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Decorporation of actinides: a review of recent research

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Abstract

This paper reports progress on some of the research priorities identified in the Guidebook for the Treatment of Accidental Contamination of Workers published in 1992. It concludes: that the oral administration of DTPA could be an effective procedure for plutonium (Pu) and americium (Am) inhaled as nitrates; that 3,4,3-LI (1,2-HOPO) is the most effective siderophore analogue yet tested for the decorporation of these actinides, and thorium (Th); and that for thorium the efficacy of treatment will be strongly dependent on the radionuclide, and hence mass, likely to be incorporated under different exposure scenarios. No effective treatment regimens appear to be available for neptunium (Np) and uranium (U). © 1998 NRPB. Published by Elsevier Science S.A.

Keywords: Decorporation; Actinides; DTPA; Siderophore analogues

1. Introduction

The *Guidebook for the Treatment of Accidental Contamination of Workers* published by the Commission of the European Communities and the US Department of Energy in 1992 [1] recommended the administration of diethylenetriaminepentaacetic acid (DTPA) for the decorporation of plutonium (Pu), americium (Am), thorium (Th) and neptunium (Np), and sodium bicarbonate ($NaHCO_3$) for uranium (U). However, the guidebook recognised that these substances were not completely effective and stressed the need for further research. Amongst the several research priorities identified were the evaluation of the oral efficacy of DTPA for inhaled Pu and Am; the evaluation of synthetic analogues of siderophores (sequestering agents produced by micro-organisms in order to obtain iron from their environment) for actinide decorporation; and the development of treatment regimens for incorporated Np and U.

The aim of this paper is to highlight the progress that has been made during the past 5 years with particular emphasis on exposure by inhalation and wound contamination.

2. Oral administration of DTPA

For the treatment of human exposure to Pu and Am by inhalation, the oral administration of DTPA would, in principle, be more convenient and acceptable than repeated intravenous injection, particularly should large numbers of people be involved. Human data on this method of treatment, usually with the calcium salt, are sparse and conclusions as to its efficacy are complicated by uncertainties on the chemical form of intake, the amount inhaled and the delay between exposure and treatment [2]. Controlled studies with laboratory animals need not suffer from these disadvantages. Preliminary studies with rats had shown that administration of the less toxic zinc salt (ZnDTPA) can be an effective method of treatment for Pu and Am inhaled as nitrate [2]. More recent work was designed to optimise the efficacy of the procedure by reducing the interval before the commencement of treatment and increasing the daily intake of the chelate [3]. In these experiments the mass concentration of Pu and Am in the rat lung simulated acute exposure by workers to 60 and 8400 times the currently recommended annual limit on intake for ^{239}Pu and ^{241}Am. The results summarised in Table 1 show that the oral administration of DTPA is highly effective despite uptake from the gastrointestinal tract being only about 3% of that administered [2]. The small amounts of Pu and Am retained in the body at 21 days were largely independent of the treatment regimens investigated; for both actinides the lowest values were obtained after repeated intraperitoneal injection [3]. When treatment was delayed for 7 days, oral administration appeared to be more effective. Importantly, histological examination of the liver, kidneys and gastrointestinal tract provided no evidence of tissue damage under all conditions [3], though the lowest concentration should be used for humans. These observations are consistent with human

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Table 1
Efficacy of ZnDTPA administered in drinking water on retention of ^{238}Pu and ^{241}Am after inhalation as nitrate

