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Experimental approaches to improve the available chelator treatments for Np decorporation

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Abstract

This paper discusses biokinetic and decorporation data in animals after contamination by Pu and Np in order to develop new experimental approaches for improving the efficacy of human treatment. Only contamination by intravenous or intramuscular injection of soluble forms has been considered here. For Pu(IV) administered as citrate, the kinetics of deposition in body tissues is slow enough so that the main circulating chemical form for potential chelation, the Pu–transferrin complex, is available for decorporation within hours after contamination. Several decorporation studies have shown a gradual decrease of the efficacy of a given chelating agent for Pu(IV), Np(IV) and Np(V) at early times after contamination. Recently, a gradual decrease of blood clearance rate has been reported for Np(V), Np(IV) and Pu(IV), and attributed to a gradual increase of the rate of actinide deposition in the skeleton. Thus, taking into account the early deposition kinetics of Np in the body tissues, the ligand 3,4,3-LIHOPO could be an effective chelating agent for removing Np(IV) from body fluids. © 1998 Elsevier Science S.A.

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1. Introduction

After internal contamination by transuranium elements, chelating agents have been used to decrease their body content. This method of treatment will decrease the dose delivered chronically to the body tissues which should decrease the risk of radionuclide-induced pathologies. Currently, DTPA can be used in humans and provides an effective treatment after contamination by most soluble forms of transuranium elements, but it is poorly effective after animal contamination by some Pu complexes, such as Pu–TBP, when administered at high masses [1], and soluble forms of Np [2]. Thus, during the last decade, the aim of most of the decorporation studies performed in our Laboratory was to test new chelating agents to provide treatment after contaminations with Pu–TBP [3–8]. At this time, 3,4,3-LIHOPO appears as much more efficient than DTPA for Pu decorporation [9,10], the ligand is of low toxicity at the human equivalent dosage of DTPA, 30 μmol kg^{-1} [7]. Recently, 3,4,3-LIHOPO was reported to decrease about half the Np retention in the skeleton when it was administered 30 min after intravenous injection of low masses of ^{239}Np–citrate [11]. Most of these experiments had been performed under experimental conditions simulating treatment after human contamination, i.e. a delay longer than 30 min. In fact, in these studies, only the decreased retention in the target organs was measured, whereas the mechanisms involved in the decorporation process was not considered, i.e. actual decorporation of the actinides deposited in the retention organs, and in the body fluids, before their deposition in the retention organs. This paper will compare available data on Pu and Np decorporation and biokinetics in order to improve the experimental approaches for Np decorporation. Only the results obtained after intravenous or intramuscular injection of Pu(IV)–citrate and soluble forms of Np(IV) and Np(V) will be considered.

2. Biokinetics of Pu and its availability for decorporation by chelating agents after contamination with Pu(IV)–citrate

Most studies on biokinetics of Pu(IV) administered as soluble forms were undertaken during the years 1970–

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1975. After intravenous administration of Pu(IV)–citrate, Pu readily forms stable complexes with transferrin both in blood and in the extracellular fluids. Then, the Pu deposition in the retention organs is mainly controlled either by the binding of Pu–transferrin to specific receptors, or the dissociation of the complex in the different extracellular compartments. Because of the kinetics of the Pu–transferrin dissociation, the Pu deposit in the main retention organs appears relatively slow compared to that of small-molecular weight Pu complexes, which are mostly encountered during the first minutes following the contamination. Thus, 6 h after contamination, less than 35% of the administered Pu is deposited in the skeleton and liver, the remaining Pu is present mostly as a 'circulating' transferrin complex in the body fluids [12]. DTPA has been shown to chelate Pu from the Pu–transferrin complex. Thus, after contamination, early DTPA administration mainly induces Pu decorporation of the body fluids, and the fast urinary excretion of Pu–DTPA prevents the Pu transfer from these fluids to the retention organs.

3. Decororation of Np(V) and Np(IV)–citrate

A few studies have been performed on Np decorporation. They have involved both Np(IV)–citrate and Np(V) at very low masses, using ^{239}Np, and at high masses, using ^{237}Np. Conflicting results have been reported and, although statistically significant decorporations have been observed [11,13–16], it was concluded that neither DTPA nor any of the new ligands tested was effective for removing Np from any part of the body [11]. In fact, the most significant Np decorporations using chelating agents of low toxicity, such as DTPA and 3,4,3-LIHOPO, have been observed after contamination with Np(IV)–citrate, up to 30–50% of the Np body burden compared to untreated animal [11,15,16], whereas no decorporation [2,11,15,16], or decorporation less than 20% [14] was obtained after contamination with Np(V). However, for ^{239}Np(V), a nearly 50% decorporation was reported using either the toxic agent LICAM C or the lower toxic DTPA/desferrioxamine (DFAO) simultaneous treatment [13]. In some cases, chelating agent administration even increased more than 3 times the transfer of ^{237}Np from the site of intramuscular administration to the skeleton [2]. Thus, a different biokinetics and affinity of Np(V) and Np(IV) for chelating agents could be expected.

