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Radioprotective Effects of Histamine H2 Receptor Antagonists Famotidine and Ranitidine on Gamma-Ray Induced Chromosome Aberration and Micronuclei *in vitro* in Human Lymphocytes

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Abstract: Histamine H2 receptor antagonist are used in the clinical treatment of peptic ulcer. *In vitro* metaphase analysis and micronucleus assay were used to test the effect of Famotidine & Ranitidine on ^{60}Cobalt gamma-ray induced clastogenic effects. Heparinised whole blood was obtained from 6 healthy volunteers and was gamma irradiated with 3Gy. Lymphocyte cultures were initiated and aqueous solution of Famotidine (150µg/ml) & Ranitidine (500µg/ml) was added at 0h and 24h. Cultures were harvested & processed at 48h & 72h for chromosome aberrations and micronucleus analysis respectively. At 0h & 24h after 3Gy gamma irradiation, cultures treated with Famotidine & Ranitidine independently showed significant decrease ($p < 0.0001$) in the frequency of chromosome aberration. At 0h & 24h Famotidine induced 60.91% & 56.42% inhibition in dicentrics & 59.39% & 56.21% inhibition was observed in total aberrations where as Ranitidine induce 52.11% & 43.54% inhibition in dicentrics and 53.06% & 46.66% inhibition in total aberrations at 0h & 24h. Significant decrease in the frequency of micronuclei was observed with Famotidine treatment after 3Gy of gamma irradiation, which induced inhibition of 48.83% ($p < 0.0001$) at 0hr & 5.02% ($p < 0.016$) at 24h. However, Ranitidine induced significant decrease ($p < 0.0001$) in frequency of micronuclei of 28.85% at 0h where as a decrease in frequency was observed of 2.88% at 24h although not significant when compared with 3Gy gamma irradiation alone. In conclusion radio protective effects of Histamine H2 receptor antagonists Famotidine and Ranitidine was observed on exposure to gamma-ray.

Keywords: Ionizing Radiation, Radioprotection, Chromosomal Aberration, Cytochalasin-B Blocked Micronuclei, Histamine H2 Receptor Antagonist, Famotidine, Ranitidine, Human Lymphocytes

1. Introduction

The use of chemical agents and phytochemicals to provide protection against radiation induced injuries has been a major field of study over 50 years. The focus of radiobiological research is to protect living organisms from radiation-induced damage. Ionizing radiation causes damage to living cells through a series of molecular events. Interaction of radiation with cell component such as DNA, have a prime biological significance on cells. Since ionizing radiation as a physical mutagen induces a variety of lesions in DNA such as SSB, DSB or clustered damages, quantification of these damages seems to be a good bio-indicator for ionizing radiation [1].

The search for more effective and less toxic radioprotectors has spurred interest in the development of different compounds. The compounds should be safe and non-toxic radio protectors which provide enough protection at a lower concentration and more tolerable in humans. Since the introduction of Cysteine as a radio protector in 1949 [2, 3], various types of natural and synthetic chemicals were tested for their radioprotective properties on various biological systems with different end points. Histamine H2 receptor antagonist also known as H2 blocker are class of drug which are used to block the action of histamine on parietal cells in stomach thus decreasing acid production by these cells. These drugs are potent scavengers of oxygen radicals, good inhibitors of histamine – stimulated gastric acid secretion, have capability for gastric acid suppression and the pepsin secretion

and in addition are potent & highly powerful hydroxyl-radical scavengers [4]. Histamine H2 receptor antagonist such as Cimetidine, Famotidine and Ranitidine are used in the clinical treatment of peptic ulcer. It was shown that H2 receptor antagonists such as Cimetidine and Famotidine exert radioprotective effects in human peripheral blood lymphocytes. [5,6]. Among them, Famotidine and Ranitidine are readily available in the market, economical and non-toxic at therapeutic doses administered. It can be administered orally. These properties of Famotidine and Ranitidine make it promising as a radioprotector for clinical use. Thus an attempt has been made to examine Famotidine and Ranitidine against gamma radiation induced DNA damage. The present study is conducted using metaphase chromosome for chromosome aberration and micronuclei analysis in order to examine the radioprotective effects of histamine H2 receptor antagonists on gamma rays induced clastogenic effects *in vitro* on human peripheral blood lymphocytes.

