Assessment of the Action of Mixed Irradiation

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Problems associated with the environmental and health perspectives of mixed irradiation are identified and the application of theoretical models is discussed. Four definitions of synergism were examined with regard to the action of mixed irradiation, and it was determined that all these definitions are inappropriate. Thus, I concluded that the term synergism or its synonym should not be used for the action of mixed irradiation unless a reasonable definition and evidence of the mechanism are provided. The Zaider–Rossi model and the extended Zaider–Rossi model, which can be applied to any type of mixed irradiation with two types of radiation, are useful for assessing the effects of mixed irradiation using the parameters for two types of single irradiation. Furthermore, models were proposed for very short and very long simultaneous mixed irradiation with multiple types of radiation. These models also would be helpful to assess the environmental and health perspectives of mixed irradiation. — Environ Health Perspect 105(Suppl 6):1455–1458 (1997)

Key words: mixed irradiation, synergism, synergistic, low dose rate, theoretical model, high linear energy transfer

Introduction

Mixed irradiation with different types of radiation is used and sometimes occurs in nature, but its action has not yet been clarified. Therefore, I examined the problems associated with and the application of theoretical models of mixed irradiation for their environmental and health effects.

It is not clear whether this combined effect is synergistic because several different definitions of the term synergism have been proposed. These definitions were examined with respect to the effect of mixed irradiation and I determined that they are inappropriate and misleading (1,2). This paper discusses the reasons why I deem these definitions inappropriate.

It is also important to assess the effect of mixed irradiation on the environment, on accidental exposure, or in space. Therefore, this paper also reports on application of the Zaider–Rossi model (3) and the Zaider–Rossi extended model (4) to evaluate the effect of mixed irradiation and proposes models for very short and long simultaneous mixed irradiation with more than two types of radiation.

To assess environmental and health risks of mixed irradiation, one must study cell killing, mutation, transformation, and carcinogenesis of the organs within which dose distribution is heterogeneous. However, this paper deals only with survival of monolayered cells because interpretation of the action of mixed irradiation is confusing at best, even in homogeneous dose distribution as discussed in this paper and because cell survival rates, most important and essential for calculating the frequency of mutation or transformation in vitro, can be obtained with more accuracy than other mechanisms.

Results

Examination of Synergism Definitions

The action of mixed irradiation is defined as synergistic in various ways, four of which are listed as follows.

When

\[ S(D_1 + D_2) < S(D_1)S(D_2) \]  \hspace{1cm} (1)

is satisfied, where \( S(D_1) \) and \( S(D_2) \) are the surviving fractions of cells irradiated with doses \( D_1 \) and \( D_2 \) of radiation types 1 and 2, and \( S(D_1 + D_2) \) is the surviving fraction of cells irradiated with dose \( D_1 \) of radiation 1 and then with dose \( D_2 \) of radiation 2 (5,6).

When

\[ \varepsilon > 1 \]  \hspace{1cm} (2)

is satisfied, where \( P_{\text{exp}} = P_1 + P_2 - P_1P_2 \), \( \varepsilon = P_{\text{obs}}/P_{\text{exp}} \) and \( P_1 \) and \( P_2 \) are the separate probabilities of the effect after exposure to radiation types 1 and 2, and \( P_{\text{exp}} \) and \( P_{\text{obs}} \) are the expected and observed probabilities of the effect after exposure to a combination of radiation types 1 and 2 (7).

When dose pairs of mixed irradiation are located below the envelope of additivity in isobolograms (i.e., iso-effect curves) (8). When

\[ S(y_1 + x) < S(x_1 + x) \]  \hspace{1cm} (3)

is satisfied. When radiation \( X \) reduces survival, a dose \( y_1 \) of radiation \( Y \) that reduces survival to \( S(y_1) \) is equivalent to dose \( x_1 \) of radiation \( X \), i.e., \( S(y_1) = S(x_2) \) (9).

Why these definitions of synergism are inappropriate is explained as follows.

The first definition, Equation 1, is always satisfied with survival curves with a shoulder including a survival curve even with a single irradiation as a special case of mixed irradiation (1,8). One exception is that one or two survival curves are semilogarithmically linear \( (S(D_1+D_2) = S(D_1)S(D_2)) \). It follows from this definition that two types of the action of mixed and single irradiation are synergistic, which is meaningless.

The second definition, Equation 2, by the United Nations Scientific Committee on the Effects of Atomic Radiation, is basically the same as Equation 1 because Equation 1 can be obtained by substituting 1–S for P in Equation 2.

According to the third definition, action of mixed irradiation with radiation 1 followed by 2 is called synergistic and that with radiation 2 followed by 1 is called additive although the effects are equal (1,10–12) (Figure 1).

According to the fourth definition, Equation 3 by the International Commission on Radiation Units and Measurements, action of mixed irradiation with radiation 1 followed by 2 is called synergistic and that with radiation 2 followed by 1 is called antagonistic although the effects are equal (1,10–12) (Figure 1).
Estimation of the Effect of Mixed Irradiation Using the Extended Zaider–Rossi Model

Zaider and Rossi (3) proposed a mathematical model of mixed irradiation based on both microdosimetric and mechanistic considerations—specific energy, which is a stochastic quantity, and the theory of dual radiation action (13). Suzuki (4) extended the Zaider–Rossi model to allow application of any type of mixed irradiation. This is given in Equation 4 and is called the extended Zaider–Rossi model in this paper.

