Dirty Bomb Pills, Shots, Weeds, and Spells

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Most of us cringe when we see news headlines about “anti-radiation pills” or “radiation antidotes” or visit Web sites that offer herbal supplements or other homeopathic remedies to protect people from dirty bombs or a nuclear attack. As the federal government, in collaboration with industry and academia, tries to make available various medical countermeasures in the event of a nuclear/radiological emergency, we can expect to see more such headlines and probably more opportunistic entrepreneurships. As health physicists, we need to have some familiarity with the subject and on occasion undo misconceptions that would inevitably arise from sensational coverage of these topics. The purpose of this article is to give a quick overview of several pharmaceuticals that have made the news in this context and provide references where additional information can be found.

Potassium Iodide (KI)

Readers of Health Physics News are very familiar with this prophylactic drug and its related issues. Average citizens, however, looking through legitimate sources of information, can come away with an unclear picture of what they should do. In principle, KI, as a potential supplementary protective action, should be perhaps the simplest and the least complicated of medical countermeasures, but years of discourse by various regulatory and private organizations have created an overall confusing picture.

Regarding distribution plans, for example, the federal policy states that KI use should be considered for the general public within the 10-mile emergency planning zone (EPZ) of a nuclear power plant (66 FR 5427, 67 FR 1355). The Bioterrorism Act of 2002 discusses planning for KI distribution, as appropriate, for the population within 20 miles of a nuclear power plant. The American Thyroid Association recommends a 200-mile radius of KI distribution. The recent report by the National Academy of Sciences (NAS) wisely recommends that KI distribution plans be based on site-specific considerations (NAS 2004). This issue is still ongoing. In the mean-

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time, the US Postal Service decided to take what it called a “proactive approach” and obtain KI tablets for any of the 750,000 workers who voluntarily requested it. For the rest of the US population, KI is widely available on the Internet and over the counter.

As another example of the confusion over the use of this drug, the Food and Drug Administration (FDA) and NAS recommend that lactating mothers taking KI may continue to breastfeed (FDA 2001, NAS 2004), while the American Academy of Pediatrics advises that exposed lactating women should temporarily cease breast-feeding (AAP 2003). If these issues, among others, are not enough to leave a concerned family perplexed, a manufacturer of KI has posted a table of recommended KI dosages for family pets.

On the plus side, the drug is inexpensive and can be obtained from domestic FDA-approved manufacturers, and there are no significant side effects even when given on a mass scale (Nauman 1993). For the most part, with the exception of people who may show allergic reactions to iodine or are taking medications that affect their serum potassium levels, no medical follow-up should be necessary after taking KI.

Prussian Blue

Among the many documented countermeasures for internal contamination with radionuclides, Prussian blue is perhaps the best known. For most of us, our familiarity with Prussian blue comes from studying the 1987 Brazilian accident in Goiânia that involved breaching of an abandoned $^{137}$Cs radiotherapy source (Farina et al. 1991; IAEA 1998). In response to this accident, 46 people internally contaminated with $^{137}$Cs were treated with Prussian blue to accelerate removal of cesium from their bodies. This was the largest single cohort of humans to be treated with this drug.

Ferric ferrocyanide, commonly called Prussian blue (PB), is administered orally. In the intestine, PB binds to cesium ions that are enterically cycled. Bound cesium is not reabsorbed, but excreted from the gut. On average, the biological half-life of cesium in untreated patients is about 110 days and is usually shorter in women and still shorter in young children (NCRP 1980). The use of PB as a decorporation agent results in reducing the biological half-life of cesium to about one-third of its usual half-life in the human body. There is negligible absorption of PB itself from the intestine and the drug is well tolerated. The primary side effects are constipation and gastrointestinal distress.