2. Materials and Methods

2.1. Sample Collection & Processing

Informed consents were obtained from 6 healthy male volunteers in the age group of 26-38 years with the inclusion criteria of having no history of exposure to clastogens, no smoking, tobacco chewing, alcohol consumption or drug taking. Blood samples were drawn from these volunteers under sterile conditions in heparinised vacutainer tubes. 0.3ml of whole blood was cultured in 4.5 ml Ham's F10 (Sigma) medium supplemented with 15% fetal calf serum (Sigma) and L-glutamine. Cell cultures were initiated with addition of 0.1ml of phytohemaglutinin (PHA) (Sigma) at a final concentration of 5μg/ml as mitogen to each culture vessel. No antibiotics were added to the cultures at any stage. Cultures were incubated at 37°C. This culture protocol was followed for CBMN. Briefly, at 24 h after culture initiation, cytochalasin B was added, resulting in a final concentration of 6μg/ml in the cultures [7].

2.2. Drug Usage

Famotidine tablets USP 20mg (Famotin*20) (Mfd. By USV Limited Mumbai India) and Ranitidine Hydrochloride Tablet IP (Zinetac*150mg) (Mfd. By GlaxoSmithKline Pharmaceutical Limited Nashik, India), were purchased from local market. Tablets were crushed and dissolved in double distilled water to get aqueous solution of Famotidine (150 μg/ml) and Ranitidine (500μg/ml) which were filtered sterilized.

2.3. Irradiation of Blood Samples

Blood samples were irradiated with ^{60}Co gamma rays at 3Gy (dose rate of 0.77Gy/min (Teletherapy Machine – Theratron Junior ^{60}Co Machine). Cultures were set from the un-irradiated and irradiated blood samples as per the standard protocol [7].

2.4. Study Design

2.4.1. The Following Sets of Experiments Were Conducted.

Set I – 0.3ml of irradiated whole blood was innoculated into 5ml of reconstituted culture medium for CA analysis and the following groups were included: (a) control (un-irradiated whole blood), (b) un-irradiated whole blood + FAM 150μg/ml or RAN 500μg/ml 0h and 24h (c) ^{60}Cobalt gamma radiation 3Gy irradiated whole blood (d) ^{60}Cobalt gamma radiation 3Gy irradiated whole blood + FAM 150μg/ml or RAN 500μg/ml 0h and 24h; total duration 48h (demecolcine added at 45h).

Set II – 0.3ml of irradiated whole blood was inoculated into 5ml of reconstituted culture medium for MN analysis and the following groups were included: (a) control (un-irradiated whole blood), (b) un-irradiated whole blood + FAM 150μg/ml or RAN 500μg/ml 0h and 24h (c) ^{60}Cobalt gamma radiation 3Gy irradiated whole blood (d) ^{60}Cobalt gamma radiation 3Gy irradiated whole blood + FAM 150μg/ml or RAN 500μg/ml 0h and 24h, total duration 72h (cytochalasin B 6μg/ml added at 24h).

Forty-eight hours after culture initiation, 0.2μg/ml demecolcine (Sigma) was added to the cultures for 2h to arrest cells at metaphase. Cells were harvested and exposed to hypotonic solution (KCl, 0.075M) for 12 minutes, then fixed in Carnoy's fixative (3:1 v/v Methanol : Glacial acetic acid). Slides were prepared using air drying technique and stained in 2% Giemsa solution (Merck). For cytoknesis blocked micronuclei assay, cells were harvested at 72h following a 5min 0.8% cold KCl treatment and fixation, including 1% formaldehyde in the second fixative. Cells were stained with 1% Giemsa (Merck) in Sorensen's buffer, *pH* 6.8, for 20 min [8, 9, 10].

200 mitoses were analyzed for the presence or absence of chromosomal aberrations for each treatment. Lesions were classified according to the international system of cytogenetic nomenclature for acquired chromosome aberrations (ISCN 1985) [11]. Major chromosomal aberrations observed in this study were of chromosome types including isochromatid gaps, isochromatid breaks and chromosomal exchanges, mainly of dicentric type.

