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Using electron beam radiation to simulate the dose distribution for whole body solar particle event proton exposure

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Abstract

As a part of the near solar system exploration program, astronauts may receive significant total body proton radiation exposures during a solar particle event (SPE). In the Center for Acute Radiation Research (CARR), symptoms of the acute radiation sickness syndrome induced by conventional radiation are being compared to those induced by SPE-like proton radiation, to determine the relative biological effectiveness (RBE) of SPE protons. In an SPE, the astronaut's whole body will be exposed to radiation consisting mainly of protons with energies below 50 MeV. In addition to providing for a potentially higher RBE than conventional radiation, the energy distribution for an SPE will produce a relatively inhomogeneous total body dose distribution, with a significantly higher dose delivered to the skin and subcutaneous tissues than to the internal organs. These factors make it difficult to use a ^{60}Co standard for RBE comparisons in our experiments. Here, the novel concept of using megavoltage electron beam radiation to more accurately reproduce both the total dose and the dose distribution of SPE protons and make meaningful RBE comparisons between protons and conventional radiation is described. In these studies, Monte Carlo simulation was used to determine the dose distribution of electron beam radiation in small mammals such as mice and ferrets as well as large mammals such as pigs. These studies will help to better define the topography of the time-dose-fractionation versus biological response landscape for astronaut exposure to an SPE.

Introduction

As a part of the near solar system exploration program, including proposed NASA Lunar and Martian exploration missions, astronauts may receive significant proton radiation exposures during a solar particle event (SPE). In the Center for Acute Radiation Research (CARR), symptoms of the acute radiation sickness syndrome induced by conventional radiation (megavoltage photons/electrons) are compared to those induced by SPE-like proton radiation. These studies will better define the spectrum of toxicities expected from astronaut SPE exposure and the relationship of these toxicities to the dose and dose rate of exposure.

Relative biological effectiveness (RBE) is defined as the ratio of the dose of a reference radiation that produces a particular effect or outcome to the dose of the investigated radiation for this same effect. Due to the emergent use of proton radiotherapy in human

patients, previous studies have attempted to define the RBE for protons using animal models (Paganetti et al. 2002; Tilly et al. 2005; Slater 2006). Most of these studies have used either the plateau or spread-out Bragg peak portions of the depth-dose distribution in proton radiation therapy, to create a relatively homogenous radiation dose for a specific organ system. However, measuring the RBE for an SPE produces several challenges. The astronaut's exposure in an SPE will be to the whole body, making dose comparisons more difficult. Moreover, the majority of protons in an SPE are at or below 50 MeV. At these lower energies, a greater proportion of the total proton absorbed dose received during an SPE will be related to a higher linear energy transfer (LET) than is seen with conventional radiotherapy. In addition to having a potentially higher than expected RBE, the energy distribution for an SPE is predicted to produce a relatively inhomogeneous total body absorbed dose distribution, with a significantly higher absorbed dose delivered to the skin and subcutaneous tissues than to the internal organs (Coutrakon et al. 2007; Hu et al. 2009).

All of these factors make it difficult to use a ^{60}Co standard for RBE comparisons in our experiments. When determining the RBE for protons without a pre-specified proton energy distribution for a specific organ, such as lung or bowel, it is possible to treat with ^{60}Co using a parallel opposed pair beam arrangement to create a relatively homogenous total body absorbed dose distribution with ^{60}Co for comparison to single proton beam with an energy distribution (i.e. spread out Bragg peak) that creates a homogenous absorbed dose distribution of protons. In this case, differences in biological effect are likely to represent true differences in RBE between these two forms of radiation. However, the proton absorbed dose distribution for an SPE in astronauts gives a high superficial absorbed dose and significantly lower internal organ absorbed dose (Hu et al. 2009). Thus, in comparing SPE protons to ^{60}Co , there is no way to match both integral body absorbed dose and absorbed dose to specific organ systems, and it would be unclear whether any observed differences in absorbed dose response arise from differences in absorbed dose distribution or radiobiological effectiveness.

