

Study points to therapy for radiation sickness

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(Medical Xpress) -- A combination of two drugs may alleviate radiation sickness in people who have been exposed to high levels of radiation, even when the therapy is given a day after the exposure occurred, according to a study led by Harvard Medical School researchers at Dana-Farber Cancer Institute and Children's Hospital Boston.

Mouse studies of other potential therapies suggest they would be effective in humans only if administered within a few minutes or hours of radiation exposure, making them impractical for use in response to events involving mass casualties. In contrast, the larger time window for administering the two-drug regimen raises the prospect that it could become a mainstay of the response to public health threats such as a nuclear power plant accident or nuclear terror attack.

In a paper published online by the journal *Science Translational Medicine*, the scientists report the beneficial effects, in mice, of a combination of a fluoroquinolone antibiotic (similar to the commonly used human antibiotic ciprofloxacin, or "Cipro") and a synthetic version of the natural human infection-fighting protein BPI. Mice that received the combination a day after being exposed to high doses of radiation fared far better than mice that received neither or only one of the agents. Whereas radiation exposures of that magnitude almost always prove fatal within a month, 80 percent of the mice that received the two agents were alive and apparently healthy a month into the study.

Faster rebound

The study's lead author is Eva Guinan, HMS associate professor of radiation oncology at Dana-Farber, and the senior author is Ofer Levy, HMS assistant professor of pediatrics at Children's Hospital Boston. The investigators also found that the ability to generate new blood cells — which can shut down in the aftermath of radiation exposure — rebounded much more quickly and vigorously in the mice treated with fluoroquinolone and rBPI21 (the synthetic version of BPI), potentially contributing to their return to health.

“Both fluoroquinolone antibiotics and rBPI21 have been shown to be quite safe in humans,” said Levy. “Their combined effectiveness in our study involving mice is an indication that they may be equally beneficial in people.”

The research potentially represents a major step in the United States government's efforts to build a stockpile of therapies to counter radiological dangers.

“There is great interest in creating systems for dealing with the short- and long-term health risks of a significant release of radiation, whether from an accident at a nuclear power plant, an act of terrorism or even a small-scale incident in which a CT machine malfunctions,” said Guinan. “Developing useful agents has proven difficult. Most existing drugs aren't effective enough and must be given within a very short time frame to provide any benefit. The recent disaster at the Fukushima nuclear power plant in Japan illustrates the need for agents that can be deployed rapidly to treat large populations.”

Severe effects

[Radiation sickness](#), also known as acute radiation syndrome, varies with the amount of radiation an individual receives. The first signs of the disease usually are nausea and vomiting, which can be followed by fever,

dizziness, weakness, bloody vomit and stools, difficulty breathing and infection. The body's blood-making tissue, nervous system, digestive tract, lungs and cardiovascular system all can be affected. At very high doses, radiation is usually fatal.

Within the body, the effects of heavy radiation may include leakage of bacteria and the toxins they produce into the bloodstream from the digestive tract or through broken skin. Radiation effects wreak havoc with the function of the heart and lungs, disrupt the process of blood coagulation and inflame tissue throughout the body.

When bacteria or certain toxins enter the blood under normal conditions, the body's immune system responds by dispatching neutrophils — white blood cells — to destroy the intruders. The neutrophils release a payload of BPI (bactericidal/permeability-increasing protein), which sticks tightly to molecules called endotoxins on the surface of the bacteria. The binding not only helps BPI kill the bacteria but also blocks inflammation caused by live or dead bacteria — something that conventional antibiotics do not do.

When a person is exposed to high levels of radiation, however, the ability to generate neutrophils is almost obliterated. “It’s a perfect storm of disease-causing events,” Guinan said. “Radiation results in bacteria and endotoxins entering the bloodstream at the same time that the body’s defenses are lowered.”

The treatment approach developed by Guinan, Levy and their colleagues takes direct aim at two potential contributors to radiation sickness: bacteria and the endotoxins on their surface. “We theorized that a two-drug therapy would be most effective,” Levy said. “Others had already shown some benefit to treatment with fluoroquinolones after [radiation](#); at least part of the benefit came from killing bacteria in the blood. The second, rBPI21, would bind to, neutralize, and ‘mop up’ the endotoxins

released by the dying bacteria, thereby removing the trigger of the inflammation process.”

Provided by Harvard Medical School

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