Cytogenetic analysis was carried out incorporating the Chromososme and Micronucleus Analysis

2.5. Chromosome Aberration Assays

The stained preparations were examined for unstable CAs [12]. CAs was scored from 100 well-spread metaphases with a minimum of 46 centromeres and 50 metaphases per slide under oil immersion at 100 X magnification.

2.6. Cytochalasin B Blocked Micronuclei Assays

Total numbers of micronucleated binucleated cells (MNBN) and total number of MN were determined in 1000 binucleated cells with well-preserved cytoplasm. The nuclear division index (NDI) was determined by scoring the number of mononucleate, binucleate, trinucleate, tetranucleate and more (polynucleate) cells in 1000 viable cells. The nuclear

division index (NDI) was calculated as:

$$\text{NDI} = \frac{[\text{M1} + (2\times\text{M2}) + (3\times\text{M3}) + (4\times\text{M4})]}{n}$$

where M1 to M4 represent the number of cells with 1 to 4 nuclei respectively; n is the total number of cells scored [9, 10, 13].

In order to study the radioprotective capability of Famotidine and Ranitidine, Chromosome aberration and CBMN assay was carried out in blood sample of 6 donors.

3. Result & Observations

3.1. Dicentric and Total Aberration Analysis

The frequencies of chromosome and chromatid breaks were found to be 0% in control cultures. Tables I and Figure 1 represents frequency of dicentrics and total aberration obtained with various treatment and Table II and Figure 2 represents the percent inhibition with various treatment in human lymphocytes in 6 individual donors. Cultures treated with 3Gy gamma irradiation showed frequency of dicentrics to be 119 + 5.68 and total aberrations to be 124 + 6.10. After 3Gy gamma irradiation, Famotidine showed a significant decrease ($p < 0.0001$) in dicentrics and total aberrations at 0h and 24h. The frequency of dicentrics and total aberrations observed was 46.50 + 2.14 and 50.50 + 3.45 /100 cell at 0h and 52.67 + 2.33 and 54.33 + 2.94 / 100 cells at 24h. Famotidine induced 60.91% and 56.42% inhibition in dicentrics and 59.39% and 56.21% inhibition in total aberrations respectively. At 0h and 24h, Ranitidine after 3Gy gamma irradiation revealed a significant decrease ($p < 0.0001$) in dicentrics and total aberrations. The frequency of dicentrics and total aberrations was observed to be 56.17 + 2.2.80 and 58.17 + 2.82 /100 cell for 0h, and 67.17 + 3.13 and 67.33 + 3.26 / 100 cells for 24h. Ranitidine induced 52.09% and 45.54% inhibition in dicentrics and 53.06% and 45.66% inhibition in total aberrations respectively. The distribution analysis was carried out and was found to be poissonian. The dispersion index and U values confirmed the distribution to be a Poisson distribution.

Table I. *Frequency of Dicentrics and Total aberration per 100 cells analyzed in human lymphocytes following gamma irradiation in the absence or presence of Famotidine (FAM) and Ranitidine (RAN) at 0h and 24h of six donors.*

Donors	**1**		**2**		**3**		**4**		**5**		**6**	
	Dic	**TA**	**Dic**	**TA**	**Dic**	**TA**	**Dic**	**TA**	**Dic**	**TA**	**Dic**	**TA**
Control	0	0	0	0	0	1	0	0	0	0	0	0
FAM 0h	0	2	0	0	0	0	0	0	0	0	0	0
FAM 24h	0	4	0	1	0	0	0	1	0	0	0	0
RAN 0h	0	2	0	0	0	0	0	0	0	0	0	0
RAN 24h	0	0	0	1	0	0	0	1	0	0	0	0
3Gy	119	129	130	136	102	104	140	144	110	114	113	117
3Gy + FAM 0h	47	54	51	63	40	42	54	56	43	43	44	45
3Gy + FAM 24h	52	59	56	59	45	47	61	64	48	48	49	49
3Gy + RAN 0h	57	58	62	63	49	50	67	69	53	53	54	56
3Gy + RAN 24h	67	67	73	73	58	58	79	80	62	62	64	64