Treatment start	Regimen dosage (μmol kg^{-1} day^{-1})	Plutonium		Americium	
		Lungs	Total body	Lungs	Total body
% controls at 21 days[a]					
1 h	3600[b]	2.3±0.5	8.3±1.1	3.6±0.9	5.4±0.7
1 h	950[c]	2.1±0.4	6.9±0.9	3.4±0.7	5.0±0.6
1 h	950[d]	2.2±0.4	8.8±1.5	3.6±0.6	6.0±0.6
1 h	95[c]	2.2±0.3	7.8±0.8	3.2±0.3	4.8±0.5
1 h	30 μmol kg^{-1}[,f]	1.7±0.3	5.2±0.7	1.7±0.6	2.5±0.4
% controls at 28 days[a]					
7 days	3600[b]	5.7±0.9	19±3.2	8.8±1.5	23±3.0
7 days	950[d]	6.1±0.7	19±3.3	9.0±1.4	23±3.4
7 days	95[c]	6.2±0.8	17±2.2	9.3±1.0	20±30
7 days	30 μmol kg^{-1}[,f]	11±1.4	25±3.6	13±1.5	29±3.5

Initial lung deposit: ^{238}Pu 676 Bq, 1.04 ng Pu, ^{241}Am 354 Bq, 2.9 ng Am.
% ILD in controls at 21 days. Pu: lungs, 41.0±3.6%; total body, 63.9±4.7%. Am: lungs, 20.1±1.6%; total body, 51.7±4.1%.
% ILD in controls at 28 days. Pu: lungs, 30.7±2.7%; total body, 60.0±4.9%. Am: lungs, 14.8±1.0%; total body, 51.3±3.8%.
[a]Mean±standard error, four animals per group.
[b]Every third day for 3 weeks (3×10^{-2} M ZnDTPA).
[c]On alternate weeks (10^{-2} M ZnDTPA).
[d]Continuously for 3 weeks (10^{-2} M ZnDTPA).
[e]Continuously for 3 weeks (10^{-3} M ZnDTPA).
[f]By i.p. injection twice weekly for 3 weeks.

experience, whereby 250 g of the free acid were administered over an interval of 16 weeks with no apparent side effects [4].

3. Development of siderophore analogues

Realistically, alternative substances to DTPA for administration to humans must be appreciably more effective under different conditions of exposure and modes of administration, and they must be of low toxicity. It has been recognised for some years that the most promising substances would be analogues of siderophores [5–7]. The rationale for this conclusion was that in mammals the biokinetics of the actinides were usually associated with the Fe(III) transport and storage systems, and that the formation constants of the actinide–ligand complexes were likely to be much higher than with DTPA. In the early developmental period, several analogues were synthesised and tested in mice after the intravenous injection of ^{238}Pu [6]. Initially the tetracatechoylate and enterobactin analogue code named 3,4,3-LICAM(C) appeared to have much potential. However, the ligand was less effective for inhaled Pu than DTPA and only enhanced minimally the excretion of Am [7,8]. Three other siderophore analogues were also considered worthy of further investigation [6]. These were a dihydroxamic derivative of DTPA, code named DTPA-DX, a hydroxypyridinone derivative of desferrioxamine, DFO-HOPO and a linear hydroxypyridinone derivative 3,4,3-LIHOPO, or more correctly 3,4,3-LI(1,2-HOPO). Subsequent studies with rats showed that after the inhalation of Pu and Am as nitrates, DTPA-DX was as effective as DTPA for removing Am from the body but less effective for Pu [9]. Whilst DFO-HOPO was considerably more effective than DTPA after the intravenous injection of Pu, it was inferior to DTPA for inhaled Pu and did not significantly enhance the excretion of Am after either mode of intake [9–11]. However, the ligand 3,4,3-LIHOPO proved to be more effective than DTPA after the inhalation of Pu–nitrate, and Pu–tributylphosphate (formed during the reprocessing of nuclear fuels), and after wound contamination with Pu and Am nitrate [7,12]. Preliminary studies showed that the substance was also more effective than DTPA for Th [7]. Toxicological studies with 3,4,3-LIHOPO in the baboon at the human equivalent dosage of DTPA, 30 μmol kg^{-1}, showed no evidence of adverse side effects, even with repeated administration [13]. However, the possible superiority of other siderophore analogues, either in terms of easier synthesis, lower toxicity or greater efficacy could not be excluded. Indeed subsequent intravenous injection studies with mice showed that the analogue code-named TREN-(Me-3,2-HOPO), abbreviated hereafter to TREN-HOPO, was as effective as 3,4,3-LIHOPO for decorporating Pu and Am [14].