Here, the novel concept of performing RBE comparisons between protons and conventional radiation using mega-voltage electron beam radiation to more accurately reproduce both the total absorbed dose and the absorbed dose distribution of SPE protons is presented. The LET of secondary electrons produced through Compton scattering by ^{60}Co and megavoltage electrons produced by a linear accelerator is very similar. Moreover, theoretical and preclinical studies have consistently found that the RBE of MeV electrons is close to 1.0. More than 25 years of clinical experience in human therapeutic irradiation has validated an RBE of approximately 1 for MeV electrons (Khalili and Takeshita 1976; Amols et al. 1986; Tilly et al. 2002). Because the absorbed dose distribution for a human SPE exposure is highly dissimilar to ^{60}Co , we hypothesized that MeV electrons might be able to produce a similar absorbed dose distribution and allow comparison to more conventional radiation form and approximation of an RBE in this situation. These studies will help to better define the topography of the absorbed dose versus biological response landscape for astronaut exposure to an SPE.

The absorbed dose that a particular target organ receives from proton radiation depends not only on the energy spectrum of the protons but also on the density of the tissues that lie between the body surface and the target organ, and the distance between the body surface and the target organ (i.e. tissue depth). When mono-energetic protons travel through tissue, they initially lose energy slowly with depth and produce a depth dose distribution curve often referred to as the "plateau" portion of the curve (Fig. 1). As the protons lose energy, they reach a threshold energy level where the remaining particle energy is transferred to the medium (tissue) in a relatively short distance; this produces the so-called "Bragg peak" on a depth dose distribution (Fig. 1a). For in vivo endpoints, protons in the 100–1,000 MeV

range have been used where the entire target is contained within the plateau portion of the depth-dose distribution (Paganetti et al. 2002; Tilly et al. 2005; Slater 2006; Kennedy et al. 2008; Wambi et al. 2009). Note that the LET of these protons is in the 0.1–1 keV/ μm range (Fig. 1b), which is similar to that of electrons that are produced from Compton-scattering by ^{60}Co photons. However, the majority of the protons in an SPE is at or below 50 MeV and shows relatively shallow Bragg peaks (<2–3 cm) and higher LET (10–80 keV/ μm , Fig. 1). At these lower energies, the tissue absorbed dose deposited comes from both the plateau and the Bragg peak portions of the depth-dose distribution curve, and a human would be expected to receive a much higher absorbed dose to skin and subcutaneous tissues than to internal organs. This raises two major problems in attempting to define the spectrum of biological responses to SPE radiation: a how to measure a meaningful RBE for SPE protons when compared to conventional radiation and b how to produce this inhomogeneous absorbed dose distribution in animals without altering the fundamental properties of the radiation. Therefore, we have focused significant effort in our first year of the CARR determining the best way to recapitulate SPE conditions in our studies.

Materials and methods

Computational modeling of absorbed dose in water phantom

For Protons and electrons, depth dose distributions were determined using GEANT4 (Agostinelli et al. 2003) to perform Monte Carlo based determinations of absorbed dose. Simulated depth dose profiles were created by transporting particles through air from the source into a $30 \times 30 \times 30$ cm water phantom and histogramming dose as a function of depth along the beam axis. In the case of electrons, the simulation included the walls of irradiation chamber and the source was designed to mimic the 6 and 12 MeV electron output of a Varian Trilogy Clinac with jaw settings of 34×34 cm and a source-to-water phantom surface distance of 5 m. For protons, single-beam geometry was simulated in the absence of specific information on the experimental proton beam line.

CT-based simulation of absorbed dose in pigs

Three 3–4-month-old (9–10 kg) Yucatan Mini-pigs were sedated using Ketamine/Xylazine and helical, 3-mm-slice CT scans were obtained. Note that the absorbed dose for this CT is negligible (~ 0.1 cGy) compared to the doses being tested in SPE ($>2,500$ cGy). The CT data (given in the Digital Imaging and Communications in Medicine (DICOM) format) were downloaded into the Varian Eclipse treatment planning software. Monte Carlo-based simulations were obtained for 6 MeV electrons delivered by a Varian Trilogy linear accelerator using a parallel opposed lateral pair beam arrangement. The simulations included the experimental set-up geometry including the 5 m source-to-skin distance and the walls of the irradiation chamber.