Until recently, PB could only be distributed in the United States under an investigational new drug (IND) status by the Department of Energy’s Radiation Emergency Assistance Center/Training Site (REAC/TS). Amid concerns about the possibility of radiological dispersal devices (RDD) being used by terrorists, and the likelihood of $^{137}$Cs being used in such a device, FDA reviewed the data in the literature and in January 2003 approved PB as safe and effective for the treatment of internal contamination with radioactive cesium and thallium. PB then made its way from scientific and technical literature to mainstream news as another “dirty bomb pill,” and the headlines touted the paint pigment as a radiation antidote. The popular online bookseller Amazon.com at one point even provided a link to a Web site offering PB.

The only FDA-approved supplier of pharmaceutical-grade PB is Heyl Chemisch-pharmazeutische Fabrik GmbH in Germany under the trademark of Radiogardase®-Cs. It

Monitoring gamma radiation from a cow given Prussian blue at a small farm in Southern Belarus. The large-scale program benefited 50,000 farmers and was supported by the Norwegian Government and the Food and Agriculture Organization (FAO/IAEA. See IAEA Bulletin 1/1993. Photo is from http://www.iaea.or.at/NewsCenter/Features/Chernobyl-15/agriculture.shtml.
is anticipated that there will soon be approved domestic suppliers as FDA is encouraging submittal of marketing applications. Radiogardase® capsules contain Ferric (III) hexacyanoferrate(II) (Fe₃[Fe(CN)₆]₃). There are other salts of PB that may have some ability to bind cesium. Recipes to make chemical grades of PB are available on the Internet and some private suppliers may market their formulations for pharmaceutical use. These formulations and suppliers have not been approved by FDA, which has certain technical specifications for approving pharmaceutical grades of the drug. These include requirements that free cyanide released in the stomach low-acid environment be low and nontoxic (for example, see Verzijl et al. 1993). The use of non-FDA approved formulations and suppliers is not advisable. PB is most efficacious when treatment is started soon after intake of cesium. However, the drug is still effective when given days after intake. This is a huge advantage over KI where the window of opportunity disappears four to six hours after intake. Therefore, predistribution issues are not a concern as long as an adequate supply is stockpiled. But there are some disadvantages. People receiving PB need to be monitored for their electrolyte levels. Cesium and potassium have similar chemical and biochemical properties and the body potassium levels may also decrease because of PB treatment. The ratio of cesium excreted in feces versus urine needs to be monitored, and the human waste is potentially highly contaminated. These limitations make it logistically challenging to administer PB to as large a group of people as is possible with KI. It is important in a 137 Cs incident to distinguish the few victims who may be internally contaminated at levels requiring treatment from a larger group of people who may have much lower but still detectable levels of internal contamination.

**DTPA**

*(diethylenetriaminepentaaacetate)*

There were also recent headlines about another radiation antidote. This was in response to the FDA announcement approving pentetate calcium trisodium (Ca-DTPA) and pentetate zinc trisodium (Zn-DTPA) for treatment of internal contamination with plutonium, americium, or curium to increase the rates of elimination of these substances from the body (68 FR 53984). In addition to their use in nuclear medicine studies, these chelating drugs have been used to treat hundreds of internally contaminated patients in the last few decades. Because of their high affinity, calcium or zinc ions of DTPA are exchanged with the transuranium element. The transuranium-DTPA complex is stable and is excreted in urine. This treatment is effective when the actinides are in the form of soluble salts such as nitrate or chloride, but it is not effective for highly insoluble compounds such as high-fired oxide (REAC/TS 2002). DTPA drugs have been available for distribution from REAC/TS under an IND for treating internal contamination. The chelating efficacy is greatest in the first hour after intake when the radionuclide is circulating in or available to tissue fluids and plasma. Because the efficiency of chelation decreases with time, DTPA should be given within six hours of exposure, if possible (REAC/TS 2002). However, DTPA treatment can still be effective when given weeks, even months after intake.