4. Comparative efficacy of HOPO ligands and DTPA for Pu and Am

With DTPA as a comparison, TREN-HOPO and another linear hydroxypyridonate, code named 5-LI-(Me-3,2-HOPO), abbreviated hereafter to LiMe-HOPO, have been examined for their ability to remove Pu and Am from the rat after inhalation or simulated wound contamination as nitrates. The data have been compared with those obtained previously for 3,4,3-LIHOPO [7,12]. The structures for the

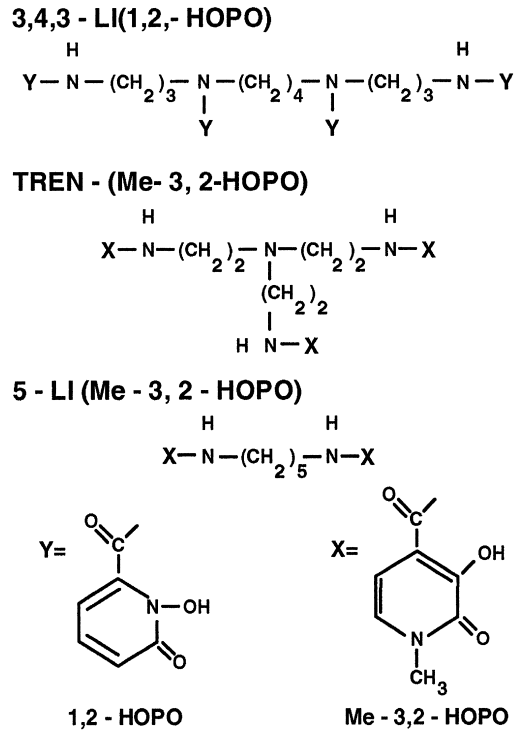

Fig. 1. Structures of hydroxypyridonate ligands.

-HOPO ligands are given in Fig. 1. A summary of the experimental results for repeated administration is given here; more detailed information and data for other treatment regimens is reported elsewhere [14–16].

In the inhalation experiment, the masses of Pu and Am deposited in the rat lung simulated acute exposure by workers to 44 and 14 700 times the ALI for ^{239}Pu and ^{241}Am. The most effective ligand for ^{239}Pu was 3,4,3-LI(HOPO) (Table 2). Repeated intraperitoneal injection of the ligands was more effective than a single administration at 30 min. In the former case, the amount of Pu retained in the body by 7 days after exposure, 4.5% of controls, was about 5 and 3 times less than with the other HOPO ligands and DTPA, respectively. For Am, TREN-HOPO, 3,4,3-LIHOPO and DTPA were considered equally effective, the body contents being reduced to about 10% of those in controls.

The -HOPO ligands and DTPA were also compared after wound contamination simulated by intramuscular injection (Table 3). In this experiment Pu and Am nitrate solutions in 10 μl 0.01 M HNO_3 were injected to a depth of 5 mm at the centre of the extensor cruris muscle block. All ligand solutions (0.1 ml in 0.14 mol l^{-1} NaCl) were injected locally at a dosage of either 3 or 30 μmol kg^{-1} at 30 min after exposure. With 3,4,3-LIHOPO, the amounts of Pu and Am retained in the body 7 days after exposure were 0.9 and 0.8%, respectively, of those in controls [12]. The value for Pu was 20 and 40 times lower than for TREN-HOPO and DTPA, respectively; the corresponding differences with Am were 20 and 34 (Table 3). However, the efficacies of 3,4,3-LIHOPO and DTPA decreased rapidly with delay in administration. When treatment commenced 1 day after exposure the amounts in the body at 7 days were, respectively, 23 and 81% of controls; the values for Am were 25 and 73% [12]. The effect of delayed administration with the other -HOPO ligands has not been investigated.

