Original Research

Rifaximin diminishes neutropenia following potentially lethal whole-body radiation

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Abstract

Terrorist attacks involving radiological or nuclear weapons are a substantial geopolitical concern, given that large populations could be exposed to potentially lethal doses of radiation. Because of this, evaluating potential countermeasures against radiation-induced mortality is critical. Gut microflora are the most common source of systemic infection following exposure to lethal doses of whole-body radiation, suggesting that prophylactic antibiotic therapy may reduce mortality after radiation exposure. The chemical stability, easy administration and favorable tolerability profile of the non-systemic antibiotic, rifaximin, make it an ideal potential candidate for use as a countermeasure. This study evaluated the use of rifaximin as a countermeasure against low-to-intermediate-dose whole-body radiation in rodents. Female Wistar rats (8 weeks old) were irradiated with 550 cGy to the whole body and were evaluated for 30 d. Animals received methylcellulose, neomycin (179 mg/kg/d) or variably dosed rifaximin (150–2000 mg/kg/d) one hour after irradiation and daily throughout the study period. Clinical assessments (e.g. body weight) were made daily. On postirradiation day 30, blood samples were collected and a complete blood cell count was performed. Animals receiving high doses of rifaximin (i.e. 1000 or 2000 mg/kg/d) had a greater increase in weight from the day of irradiation to postirradiation day 30 compared with animals that received placebo or neomycin. For animals with an increase in average body weight from irradiation day within 80–110% of the group average, methylcellulose rendered an absolute neutrophil count (ANC) of 211, neomycin rendered an ANC of 334, rifaximin 300 mg/kg/d rendered an ANC of 582 and rifaximin 1000 mg/kg/d rendered an ANC of 854 ($P = 0.05$ for group comparison). Exposure to rifaximin after near-lethal whole-body radiation resulted in diminished levels of neutropenia.

Keywords: rifaximin, whole-body radiation, radiation enteritis, normal tissue toxicity, acute radiation syndrome

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Introduction

The deadly effects of whole-body exposure to radiation have been characterized in animal models and humans.[1–3] Immediately following exposure to whole-body radiation, nausea, vomiting, headache, erythema, increased body temperature and malaise may be present and last for several days.[4] In addition, longer-lasting and potentially fatal effects, including intestinal and cardiovascular damage and reductions in red and white blood cell counts, may occur. The decrement of immune functioning because of decreased numbers of white blood cells may increase susceptibility of infections caused by bacteria present in the environment and within the gastrointestinal (GI) tract. In addition, irradiation may alter the GI flora, promote bacterial overgrowth and increase bacterial translocation across the GI mucosa.[5,6] Because of these alterations, if left untreated and allowed to interact with members of the general public, 50% of humans would likely succumb following exposure to whole-body radiation in the range of 4 Gy.[3] Because of the potential mass mortality of radiation exposure, the use of radiation as a component of terrorist attacks is both dreadful and logical. Accordingly, development of countermeasures for low-to-intermediate whole-body radiation exposures is a defense research priority, considering optimal medical care may increase survival.[3,7]

Current treatment algorithms for radiation exposure recommend administration of filgrastim and potassium iodide to promote granulocyte production and protect the thyroid gland.[8] In addition, prophylactic antibiotics may be administered to guard against infection.[3,8] The efficacy of the non-systemic antibiotic, neomycin, in the reduction of mortality after total body irradiation has been detailed comprehensively in a paper by Rosoff in 1963.[2] In the

Rosoff study, six- to eight-week-old female Wistar rats were used to determine the dose of radiation necessary to achieve uniform lethality. Exposure to 550 R whole-body radiation achieved lethality within the observation period of 30 d. Administering a sufficient dose of neomycin (25 mg/d) throughout the study period yielded 100% survival if administered before or within one hour of radiation exposure. Survival decreased to 67% if neomycin was first administered within two hours of radiation exposure, to 50% if the drug was first administered within eight hours of radiation exposure and to 6% if neomycin was first administered within 30 h of radiation exposure. Although the results of this study are compelling, the long-term use of neomycin as a countermeasure for whole-body radiation may be problematic because of the potential for adverse events (e.g. neurotoxicity, ototoxicity and nephrotoxicity).[9,10] This suggests that a non-systemic antibiotic with a favorable long-term tolerability profile is needed.

