 mg/kg cimetidine was found to be more potent to increase survival rate compared to other doses used in this study.

Determination of $LD_{50/30}$ for optimum dose of cimetidine

In these experiments, a total number of 180 mice in groups of 10 were irradiated with doses of 590, 678, 780, 897 and 1032 cGy in combination with optimum protective dose of cimetidine (15 mg/kg). A result of triplicate observations is shown in figure 3. As seen, irradiated animals with the highest radiation dose (1032 cGy) in the presence of cimetidine survived up to 12 days. However, survival of

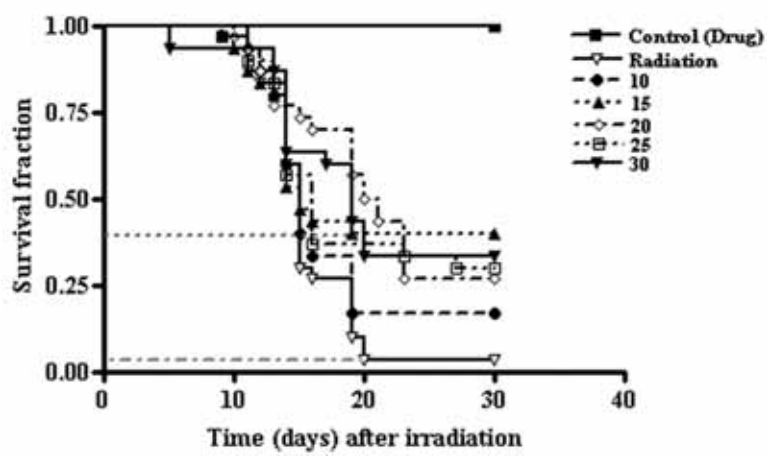

Figure 2. Groups of 10 male mice irradiated with 801 cGy at a dose rate of 93.3 cGy/min. The mice were injected various doses of cimetidine intraperitoneally 1 hour before irradiation. Dose of 15 mg/kg cimetidine is found to be optimum protecting dose at the dose range used. All data points are results of triplicate experiments.

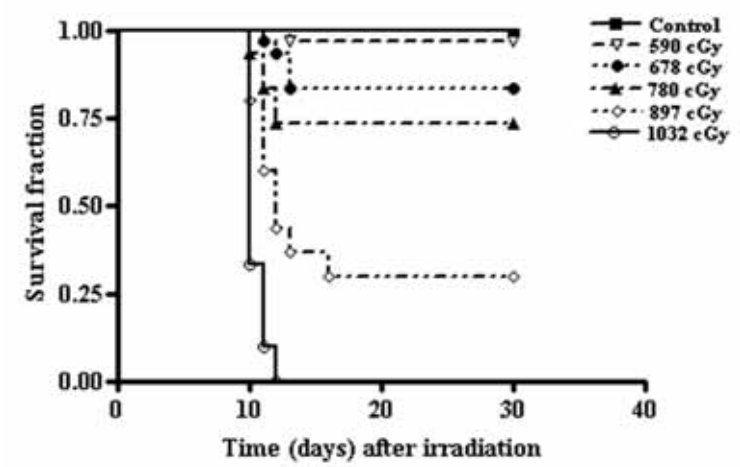

Figure 3. Survival in groups of 10 male NMRI mice irradiated with various doses of gamma rays at a dose rate of 93.3 cGy/min in the presence of optimum protecting dose cimetidine (15 mg/kg). Cimetidine was injected intraperitoneally 1 hour before irradiation. All data points are results of triplicate experiments.

those groups irradiated with 879 cGy in combination with cimetidine increased considerably to 25%. Pre-treatment of animals with cimetidine increased the survival of 780 cGy gamma irradiated animals to 75%. This value is about 30% higher than the $LD_{50/30}$ value observed for radiation alone.

Effect of various doses of famotidine on whole body gamma irradiated mice

In order to determine the optimum protective dose of famotidine, a total number of 270 male mice were used. Mice in groups of 10 were irradiated with a dose of 801 cGy in combination with a dose range of famotidine (0.62, 1.25, 2.5, 5 and 10 mg/kg) intra-peritoneal injected 1 hour before irradiation. A group of mice with only solvent injection and a group receiving the highest dose of famotidine (10 mg/kg) were also considered as controls. Results of triplicate experiments are shown in figure 4. As seen in figure 4, the survival of only gamma irradiated mice with a dose of 801 cGy was about 25%. This survival rate was not increased significantly for most of the doses of famotidine used. Only doses of 2.5 and 10 mg/kg famotidine could improve the survival of gamma irradiated mice in which the latter increased the survival rate to 37.5%. These observations suggested that the dose of 10 mg/kg famotidine was more potent to increase survival rate compared to other doses used in this study.