In this equation, \( S \) is the surviving fraction of cells, \( \alpha_i \) and \( \beta_i \) are the parameters of the survival curve with radiation \( i \), \( D_i \) is the dose of radiation \( i \), \( t \) is the irradiation time, \( q(t) \) is the reduction factor for irradiation time \( t \), \( T \) is the time between the end of the first irradiation and the beginning of the second irradiation, \( q_{12}(t_1, t_2, T) \) is the interaction factor for two doses of radiation, and \( t_0 \) is the time constant for recovery. Both \( q(t) \) and \( q_{12}(t_1, t_2, T) \) are equally considered as functions of recovery as time. Although Equation 4 with \( q_1, q_2, q_{12} \), and \( A(T) \) seems complicated, any type of mixed irradiation (e.g., irregular exposures in the environment, accidental exposure, or in space) can be analyzed numerically if the parameters \( \alpha_i \) and \( \beta_i \) of single irradiations and the conditions of irradiation are known. It is important to pay attention to the sign (+, −, or 0) of \( T \), which is the time between two types of irradiation. \( T \) is negative when the second irradiation starts before the end of the first one.

Mixed irradiation in nature, such as in the environment, accidental exposure, and in space, often occurs simultaneously. Thus, examples of simultaneous mixed irradiation are shown in Equations 5 and 5.1. In this case, the reduction factor is equal to the interaction factor (3).

\[
q_1(t) = q_2(t) = q_{12}(t)
\]

Thus,

\[
S = \exp\left\{ -\alpha_D D + \sum \alpha_i D_i + \sum \beta_i D_i \right\}
\]

\[
q(t) = \frac{2t_0}{t} - 2\left(\frac{t_0}{t}\right)^2 \left[ 1 - \exp\left(-\frac{t}{t_0}\right) \right] \quad [5.1]
\]

For a very short irradiation time of simultaneous mixed irradiation, \( q(t) \) is almost unity \((x = t/t_0 \ll 1)\) from Figure 2

\[
\alpha = \sum_{i=1}^{n} k_i \alpha_i \quad [7.1]
\]

\[
\beta = \sum_{i=1}^{n} k_i^2 \beta_i + 2 \sum_{i=1}^{n} \sum_{j=i+1}^{n} \sqrt{\beta_i \beta_j} k_i k_j \quad [7.2]
\]

\[
k_i = \frac{D_i}{\sum_j D_j} \quad [7.3]
\]

Figure 1. Survival curves for Chinese hamster V79 cells irradiated with 60Co γ-rays alone (G, open square), 6 MeV neutrons alone (N, closed square), neutrons after 4 Gy of 60Co γ-rays (O, open circle), and 60Co γ-rays after 2 Gy of neutrons (g, closed circle).
such high doses, $q(t)$ (Equation 5.1) is almost 0 (e.g., $q(1\text{ week})=0.01$ assuming $t_0=70\text{ min}$). Then,

$$S = \exp(-\alpha D) = S(D_1) \ast S(D_2)$$  \hspace{2cm} [8]

where
$$\alpha = k_1 \alpha_1 + k_2 \alpha_2,$$
$$D = D_1 + D_2,$$
$$S(D_1) = \exp(-\alpha_1 D_1),$$
$$S(D_2) = \exp(-\alpha_2 D_2).$$

In general,

$$S = S(D_1) \ast \cdots \ast S(D_n)$$  \hspace{2cm} [9]

was easily obtained for mixed irradiation with multiple types of radiation, where $S(D) = \exp(-\alpha D)$. However, it is not necessary to obtain $\alpha$ at lower dose rates because $\alpha$ is considered to be independent of dose rate.

For an intermediate irradiation time with simultaneous mixed irradiation, $q(t)$ must be calculated.

**Discussion**

The inappropriateness of the four definitions of synergism with mixed irradiation discussed here is probably attributable to treating the resulting phenomena—cell survival in most cases—without adequately considering the underlying biological mechanisms in defining the synergism in mixed irradiation. Radiobiological studies suggest that unreparable DNA double-strand breaks are the main cause of cell death by radiation (i.e., lethal lesions) and that repairable double-strand breaks and/or single-strand breaks interact among themselves leading to a lethal lesion. This sublesion—sublesion interaction of a single irradiation should be defined not as synergistic but additive in the common sense of the term synergism. As defined by Equations 1 and 2, the sublesion—sublesion interaction is synergistic. The number of sublesions differs at the same survival level depending on the type of radiation ($D_1$). Synergism would occur, if any, when the sublesion—sublesion interaction by different types of radiation is more effective in forming lesions than the same radiation type. Therefore, aside from the experimental feasibility of this kind of comparison, comparison should be started at the same number of sublesions not at the same survival level. Definitions by both Equation 3 and the isobologram compare the effect at the same survival level, which would be inappropriate to define the action of mixed irradiation. In summary, to avoid misunderstanding, concepts 1 through 4 should not be used to define synergism of mixed irradiation, even if there is no simple substitute, and the terms synergism and synergistic also should not be applied to mixed irradiation unless a reasonable definition and evidence are provided.

Theoretical models for mixed irradiations have been presented by Zaider and Rossi (3), Suzuki (4), Scott (15), Tobias et al. (16), Ager and Haynes (17), and Lam (18). The Zaider—Rossi model (3) and its extended model, which can be applied to any type of mixed irradiation with two types of radiation (Equation 4) (4), seem the most appropriate to estimate the effect of mixed irradiation using parameters $\alpha$ and $\beta$, a dose rate, and irradiation time of each radiation. Also, models for simultaneous mixed irradiation with multiple types of radiation are presented in this paper, although the conditions are limited (i.e., $q(t) = 1$ and 0 at very high and low dose rates, respectively). These models may prove useful for health perspectives because no model has been reported for mixed irradiation with multiple types of radiation.

The study of mixed irradiation has progressed in recent years, but to assess realistic risks of environmental or accidental radiation or radiation in space, which often are composed of two or more types, there must be further investigations that include defining synergism and analyzing the organs in which dose distribution is heterogeneous.

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