The non-systemic antibiotic, rifaximin, has been available in the United States since 2004 and is approved by the US Food and Drug Administration (FDA) for the treatment of travelers' diarrhea.[11] It demonstrates systemic absorption of $<0.4\%$,[12] broad-spectrum antimicrobial activity,[12] no clinically relevant bacterial antibiotic resistance[13] or alteration of GI flora[14] and has a tolerability profile similar to placebo.[12] In addition, rifaximin has been shown to prevent bacterial translocation in an animal model of colitis[15] and eradicates small intestinal bacterial overgrowth.[16–18] Given these data, rifaximin may be a safe countermeasure against lethal radiation exposure. In this study, we examined the ability of rifaximin to prevent radiation-induced weight loss and neutropenia in a rat model of full-body irradiation.

Materials and methods

Animals

Female Wistar rats approximately eight weeks of age ($N = 72$) were obtained from Harlan Laboratories (Prattville, AL, USA) and housed two to three per cage in a facility accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International under standard conditions (i.e. 22–24°C, 12-h light cycle). In addition, chew bones were provided to ameliorate stress.

Animals were weighed daily and assessed for subjective signs of stress (i.e. porphyrin staining, eyelids partially or completely closed, rough hair coat and/or hair loss, poor grooming, recumbent position with head tucked into abdomen, aggressive vocalization when handled, lack of social activity [e.g. guarding] and reduced exploratory behavior) by a veterinarian or a specially trained animal care expert. All animal procedures were approved by the Auburn University Institutional Animal Care and Use Committee prior to study initiation.

Irradiation

Animals were restrained in plastic immobilizers and irradiated in two series of 36 animals each. Each animal received 550 cGy whole-body radiation using either a Siemens Mevatron or a Siemens Primus linear accelerator (Siemens Oncology, Concord, CA, USA) with a 6-MV anteroposterior/ventrodorsal beam prescribed to a depth of 4 cm (corresponding approximately to spinal column depth in an average animal). An additional 1 cm of tissue-equivalent bolus material was placed under the plastic immobilizer to create an appropriate radiation dose build-up region.

Confirmation of dose calculation and accuracy of delivery was accomplished by measuring the delivered radiation dose at multiple points on and within a dosimetric phantom made of tissue-equivalent bolus material using the OneDose™ diode system (Sicel Technologies, Morrisville, NC, USA). An additional measurement was made using the same system on the dorsal edge of a randomly selected animal. Because of limitations of the diode system, these evaluations were performed using half the intended experimental dose (i.e. 275 cGy). A variation in radiation dose of 5% was deemed acceptable.

Preparation of medication

Methylcellulose (USP-grade; Sigma-Aldrich, St Louis, MO, USA) and neomycin (Pharmacia Animal Health, Basking Ridge, NJ, USA) were diluted in water by a veterinary pharmacist and stored according to the manufacturer's instructions. Rifaximin (Xifaxan®, Salix Pharmaceuticals, Morrisville, NC, USA) was dissolved/suspended in methylcellulose. Effort was made to ensure that all animals were administered an equal volume of medication for uniformity of effect.

Treatment

Animals were randomly assigned to receive either placebo (i.e. methylcellulose, $n = 12$), neomycin 179 mg/kg/d ($n = 12$), or rifaximin 150 mg/kg/d ($n = 12$), rifaximin 300 mg/kg/d ($n = 12$), rifaximin 1000 mg/kg/d ($n = 12$), or rifaximin 2000 mg/kg/d ($n = 12$) by oral gavage in two divided daily doses within one hour after full-body irradiation, and then daily throughout the study period. Dose calculations for all treatments were based on the average weight for the treatment group; no dose correction was made for specific animals or for weight lost or gained during the study. The dose of neomycin coincided with the dose used in Rosoff's study (i.e. 25 mg per 140 g body weight).[2]