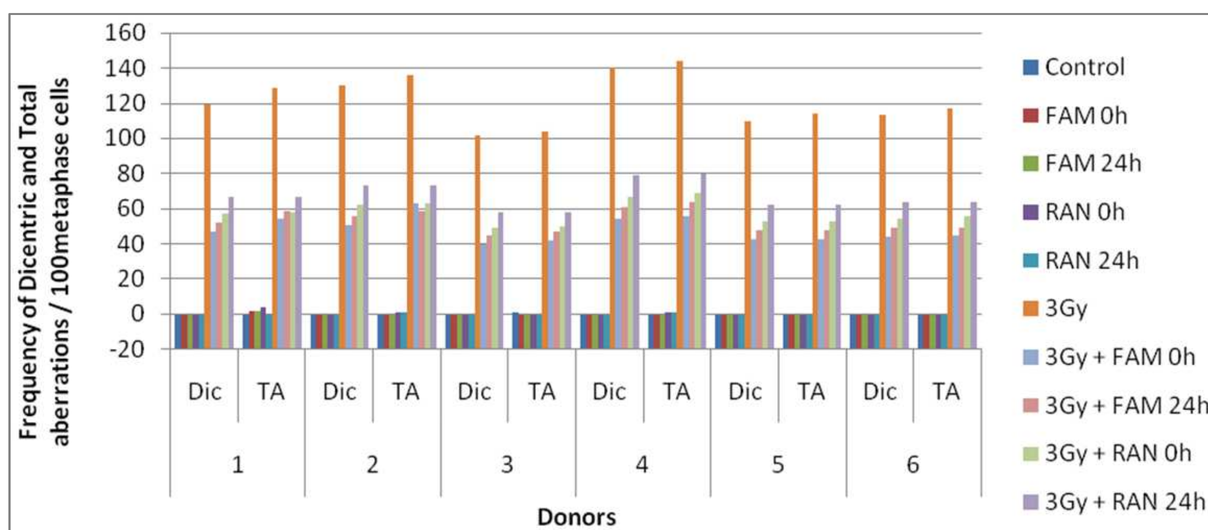

Fig. 1. *Frequency of Dicentric and Total aberrations per 100 metaphase cells among the six donors following 3 Gy of gamma irradiation in the absence or presence of various doses of Famotidine (FAM) and Ranitidine (RAN) at 0h and 24h [Y axis represents frequency of Dicentric and Total aberrations per 100 metaphase cells and X axis represents six donors frequency of Dicentric and Total aberrations].*

Table II. *Percent Inhibition of Dicentrics and Total aberrations analyzed in human lymphocytes following gamma irradiation and Famotidine (FAM) or Ranitidine (RAN) treatment at 0h and 24h among the six donors.*

	% Inhibition							
Donor	**3Gy + FAM 0h**		**3Gy + FAM 24h**		**3Gy + RAN 0h**		**3Gy + RAN 24h**	
	Dic	TA	Dic	TA	Dic	TA	Dic	TA
1	60.50	58.13	56.30	54.26	52.10	55.04	43.69	48.06
2	60.76	53.68	56.92	56.62	52.30	53.68	43.85	46.32
3	60.78	59.61	55.88	54.81	51.96	51.92	43.14	44.23
4	61.42	61.11	56.43	55.55	52.14	52.08	43.57	44.44
5	60.91	62.28	56.36	57.89	51.82	53.51	43.64	45.61
6	61.06	61.54	56.64	58.12	52.21	52.14	43.36	45.30