It is noteworthy that the early administration (30 min) of 3,4,3-LIHOPO is also effective when the mass of Pu deposited at the wound site is 3 orders of magnitude greater than that cited in Table 3. In this case the amounts of Pu retained at the wound site and in other tissues at 7 days were 4.3 and 0.8% of the initial deposit [12].

Table 2
Comparative efficacies of hydroxypyridinonates and DTPA on retention of ^{238}Pu and ^{241}Am after inhalation as nitrate

Ligand	Dosage (μmol kg^{-1})	Plutonium		Americium	
		Lungs	Total body	Lungs	Total body
% of controls at 7 days ($\bar{x}$±SE)[a]					
TREN-HOPO	30[b]	34±2	37±3	26±2	34±2
	30[b]+30[c]	23±1	21±2	10±1	12±1
LIMe-HOPO	30[b]	31±2	46±3	34±2	40±2
	30[b]+30[c]	14±1	21±2	15±1	18±1
3,4,3-LIHOPO	30[b]	11±1	11±1	41±4	31±3
	30[b]+30[c]	1.8±0.3	4.5±0.4	13±2	11±2
DTPA[d]	30[b]	16±2	18±2	21±2	15±1
	30[b]+30[c]	14±1	13±1	13±2	10±1

Initial lung deposit: ^{238}Pu 550 Bq 0.8 ng Pu, ^{241}Am 700 Bq 5.6 ng Am.
% ILD in controls at 7 days. Pu: lungs, 60.8±4.1%; total body, 84.0±4.2%. Am: lungs, 45.9±2.8%; total body, 75.0±2.8%.
[a]Mean±standard error, five animals per group.
[b]Intraperitoneal injection at 30 min.
[c]Intraperitoneal injections at 6 h, and 1, 2 and 3 days.
[d]CaDTPA at 30 min, ZnDTPA at other times.

Table 3
Comparative efficacies of hydroxypyridinonates and DTPA on retention of ^{238}Pu and ^{241}Am after intramuscular injection as nitrate

Ligand	Dosage (μmol kg^{-1})	Plutonium		Americium	
		Wound site	Total body	Wound site	Total body
% of controls at 7 days ($\bar{x}\pm$SE)[a]					
TREN-HOPO	3[b]	20±1	24±1	19±2	23±1
	30[b]	16±1	18±1	12±1	16±1
LIMe-HOPO	3[b]	5.7±0.3	10±1	5.4±0.4	7.4±0.3
3,4,3-LIHOPO	3[b]	4.8±0.4	5.9±0.3	8.5±0.9	8.8±0.6
	30[b]	0.9±0.2	0.9±0.1	0.6±0.2	0.8±0.1
CaDTPA	30[b]	29±1	37±1	25±1	27±1

Initial intramuscular deposit: ^{238}Pu 350 Bq, 0.5 ng Pu, ^{241}Am 350 Bq, 2.8 ng Am.
% IMD in controls at 7 days. Pu: wound site, 66.8±1.1%; total body, 94.4±0.2%. Am: wound site, 66.9±0.8%; total body, 94.8±0.2%.
[a]Mean±standard error, four animals per group.
[b]Local administration at 30 min after exposure.

5. Comparative efficacy of HOPO ligands and DTPA for Th and Np

The substance recommended for the decorporation of Th is DTPA [1]. However, the evidence available from animal experiments with nitrate [17] suggests that it will be ineffective when any chemical form of ^{232}Th is inhaled by humans [17].

The efficacies of DTPA and 3,4,3-LIHOPO when the initial lung deposit of Th (4 ng) in the rat lung simulated acute exposures by workers to 3×10^6 and 50 times the ALIs for ^{228}Th and ^{230}Th, respectively, are shown in Table 4. The results show that the repeated administration of 3,4,3-LIHOPO was appreciably more effective than of DTPA, the body contents being reduced to 17 and 78%, respectively, of those in controls. However, for a mass concentration which simulates the ALI for ^{232}Th (4.2 μg Th), the efficacy of treatment is reduced substantially.

