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Early biokinetics of actinides after intravenous administration of soluble forms of Pu(IV), Np(IV) and Np(V)

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Abstract

We have compared the early biokinetics of actinides after intravenous administration of Pu(IV)–citrate, Np(IV)–citrate or Np(V)–nitrate in male Sprague-Dawley rats. Blood samples, the liver, the kidneys and the femurs were removed 1, 2, 6 and 24 h after contamination for radioactive measurements. Our results demonstrate significant differences in blood and bone actinide retention for each compound studied. We conclude that the biological Np behavior varies depending on its valency state. Np(V) readily binds to the skeleton, whereas a gradual delay in the bone retention kinetics was observed for Np(IV) and Pu(IV), respectively. © 1998 Elsevier Science S.A.

Keywords: Biokinetics; Neptunium; Plutonium

1. Introduction

Previous studies have shown that, within minutes after contamination by soluble forms of Np(V), more than 90% of the actinide entering the bloodstream was bound to transferrin [1]. Thus, the kinetics of Np deposition in the main organs of retention, skeleton and liver, might be controlled mostly by the behavior of the transferrin complex, as for the other actinides, such as trivalent americium or tetravalent plutonium [2,3]. However, no information is available on the actual form of Np in the blood compartment, especially concerning its valency state. By contrast, reported results in a few studies suggest that the behavior of soluble Np(V) or Np(VI) administered by intravenous injection was quite different from that of soluble actinides administered as Np(IV). The half-life of more than 80% of the administered Np(VI) in blood was less than 1 h [4], whereas for Pu(IV) citrate 50% of the injected activity was cleared from the bloodstream in less than 15 min, and the remaining had a half-life of 24 h [5]. Most of the bone Np was deposited within 1 h following the intravenous administration of ^{239}Np(V)–nitrate [6]. Moreover, 1 and 4 h after injection, significant differences in Np retention in the blood, liver, skeleton and kidneys were observed, depending on the chemical forms of Np(IV) and Np(V) administered, such as citrate, phytate, EDTA and DTPA complexes [7].

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The aim of this work was to compare the early biokinetics of Pu(IV)–citrate, Np(IV)–citrate and Np(V)–nitrate in the blood, skeleton, liver and kidneys after intravenous administration to rats.

2. Experimental details

Two isotopes were used, ^{237}Np and ^{238}Pu. Np(V) was prepared by adding $NaNO_2$ to a stock solution of Np in 1 M HNO_3 that was diluted 10 times in distilled water just before administration. Np(IV)–citrate was obtained by diluting the HNO_3 stock solution in 0.1 M citric acid, and a complete reduction was achieved by adding rongalite. The valency state of the Np solutions was determined by specific D_2EHPA solvent extraction of valency (IV) forms [8]. Less than 5% of Np from the Np–nitrate solution was extracted, whereas more than 90% of Np from the Np–citrate and 99% of Pu from Pu–citrate was extracted. Ultrafilterability of the actinides measured before each administration (filter Millipore: GTTP, 0.01 μm) was more than 95%.

Three groups of 12 male Sprague-Dawley rats at 3 months of age were given intravenous injection, under anesthesia, of Pu(IV)–citrate, Np(IV)–citrate or Np(V) solutions (6.5–9.5 kBq). Groups of three rats were killed 1, 2, 6 and 24 h after contamination. Weighed blood samples, liver, kidneys and femurs were removed and mineralized by combined heat and acid treatments.

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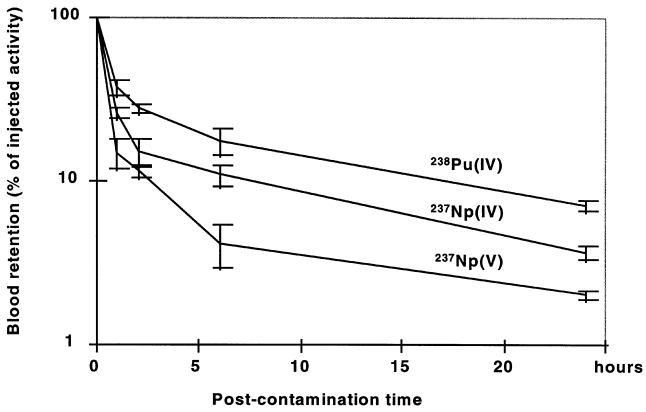

Fig. 1. Blood retention at different times after injection of Np(IV)–citrate, Np(V)–nitrate and Pu(IV)–citrate. Mean values±standard deviation (n=3).

