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Author(s)	岡村, 重昭; 馬屋原, 晟; 古賀, 充 他
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THE INFLUENCE OF S-2-AMINOETHYL ISOTHIURONIUM Br-HBr ON THE EQUAL EFFECT RATIO BETWEEN 200kVp X-RAYS AND ^{60}Co γ-RAYS

by

Shigeaki Okamura

Department of Experimental Radiology (Director: Prof. H. Yoshinaga), Faculty of Medicine, Kyushu University

Akira Umayahara Mitsuru Koga, Toshikazu Takeshita and Akira Yasukochi

Department of Radiology (Director: Prof. H. Irie), Faculty of Medicine, Kyushu University, Fukuoka, Japan

200 kVp X線と ^{60}Co r線の等効果比に及ぼす S-2-Aminoethylisothiuronium Br-HBr の影響

九州大学医学部放射線基礎医学教室（指導　吉永春馬教授）

岡　村　重　昭

九州大学医学部放射線科学教室（指導　入江英雄教授）

馬屋原　晟　古賀　充　安河内　彰　竹下　寿七

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雄性及び雌性の CF#1 10～11週令のハツカネズミを用い，その $LD^{50}/_{30}$ を指標にした 200 kVp X線と ^{60}Co γ線の等効果比に及ぼす S-2-Aminoethylisothiuronium Br-HBr（以後ＡＥＴと略する）の影響を検討した．

$LD^{50}/_{30}$ はX線群の雄 560 rads, 雌 553 rads, X線＋ＡＥＴ処置群で雄 810 rads, 雌 902 rads, γ線群で雄 874 rads, 雌 857 rads, γ線＋ＡＥＴ処置群で雄1248 rads, 雌1325 rads となつた．

これよりＡＥＴの dose-reduction factor を求めるとX線群で雄 1.5, 雌 1.6, γ線群で雄 1.4, 雌 1.5となり，等効果比を求めるとＡＥＴ非投与群では雄0.6_4, 雌0.6_5：ＡＥＴ投与群では雄 0.6_5, 雌0.6_8となつた．

この結果から考えるとＡＥＴの dose-reduction factor はX線でもγ線でもほぼ等しく，又ＡＥＴの投与はX線とγ線の等効果比に影響を及ぼさないと考えられる．

何故ＡＥＴがX線とγ線の等効果比に影響しなかつたかについて考察し，通常用いられている Gray や Cormack の計算したＬＥＴ値よりも Burch の計算したＬＥＴ値の方がより適切であろうと述べた．

Introduction

Numerous reports have been made on the protective agents against radiation injuries. Since the report of Doherty et al,[1)2)] S-2-Aminoethylisothiuronium Br-HBr (AET) in particular has been recognized to be the most effective protective agent against radiation damage.

On the other hand, many experiments have geen conducted on the relative biological effectiveness (RBE) between radiations of different qualities.[3] Particularly, the RBE between 200 kVp X-rays and high energy radiations has been studied by Irie and his coworkers with the support of the scientific research grant provided by the Ministry of Education of Japan[4][5][6][7].

However, there is hardly any report in literature which compares the effect of protective agents against radiations of different qualities.

In the present study the difference in effect of AET on the $LD^{50}/_{30}$ of mice between 200 kVp X-rays and ^{60}Co γ-rays was investigated.

Experimental Procedure

CF ♯ 1 male and female mice, 10 to 11 weeks old, were divided into the following four groups. Each exposure was graded in these four groups, as described below.

X-ray groups (for both sexes)		480, 550, 630, and 725 R
X-ray+AET groups	(for male)	630, 725, 800, 900, and 1000 R
	(for female)	800, 900, 1000, and 1100 R
X-ray groups (for both sexes)		725, 800, 900, and 1000 R
X-ray+AET groups	(for male)	1100, 1200, 1300, 1400, and 1500 R
	(for female)	1200, 1300, 1400, and 1500 R

Radiation sources and exposure conditions are as follows.