DTPA is usually administered intravenously, but it can also be administered by intramuscular injection. When radionuclide intake is only by inhalation, the drug can be administered as a nasal inhalant. Currently, there is no approved DTPA product that can be administered orally, although that may become available soon.
**Amifostine (WR-2721 or Ethyol®)**

Radioprotectants are a class of drugs that are used to protect tissues against oxidative damage at the cellular level. The best known of these radioprotective drugs is amifostine, also known as WR-2721. “WR” stands for Walter Reed as this drug was originally a product of classified military research to identify compounds to protect US troops from radiation injury during nuclear warfare. The synthesis of this drug, which is an analog of cysteamine, was based on observations more than 50 years ago that sulphydryl-containing amino acid cysteine had radioprotective properties (Patt 1949). Research on this subject was also advanced in the area of cancer research with the goal of protecting normal tissue from cytotoxic effects of radiotherapeutic and chemotherapeutic agents (Culy 2001).

In tissue, amifostine becomes dephosphorylated to its active form, WR-1065, which is a free thiol. In this form, it is taken up into the cells and acts as a free radical scavenger. Amifostine has been shown in vitro and in animal models to protect against cell death, carcinogenesis, and mutagenesis. Amifostine is what is referred to as a broad-spectrum cytoprotective agent in the sense that it protects against a broad array of cytotoxic therapies in multiple organ systems (Capizzi 1999).

Amifostine is marketed by MedImmune, Inc., under its trade name Ethyol® and has been approved by FDA for use as a protectant of normal tissues during radiotherapy of head and neck cancers. The use of this drug is limited by its side effects. At concentrations necessary to protect against acute radiation injury, there are significant toxic side effects such as nausea, vomiting, and hypotension. This makes its prophylactic use on a mass basis questionable and there is no evidence that amifostine offers any protective value when given after exposure to ionizing radiation.

At lower concentrations (no toxicity), amifostine loses much of its ability to protect against acute effects of radiation, but appears to retain its anticarcinogenic effects (Grdina 2002). In the context of radiation oncology, it has been suggested that low-dose amifostine may be effective in preventing treatment-related secondary malignancies, a particular concern in pediatric oncology. In the context of emergency response to a nuclear/radiological incident, there is a theoretical possibility to reduce stochastic risks for responders prior to entering a high-radiation area (NCRP 2001, DHS 2003). For this purpose, a compound (WR-3689) which is structurally very similar to amifostine is being developed by Hollis-Eden Pharmaceuticals (http://www.holliseden.com) under the trade name Phosphonol™.

**Androstenediol (HE2100 or NEUMUNE™)**

Androstenediol was one of the first “radiation drugs” to make the post-9/11 news headlines. There are several native steroid hormones that upregulate (boost) the immune system and can increase resistance to bacterial and viral infections. A few years ago, researchers from the Medical College of Virginia and the Armed Forces Radiobiology Research Institute (AFRRI) demonstrated that one such immune regulating hormone, 5-androstenediol (5-AED), stimulates myelopoesis (regeneration of bone marrow) and increases the number of circulating platelets and certain white blood cells of the innate immune system (neutrophils, monocytes, and natural killer cells). These changes persist for several weeks after treatment, resulting in enhanced resistance to infection and significantly better survival in gamma-irradiated mice (Whitnall et al. 2001). AFRRI is in a Cooperative Research and Development Agreement with Hollis-Eden Pharmaceuticals to develop this drug, also referred to as HE2100, for eventual use in humans exhibiting acute radiation syndrome.

The hematopoietic syndrome is characterized by a compromised immune system and low levels of circulating white blood cells. One diagnostic indicator is the number of circulating neutrophils. When that drops below a certain value, the condition is described as severe neutropenia and the patient is at high risk of developing infections. The effectiveness of a medical countermeasure in this context is in shortening the duration of neutropenia. This will reduce probability of infections and increase the chances of survival. HE2100 with the trade name of NEUMUNE™ has been shown to be effective in
mice, dogs, and monkeys. NEUMUNETM can be administered prophylactically 24 hours before exposure or two to four hours after exposure.