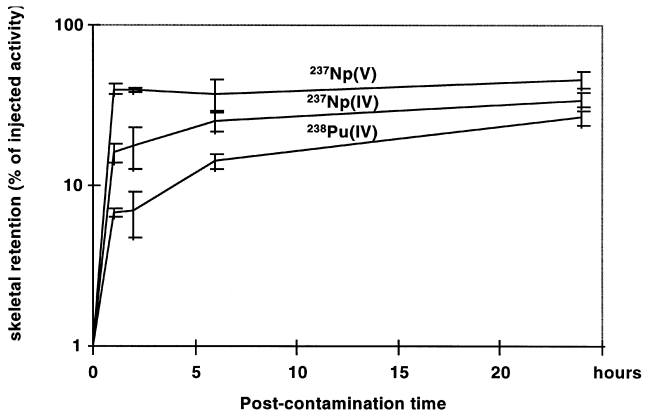

Fig. 2. Skeletal retention at different times after injection of Np(IV)–citrate, Np(V)–nitrate and Pu(IV)–citrate. Mean values±standard deviation (n=3).

Radioactivity measurements were performed by liquid scintillation counting of total α (Instagel-Plus, Packard Tri-Carb 2500 TR/AB). The total skeleton retention was assumed to be 10 times the retention in two femurs and the total blood retention was calculated assuming that blood corresponded to 1/13 of the body weight.

3. Results

Fig. 1 shows the retention of the actinides in blood as a function of time following intravenous administration. During the first 6 h, a gradual decrease of the blood clearance rate was observed for Np(V)–nitrate, Np(IV)–citrate and Pu(IV)–citrate, and at 6 h, 4.2, 10.9 and 17.7% of the actinides were still in the blood compartment, respectively. By contrast, between 6 and 24 h, the blood actinide clearances were very similar for the three different actinide forms with an half-life of about 24 h. Fig. 2 shows the retention of the actinides in the skeleton as a function of time following intravenous administration. After administration of Np(V)–nitrate, most of the Np deposited in bone within 1 h, which corresponded to 87.4% of the retention measured at 24 h. By contrast, after 1 h, these percentages were 46.5% for Np and 25.7% for Pu after administration of Np(IV)–citrate and Pu(IV)–citrate, respectively. Thus, kinetics of actinide bone deposition appeared closely related to their blood clearance.

Table 1 shows the actinide retention in blood, skeleton, liver and kidneys as a function of time following intravenous injection. The skeleton appeared as the main retention organ, whereas even after 24 h after contamination, the retention in liver and kidney was less than 7 and 3% of the injected activity, respectively. For each post-contamination

Table 1
Retention of actinides in blood, skeleton, liver and kidneys expressed as percent of injected activity at different post-contamination times