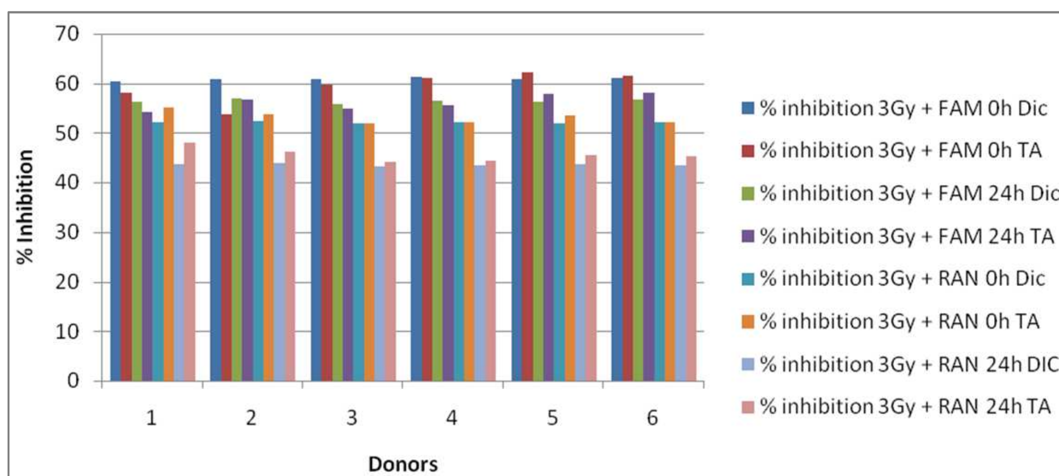

Fig. 2. *Percent Inhibition of Dicentrics and Total aberrations analyzed in human lymphocytes following gamma irradiation in the absence or presence of various doses of Famotidine (FAM) and Ranitidine (RAN) in 6 donors. [Y axis represents % inhibition and X axis represents six donors].*

3.2. Micronuclei Analysis

Frequency of micronuclei analyzed in human lymphocytes following gamma irradiation in the absence or presence of Famotidine (FAM) and Ranitidine (RAN) and with various treatments is depicted in Tables III and figure 3 and percent inhibition with various treatments in human lymphocytes in 6 individual donors is represented in Table IV and figure 4. Tables III and Figure 3 represents frequency of Micronuclei per cell at various treatment and total number of binucleated cells scored were 1000. Table IV and Figure 4 represents the percent inhibition in micronuclei with various treatment.

Cultures treated with 3Gy gamma irradiation showed a frequency of 1.010 + 0.01366 micronuclei in binucleate cells. At 0h and 24h, Famotidine after 3Gy gamma irradiation revealed a significant decrease ($p < 0.0001$ for 0h & $p < 0.016$ for 24h) in micronuclei in binucleate cells. The frequency of micronuclei was observed to be 0.52 + 0.0074 and 0.96 + 0.0083 /BN cell, and 48.83% and 5.02% inhibition in micronuclei at 0h and 24h respectively. After 3Gy gamma radiation, Ranitidine showed a significant decrease ($p < 0.0001$) in the frequency of micronuclei in binucleated cell to be 0.72 + 0.0262 / BN cells at 0h where as 28.85% inhibition in micronuclei when compared with 3Gy gamma irradiation alone. However a decrease in the frequency of micronuclei in binucleated cell are found to be 0.98 + 0.0052 /BN cell for 24h although the decrease was not statistically significant ($p < 0.14$) where as Ranitidine showed 2.88% inhibition in micronuclei when compared with 3Gy gamma irradiation alone.

Table III. *Frequency of Micronuclei analyzed in human lymphocytes following gamma irradiation in the absence or presence of Famotidine (FAM) and Ranitidine (RAN) at 0h and 24h among 6 donors is depicted.*

Donors		**1**	**2**	**3**	**4**	**5**	**6**	**Mean + SE**
	Total No of BN cells	**MN/cell**	**MN/cell**	**MN/cell**	**MN/cell**	**MN/cell**	**MN/cell**	
Control	1000	0.005	0.004	0.003	0.003	0.004	0.005	
FAM 0h	1000	0.005	0.005	0.004	0.003	0.004	0.006	
FAM 24h	1000	0.004	0.004	0.006	0.003	0.003	0.004	
RAN 0h	1000	0.005	0.004	0.005	0.006	0.006	0.004	
RAN 24h	1000	0.004	0.004	0.006	0.005	0.003	0.003	
3Gy	1000	1.010	1.040	0.980	0.960	1.040	1.030	1.0100 + 0.01366
3Gy + FAM 0h	1000	0.528	0.542	0.490	0.510	0.530	0.520	0.5200 + 0.00741
3Gy + FAM 24h	1000	0.964	0.978	0.930	0.968	0.940	0.980	0.9600 + 0.00837
3Gy + RAN 0h	1000	0.772	0.802	0.722	0.620	0.720	0.684	0.7200 + 0.02629
3Gy + RAN 24h	1000	0.988	0.974	0.998	0.978	0.960	0.982	0.9800 + 0.00527