A few studies have been reported on the effect of time elapsing between Np contamination and chelating agent treatment. A local treatment by DTPA (30 μmol/kg) following intramuscular administration of ^{239}Np(IV)–citrate caused a significant increase of the cumulative urinary and fecal Np excretion over 3 days when the chelating agent was administered 2 and 20 min after contamination. On the other hand, no effect was observed at 60 min when compared to untreated controls. Twenty min after the ^{237}Np(IV)–citrate contamination, a similar efficacy of DTPA was measured for Np masses up to 10 μg, corresponding to a 30% decrease of the Np retention in the skeleton compared to untreated controls. No decorporation was obtained after contamination with Np(V). Thus, a significant Np decorporation can be obtained by a DTPA treatment for Np(IV) forms within minutes after contamination, the efficacy of which gradually decreased with time [15,16]. After intravenous administration of ^{239}Np(V), a significant decrease of the Np retention in the muscles and the kidneys was measured 7 days after contamination when a combined DTPA/DFAO treatment was initiated 48 h after contamination. The treatment efficacy gradually decreased from 80–60% to about 50% of the tissue retention measured in untreated controls when it was performed from 1 to 48 h post-contamination. By contrast, no significant difference was observed for bone and liver Np retention from 6 to 48 h post-contamination which was about 10 and 50%, respectively, whereas these decorporations were 35 and 70% for a 1-h delayed treatment [13]. Thus, most of the Np retained in soft tissues seems to be available for chelating agent decorporation within hours after contamination, but this available Np fraction is negligible after Np deposition in the skeleton and in the liver.

4. Biokinetics of Np(V) and Np(IV)-soluble forms

Recently, some authors have concluded that the behavior of Np was similar to that of Pu and, thus, its deposition in the main retention organs is controlled by the physico-chemical properties of the Np–transferrin complex [11,17]. This was based on qualitative studies that identified Np–transferrin as the main Np chemical form in blood 30 min after intravenous administration of Np(V) [18] or 24 h after administration of either Np(V) or Np(IV)–citrate [17]. Thus, it has been concluded that Np(IV) and Np(V) have a similar biological behavior, probably due to the fast reduction of Np(V) to Np(IV) under physiological conditions. With such an experimental approach, the lack of DTPA efficacy to decorporate Np after early treatment ($<$1 h) appears to be due to the formation of a very stable Np(IV)–transferrin complex which cannot be dissociated neither by DTPA or by other chelating agents [11].

Some earlier studies have shown a very fast clearance of ^{239}Np from blood after intravenous administration of ^{239}Np(VI) [19] and quite different early biokinetics of Np in blood, skeleton, liver and kidneys after intravenous administration of different soluble forms of ^{239}Np(V) and ^{239}Np(IV) [20]. A similar behavior of Np(V) in diluted HNO_3 was observed when it was administered at physio-

logical pH and after dilution in 1 mM citrate, EDTA or DTPA. By contrast, significantly different behavior was observed after administration of Np(IV)–citrate, Np(IV)–EDTA and Np(IV)–DTPA. For this last form, almost all the administered Np was excreted in the urine [20]. This clearly demonstrates that a stable Np(IV)–DTPA complex can be formed so that it prevents the deposition of the actinide in the retention organ, whereas, Np(V) does not form stable complexes with DTPA. Recently, a comparison of the early biokinetics of ^{239}Pu(IV)–citrate, ^{237}Np(IV)–citrate and ^{237}Np(V) has been reported after their intravenous administration [21]. A gradual decrease of the actinide deposition rate was observed from Np(V) to Np(IV)–citrate and Pu(IV)–citrate. Thus, after 1 h, the fraction of actinide retention in bone was about 85, 45 and 25% of that measured after 24 h for Np(V), Np(IV)–citrate, and Pu(IV)–citrate, respectively. This was related to a gradual increase of the actinide clearance rate in blood from Pu(IV)–citrate to Np(IV)–citrate and Np(V). Obviously, this phenomenon was due to difference in the actinide forms in the circulating compartment. Nevertheless, from 2 to 24 h, very similar blood clearance parameters were observed for the different forms administered, suggesting that similar actinide complexes were present, probably Pu(IV) and Np(IV)–transferrin complexes.

5. The mechanisms involved in Np decorporation

From most of the biokinetic and decorporation results that have been previously reported we can hypothesise on the mechanisms involved in the Np decorporation process. Because of the lack of stable Np(V)–chelating agent complexes, no early decorporation of Np can be obtained after contamination with soluble Np(V) forms. Thus, as previous suggested [14], the low decorporation observed at early times after Np(V) contamination might be due both to the spontaneous reduction of Np(V) to Np(IV), which forms stable complexes with physiological or the administered chelating agents, and to the very fast Np deposition in the retention organs.

For Np(IV), the decorporation mechanisms are the same as those of Pu(IV). Because, once deposited in the skeleton Pu and Np are similarly poorly available for decorporation, the lower early decorporation observed for Np(IV) than for Pu(IV) is very easily explained by the faster deposition of Np than Pu in bone [21]. In fact, efficient chelating agents are available for decorporation of both low-molecular weight Pu(IV) and Np(IV) complexes and Pu(IV) and Np(IV) transferrin complexes in blood and extra-cellular fluid compartments. Thus, the amount of Np(IV) decorporated after a 3,4,3-LIHOPO administration is quantitatively similar to the amount of Np in these compartments at the time of treatment [11,21].

6. Conclusion

Combined biokinetics and decorporation studies are a suitable experimental approach to understand the mechanisms involved in the decorporation of Np and should be used to improve the decorporation of the different actinides by chelating agents. After contamination with Np(V), no efficient decorporation can be obtained. By contrast, decreasing the delay between contamination with Np(IV)-soluble forms, and the treatment with efficient chelating agents, such as 3,4,3-LIHOPO, should provide very significant decorporation. For that purpose, further studies will be performed depending on the availability of the chelating agent.

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