Irradiation of animals

Three pigs were irradiated with 2.5 Gy per side using 6 MeV electrons delivered by a linear accelerator. The age at irradiation was 3–4 months and the weight was 9–10 kg. Custom Plexiglas chambers measuring $33 \times 25 \times 75$ cm (height $\times$ depth $\times$ width) were designed to allow animal's comfortable access to food and water, while limiting mobility to allow homogeneous irradiation. For pigs, the chambers were constructed with 5-mm-thick chamber walls with multiple 9-mm holes for air exchange. The entire dose was delivered over a 3-h period resulting in a dose rate of 3.3 Gy/h. The radiation dose was delivered in 2.5 Gy increments to one side of the long axis of the pig's body, after which the entire irradiation chamber was rotated 180 degrees and the dose was delivered to the opposite side of the pig. All animal procedures involved in this study were performed using a protocol approved by the University of Pennsylvania Institutional Animal Care and Use Committee.

Facilities housing the animals involved are accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International (AAALAC).

Measurement of absorbed dose

Absorbed doses (surface) to specific areas of animal's surface were measured using OneDose MOSFET dosimeters (Sicel Technologies, Morrisville, NC) according to manufacturer's instructions. Briefly, the serial number for each dosimeter was recorded and the dosimeter was zeroed using the OneDose reader. Five OneDose dosimeters were attached to each animal on the left and right anterior surface (cephalad above shoulder), left and right flank (above hip), and spine (ventral midline at a level between shoulders and hips) using paper tape prior to irradiation. After irradiation, each dosimeter was removed and the absorbed dose was determined using the OneDose reader. This system has an established accuracy of $\pm 5\%$ when compared to an ion chamber (per product literature/package insert). Experiments to verify the accuracy of these dosimeters were performed using an Ion Beam Associates Dosimetry PPC40 parallel plate ionization chamber (Bartlett, TN) and a PTW counter (Hicksville, New York). The PPC40 response was calibrated in a 6-MeV linac beam with SSD of 100 cm, 1.4 cm buildup, and using a 10×10 cm electron cone. In this configuration, the linac is calibrated to output 1 cGy/MU. The results of these experiments demonstrate that OneDose dosimeters show a linear dose-response up to 7.5 Gy under these irradiation conditions (Fig. 2).

Results

Depth dose curves calculated for a water phantom

RBE is typically defined as the ratio of radiation dose needed to achieve a particular biological effect for the test radiation to the dose of ^{60}Co radiation needed to produce the same effect. In a human exposure to SPE protons, the typical dose distribution is relatively inhomogeneous with the surface receiving 5–10 times higher dose than the internal organs (Hu et al. 2009). We have performed simulations in a water phantom that demonstrate the remarkable difference of SPE proton dose distribution when compared to the dose distribution produced by ^{60}Co photons using GEANT4 and the fluence rate spectrum of the September 1989 SPE (Fig. 3). This raises a fundamental problem in measuring RBE for SPE protons in terms of acute radiation sickness (ARS). ARS represents an integrated, multi-system response to ionizing radiation exposure that involves interactions between the hematopoietic, immune, central nervous and gastrointestinal systems, and that qualitatively and quantitatively depends strongly on which organ systems were exposed to the radiation dose. Therefore, to accurately measure RBE for ARS, it would be desirable to produce similar dose distributions with protons and a conventional (i.e. radiation form with RBE = 1) form of radiation. To determine whether MeV range electrons that can be produced by a linear accelerator could mimic the dose distribution of SPE protons, we performed iterative test simulations using different beam energies alone and in combination. From these simulations, we determined that 6-MeV electrons as a single energy beam closely matched the dose distribution for the 1989 SPE and that a mixture of energies consisting of 80% 6-MeV electrons and 20% 12-MeV electrons even more closely matches the SPE dose distribution (Fig. 3). Note that simulated beam geometries (using a water phantom) are consistent with those of the total body irradiation mode used in the animal studies.

Depth dose curves calculated using clinical treatment planning software

Note that the GEANT4 simulations described above were performed in a rectangular water phantom and do not take into account the changes in dose distribution caused by inhomogeneities in tissue electron density that would occur when irradiating an animal or a human with SPE protons. As a first step towards accounting for these inhomogeneities,

computational modeling of these dose distributions has been performed using techniques adapted from radiation therapy planning for human patients. This was performed by obtaining a high-resolution helical CT scan for the animals to be studied. This scan was then imported into clinical treatment planning software (Varian Eclipse) and total body predicted dose distribution was determined using the Varian Monte Carlo electron dose calculation algorithm (eMC) (Fig. 4). Note that the software automatically incorporates inhomogeneities in tissue electron density as determined from the planning CT scan into the dose calculations so that the final electron treatment plan accurately reflects the expected dose distribution of electrons in tissues of varying electron density (i.e. the body of the animal when compared to a water phantom).