Assessments

Stool cultures

Stool cultures were performed on all animals in the first irradiation series ($n = 6$ per treatment group) on postirradiation days 3 and 30. Stool cultures from each animal were obtained by rectal swabs and streaked on media in four successive quadrants according to standard clinical microbiology methods. The total bacterial concentration and the concentration of *Streptococcus/Enterococcus* species, *Lactobacilli* species, Gram-negative enterics, *Clostridium* species, Gram-negative anaerobes and *Bacteroides fragilis*

were semi-quantitatively examined by observing the number of quadrants on each plate that displayed growth.

Complete blood cell count

Blood was collected from all animals via intracardiac blood sampling on postirradiation day 30 and complete blood cell count (CBC) was ascertained using an automated clinical blood counter. Analysis of absolute neurophil count (ANC) was limited to animals within the range of 80–110% of the entire group average to limit the effect of animal size on radiation dose distribution.

Statistical analyses

Data were captured and reviewed for completeness daily with the use of the RealTouch Internet-based data capture system (Assurance Oncology Services, LLC, Chelsea, AL, USA). Bacterial counts were presented as descriptive statistics. Complete blood count and ANC were analyzed with one-way analysis of variance using InStat 3 (GraphPad Software, La Jolla, CA, USA). In addition, differences in ANC between antibiotic treatment groups and placebo were analyzed via MEANS testing (SAS, Cary, NC, USA). A P value <0.05 was considered statistically significant in all analyses.

Results

Irradiation

Dosimetric evaluation on the phantom demonstrated an entry dose (ventral surface) that was 112.7% of the prescribed dose, a mid-body dose that was 113.4% of the prescribed dose, and an exit dose (dorsal surface) that was 102.5% of the prescribed dose. Furthermore, the exit dose (dorsal surface) for the animal on which radiation level was detected was 96% of the prescribed dose.

Animal survival

No animals displayed visible signs of stress during the treatment period, although porphyrin staining indicative of mild-to-moderate pain and distress was observed after administration of radiation. Four of 72 animals (1 each in the neomycin, rifaximin 150 mg/kg/d, rifaximin 1000 and 2000 mg/kg/d groups) receiving radiation exposure died. Because two of these deaths were thought to be related to the viscosity of the rifaximin 1000 and 2000 mg/kg/d dosing preparations, these doses were not administered to animals in the second irradiation group. The death of the animal receiving neomycin was thought to be related to accidental tracheal gavage.

Effect of antibiotic treatment on enteric microflora

The average number of microbiological plate quadrants that displayed growth for each bacterial species and treatment group on postirradiation days 3 and 30 is shown in Table 1. Growth was apparent on postirradiation days 3 and 30 for all bacteria species, except *Clostridium* spp. Animals that received placebo had a relative decrease in total bacterial growth and growth of *Streptococci/Enterococci*, *Lactobacilli*, Gram-negative enterics, Gram-negative anaerobes and *Bacteroides fragilis* on postirradiation day 30 compared with postirradiation day 3. In contrast, the total concentration of bacteria and the concentration of *Streptococci/Enterococci* and *Lactobacilli* increased from postirradiation day 3 to postirradiation day 30 in all antibiotic-treated animals. All doses of rifaximin elicited a reduction in the concentration of Gram-negative enterics from postirradiation day 3 to postirradiation day 30.

Effect of antibiotic therapy on weight

Animals receiving rifaximin 1000 mg/kg/d had a higher body weight on postirradiation day 30 compared with animals receiving placebo or neomycin (Figure 1a) or low doses (i.e. 150 and 300 mg/kg/d) of rifaximin (Figure 1b). Weight was similar between animals that received rifaximin 1000 mg/kg/d and rifaximin 2000 mg/kg/d on postirradiation day 30.