200 kVp X-rays: Shinai X-ray machine (manufactured by Shimazu Co.) operated at 15 mA with a filtration of 0.7 mm Cu+0.5 mm Al. The distances from X-ray target to the mouse were 55 cm and 33 cm and dose rates were 52.5 R/min and 151.0 R/min for each distance, as measured in the air with a Victroeen ionization chamber (No. 154).

^{60}Co γ-rays : 1.17 MeV and 1.33 MeV γ-rays from a 3000 -curie teletherapy unit (Shimazu). The distances from the source to the mouse were 106 cm and 67 cm and dose rates were 46.7 R/min and 128.0 R/min for each distance, as measured in the air with a Victoreen chamber (No. 621).

The high dose rates of X-ray and γ-ray were used in the cases irradiated over 800 R or 900 R. Whole body irradiation was delivered in a rectangular wooden container, covered with X-ray film for X-ray irradiation and with acrylate resin plate (thickness of 5 mm) for γ-ray, respectively.

A dose of 7 mg of AET neutralized by 0.1 N NaOH (namely, AET changes to Mercaptoethy lguanidine in this condition) was injected intraperitoneally and the corrected administration time[8] ("time from administration to irradiation" $+\frac{\text{irradiation time}}{2}$) was 20 minutes.

Results

The dose, the number of mice, the number surviving 30 days after exposure, and the survival rate (probit) are shown in Table I.

Attempts were made to develop an empirical transformation formula which would give values decreasing linearly with irradiation dose. A modified logarithmic transformation formula was found to be satisfactory.

$$S=-aD+b$$

where D is irradiation dose in log. scale, S is the most reliable survival ratio in the probit scale, and a

Fig. I. The relationship between exposure and survival rate (male) is illustrated.

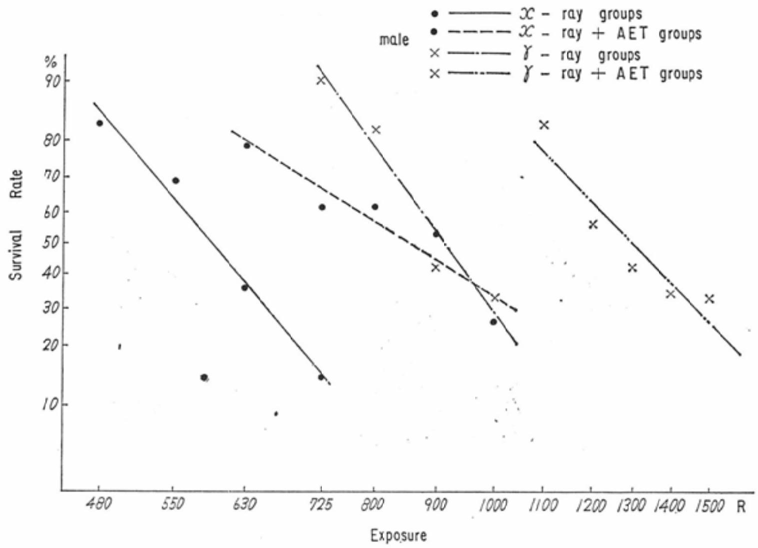
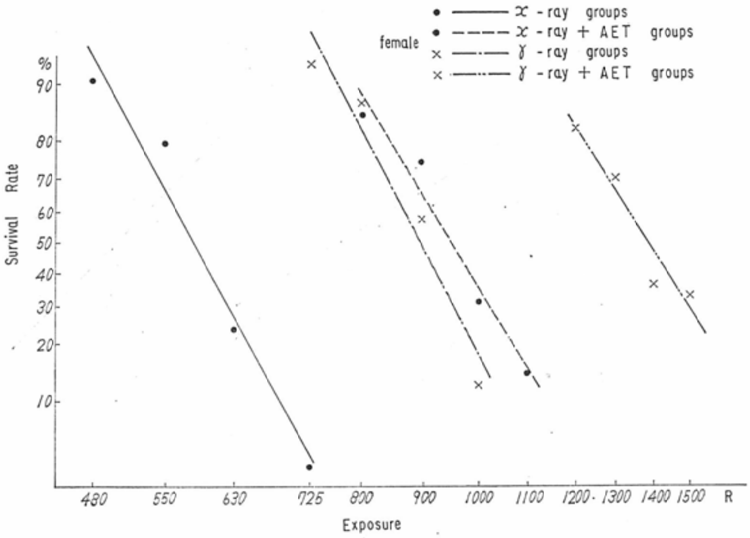


