Medical countermeasures against radionuclide contamination: An overview

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1 Introduction

Radionuclides (RN) are extensively used around the world in a broad spectrum of industrial (e.g. electric power generation), medical (e.g. therapies, imaging), and military applications (e.g. armor-piercing weapons), thus causing opportunities for accidental intake by individuals. Although this hazard primarily concerns workers and soldiers, the population can also be affected in the case of major nuclear accidents resulting in a large release of RN into the environment, or following the possible terrorist use of a RN dispersal device.

Internal contamination of RN can result from inhalation, ingestion, wound or penetration through intact skin. Following internalization, a fraction of RN will be absorbed into the blood prior to deposition in target organs. During their retention which depends on their biological half-lives, RN have the potential to cause radiation-induced health effects or to even impair physiological systems.

RN of health concern are actinides, especially uranium (U) and plutonium (Pu) isotopes, but also americium (^{241}Am), neptunium (^{237}Np) and curium isotopes (Cm), the fission and activation products iodine-131 (^{131}I), cesium-137 (^{137}Cs), strontium-90 (^{90}Sr), tritium (^{3}H), and cobalt-60 (^{60}Co).

2 Current treatments and recommendations

The only practical way to reduce RN body burden and associated health risks is to apply countermeasures, i.e. decorporation and decontamination methods, that consist in minimizing blood absorption and/or accelerating excretion of RN. The therapeutic arsenal includes non-specific methods. For ingested RN, intestinal absorption can be reduced by gastric lavage, enemas or by gastric dressing with antacids. An intact skin or wound can be decontaminated by washing with tepid water, a decontaminant solution or soap (e.g. Trait rouge®), or applying Osmogel®, green clay… A surgical excision of the wound site will be considered for a puncture wound with high specific activity RN. In case of massive inhalation of insoluble forms of highly radioactive transuranics such as ^{238}Pu oxides, the removal of macrophage-internalized RN particles by lung lavages could be envisaged.

Other strategies are more specific. The countermeasure against ^{131}I is the oral intake of potassium iodide tablets to prevent thyroid uptake by saturating binding sites. Similarly, the method of isotopic dilution with a stable isotope or a chemical analog is recommended for competing with the RN, so accelerating excretion. Sr lactate or calcium gluconate can be

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given parenterally for ^{90}Sr contamination, and drinking large amounts of water can facilitate tritium clearance. Also, Co oligosol administration may be useful to accelerate ^{60}Co body turnover. For U intake, the administration of sodium bicarbonate *per os* or by i.v. infusion is recommended. This can promote the formation of U-carbonate complexes in blood that are stabilized by urine alkalization, thereby preventing kidney deposition of U [1]. The medication against ^{137}Cs ingestion is the long term oral treatment with insoluble Prussian Blue (Radiogardase®) that contains crystals of ferric ferrocyanide. This traps available Cs in gut by ion-exchange so minimizing intestinal absorption and reabsorption by blocking Cs enterohepatic circulation. The only available decorporation therapy for transuranics Pu, Am or Cm is the i.v. infusion of the marketed solution containing the octadentate chelator diethylenetriaminepentaacetic acid (DTPA) as calcium or zinc trisodium salts. Inhalation of nebulized DTPA is authorized for treating inhaled RN and irrigation with the solution is recommended for skin or wound decontamination. EDTA or DTPA are sometimes recommended for Co since some animal studies have shown a modest efficacy.

3 Animal research for improvement of decorporation treatment

There is a vast body of studies which aims at improving treatments mainly with chelators, either by finding or developing new ones, or by reformulating those available to enhance systemic efficacy, to target the site of RN entry, or to facilitate administration.

3.1 Evaluation of already-marketed drugs or available natural compounds

Natural compounds or licensed drugs have been evaluated in animals for decorporating RN, such as the amino acid N-AcetylCysteine (NAC), the tripeptide L-glutathione (GSH), a dithiol lead chelator (dimercaptosuccinic acid, DMSA), copper chelators (D-penicillamine and trientine) and polysaccharides. In many cases, results are mixed or modest. A few examples. Injections of GSH or NAC may decrease hepatic and splenic contents of Co [2]. Of interest an older study showed that a repeated treatment with DTPA was better when the chelator given as Co salts rather than as Ca or Zn salts [3]. Chitosan lactate, cysteine and D-penicillamine may also have potential for Co decorporation [4-6]. Alginate can remove ingested Sr [4]. However, phytate (Zn-InsP6) seems to inhibit more effectively Sr intestinal absorption [7]. Trientine and D-penicillamine modestly increase the clearance of Sr and Cs, respectively [6]. The consumption of pectins to eliminate the chronically ingested Cs may be useful as shown by some studies conducted on contaminated children [8, 9]. As for Pu, chelators primarily designed for treating iron overload such as desferrioxamine have been tested but none is better than DTPA. An active substance of drugs for treating Ca-related bone diseases, the bisphosphonate etidronate (EHBP), limits U retention [10, 11].