Last year, Hollis-Eden made headlines by announcing some of its preliminary findings on the efficacy of this new drug in nonhuman primates. Most recent results were presented in October of this year at the 2004 annual meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO) in Atlanta, Georgia. This study demonstrated again that treatment of irradiated Rhesus macaques with NEUMUNETM (two to four hours after whole-body irradiation) significantly reduced the duration of neutropenia as well as occurrence of severe thrombocytopenia (low platelet counts) in treated animals. Based on these pilot studies, Hollis-Eden is apparently in the process of planning a larger efficacy study using nonhuman primates. If those results turn out to be as positive, NEUMUNETM will get one major step closer to obtaining FDA approval.

It should be noted that the FDA amended its regulations in 2002 so certain drugs can be approved for marketing based on evidence of effectiveness from appropriate animal studies (67 FR 37988). This rule applies when adequate and well-controlled clinical studies in humans cannot be ethically conducted and field efficacy studies are not feasible. This is particularly important for availability of some products intended to protect against weapons of mass destruction.

As for NEUMUNETM, the manufacturer appears to promote a potential for administering this drug to a large population after a nuclear attack in an outpatient setting without the need for hospitalization. The feasibility of such a treatment approach needs careful examination. However, this drug appears to offer advantages. It does promote regeneration of more than one cell type in the bone marrow and its manufacturing cost is likely to be lower than other products that stimulate hematopoiesis.

**Filgrastim (Neupogen®)**

Filgrastim is a human granulocyte colony-stimulating factor (G-CSF) produced by recombinant DNA technology, that is, the drug is actually produced by E. coli bacteria into which the human G-CSF gene has been inserted. The drug is marketed by Amgen under the trade name Neupogen®. FDA has approved this drug specifically for use in neutropenic patients receiving myelosuppressive anticancer therapy.

Cancer patients who undergo aggressive cancer therapy can suffer from bone marrow suppression and become neutropenic (that is, severely low levels of neutrophils in serum). There is extensive clinical history of using cytokines to help these patients recover from neutropenia and increase their chances to fight infections. These products work in general by stimulating bone marrow stem cells to proliferate and differentiate into a wide variety of mature cell types. As such, they can be effective in treating the hematopoietic syndrome following exposure to high doses of radiation.

Unfortunately, using this drug for radiation-induced neutropenia would be an “off-label” use. In individual cases, this would not necessarily be an issue. However, emergency-response planning demands the capability to treat potentially large numbers of patients following a nuclear/radiological event. The Centers for Disease Control and Prevention (CDC), with approval from its Institutional Review Board, has submitted an IND protocol for Neupogen® to the FDA. This is in preparation to make this drug available through the Strategic National Stockpile for treating patients suffering from the acute radiation syndrome (ARS) in the event of a nuclear/radiological incident.

Neupogen® can be administered intravenously or by subcutaneous bolus injections on a daily basis until the patient has recovered from neutropenia. Treatment can continue for up to two weeks. The cost for a full course of Neupogen® treatment is relatively high.

A closely related drug is its long-acting form, pegfilgrastim. The “peg” in pegfilgrastim refers to a polyethylene glycol unit that is added to the filgrastim protein, increasing its half-life in the body. This allows administration of a single dose instead of multiple daily administrations. This drug is available from Amgen under the trade name Neulasta®, and it is FDA approved for treating neutropenic patients undergoing cancer therapy. Use of this drug to treat radiation-related neutropenia would be “off label.”

**Homspera™**

Homspera™ is not an FDA-approved product, but its press releases have been picked up by a few newswire services. The drug is being developed by ImmuneRegen Biosciences, Inc., in Scottsdale, Arizona. It is an analog of substance P, a naturally occurring immunomodulator. Substance P is a peptide (a short chain of amino acids) and is widely present in...
n numerous tissues, including the central nervous system and gastrointestinal tract. It has been shown to have many physiological effects, including neurotransmission, blood vessel dilation, histamine release, and activation of the immune system. ImmuneRegen claims its studies in mice have shown that Homspera™ has a high degree of efficacy in treating acute radiation syndrome. These data are apparently not published and they may be proprietary information. ImmuneRegen is interested in gaining FDA approval for Homspera™ for treating ARS and other ailments such as acute respiratory distress syndrome and hair-loss replacement, among others.