Studies have also been undertaken on the comparative efficacy of 3,4,3-LIHOPO and DTPA after intramuscular injection of Th nitrate [18]. The experimental conditions were similar to those described previously for Pu and Am. After the repeated administration of the ligands commencing 30 min after exposure, the amounts of Th retained in the body by 7 days were about 4 times less with 3,4,3-LIHOPO than with DTPA. However, when this treatment protocol was delayed for 1 day, the efficacy of treatment fell appreciably; under these conditions the body contents of Th differed by two-fold (Table 5). The efficacy of 3,4,3-LIHOPO for treating wound contamination has also been confirmed by others [19].

The recommended agent of choice for Np is also DTPA [1]. On the basis of the experimental evidence available it is concluded that DTPA, 3,4,3-LIHOPO, TREN-HOPO and phosphonic acid derivatives are only minimally effective [14,20,21], and that the decorporation of Np remains an outstanding problem.

6. Decorporation of uranium

Soluble compounds of natural and low enriched uranium are nephrotoxic. Due to the rapid absorption of uranium from lungs to blood, conclusions concerning the efficacy of chelating agents would, in this case, be valid on the basis of intravenous injection experiments. The recom-

Table 4
Comparative efficacies of 3,4,3-LI(1,2-HOPO) and DTPA on retention of Th after deposition in the lungs as nitrate

Ligand	Dosage (μmol kg^{-1})	Thorium[b]		Thorium[c]	
		Lungs	Total body	Lungs	Total body
% of controls at 7 days ($\bar{x}\pm$SE)[a]					
3,4,3-LIHOPO	30[d]	36±3	29±2	93±7	87±5
3,4,3-LIHOPO	30[d]+30[e]	17±2	17±2	73±6	69±5
DTPA	30[d]+30[e]	73±4	78±3	93±6	91±5

[a]Mean±standard error, four animals per group.
[b]ILD 4 ng Th. % ILD in controls: lungs, 50.7±1.9%; total body, 69.9±3.5%.
[c]ILD 4.2 μg Th. % ILD in controls: lungs, 69.9±4.5%; total body, 78.1±4.6%.
[d]Intraperitoneal injection, 30 min.
[e]Intraperitoneal injection, 6 h, and 1, 2 and 3 days.
[f]CaDTPA at 30 min, ZnDTPA at other times.

Table 5
Comparative efficacies of 3,4,3-LIHOPO and DTPA on retention of ^{228}Th after intramuscular injection as nitrate

Ligand	Delay[b]	Dosage, (μmol kg^{-1})	Wound site	Total body
% of controls at 7 days ($\bar{x}\pm$SE)[a]				
3,4,3-LIHOPO	30 min	30[c]	14±1	20±1
		30[c]+30[d]	12±1	15±1
DTPA		30[c]	60±3	65±3
		30[c]+30[d]	50±3	55±2
3,4,3-LIHOPO	1 day	30[c]	43±3	52±2
		30[c]+30[d]	38±2	40±2
DTPA		30[c]	82±3	82±3
		30[c]+30[d]	79±3	79±3

Initial deposit: 600 Bq ^{228}Th, 0.1 ng Th.
% IMD in controls at 7 days: wound site, 64.8±1.5; total body, 91.5±1.7.
[a]Mean±standard error, n=4 except controls when n=8.
[b]Interval before exposure and treatment.
[c]Local injection of CaDTPA.
[d]ZnDTPA by i.p. injection at 6 h, and 1, 2 and 3 days after exposure.

mended substance for uranium decorporation is $NaHCO_3$, despite the possibility of undesirable side effects, such as hypokalaemia, alkolosis, etc. [1]. Since there appears to be no substantial evidence that bicarbonate is effective, several alternative substances have been investigated. Amongst these were phenolic chelating agents such as sodium 4,5-dihydroxybenzene-1,3-disulphonate (Tiron). Whilst Tiron was shown to avert uranium poisoning in mice [22], it was a much less effective antidote in rats [23]. Moreover, after the administration of sublethal amounts of uranium to rats, its excretion was not enhanced appreciably by the chelate [24].