Target organs	Time (h)	^{238}Pu(IV)–citrate	^{237}Np(IV)–citrate	^{237}Np(V)–nitrate
Blood	1	37.1+4.1 (aa)	25.8 ± 1.9 (cc)	15.0+3.1 (bb)
	2	27.7±1.5 (aa)	15.0±2.8 (nsc)	11.5±1.0 (bbb)
	6	17.7±3.1 (a)	11.0±1.6 (cc)	4.2±1.2 (bb)
	24	7.1±0.5 (aaa)	3.7±0.4 (cc)	2.0±0.1 (bbb)
Skeleton	1	6.8±0.4 (a)	16.0±2.2 (c)	40.1±3.1 (bb)
	2	7.0±2.3 (aa)	17.9±5.3 (nsc)	39.6±1.7 (b)
	6	14.2±1.3 (a)	25.3±3.7 (cc)	37.1±8.8 (bbb)
	24	26.5±2.7 (aa)	34.5±3.7 (ccc)	45.9±5.7 (bbb)
Liver	1	4.6±0.9 (nsa)	3.5±0.6 (nsc)	2.9±0.8 (nsb)
	2	4.9±1.0 (nsa)	3.1±0.6 (nsc)	3.2±0.7 (bb)
	6	5.1±0.2 (nsa)	4.0±0.4 (nsc)	3.5±1.1 (nsb)
	24	6.5±1.4 (nsa)	5.3±0.6 (nsc)	3.8±1.8 (nsb)
Kidneys	1	1.0±0.3 (aa)	2.3±0.3 (nsc)	2.8±0.3 (bb)
	2	1.0±0.01 (aa)	2.3±0.5 (nsc)	2.0±0.3 (bb)
	6	0.7±0.3 (aa)	2.4±0.2 (nsc)	1.6±0.5 (b)
	24	0.6±0.1 (aaa)	2.6±0.4 (c)	1.7±0.4 (bb)

Mean values±standard deviation (n=3). Student's test calculation for the same time post-contamination:
Comparison with Np(IV), (a) $P<0.05$, (aa) $P<0.01$, (aaa) $P<0.001$. nsa, no significant differences.
Comparison with Pu(IV), (b) $P<0.05$, (bb) $P<0.01$, (bbb) $P<0.001$. nsb, no significant differences.
Comparison with Np(V), (c) $P<0.05$, (cc) $P<0.01$, (ccc) $P<0.001$. nsc, no significant differences.

time studied, significant differences in actinide retention were observed in the blood and in the skeleton, depending on the chemical form administered. No difference was observed for the liver, but in the kidneys a difference was only observed for Pu(IV) as compared to both Np(IV) and Np(V).

4. Discussion

This study shows significant differences in the retention kinetics of Np and Pu in the blood and skeleton depending on the chemical form administered. For Pu, we observed very similar results to those previously reported by Durbin et al. [5]. However, at 24 h post-administration, a lower retention in the liver was observed. For Np, some differences were observed as compared with biokinetics reported after intravenous administration of ^{239}Np(IV)–citrate and ^{239}Np(V) added to 1 mM citrate, especially with regard to blood retention [7]. A mass effect could explain these discrepancies. Nevertheless, in both cases the deposition of Np in the skeleton appeared much faster for Np(V) than for Np(IV) forms and, after administration of Np(V), the kinetics of Np deposition in bone was similar to that previously reported [6,7].

The significant differences observed between Np(IV) and Np(V) blood retention kinetics can be only explained by the presence of different Np forms during the first hour following the contamination. Obviously, we cannot conclude that the kinetics of Np deposition in the skeleton is controlled by the behavior of a Np–transferrin complex. Our results suggest that only a small fraction of Np(V) is reduced immediately to Np(IV) on entering the blood. The fast bone deposit of Np probably involves low-molecular weight Np complexes and, in the case of Np(V), neptunyl cations [9].

The behavior of Pu(IV) and Np(IV) was significantly different in blood and skeleton. Two different hypotheses might explain this phenomenon: (1) the kinetics of an actinide–transferrin complex is faster for Pu than for Np, due either to a mass effect or to different association constant depending on the actinide; and (2) an oxidation of some Np(IV) to Np(V) might occur. Although it has been suggested that Np(V) spontaneously reduces to Np(IV) in biological media, this has not been demonstrated experimentally. By contrast, at physiological pH, for low concentrations of Np and low concentrations of Np(IV) chelating agents, Np(IV) spontaneously oxidizes to Np(V) [7].

These different behaviors of Np(IV), Np(V) and Pu(IV) could explain the different efficacy of a DTPA treatment for actinide decorporation [6,9–12]. DTPA could not remove Np(V), whereas a significant decorporation of Np(IV) could only be obtained by treatment within minutes after contamination [12]. Thus, new experiments are needed to improve chelating agent decorporation of Np, and to characterize the Np chemical form in blood early after intravenous administration of either Np(IV) or Np(V) [13].

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