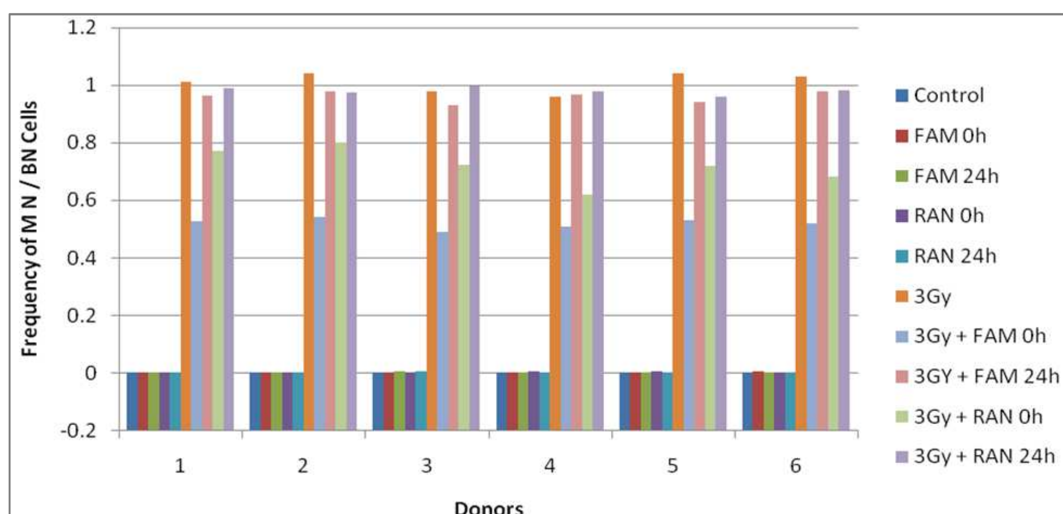

Fig. 3. *Frequency of Micronuclei analyzed/BN cells in human lymphocytes following gamma irradiation in the absence or presence of Famotidine (FAM) and Ranitidine (RAN) at 0h and 24h in 6 donors [Y axis represents frequency of Micronuclei per BN cells and X axis represents six donors].*

Table IV. *Percent Inhibition of Micronuclei analyzed in human lymphocytes following gamma irradiation and Famotidine (FAM) or Ranitidine (RAN) at 0h and 24h among the six donors is depicted.*

	% Inhibition of MN			
Donor	**3Gy + FAM 0h**	**3Gy + FAM 24h**	**3Gy + RAN 0h**	**3Gy + RAN 24h**
1	47.72	4.47	23.56	2.10
2	47.93	5.96	22.88	6.35
3	50.05	5.40	26.48	-1.60
4	48.96	-0.008	35.73	-1.66
5	49.04	9.53	30.90	7.60
6	49.56	4.76	33.53	4.47

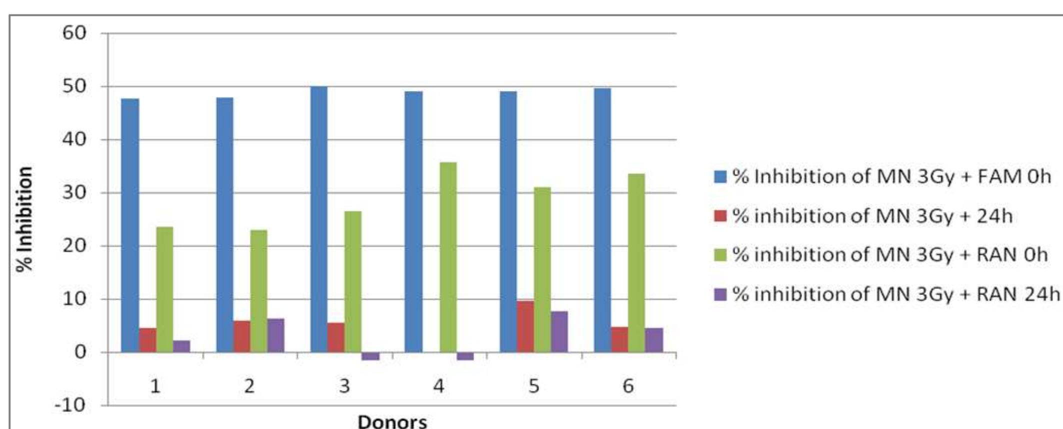

Fig. 4. *Percent Inhibition of Micronuclei analyzed in human lymphocytes following gamma irradiation and Famotidine (FAM) or Ranitidine (RAN) at 0h and 24h in 6 donors [Y axis represents % inhibition and X axis represents six donors].*

The nuclear division index (NDI) ranged between 1.532 to 1.708, and was determined by scoring the number of mononucleate, binucleate, trinucleate, tetranucleate and more (polynucleate) cells in 1000 viable cells.

