Radiation Protection In Humans

Extending The Concept Of As Low As Reasonably Achievable (ALARA) From Dose To Biological Damage

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Next Section

Ionizing radiation has proven to be a double-edged sword since its discovery by Dr Roentgen in 1895. Radiation is a potent mutagen and carcinogen; however, it is also used in the diagnosis and treatment of human diseases. Background radiation consists of cosmic radiation and radiation emitted from radioactive substances present in the ground or commercial sources. Thus, all living organisms have been exposed to background radiation since their appearance on Earth. The appearance of oxygen some 4.5 billion years ago, allowed the appearance of aerobic organisms that used oxygen for their survival. The usage of oxygen generated toxic chemical species, free radicals, as byproducts. The interaction of radiation with oxygen may have caused increased production of free radicals. In order to cope with these adverse conditions, aerobic organisms that survived have antioxidant defence systems to quench excessive levels of free radicals and repair systems that can correct mutagenic changes.

Today, humans, well equipped with antioxidant systems (from dietary and endogenous sources) and efficient repair mechanisms, are constantly exposed to varying levels of background radiation, depending upon the region and altitude where they live. In the USA, the average annual effective dose equivalent from natural sources to a member in the population is about 3.0 mSv (2.0 mSv from radon and 1 mSv from cosmic, terrestrial and internal) [1]. Medical exposure, consumer products, occupational, fallout, nuclear fuel cycle and miscellaneous contribute to about 0.6 mSv [1]. Patients can receive medical radiation exposure of varying levels up to 100 mSv, generally about 20 mSv or less, for diagnostic purposes. The use of radiation in medicine has always been rationalized on the basis of risk *vs* benefit. Owing to the growing use of nuclear energy in the world, especially in developed countries for civilian and military purposes, the concept of risk was applied to all personnel involved with radiation. In order to further safeguard against potential radiation damage, the concept of maximum permissible dose (MPD) was developed for the two major population groups. The annual MPD value for the general population for stochastic-effects, where the probability of the biological effect is proportional to the dose (linear no-threshold effect) is about 50 times less (1 mSv) than that recommended for radiation workers (50 mSv). In the UK, the radiation worker standard is 20 mSv as effective dose [2]. Although the value of MPD for radiation workers for the above effect has remained fairly constant during the last several decades, this value for the US population was recommended to be reduced by a factor of 5 in 1991 [3] and made law in 1993. This is due to the emergence of new data on low doses of radiation on somatic and heritable mutations in mammals and in mammalian cells in culture [4–7], the synergistic effect of the interaction of radiation with other chemical and biological carcinogens and tumour promoters on cancer incidence and mutations, and epidemiological studies in humans. To address the growing concerns of radiation-induced somatic and heritable mutations, the

concept of ALARA (as low as reasonably achievable) with respect to dose was recommended by national and international radiation protection agencies for radiation workers [2, 3].

Efforts to protect normal tissues were started soon after the discovery of X-rays. However, the observation by Dr Muller of Columbia University in 1927, that radiation causes gene mutations in *Drosophila melanogaster* (common fruit fly) provided new impetus to reduce exposures [5]. The initial concept of radiation protection involved three physical principles: (a) shielding (usually by lead) of unexposed areas, especially radiosensitive organs such as bone marrow, gonads and thyroid; (b) increased distance between the radiation source and radiation workers or patients; and (c) reduction of exposure time. Each of these factors has been very useful, but they have limitations. For example, during fluoroscopy, it may not be possible to protect the gastrointestinal tract (one of the most radiosensitive organs) against radiation damage by lead shielding. Increasing the distance between the radiation source and exposed individuals may not be practical for many radiation workers, patients, civilian or military personnel. Reducing exposure time may also not be pertinent to all populations, except those that are involved in taking care of patients who have received gamma-emitting radioisotopes for medical purposes or who are responsible for radioactive decontamination as a result of accidents or attack. Nevertheless, radiation protection based on physical factors has served a useful purpose and has been successful in reducing the level of unnecessary medical exposure to patients and to radiation workers. In order to protect normal tissues from potential radiation damage, it would be important to identify biological or chemical agents which, when given before radiation exposure, could protect all normal tissues. Such radioprotective agents would help to extend the concept of ALARA from dose to biological damage. They would also protect patients against radiation damage during diagnostic procedures.

The search for non-toxic radioprotective agents which can protect normal tissue against radiation damage began soon after World War II. Extensive radiobiological research yielded numerous agents which, when given before radiation exposure, protected animals (primarily rodents) against radiation injuries [5]. From these studies it became clear that agents, which scavenge free radicals and/or cause hypoxia, may be of radioprotective value. Unfortunately most of these compounds at radioprotective doses were found to be toxic to humans. With the decreased risk of nuclear confrontation experienced during the evolution of the cold war and later, the interest in the study of radioprotective agents markedly decreased. Due to rapid growth of X-ray-based diagnostic equipments and increased use of radiological procedures in the early diagnosis of disease, concerns are being raised about increased frequency somatic and heritable mutations that can enhance the risk of gene-linked diseases in present and future generations. Therefore, it has become imperative that normal tissues be protected against potential radiation damage no matter how small that damage might be.