Table I. The doses, the number of mice, the number surviving 30 days after exposure, and the survival rate (probit) are shown.

	Male				Female			
X-ray groups								
Dose	No. of mice	30 days survival	survival rate	probit	No. of mice	30 days survival	survival rate	probit
480R	12	10	83.3%	5.97	32	29	90.6%	6.32
550R	13	9	69.2%	5.50	33	26	78.8%	5.80
630R	11	4	36.4%	4.65	33	8	24.2%	4.30
725R	14	2	14.3%	3.93	29	1	3.4%	3.17
X-ray + AET groups								
630R	14	11	78.6%	5.79				
725R	13	8	61.5%	5.30				
800R	13	8	61.5%	5.30	33	28	84.8%	6.03
900R	15	8	53.3%	5.09	36	27	75.0%	5.67
1000R	15	4	26.7%	4.38	35	11	31.4%	4.51
1100R					35	5	14.3%	3.93
γ-ray groups								
725R	11	10	90.9%	6.33	28	26	92.9%	6.47
800R	11	9	81.8%	5.91	31	27	87.1%	6.13
900R	14	6	42.9%	4.82	33	19	57.6%	5.19
1000R	12	4	33.3%	4.57	33	4	12.1%	3.82
γ-ray + AET groups								
1100R	12	10	83.3%	5.96				
1200R	14	8	57.1%	5.18	34	28	82.4%	5.93
1300R	14	6	42.9%	4.82	34	24	70.6%	5.54
1400R	14	5	35.7%	4.63	36	13	36.1%	4.64
1500R	12	4	33.3%	4.57	30	10	33.3%	4.57

Fig. II. The relationship between exposure and survival rate (female) is illustrated.



and b are constant.

This linearity in relationship between survival ratio and exposure is demonstrated in Figure I and II.

The relationship between survival ratio and log. dose is calculated [9] as follows.

Male

X-ray groups	$S=-11.698D+37.41$
X-ray+AET groups	$S=-6.111D+22.91$
γ-ray groups	$S=-13.588D+45.21$
γ-ray+AET groups	$S=-10.053D+36.30$

Female

X-ray groups	$S=-18.381D+55.82$
X-ray+AET groups	$S=-16.215D+53.01$
γ-ray groups	$S=-18.935D+60.86$
γ-ray+AET groups	$S=-15.462D+53.55$

In the above, D is roentgen in log. scale, S is the most reliable value of survival ratio in the probit scale.

Table II $LD_{50/30}$ values of CF# 1 male and female mice on X-ray groups, X-ray + AET groups, γ-ray groups, and γ-ray + AET groups are shown.

	male	female
X-ray groups	590 R (560 rads)	582 R (553 rads)
X-ray + AET groups	853 R (810 rads)	949 R (902 rads)
γ-ray groups	910 R (874 rads)	891 R (856 rads)
γ-ray + AET groups	1299 R (1247 rads)	1380 R (1325 rads)

Table III The dose-reduction factor on X-ray and on γ-ray is shown.

$\frac{LD_{50/30} \text{ of X-ray + AET groups}}{LD_{50/30} \text{ of X-ray groups}}$	1.4 (male)	1.6 (female)
$\frac{LD_{50/30} \text{ of } \gamma\text{-ray + AET groups}}{LD_{50/30} \text{ of } \gamma\text{-ray groups}}$	1.4 (male)	1.5 (female)

Table IV. The equal effect ratio between X-ray and γ-ray with or without AET treatment is shown.