Effect of antibiotic therapy on blood cell count

CBC analysis was performed on animals on postirradiation day 30; however, experimental difficulties (i.e. clot formation and low blood sample volume) rendered some samples unusable for analysis. Successful CBCs were obtained from nine animals in the placebo group, eight neomycin-treated animals, nine animals treated with rifaximin 150 mg/kg/d, 12 animals receiving rifaximin 300 mg/kg/d, three animals treated with rifaximin

Table 1 Mean number of microbial plate quadrants that displayed bacterial growth

	All bacteria		*Streptococcous* spp./ *Enterococcous* spp.		*Lactobacilli* spp.		Gram-negative bacteria		*Clostridium* spp.		Gram-negative anaerobes		*Bacteroides fragilis*	
No. of days postirradiation	3	30	3	30	3	30	3	30	3	30	3	30	3	30
Placebo	3.83	3.40	3.83	3.00	3.00	3.00	2.67	2.60	0.00	0.00	3.00	1.40	1.83	1.20
Neomycin	3.33	3.40	2.17	2.40	1.00	2.80	1.33	2.20	0.00	0.00	3.33	1.60	2.33	2.40
Rifaximin x (mg/kg/d)														
150	3.17	4.00	3.00	3.80	1.33	2.80	2.67	1.80	0.00	0.00	2.33	2.20	1.67	1.40
300	3.50	4.00	3.50	3.80	1.67	3.00	2.17	2.00	0.00	0.00	1.50	2.20	1.50	1.00
1000	3.17	3.80	3.00	3.40	0.67	3.00	2.00	1.60	0.00	0.00	1.67	3.20	0.83	1.40
2000	3.50	3.60	3.50	3.60	1.50	2.80	1.80	1.80	0.00	0.00	2.17	2.60	1.50	1.60

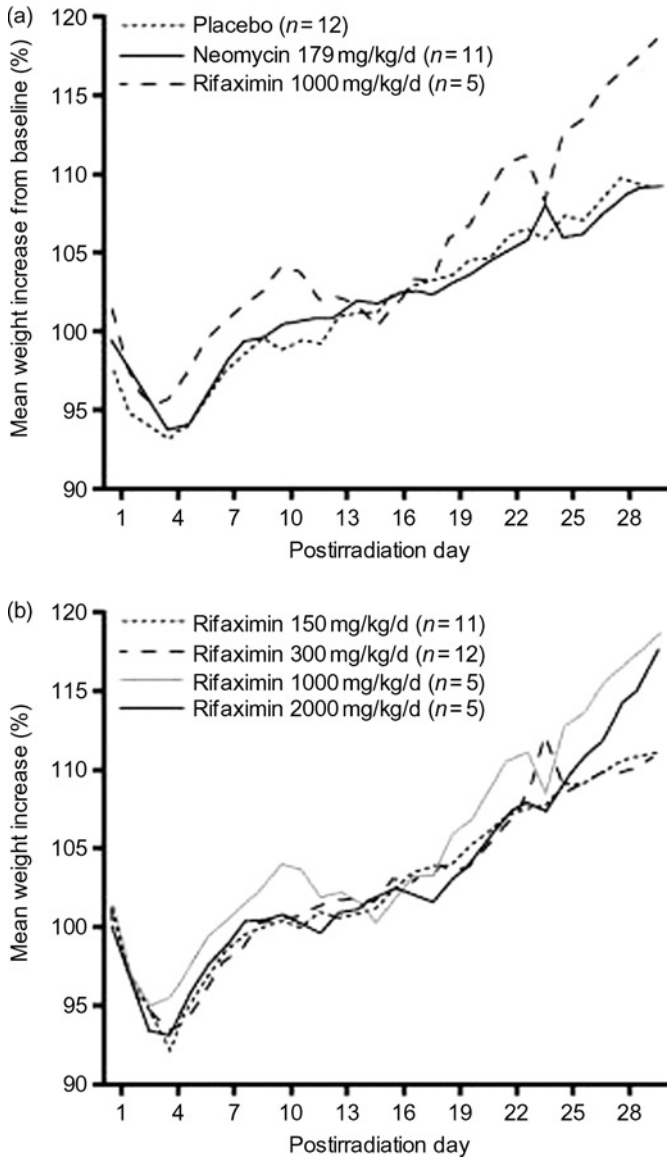

Figure 1 Mean daily weight change from day of irradiation. Animal weights were recorded daily and an average change in weight was calculated for each treatment group. On postirradiation day 30, animals that received rifaximin 1000 mg/kg/d had greater weight gain than animals receiving placebo or neomycin (a) or lower rifaximin doses (b)

1000 mg/kg/d and two animals in the rifaximin 2000 mg/kg/d group.

