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Research Paper

Predicting Plutonium Decorporation Efficacy after Intravenous Administration of DTPA Formulations: Study of Pharmacokinetic–Pharmacodynamic Relationships in Rats

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Purpose. The objectives of this study were: 1) to assess the relationship between plutonium decorporation (increased excretion and reduced retention in main organs of deposition) induced by intravenous liposome formulations of the chelating agent diethylene triamine pentaacetic acid (DTPA) and its pharmacokinetics, and 2) to model the renal excretion of plutonium after treatment with liposome-encapsulated DTPA in order to predict its efficacy and to optimise treatment schedules.
Materials and Methods. Pharmacokinetic parameters from plasma or urinary data (days 0–16 sample collections) were modelled *versus* decorporation efficacy, and best correlations were selected for their goodness of fit.
Results. The plutonium decorporation enhancement by DTPA liposomal formulations was well described by logistic models and the best correlation was observed with the area under the DTPA concentration curve of each formulation. The plutonium urinary excretion rates decreased mono-exponentially as a function of time after a single dose and the proposed model allowed a simple determination of the elimination half-life of the Pu–DTPA complex, a reasonably good approximation of the long-term efficacy of the treatments from truncated urinary data.
Conclusions. Both liposomal formulations of chelating agents and pharmacokinetic approaches to plutonium decorporation should be helpful in optimising treatment protocols.

KEY WORDS: DTPA; excretion rate; liposome; PK/PD correlation; plutonium decorporation.

INTRODUCTION

In accidental internal contamination by plutonium (Pu), decorporation treatment, if necessary, consists in reducing the radiological risk by increasing the rate of elimination of the contaminant from the body. This can be achieved by administering a chelating agent able to form a soluble complex with the radionuclide, which is therefore more readily excreted in the urine or faeces. To date, diethylene triamine pentaacetic acid (DTPA) is the only molecule admitted for use in humans (1,2) as its efficacy towards Pu has been demonstrated by animal experiments (3). However, DTPA therapy has serious drawbacks which are attributed to the physicochemical properties of the molecule. In spite of its ability to chelate Pu in body fluids, DTPA is hydrophilic and thus does not penetrate cells to any great extent (4). Besides, early pharmacokinetic studies in animals (5,6) and in humans (7) showed that DTPA is generally very poorly distributed to tissues and is rapidly eliminated from the body after inhalation or intravenous injection.

To overcome these drawbacks, we have previously reconsidered a useful strategy first proposed by Rahman *et al.* (8) which consisted of encapsulation of DTPA in liposomes in order to promote its capture by macrophages of the reticulo-endothelial system. In addition, we justified this strategy by adding a pharmacokinetic approach and designed novel long-circulating liposomes of DTPA in order to modify its fate *in vivo* after intravenous administration. In rats, this optimised strategy extended the biological residence time of DTPA and increased its distribution to the liver and the

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ABBREVIATIONS: C-MLV, conventional multilamellar vesicle; CL, conventional liposome; CL-100 nm, conventional liposome sized at around 100 nm; DTPA, diethylene triamine pentaacetic acid; IA, injected activity; MLV, multi-lamellar vesicle; Pu, plutonium; S-MLV, stealth multi-lamellar vesicle; SL, sterically stabilized (Stealth®) liposome; SL-100 nm, stealth liposome sized at around 100 nm.

skeleton, which are the two main Pu target organs. Then, in Pu decorporation experiments in rats, we verified that these advantageous pharmacokinetic modifications were associated with a substantial reduction of Pu retention in liver and bones and concurrently an increased urinary excretion (9).

In order to confirm the usefulness of DTPA encapsulation in liposomal formulations and the interest of pharmacokinetic studies as a tool to select more effective formulations for Pu decorporation, the first objective of the present study was to assess the relationship between DTPA pharmacokinetic parameters modified after its encapsulation in different liposomal formulations and the resulting enhanced pharmacological effect, i.e., an increased excretion of the radionuclide in comparison with the conventional treatment with the solution of free DTPA. Assuming that urinary excretion is the predominant elimination pathway of Pu after DTPA treatment, and in order to confirm the benefit of the pharmacokinetic approach, we then analysed the Pu urinary excretion data using a simple pharmacokinetic model, in order to provide a tool to predict the efficacy of decorporation treatment with encapsulated DTPA and also to provide radiation toxicologists and other physicians with information regarding the treatment schedule.