The accuracy of the simulation was then tested using in vivo dosimetry by fixing OneDose MOSFET dosimeters (Sicel Technologies, NC) to the body surface of the test animals during irradiation. Using the OneDose MOSFET dosimeters to verify the treatment plans of two animals exposed to 2.5 Gy per side revealed that the dose measured matched the dose predicted from treatment planning within 25% and that the maximal variation in body surface dose in these animals was less than 30% (Table 1).

Discussion

The depth dose distributions for SPE protons, ^{60}Co photons and electrons have been compared, in a water phantom (Fig. 3). These studies show that electrons can be used to create inhomogeneous dose distributions similar to those of an SPE exposure, and that clinical radiotherapy planning techniques can be applied to predict dose in animal irradiation experiments (Table 1). Importantly, electrons, in the 1–20 MeV energy range, have a linear energy transfer (LET) that is nearly identical to that of MeV secondary electrons produced through Compton scattering by ^{60}Co photons. Using both in vitro and in vivo models, multiple investigations have concluded that MeV electrons are radiobiologically quite similar to MeV photons and the RBE estimation of 1.0 has been validated by nearly 30 years of wide-spread clinical usage for MeV electrons and photons in human treatments (Khalili and Takeshita 1976; Amols et al. 1986; Tilly et al. 2002). Therefore, electrons can be used to mimic the dose distribution of an SPE and by virtue of their radiobiological similarity to ^{60}Co photons, the radiobiological data from experiments with electrons can be used to determine an RBE value for an SPE. These data could be used in estimating the overall risk of astronaut SPE exposure. This particular solution is conceptually and experimentally simple and can be applied to animals such as pigs that have a similar diameter as humans.

The problem of whether to scale the energy of the proton radiation to account for the smaller size of the experimental animal relative to the size of a human astronaut has no easy solution. Clearly, the overriding clinical concern is to predict as accurately as possible the time-dose-response relationship for acute radiation-induced signs and symptoms in astronauts exposed to proton radiation in an SPE. For a particular energy spectrum, dose rate and exposure time for proton radiation in an SPE, the anticipated dose to the total body (represented by the mean dose) or the dose to specific organ systems of interest can be calculated for both humans and laboratory animals. However, because of the size (depth from beam entrance) differences between humans and laboratory animals, both the total radiation dose deposited as well as the distribution of this dose in tissues will be fundamentally different. When testing the biological effects of SPE protons in animals that are relatively close to human dimensions (e.g. pigs with a approximate transverse (axial) diameter axis of 20 cm versus humans with an approximate transverse (axial) diameter of 30 cm), the internal dose distribution will be similar even without scaling the energy of the radiation to match the relatively smaller dimensions of the test animal. However, the solution of “scaling down” the proton energy spectrum to account for these size differences

to produce nearly equivalent dose distributions can also be used, in these larger animals. For example, 50-MeV protons treating a 30-cm-diameter human would need to be scaled down to 40 MeV for a 20-cm pig (Fig. 5). For smaller test animals such as mice that have an approximate diameter of 3 cm, 50-MeV protons in a human would compare to 15-MeV protons in the mouse (Fig. 5). While accounting for total dose, however, this method does not take into account the potential for increase in the RBE for protons that occurs at energies less than 10–15 MeV, due to the significantly higher LET (Fig. 1). For proton beams with maximum energies in this range, almost all of the energy deposited into tissue comes from protons with a higher RBE. In contrast, for proton beams with maximum energies in the 50–200 MeV range, a proportionally smaller portion of the energy deposited comes from high RBE protons. Thus, by scaling the proton energy spectrum down to account for the smaller size of test animals compared to humans, the RBE spectrum of the protons used increases significantly and there is a risk of dramatically over-estimating the magnitude or possibly even the fundamental characteristics of the dose–response curve for SPE protons.