Radiobiological studies have identified several radioprotective compounds some of which are non-toxic to humans. The identification that sulfhydryl (SH)-compounds are potent radioprotective agents is considered as one the most important discoveries in applied radiobiological research [5]. Unfortunately, most widely studied SH-compounds like cysteamine, cystamine and aminoethylisothiourea dihydrobromide (AET) and a cysteamine analogue, amifostine, were toxic to humans [5, 8]. However, compounds such as N-acetylcysteine (NAC) and alpha-lipoic acid that are rapidly absorbed and elevate intracellular levels of glutathione (perhaps the most ubiquitous endogenous SH-compound in ameliorating sources of oxidative stress), are of radioprotective value [5–9] and are, within certain dose ranges, non-toxic to humans. Dietary antioxidants such as vitamins E, C and beta-carotene are of radioprotective value [5, 10–21], but very little attention has been given to these compounds with respect to their use in protecting normal tissue against radiation damage in humans. It is therefore possible to develop a non-toxic, cost-effective mixture of antioxidants (dietary and glutathione-elevating agents) that can provide biological protection against radiation damage based on several criteria

including mutations. Indeed, such radioprotective products have been patented (pending), and are available commercially. *In vitro*, animal and human studies that support the rationale of these radioprotective products are described below.

It has been reported that mitotic cells, which are most sensitive to radiation, have the lowest levels of SH-compounds, whereas S-phase cells, which are the most resistant to radiation, have the highest levels of these compounds [5]. The role of SH-compounds in radiation protection was further substantiated by the fact that an elevation of the intracellular levels of these compounds in mitotic cells makes them radioresistant to the same level as S-phase cells [5]. It has been shown that dietary antioxidants are also of radioprotective value. For example, vitamin E and selenium reduced radiation-induced transformation in cell culture; the combination was more effective than the individual agents [5]. Natural beta-carotene protected against radiation-induced neoplastic transformation in cell culture [5]. Vitamin E and C reduced radiation-induced mutations and chromosomal damage in mammalian cells [9–13, 21], and radiation-induced lethality [5].

Animal studies support the radioprotective role of SH-compounds. For example, SH-compound such as cysteamine, cystamine and AET protected mice against bone marrow syndrome with a dose reduction factor of 1.3–1.6 [5]. The mechanisms of radiation protection involved scavenging of free radicals and inducing hypoxia. Alpha-lipoic acid, a glutathione-elevating agent, increases the LD_{50} in mice with a dose-reduction factor of 1.26 [5]. Vitamin E, Vitamin C and beta-carotene protected rodents against the acute effects of irradiation [5, 15–17]. Vitamin A and beta-carotene protected normal tissue during radiation therapy of cancer in an animal model [20]. A combination of vitamin A, C and E protected against radiation-induced myelosuppression during radiation therapy of cancer in an animal model [20].

All radioprotective SH-compounds discovered in early investigations were toxic to humans [5]. Amifostine, an analogue of cysteamine, was relatively less toxic, but at radioprotective doses it caused hypotension and bone marrow hypoxia when administered intravenously. Subcutaneous injection causes relatively less toxicity [8]. Therefore, amifostine may not be suitable for protecting normal tissue during diagnostic procedures. Vitamin A and a glutathione-elevating agent, N-acetylcysteine (NAC), may be effective against radiation-induced carcinogenesis [9]. Alpha-lipoic acid (another glutathione-elevating agent) treatment for 28 days lowered lipid peroxidation among children chronically exposed to low doses of radiation in the area contaminated by the Chernobyl nuclear accident [21]. In another study, beta-carotene reduced cellular damage in the above population of children [19]. A combination of vitamin E and alpha-lipoic acid was more effective than the individual agents [21]. Beta-carotene also protected against radiation-induced mucositis during tumour radiation therapy [20]. A combination of dietary antioxidants was more effective in protecting normal tissue during radiation therapy than the individual agents [20].

Radiobiologists have been struggling to estimate the health risks from low doses of radiation in humans for decades. Health risks involve not only neoplastic diseases, but also somatic mutations that may contribute to other illnesses (including birth defects and ocular maladies) and heritable mutations that may increase the risk of diseases in future generations. Most radiobiologists believe that diagnostic doses of ionizing radiation should not be considered insignificant for risks of somatic and heritable mutations, neoplastic and non-neoplastic diseases in humans [2, 5], whereas some radiation scientists suggest that diagnostic doses of radiation do not contribute to health risks in humans [22]. We have proposed that a combination of dietary antioxidants and glutathione-elevating agents could be useful in protecting normal tissue against radiation damage, no matter how small that damage might be. The amounts of individual antioxidants present in the mixture may depend upon the level of diagnostic doses of radiation.

Dietary antioxidants (vitamin C and E, beta-carotene and selenium) and glutathione-elevating agents (NAC and alpha-lipoic acid) have been consumed by humans for decades, and within certain dose ranges, no toxicity of these nutrients have been reported. However, higher doses of these nutrients can produce some toxicities. For example, doses of 10 g or more of vitamin C as ascorbic acid can cause upset stomach in some individuals, and may increase the risk of kidney stones after long-term consumption among those who are susceptible to develop this complication. Vitamin E at doses 2000 IU or more after prolonged consumption may induce clotting defects in some individuals. Beta-carotene at doses of 60 mg or more can induce bronzing of skin that is reversible after discontinuing the intake. Vitamin A at doses of 10 000 IU or more can cause birth defects in pregnant women. Higher doses of vitamin A can cause liver and skin toxicity. NAC at a daily dose of 800 mg can increase the excretion of zinc in the urine. The references for the above studies have been provided in a review [23].

Data on laboratory experiments *in vitro* and *in vivo*, and in limited human studies suggest that a mixture of dietary antioxidants and glutathione-elevating agents at appropriate doses can be formulated to protect normal tissues against somatic and heritable mutations, as well as cancer and birth defects. Thus, the use of such antioxidant preparations can extend the concept of ALARA from dose to biological damage for radiation workers. In addition, such antioxidants can also protect patients receiving diagnostic doses against radiation damage, no matter how small that damage that might be. A clinical study to evaluate the radioprotective value of antioxidants should be evaluated among patients receiving diagnostic radiation, using measures of oxidative stress and frequency of mutations (chromosomal damage).

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