4. Discussion

In the present investigation, evaluation of radioprotective effects of Histamine H2 receptor antagonists is comprehensively investigated; Famotidine and Ranitidine on gamma-ray induced chromosome aberration and Micronuclei *in vitro* in human lymphocytes of six donors. CA and CBMN formation is used as the end points. The data indicated that the control (untreated) lymphocytes, did not exhibit any type of chromosomal damage.

It is a well known fact that ionizing radiations such as X-rays and gamma rays produce biological damages/effects due their indirect-effect through formation of free radicals. A major proportion of single and double strand breaks in DNA molecule is caused by the formation of hydroxyl radicals [14, 15]. It is also observed that $-OH^-$ scavengers played an effective role in preservation of the DNA strands against

breakage [16]. Such scavengers are known as radioprotectors which are designed compounds to reduce radiation induced damage in normal tissue on exposure to radiation. Famotidine and Ranitidine, H2 receptor antagonists have exerted radio protective effect in many systems such as in mouse bone marrow erythrocytes, Famotidine and Ranitidine showed radioprotective effects when applied *in vivo* [17]. Studies carried out by Lappena *et al* [18] have shown that Famotidine and Ranitidine as such do not have immunomodulatory role in the body but these drugs are potent oxygen radical scavengers. Ching *et al* [19] have demonstrated that histamine H2 receptor antagonists such as Famotidine and Ranitidine were good inhibitors of histamine – stimulated gastric acid secretion and also posses the capability for gastric acid suppression and pepsin secretion [4]. These are potent and highly powerful hydroxyl-radical scavengers. Based on the study of Ching et al [20] on HOCl scavenging properties of these drugs, it was concluded that the presence of sulphur atom in the compound is important for their scavenging activity.

Lymphocytes treated with Famotidine and Ranitidine at 0h and 24h did not show any increase in frequency of dicentric and total aberration. Ionizing radiation such as gamma radiation (3Gy) alone caused increased in chromosomal damage resulting in dicentrics, centric rings and fragment formation. Lymphocytes treated with Famotidine and Ranitidine at 0h and 24h after irradiation with gamma ray (3Gy) showed decrease in the frequency of dicentric and total aberration. The MN test is a reliable and effective test for the evaluation of clastogenic effects of physical and chemical agents [21, 22]. Lymphocytes treated with Famotidine and Ranitidine at 0h and 24h did not show any increase in frequency of micronuclei when compared with controls. 3Gy of gamma radiation exposure alone caused increase in micronuclei frequency. Lymphocytes treated with FAM and RAN at 0h and 24h after irradiation with gamma ray (3Gy) also showed a decrease in the frequency of micronuclei. The results and observation of the experiments conducted indicated that histamine H2 receptor antagonists are radioprotectors in nature when used in vitro as shown by Ghorbani and Mozdarani [5, 23]. The mechanism in which these drugs reduce clastogenic effect of gamma-radiation is not fully understood. It might be due to their antioxidant and free radical-scavenging properties.

Reduction of the frequency of chromosomal aberrations in the lymphocytes treated with Famotidine and Ranitidine at 0h and 24h after irradiation with gamma ray (3Gy) indicate that drugs might reduce the clastogenic effect of radiation via radical scavenging mechanism and famotidine is more effective than the ranitidine – histamine H2 receptor antagonists studied.

5. Conclusion

Radioprotective effects of Histamine H2 receptor antagonists; Famotidine and Ranitidine on gamma-irradiation induced chromosome damage were observed and the drugs effectively reduced the frequency of radiation induced chromosome aberrations and micronucleus particularly at 0h, as compared to 24h. Famotidine was found to be more effective, thus these features makes it suitable for use as chemical radioprotector especially for radiotherapy patients.

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