The most notable difference in CBC parameters was seen for ANC; no differences in the number of red blood cells or platelets were observed between groups. Animals that received any dose of rifaximin had a higher number of neutrophils compared with animals that received placebo or neomycin (Figure 2; $P = 0.05$). In addition, animals in the high-dose rifaximin (i.e. 1000 mg/kg/d) group had a significantly higher ANC than animals in the low-dose rifaximin (i.e. 150 and 300 mg/kg/d) groups (Figure 2; $P = 0.05$). Using the MEANS procedure, a statistically significant difference was noted between animals in the rifaximin 300 mg/kg/d group versus animals that received placebo (Figure 2; $P = 0.02$). Additional analysis of ANC per initial gram of body weight on the day of irradiation demonstrated

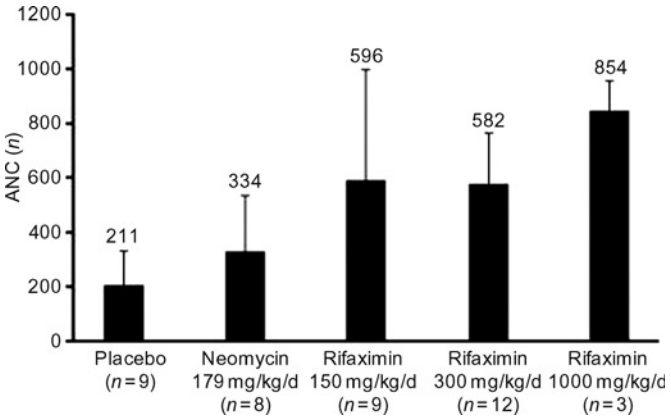

Figure 2 Average absolute neutrophil count 30 d after irradiation. Animals in the rifaximin 1000 mg/kg/d group had significantly elevated ANC versus placebo, neomycin and other doses of rifaximin ($P = 0.05$ using ANOVA; $P = 0.02$ using MEANS procedure). ANC, absolute neutrophil count; ANOVA, one-way analysis of variance

a similar trend for ANC (Figure 3; $P = 0.037$ for all), with animals treated with rifaximin 1000 mg/kg/d having more than four times as many neutrophils per gram of initial body weight on postirradiation day 30 than animals receiving placebo ($P = 0.037$).

Discussion

Radiation exposure after catastrophic events (e.g. terrorist attacks) requires prompt medical intervention for exposed individuals; however, procedures for accurate measurement of radiological exposure in the field are limited. Because of this, the most important criterion in selecting an agent for use as a radiological countermeasure is that it must have few, if any, ill effects so that it may be administered safely to individuals regardless of the magnitude of radiological exposure. Previous studies in humans suggest that the nonsystemic antibiotic, rifaximin, is safe and has a tolerability profile similar to that of placebo.[12,16–18] Given the antimicrobial properties of rifaximin, its demonstrated efficacy in the treatment of small intestinal bacterial overgrowth,[16–18]

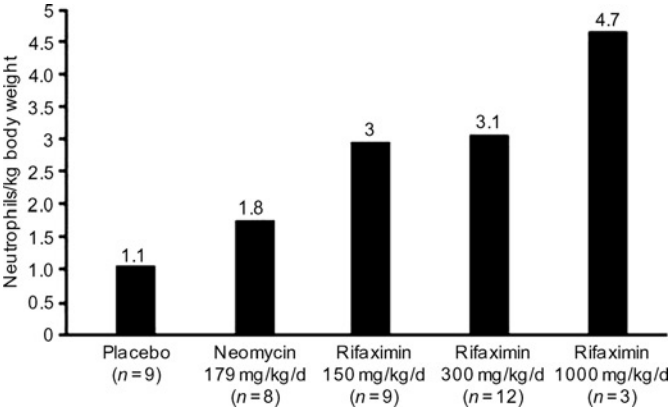

Figure 3 Mean ANC 30 d postirradiation per gram of animal weight at irradiation day. Animals in the rifaximin 1000 mg/kg/d group had significantly elevated ANC versus animals that received placebo, neomycin and other doses of rifaximin ($P = 0.037$ for all). ANC, absolute neutrophil count