The solution described in the present paper for comparing conventional versus SPE proton radiation to determine RBE using MeV electrons as the reference radiation works best for larger animals such as pigs. Indeed, we have begun initial testing of the biological effects of inhomogeneous SPE-like radiation dose distributions using 6-MeV electrons in pigs. This leaves the problem of accurately measuring both the effects and an RBE value for SPE exposure using smaller animals. Clearly, many important biological models for effect seen in the ARS syndrome such as fatigue, malaise, hematologic and immunologic dysfunction have been developed and refined in mice. These models either have not been developed or are significantly less refined or studied in larger animal species. One solution for this would be to use protons in a similar energy range as an SPE, but with relatively homogenous, ^{60}Co -like dose distributions in mice. While this would provide one of the only feasible means to define a useful RBE for SPE protons in these small animal models, this solution does not take into account the dramatic dose inhomogeneity for SPE protons (Figs. 2, 3, 4). Another solution to this problem would be to simulate the desired dose distribution in small animals using electrons (e.g. 1–3 MeV). This would produce the desired inhomogeneous dose distribution and make it possible to estimate the effects of SPE protons using the electron-proton RBE determined from comparisons of MeV electrons with SPE-like protons in larger animals.

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Fig. 1. 50-MeV proton depth dose distribution. **a** This plot demonstrates the classic plateau and Bragg peak regions of the proton depth dose distribution. **b** This plot demonstrates the energy deposited per depth as unrestricted collisional stopping power versus incident proton energy and was created using the online PSTAR program from the National Institute of Standards and Technology (<http://physics.nist.gov/PhysRefData/Star/Text/PSTAR.html>)

Fig. 2.

Dose response for OneDose MOSFET dosimeters. Three One-Dose MOSFET dosimeters were exposed to the indicated electron radiation dose and read using a OneDose reader. The results are presented as average $\pm$ standard deviation and are compared to the delivered dose as measured using an ionization chamber

Fig. 3. Dose distributions for ^{60}Co when compared to SPE protons and electrons. Depth dose distributions for electrons or the September 1989 SPE were produced using the GEANT4 Monte Carlo simulation tool-kit (Agostinelli et al. 2003). Simulated radiation field geometry is consistent with the total body irradiation treatment mode used during the animal studies (see “Materials and methods”). However, the simulations themselves were performed using a rectangular water phantom

Fig. 4. Cross-section of dose color map for 6 MeV and 6 + 12 MeV electrons in pigs. **a** The dose distribution of 6-MeV protons for a surface dose of 2.5 Gy per side approximates the dose distribution of SPE protons. **b** The same dose is given using mixed 6 MeV (80% of total fluence) and 12 MeV (20% to total fluence) electrons

Fig. 5.

Comparison of proton range and proton energy. The proton energy for a 30-cm human or 20-cm pig is similar, which would give similar LET and RBE values for SPE protons, even with geometrical/energy scaling to account for the different animal sizes. However, for mice, to scale the energy of the protons to match the significantly smaller geometrical size would entail the use of higher LET/RBE protons. The proton range versus energy plot was created using the online PSTAR program from the National Institute of Standards and Technology (<http://physics.nist.gov/PhysRefData/Star/Text/PSTAR.html>)

Table 1

Example of dosimetry results using OneDose MOSFET dosimeters

Site	Calculated Dose (cGy)	Animal 17.6 Dose (cGy)	Animal 14.1 Dose (cGy)
Right anterior	180–200	180 ± 9	196 ± 10
Right flank	180–200	182 ± 9	–
Spine	180–200	210 ± 10	257 ± 13
Left anterior	180–200	225 ± 11	243 ± 12
Left flank	180–200	246 ± 12	234 ± 12

Dosimetry results from two pigs that were exposed to 2.5 Gy per side calculated at the depth of maximum dose (Dmax) using 6-MeV electrons as described in the “Materials and methods”. In all, three pigs were irradiated with 2.5 Gy/side. Dosimetry information was not obtained from the other pig irradiated at this dose. Expected body-surface entrance doses were determined from radiation simulations and vary from 1.8 to 2.0 Gy in the region where the dosimeters were affixed. Note that the dose on the surface of the animal will vary considerably because the animal is not rectangular and therefore the actual surface dose varies due to the changing angle of incidence for the beam to the animal’s surface. Measured doses are presented as value ±5%, which is the maximum error of measurement stated in the product literature