Determination of $LD_{50/30}$ for optimum dose of famotidine

In these experiments, a total number of 180 mice in groups of 10 were irradiated with doses of 590, 678, 780, 897 and 1032 cGy in combination with optimum protective dose of famotidine at the dose range used (10 mg/kg). A result of triplicate observations is shown in figure 5. As seen, irradiated animals with the highest radiation dose (1032 cGy) in the presence of famotidine survived up to 14 days. However, survival of those groups irradiated with 879, 780 and 628 cGy in combination with famotidine was 25, 50 and 75% respectively that are significantly different with each other ($p<0.05$). Survival rates observed for doses of 590 and 678 cGy were not significantly different. These results showed that pre-treatment of animals with famotidine increased the survival rate slightly above the observed $LD_{50/30}$ value with radiation alone, which is not significantly different with each other.

DISCUSSION

Results of whole body gamma irradiated mice with various doses indicate that there is a dose response relationship for radiation

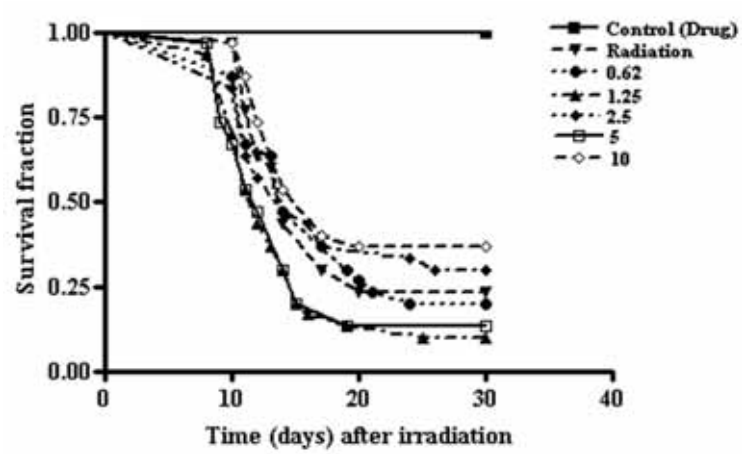

Figure 4. Groups of 10 male mice irradiated with 801 cGy at a dose rate of 93.3 cGy/min. The mice were injected various doses of famotidine intraperitoneally 1 hour before irradiation. Dose of 10 mg/kg famotidine is found to be optimum protecting dose at the dose range used. All data points are results of triplicate experiments.

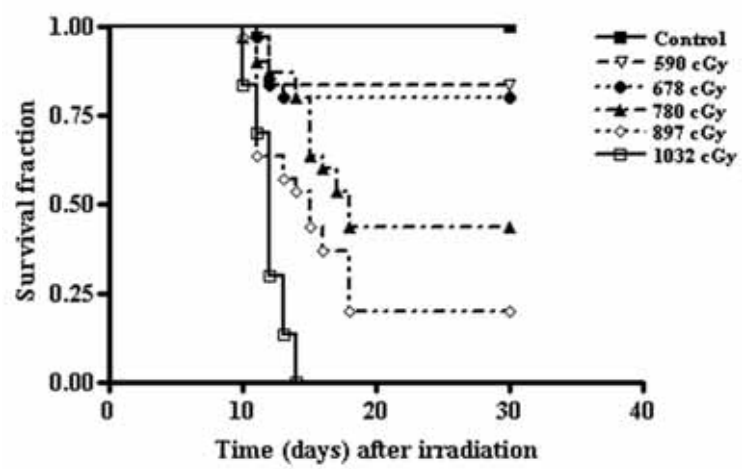

Figure 5. Survival in groups of 10 male NMRI mice irradiated with various doses of gamma rays at a dose rate of 93.3 cGy/min in the presence of optimum protecting dose of famotidine (10 mg/kg). Famotidine was injected intraperitoneally 1 hour before irradiation. All data points are results of triplicate experiments.

lethality (figure 1). Mean $LD_{50/30}$ calculated for radiation alone is about 723.7 cGy in which based on this value the DRF for drugs is calculated (table 1). The $LD_{50/30}$ obtained in this study is nearly similar to those reported earlier for mice [2], although, there might be small variations in the reported values for different strains. The survival of animal would depend on multisystem efforts of the organism to combat infection and maintain vital functions and also integrity of the body during the period of repair at cellular level. Radiation induced lymphohematopeitic syndrome is anticipated when a dose of radiation greater than 100 cGy is received. The resulting clinical situation is life threatening because of opportunistic infections and gradual decline in immune capacity due to irradiation. Certain drugs such as aminothiols, antioxidants, hemopoetic stimulants and immuno-stimulants are capable of protecting against radiation induced tissue injuries [18]. Histamine H_2 receptor antagonists such as cimetidine and famotidine are used clinically for peptic ulcer treatment [19, 20]. Apart from their capability for gastric acid suppression and the pepsin secretion [21], most of them are potent hydroxyl radical scavengers [22].