Since uranium has a known affinity for the phosphonic acid moiety, another approach has been to investigate the efficacies of polyaminophosphonic acids, bisphosphonates and phosphoalkylphosphinates [25,26]. In some cases, large reductions in the kidney and skeletal contents have been observed when the substances have been administered immediately after uranium [25–27]. The most effective derivative tested so far under these conditions is diethylenetriaminepentamethylenephosphonic acid (DTPMP) and its administration to humans has been recommended [25]. However, under more meaningful conditions relevant to human exposure and treatment, delays of 30 min or more, it is only partially effective (Table 6). The efficacy of 3,4,3-LIHOPO after prompt and delayed administration is superior to that of bicarbonate [27] but the effect of delayed treatment is similar to that for DTPMP (Table 6). Recent studies with mice show that other HOPO ligands have a similar efficacy to 3,4,3-LIHOPO [28].

It is concluded that the effective decorporation of uranium remains an outstanding problem in radiological protection.

7. Summary and future considerations

The experimental data reviewed here show that the oral administration of ZnDTPA is potentially an effective method of treatment for workers overexposed to Pu and Am nitrates by inhalation. This mode of uptake of ZnDTPA should also be appropriate for less transportable compounds such as AmO_2. In such cases the administration of ZnDTPA by any route may not accelerate absorption into blood. On the other hand, the maintenance of low concentrations of ZnDTPA in the bloodstream should inhibit substantially the deposition of these actinides in body tissues as has been demonstrated after subcutaneous infusion [29]. In principle the efficacy of oral ZnDTPA could be improved by the use of drugs which increase intestinal permeability. Whether any advantage would be lost by the possibility of any unacceptable side effects is at present uncertain.

Table 6
Comparative efficacies of 3,4,3-LIHOPO and DTPMP on retention of uranium after intravenous injection as nitrate

Ligand	Delay (min)	Dosage (μmol kg^{-1})	Kidneys	Total body
% of controls at 4 days ($\bar{x}\pm$SE)[a]				
3,4,3-LIHOPO	0.1	30	18±2	51±2
	30	30	36±3	66±5
DTPMP	0.1	300	8±1	32±3
	30	300	51±6	72±6

Injected activity: 300 Bq ^{233}U, 10 μg U.
% in controls at 4 days: kidneys, 9.94±0.87; total body, 27.3±1.3.
Mean±standard error, four animals per group.

The data reported for the comparative efficacy of the hydroxypyridonates and DTPA suggests that 3,4,3-LIHOPO is the most potent ligand for the decorporation of Pu and Am. As such it remains at present the most appropriate substance for comprehensive toxicity testing prior to its possible use in humans. For wound contamination, its incorporation into transdermal gels should be considered as an alternative to local injection.

The ligand 3,4,3-LIHOPO is also much more effective than DTPA for Th when the mass of the element is likely to be low, e.g. after incorporation of ^{228}Th and ^{230}Th. However, the reduction in the body content is lower than for Pu, and the potential of other substances should be investigated. The removal of ^{232}Th from the body remains an outstanding problem.

At present no effective regimens appear to exist for the decorporation of Np and U.

Finally it should be noted that an 'action group' sponsored by the Commission of the European Communities under the Fourth Framework Programme has been charged with the preparation of a state-of-the-art report on decorporation by late 1999. This report will include the most recent research progress, advice on treatment for industrial and environmental forms of the actinides based on material specific absorption data, and a medical overview by practitioners in the field.

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