**Other Available Products**

A whole class of products marketed as dietary supplements is not subject to vigorous premarket safety evaluations under the Dietary Supplement Health and Education Act of 1994. These nutraceuticals include not only the traditional vitamins, minerals, and proteins, but also herbal and other botanical products, enzymes, and glandulars, in addition to any mixtures of these. The ever-expanding world of Internet-based marketing undoubtedly presents a challenge to FDA to keep this growing industry within bounds.

Some products claiming to have radioprotective properties are legitimate and at a minimum have a sound basis. For example, the radioprotective effect of vitamin E has been known for decades. Recently, AFFRI evaluated the efficacy of vitamin E in mice and found radioprotective properties against lethal doses of gamma radiation, particularly when vitamin E was given subcutaneously (Kumar 2002).

Alginates (salts of alginic acid extracted from brown sea algae) are known to inhibit intestinal absorption of radioactive strontium (NCRP 1980). Some entrepreneurs market seaweed as a product that detoxifies the body following exposure to harmful radiation, even the radiation coming from cell phones and computer monitors. Some herbalists recommend servings of miso soup with added seaweed for general protection against radiation.

There is an abundance of homeopathic approaches, including soaking in detoxification baths, eating special foods, drinking certain teas, and growing specific plants around the house. Such plants are purported by homeopathic healers to be useful in treating radiation burns and also as natural alarms—when the plants change color it signals the presence of excess radioactivity in the environment. In addition, some spiritual healers assert that they can provide remote healing, facilitate the exit of possessing spirits, and also completely eliminate harmful radiation or convert the harmful radiation to the benefit of their clients. Some spiritual/energy healers claim that in the special state of connectedness, they emit a field that can significantly reduce ionizing radiation levels, including alpha, beta, and gamma radiation.9

Average citizens are barraged with information and misinformation on radiation and radiation countermeasures through the Internet, newspapers, magazines, and of course dramatic television programming. It is against this backdrop that the health physics community and public health professionals must work to communicate public information messages.

**Future Products**

Many other products in various stages of development are competing for government support. Some drug information is proprietary and some appears in open literature. As new information makes headlines, we can expect some overstatements.

The idea of developing a generic radioprotective drug remains elusive. Basic research, particularly in the area of gene expression, may present opportunities to come closer to that goal in the future. In terms of treating radiation injury, the ability to treat the hematopoietic syndrome following “moderate” doses of radiation is likely to improve in the near future. As that happens, injury to other tissues (for example, the gastrointestinal tract, lung, kidney) and increased rates of stochastic effects may demand development of new complementary approaches to treatment. For a discussion of these topics, two recent publications are highly recommended, Coleman, et al. 2003 and Waselenko, et al. 2004.

**Final Thought**

The focus of this article was on pharmaceutical radiation countermeasures. However, in a mass casualty event involving radiation or radioactive materials, the importance of having trained health-care professionals available to effectively deal with the victims can not be overstated. Emergency room physicians, surgeons, and nurses who are trained in effective triage and treatment of radiation accident victims would be our greatest asset in terms of being prepared to deal with such an emergency. Much progress has been made in this area, but a lot more remains to be done.

**Further Reading**

On the subject of treating internal contamination, NCRP Report No. 65 is a valuable resource. Goan (2001) provides an excellent review. The
Footnotes
1 The content of this article was not reviewed by my employer and therefore does not in any way represent the policies or opinions of the Centers for Disease Control and Prevention. Trade names when used are only for clarification.
9 I avoided giving specific references here, but interested people can search for these on the Internet.

References

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