and its prevention of bacterial translocation,[15] rifaximin may be safe and beneficial for individuals exposed to potentially lethal doses of radiation.

In the current study, administration of rifaximin 1000 mg/kg/d to rats exposed to near-lethal doses of radiation had a favorable impact on the overall wellbeing of animals as evidenced by weight gain during the 30-d observation period. In addition, favorable changes in the fecal flora of animals that received rifaximin were observed, with increased *Lactobacilli* concentrations on postirradiation day 30 compared with postirradiation day 3 and a reduction in Gram-negative bacteria concentration during the same period.

A recent study from Spain suggests that the presence or absence of certain bacterial groups can have a substantial impact on the type and magnitude of symptoms experienced by patients after exposure to abdominopelvic radiation.[19] In addition, the treatment of mild diarrhea, including radiation-induced diarrhea, with yogurt is well established. Yogurt may promote or establish the growth and development of beneficial *Lactobacilli* in the GI tract and, in so doing, partially assuage diarrhea and other aspects of GI toxicity.[20] Given these data, the increased *Lactobacilli* concentration seen in rifaximin-treated animals may have contributed to their overall improved outcome (e.g. weight gain). It is also logical that decreased concentrations of Gram-negative enterics (seen with rifaximin, but not neomycin or placebo) contributed to a more favorable outcome in rifaximin-treated animals because these pathogens are commonly associated with postirradiation sepsis.[21]

In addition to alterations of the bacterial flora, treatment with rifaximin preserved neutrophils, as measured by ANCs. The mechanism for this preservation is unclear, although it may be related to suppression of the concentration of bacteria most likely to become invasive (e.g. Gram-negative bacteria). In addition, it is possible that fewer immune resources are expended to defend against opportunistic bacteria invading from within the gut of animals treated with rifaximin. Accordingly, more of these resources may be available to deter invasion of potential pathogens from external sources, thus rendering a higher ANC. In addition, rifaximin has been shown to alter the production of cytokines that may regulate neutrophil proliferation, apoptosis and trafficking.[15]

Several limitations of the current study should be noted. First, no animals were lost due to radiation exposure, which contrasts with findings from Rosoff.[2] The reason for this discrepancy is unknown, but may be because of increased sanitization in animal housing facilities. For example, individuals who have an ANC of approximately 200 would almost certainly die or at least be incapacitated after exposure to pathogens in a general public setting, but the same patients may survive in a more sanitized environment. Second, rifaximin was diluted in methylcellulose, which deterred easy administration via oral gavage. Animals that received high-dose rifaximin (i.e. 1000 or 2000 mg/kg/d) were seen to struggle more during handling than animals in other treatment groups. This struggling may have led to complications in gavage dosing and ultimately to the deaths of two animals.

Despite these caveats, rifaximin appears to be beneficial after full-body irradiation by promoting the growth of favorable GI bacterial species and preserving neutrophils. This conclusion is supported by another study, which showed a beneficial effect of rifaximin for radiation-induced GI effects.[22] The ease of rifaximin administration, along with rifaximin's long-term stability and existing FDA approval for other indications, make it a prime candidate for ongoing evaluation as a radiation countermeasure and a potential therapeutic option for radiation toxicity in human oncology patients. Further testing to support the use of rifaximin as a radiation countermeasure and to identity mechanisms associated with neutrophil perseveration is warranted.

Author contributions: All authors participated in the design, interpretation of studies and data analysis, and review of the manuscript. In addition, all authors were meaningfully involved in the conduct of experiments. The manuscript was written by CDJ.

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