In the present experiments, survival of exposed mice to 801 cGy gamma rays after 30 days was 5%. Presence of cimetidine enhanced survival of mice and the optimum protective effect of cimetidine was found at a dose of 15 mg/kg in which increased the survival rate to 37.5% (figure 2). This result is consistent with previous reports indicating the protective effect of cimetidine on lymphohematopoetic system [11].

As seen in figure 3, $LD_{50/30}$ for radiation in the presence of 15 mg/kg cimetidine is about 850 cGy making the DRF about 1.17. However, mean $LD_{50/30}$ for radiation in the presence of cimetidine was 805.7 cGy leading to a mean DRF of 1.11 for cimetidine (table 1). Similar DRF has been

Table 1. Values calculated for $LD_{50/30}$ for each experiment performed with various doses of radiation alone (528-801 cGy) and higher doses of radiation (590-1032 cGy) in the presence of cimetidine (15 mg/kg) or famotidine (10 mg/kg) and resulting DRF. DRF is calculated as the ratio of $LD_{50/30}$ of either drug to the $LD_{50/30}$ of only irradiated animals.

Experimental group	Experiment No.	$LD_{50/30}$ (cGy)		Mean $LD_{50/30}$ (cGy)	DRF
		Value	95% confidence intervals		
Radiation alone	1	734.3	702.4-767.7	723.7	
	2	738	698-780.2		
	3	721.8	656.6-793.6		
	4	700.6	648.1-757.5		
Radiation + cimetidine (15 mg/kg)	1	811.3	756-870.6	805.7	1.11
	2	780.4	737.4-825.9		
	3	825.3	771.1-883.2		
Radiation + famotidine (10 mg/kg)	1	727.7	674.4-785.2	758.3	1.05
	2	766.9	703.3-836.2		
	3	780.4	710-857.8		

reported for oxymetholone, an alkylated anabolic steroid, capable of stimulating bone marrow cells and used for treatment of anemia, although with much higher doses for achieving such DRF (640 mg/kg) [23]. Other immunomudelators lithium chloride showed no radioprotective effect and OK432, a drug known to reduce radiation-induced leukopenia [24-27] had only slight radioprotective effects in spite of its stimulatory effects on GM-CFC and reducing effects on radiation induced leucopenia [28]. Radioprotective effect of cimetidine observed in this study (figures 2 and 3) as well as previous reports concerning potential protective effects of cimetidine against radiation induced lymphohematopoetic injury [11], clastogenic effects of gamma rays [12, 29] and low dose neutron [13] might be due to the augmentation of the proliferative capacity of lymphatic cells by cimetidine [30]. This and many other investigations indicate that administration of cimetidine before irradiation leads to the inhibition of T suppressor cells and increase the proliferation of CD4+ lymphocytes. This process causes production of glutathione reductase and catalase enzymes which prevent DNA damage and eventually reduced the clastogenic effects of radiation [12, 13, 29].

Using optimum dose of famotidine did not improve radiation lethality. Mean $LD_{50/30}$ calculated for famotidine was 758.3 cGy. Accordingly the DRF calculated for famotidine was 1.05 (table 1). This value is found to be much lower than that observed at cellular and molecular level. Famotidine dose not have immunomedulatory role in immune system but it has been shown that is a potent radical scavenger of oxygen radicals [31]. This effect of famotidine is shown to reduce clastogenic effects of gamma rays against micronuclei and chromosomal aberration formation [14, 32] as well as radiation induced DNA damage [16]. Therefore it appears that famotidine is effective against radiation insult in short terms. Similarly, the radioprotective effects of structurally different flavonoids [33, 34] and 2-iminothiazolidine derivatives have been investigated against gamma irradiation in mice [35, 36]. These compounds although toxic, did not produce a significant DRF either.

In conclusion, cimetidine was found more effective than famotidine to maintain long term survival following whole body gamma irradiation of mice. Cimetidine has a widespread clinical use with no apparent side effects at doses much higher than therapeutic levels and is administered orally. Therefore it might have the potential for usage for radiotherapy patients as well as radiation workers.

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