Evaluation Of Protracted Chelation Treatments To Decorporate Plutonium After Rat Lung Contamination

Laurent Miccoli[1], *Sylvie* Coudert[1], *Pierre* Laroche[2], and *Olivier* Grémy[1]

[1]Laboratoire de RadioToxicologie, CEA, Université de Paris-Saclay, Bruyères-le-Châtel, France
[2]Orano, Courbevoie, France

In the electronuclear industry, accidental release of alpha-emitting transuranic actinides such as plutonium (Pu) may occur at the work place. As a consequence, internal contamination *via* inhalation is a potential hazard for nuclear workers handling Pu. After deposition in the lungs, the transportable fraction of Pu translocates from the lungs to the bloodstream. The importance of this fraction and its translocation kinetic depend on numerous variables, including the physicochemical form of the inhaled Pu compound. Although a small fraction of the systemic burden is cleared in urine, most of the transferred activity is retained in extrapulmonary tissues, mainly in liver and bones [1].

The only medical approach available nowadays for reducing the committed radiological dose in target tissues, and consequently the risk of radiation-induced pathologies, is the removal of Pu from the body by chelation therapy with diethylenetriaminepentaacetic acid (DTPA used as Ca or Zn trisodium salt) [2]. Unfortunately, DTPA has serious drawbacks because of a very rapid elimination from the body and a poor distribution in Pu retention sites [3]. The success of a DTPA treatment in removing internalized Pu varies greatly, depending not only on its physicochemical form [4], but also on the treatment methods and regimens used (i.e., dose level, single or repeated administrations, frequency, administration route, and delay post-exposure). Once deposited in target tissues Pu becomes very difficult to remove. Thus, repeated administrations of DTPA which are more effective than a single one are needed [5].

For a decorporating treatment based on multiple DTPA injections, several therapeutic variables should be considered such as the number and the frequency of injections, or the dose level per injection. However, even though various data are available in the literature, they remain fragmentary and not sufficient, in our opinion, to draw definitive general conclusions for an optimal protracted chelation therapy.

In this context, the aim of the present work was to better understand the influence of important therapeutic variables on the overall efficacy of a repeated DTPA chelation treatment. This new useful information may help to design better treatment schedules that can be both efficient and the least burdensome as possible for the patient. Thus, our experimental work design featured: (1) all DTPA treatment schedules commenced several days or weeks following contamination in order to consider only Pu firmly-fixed in tissues and not the available pool of circulating Pu just after contamination; (2) the various DTPA treatment regimens tested used comparable cumulated total dose to assess only the effects of the distribution and/or the frequency of multiple injections as therapeutic variables; (3)

the effects of the variables on the efficacy were evaluated in both systemic tissues and lungs.

We here designed animal experiments to assess mainly the impact of the fractionation of a given dose and that their frequency totaling the same dose. Firstly, rats were contaminated intravenously with Pu then treated several days later with DTPA given at once or as various split-dose regimens cumulating to the same total dose and spread over several days. Similar efficacies were induced by the injection of the total dose or by splitting the dose in several smaller doses independently of the number of doses and the dose level per injection. Secondly, rats were pulmonary contaminated with a moderately form of Pu nitrate then received three weeks later a DTPA dose eleven-fold higher than the maximal daily recommended dose, administered either as a single bolus or as numerous multiple injections cumulating the same dose according to schedules differing in their injection frequencies. Independently of the schedule, the various split-dose regimens spread over weeks/months were as effective as the single delivery of the total dose for mobilization of lung plutonium, and had a therapeutic advantage for removal of retained hepatic and bone plutonium burdens.

We concluded that the cumulative dose level was a therapeutic variable more important than the distribution of split doses for the success of a repeated treatment regimen on retained tissue Pu. Lastly, a pulmonary administration of clodronate which aims at killing alveolar macrophages, thereby releasing their Pu content, associated with a continuous DTPA infusion regimen suggested that the efficacy of injected DTPA in decorporating lung deposit is limited in our conditions because of its restricted penetration into alveolar macrophages and not because of Pu is as a physico-chemical form not available for chelation.

Results presented here were obtained in the frame of the Orano-CEA collaboration.

References

1. L. Grappin, P. Berard, P. Beau, L. Carbone, C. Courtay, X. Castagnet, JP. Le Goff, MO. Neron, J. Piechowski. Radioprotection **42**, 163 (2007)
2. MH. Bhattacharyya, BD. Breitenstein, H. Métivier, BA. Muggenburg, GN. Stradling, V. Volf. Radiat. Prot. Dosim. **41**, 1 (1992)
3. W. Stevens, FW. Bruenger, DR. Atherton, DS. Buster, G. Howerton. Radiat. Res. **75**, 397 (1978)
4. E. Ansoborlo, B. Amekraz, C. Moulin , V. Moulin, F. Taran, T. Bailly, et al. C. R. Chimie **10**, 1010 (2007)
5. GN. Stradling, SA. Gray, JC. Moody, A. Hodgson, KN. Raymond, PW. Durbin, et al. Int. J. Radiat. Biol. **59**, 1269 (1991)