$\frac{LD_{50/30} \text{ of X-ray groups}}{LD_{50/30} \text{ of } \gamma\text{-ray groups}}$	0.6_4 (male)	0.6_5 (female)
$\frac{LD_{50/30} \text{ of X-ray + AET groups}}{LD_{50/30} \text{ of } \gamma\text{-ray + AET groups}}$	0.6_5 (male)	0.6_8 (female)

With this formula, $LD^{50}/_{30}$ of each group was calculated and is shown in Table II.

In this calculation, factors used in converting roentgens to rads were 0.95[10] for X-ray and 0.96[11] for γ-ray, respectively.

The dose-reduction factor of AET is shown in Table III.

The dose-reduction factor of AET for X-ray is 1.4 for male and 1.6 for female, and for γ-ray it is 1.4 for male and 1.5 for female, respectively.

The equal effect ratio between X-ray and γ-ray is shown in Table IV.

The equal effect ratio between X-ray and γ-ray without AET treatment is 0.6_4 for male and 0.6_5 for female and with AET treatment it is 0.6_5 for male and 0.6_8 for female, respectively.

Discussion

The RBE Committee has recommended that the term "equal effect ratio" should be used instead of "RBE" for the comparison of effects between radiations of different qualities, such as $LD^{50}/_{30}$. Because $LD^{50}/_{30}$ is a measure of effects which, although equal in number of fatalities one month after irradiation, can involve very different mechanisms leading to death.

Many authors have made studies to determine the optimum administration time of AET. Some give 30 minutes[13] before irradiation as the best administration time of AET, while others give 10 minutes[14] and 10–15 minutes[15] as the best administration time of MEG, but their irradiation time (or dose rate) differs. The length of irradiation time bears upon the survival rate in the use of protective agents, because the distribution of protective agent in the critical organs changes after administration even during irradiation. Therefore, the length of irradiation may affect the optimum administration time. In 1961 the authors proposed[8] the corrected administration time which takes consideraion into interval time between administration and irradiation (the administration time) and the interval time between the beginning and end of irradiation (the irradiation time). In 1965 this concept of corrected administration time was supported by the report on "the distribution of radioactivity following AET-^{35}S administration"[16]. Thus, the problem of how to determine the administration time in the cases of different irradiation time (or of different irradiation dose) can be resolved by the use of this corrected administration time. In practice, two dose rates were used in order to reduce the difference between the longest and shortest irradiation time.

According to the recent reports made by Oldfield et al[17][18] on the chemical protection against 440 MeV protons in mice pretreated with Mercaptoethylamine (MEA) and p-Aminopropiophenone (PAPP), RBE (or the equal effect ratio in this report) was found to be 0.66 in the control, 0.57 by MEA treatment and 0.70 by PAPP treatment. They ascribe the variation in RBE value to the difference in dose-reduction factors of MEA and PAPP between protons and X-rays. It should be noted that both MEA and PAPP were administered 5 minutes before irradiation and the change in concentration of the protective agent in the critical organs was disregarded. They may have committed a severe error in the experiment by using a definite administration time. For this reasons the authors can not agree to their finding that the dose-reduction factors of these agents differ between 440 MeV protons and 250 kVp X-rays, and that RBE when MEA or PAPP is used differs from the control value.

In the present experiment the dose-reduction factor of AET on X-ray and γ-ray is 1.4～1.6, a value which is considered to be almost equal. As for the equal effect ratio, an almost equal value of $0.6_{4\sim8}$ was also obtained in the case of AET treatment. In other words, the dose-reduction factor of AET is almost equal in both X-ray and γ-ray, and AET has not affected the equal effect ratio between X-ray and γ-ray.