3.2 Approaches for high affinity chelating agents

For Pu decorporation, derivatives of DTPA have been designed by altering their structure, adding or replacing chelating moieties, e.g., the dihydroxamic derivative DTPA-DX. Nonetheless none have proved to be more effective than native DTPA.

Considering the similar chemical properties and the close *in vivo* behavior of Fe(III) and Pu(IV)), numerous chelators have been synthetized by varying the molecular backbones and geometry, as well as the siderophore-inspirated chelating moieties and number (denticity) [12]. Based on their decorporation efficiency and their toxicity in animals [13, 14], two of those synthetic chelators have emerged as lead candidates due to their far greater efficacy than DTPA for Pu removal and their ability to sequester other

actinides including Am, Np and U: the octadentate 3,4,3-LI(1,2-HOPO) and the tetradentate 5-LIO(Me-3,2-HOPO), both containing hydroxypyridinone chelating moieties grafted to linear polyamine backbones. More recently, 3,4,3-LI(1,2-HOPO) was preferred to take forward through pre-clinical studies of efficacy, toxicology, and pharmacology [15]. Some chelators bearing catecholamide functions such as 3,4,3-LICAM(C) for Pu removal, or 5-LICAM(S) and CBMIDA for U [10, 14] were also promising but were later shown to be nephrotoxic and less efficient than HOPO-based chelators.

The affinity of a phosphonic acid moiety for U has been also an area of research for U decorporation improvement. For example, dipodal and tripodal U-binding diphosphonate chelators with amine as scaffold have been synthetized [16]. The most potent for reducing U retention was the dipodal designated 3C which is slightly better than EHBP but less efficient than 5-LICAM(S) for bone deposits.

Chelators with macrocyclic structures have been also tested. Thus, for decontamination of intact skin, a calix[6]arene bearing carboxylic groups (p-tert-butylcalix[6]arene) has been formulated in an oil-in-water emulsion [17]. It is efficient for U removal but may have the ability to trap other actinides. Heterocyclic crown ether compounds can promote body clearance and reduce tissue retention of Sr [18].

The use of functionalized macromolecules bearing numerous chelating sites per area unit is under investigation. For example, the functionalized methy-carboxylated poly(ethylenimine) (PEI-MC) has an high affinity for U but no animal studies have been performed yet [19]. Also, a mesoporous silica (SAMMS^{TM}) with ferrocyanide moieties has a greater capacity for Cs loading than Prussian Blue but is not more efficient *in vivo* [20].

3.3 Strategies for oral delivery enhancement of chelators

The parenteral route for treating many people would be challenging and make a long-term therapy particularly cumbersome for patients. Orally effective chelators would be very useful but the available DTPA is very poorly absorbed from the intestine (3-5%).

Partially lipophilic analogs and derivatives of DTPA were developed to facilitate passage through the intestinal barrier. Long alkane chains were grafted to a nonadentate analog of DTPA named triethylenetetramine hexaacetic acid (TTHA), resulting in a series of compounds of which the most interesting is C_{22}TT for Pu/Am decorporation [21]. Another approach was to create a prodrug such as the penta-ethyl ester (C2E5) of DTPA [22]. In addition, pharmacological approaches have been employed to enhance intestinal penetration of native DTPA. Indeed, DTPA associated with permeation enhancers as a tablet form [23] or entrapped within enteric-coated capsules [24] have been formulated. Also, a water-in-oil microemulsion of DTPA has been developed for buccal transmucosal delivery (Medesis Pharma; personal data). However, all these DTPA galenic forms need repeated administrations at higher doses to be as effective as parenteral DTPA. We note that the aforementioned HOPO-based chelators already display a good oral efficiency [13] which could be undoubtedly improved further by a permeation enhancer.

3.4 Strategies targeting the site of entry or a systemic retention tissue of RN

A rapid delivery of chelators at the site of entry (lung, wound site and intestine) aims at preventing RN absorption into the blood as non-chelated form, which will lead to a better overall decorporation than a systemic delivery that must trap RN in circulation or in tissue.

Thus, DTPA has been formulated into porous particles by spray-drying for improving local treatment in case of inhaled RN. Its insufflation in rats induced a good mobilization of available Pu deposited in lungs and prevented deposition in systemic tissues [25].

Along with bone, the liver is a target organ for transuranics. The encapsulation of DTPA within liposomes allows better penetration into hepatic cells so improving decorporation for liver-retained Pu [26].

4 Conclusion

The treatments for RN contamination are restricted to a small number of non-specific methods and strategies using specific chelators. Some RN remain without any or really satisfactory treatment such is the case for Np, Co and polonium.

So far, work has focused mainly on Pu and U, while considerably less study has been directed towards other RN. Efforts still need to be made to complete the poor therapeutic arsenal against RN internalization with efficient drugs. Today, the best candidate is undoubtedly 3,4,3-LI(1,2-HOPO) with a greater efficacy of Pu/Am decorporation than DTPA, as well as an ability to chelate U and Np. It received approval by the US FDA for phase I clinical trials in 2014.

Pending approval and licensing of new chelators, the development of novel drug-delivery systems for already available chelators to increase their bioavailibility may be a strategy for decorporation improvement, and simpler for attainment of regulatory approval.

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