The mechanism of the ionizing radiation is considered to have direct action and indirect action. According to the calculation made by Gray[19] and Cormack et al[20], the mean LET of 200 kVp X-rays and that of ^{60}Co γ-rays have different values, i.e. about 3 keV/micron and 0.3 keV/micron, respectively. It may be possible that the contribution ratio of direct action and indirect action on irradiation effect might differ according to X-ray or γ-ray.

Why do the dose-reduction factors of AET on X-ray and γ-ray have an almost equal value of 1.4～1.6? Why does the equal effect ratio have a nearly equal value of $0.6_{4\sim8}$ even when AET is used? The reason involved will be discussed.

If we assume that AET modifies both the direct and indirect action (e.g. promotion of recovery from radiation injury), a number of other assumptions would be necessary to satisfy the result of the present experiment that the dose-reduction factor of AET in X-ray and γ-ray is of almost equal values.

If however we assume that, as Doherty et al. say, AET modifies the indirect action, the degree of contribution of the direct action to radiation effects by both X-rays and γ-rays can be assumed to be very small in comparison with that of indirect action: and the degree of modification on the indirect action by AET can be assumed to have hardly any difference between X-ray and γ-rays. This would satisfy the result of our experiment that the dose-reduction factor is of an almost equal value regardless whether X-ray or γ-ray is used. This assumption seems to be more reasonable than the former assumption. Accordingly, AET would have no influence on the equal effect ratio between X-ray and γ-ray, and this agrees with the result of our experiment that the equal effect ratio between X-ray and γ-ray has a nearly equal value regardless whether AET is used or not.

The following LET has been reported:

The mean LET of 200 kVp X-rays ....3.25 keV/micron (Gray's)
1.79 keV/micron (Cormack's)
The mean LET of ^{60}Co γ-rays ....0.36 keV/micron (Gray's)
0.245 keV/micron (Cormack's)

As shown above, the mean LET of 200 kVp X-rays is 7～9 times larger than that of ^{60}Co γ-rays. However, the equal effect ratio of X-ray and γ-ray is about 0.6～0.7 as demonstrated in the present experiment. Although the equal effect ratio is usually explained with relation to LET, the difference between this equal effect ratio and the ratio of LET appears to be very large.

The indirect action of -Xrays and γ-rays is assumed to be chiefly due to δ-rays and it is considered that δ-rays of both X-rays and γ-rays do not give any qualitative difference in effect, since δ-ray has the same character with regard to both radiations. In the mean LET computed by Gray and Cormack δ-track formation is ignored. According to Burch[21] the mean LET values allowing for δ-tracks are 25.8 keV/micron for 200 kVp X-rays and 19.6 keV/micron for ^{60}Co γ-rays. Based on our experiment, the mean LET values allowing for δ-tracks by Bruch are considered to be more reasonable than those calculated by Gray and Cormack.

Summary

A study was made on the equal effect ratio between 200 kVp X-rays and ^{60}Co γ-rays based on $LD^{50}/_{30}$ of CF#1 male and female mice with or without S-2-Aminoethylisothiuronium Br-HBr treatment.

The problem of length of irradiation, which influences the survival ratio when protective agents are used, was solved by using the corrected administration time. This was reported earlier.

The dose-reduction factor of AET on X-ray is 1.4 for male and 1.6 for female, and on γ-ray it is 1.4 for male and 1.5 for female, respectively.

The equal effect ratio between 200 kVp X-rays and ^{60}Co γ-rays without AET treatment was 0.6_4 for male and 0.6_5 for female and with AET treatment 0.6_5 for male and 0.6_8 for female.

These results suggested that the dose-reduction factor of AET on X-ray and γ-ray is almost equal and that the equal effect ratio between X-ray and γ-ray is almost equal regardless of AET treatment.

Discussion was made on the reason why AET treatment has not influenced the equal effect ratio and why the mean LET values calculated by Burch are more appropriate than those reported by Gray and Cormack.

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