MATERIALS AND METHODS

Chemicals

Unlabelled DTPA, as calcium salt aqueous solution $CaNa_3$–DTPA, was from the Pharmacie Centrale des Armées (P.C.A., Orléans, France). [^{14}C]-DTPA labelled at carbon-2 in the acetate moiety was from NEN Life Science Products (Boston, USA). Dioleoylphosphatidylcholine (DOPC), cholesterol (CH) and phosphatidylglycerol (PG) from Sigma–Aldrich (St Quentin Fallavier, France) were used for the formulation of conventional liposomes (CL). DOPC, CH and distearoylphosphatidylethanolamine-polyethylene glycol 2000 conjugate (DSPE-PEG) (Sigma–Aldrich, France) were used for the formulation of stealth liposomes (SL) i.e., PEGylated liposomes. Solutions of ^{239}Pu-phytate and ^{238}Pu-phytate (87% of Pu (IV)) were prepared by dilution of a stock solution of predominantly ^{239}Pu or ^{238}Pu in nitric acid (2 N) in a 0.2 mM solution of phytic acid to obtain a Pu activity of about 500 Bq/100 μL. These solutions were filtered (porosity: 0.22 μm; Schleicher & Schuell FP 30/0.2 CA) before injection. All other chemicals were of reagent grade.

Animals

Animal use procedures were in accordance with the recommendations of the EEC (86/609/CEE) and the French National Committee (decree 86/848) for the care and use of laboratory animals. Twelve-week-old male Sprague–Dawley rats (Charles River Laboratories, Les Oncins, France) weighing from 300 to 325 g and from 200 to 220 g were used in pharmacokinetic and in Pu decorporation experiments, respectively. Rats were separated into groups of three animals and housed in metabolism cages. Food and water were given *ad libitum*.

Liposome Preparation

Conventional (CL) and stealth (SL) liposomes were composed of DOPC/CH/PG and DOPC/CH/DSPE-PEG of molar ratios 60/30/10 and 64/30/6, respectively, with a total lipid concentration of 100 mM. Methods to obtain large multilamellar vesicles (MLV) or liposomes calibrated to a diameter of around 100 nm of both types and which will be designated as C-MLV, S-MLV, CL-100 nm and SL-100 nm were extensively described previously (10). To summarise, MLVs were formulated according to Bangham's lipid hydration method and sized liposomes were obtained from MLVs by an extrusion procedure. DTPA was encapsulated in liposomes following a freeze-thaw procedure (10).

In vivo Studies

The pharmacokinetics of free DTPA and of [^{14}C]-DTPA-loaded liposomes were tested 48 hours and up to 16 days after a single intravenous injection of each formulation in anaesthetised rats (n = 3 rats per formulation) as described previously (10). Blood, organs (liver, spleen, kidneys, and femurs), daily urine and faeces were sampled and assayed for their ^{14}C content. In Pu decorporation studies, anaesthetised rats were contaminated intravenously with Pu solutions 1 h before treatment (n = 5 rats per treatment) by intravenous injection of a calcium salt aqueous solution of unlabelled DTPA (approximately 4 and 30 μmol kg^{-1}) or formulations of unlabelled DTPA encapsulated in liposomes. DTPA encapsulated doses depended on percentages of encapsulation which were assumed to be equal to those obtained with liposomes containing [^{14}C]-DTPA formulated at the same time (48% for S-MLV liposome, 30% for C-MLV and CL-100 nm and 7% for SL-100 nm liposomes). Cumulative samples of urine and faeces were collected. Sixteen days after treatment, rats were euthanatised and tissue samples (femurs, liver, kidneys and spleen) were dissected and mineralised. Pu content was determined by liquid scintillation counting and Pu retention was expressed in terms of the percentage of the injected radioactivity. Pu retention in the body was estimated as the Pu content in liver, skeleton (estimated to be 20 times the femur content (1)), spleen and kidneys.

Data Analysis

DTPA principal pharmacokinetic parameters were calculated from plasma data using a non-compartmental analysis and Kinetica 3.0 software (InnaPhase Corporation, Philadelphia, PA, USA). Each parameter was evaluated for best fit and correlation with Pu decorporation results (PK–PD relationship) by using Origin 6.1 software (OriginLab Corporation, Northampton, MA, USA). Potential models were discriminated by selecting the smaller chi square value of fit (χ^2) and the higher coefficient of determination (r^2). Selected doses, pharmacokinetic parameters for each DTPA formulation and Pu decorporation results are listed in Table I. In the last part of this study, excretion rates of Pu–DTPA complex in urine after a single DTPA treatment with either free DTPA or SL-100 nm were calculated from data listed in Table II. The change of excretion rates as a function of time was analysed assuming that Pu–DTPA

Table I. Plasma Pharmacokinetic Parameters of [^{14}C]-DTPA Injected in Different Formulations and Plutonium Decorporation Efficacy of $CaNa_3$–DTPA Formulations 16 days after a Single Intravenous Administration to Rats

	Control		Free DTPA	C-MLV	CL-100 nm	S-MLV	SL-100 nm
AUC_{tot} (% dose/ml h)	–		0.41	1.22	7.79	8.10	35.34
$t_{1/2}$ beta (h)	–		0.53	4.17	3.68	8.71	12.57
MRT (h)	–		0.73	2.90	5.17	7.48	17.62
V_d (ml)	–		182.6	524.2	78.4	155.1	51.3
Cl (ml/h)	–		250.5	87.8	14.8	12.4	2.8
DTPA dose (μmol kg^{-1})	0	4.25	30.0	5.2	6.0	21.9	3.2
Pu excretion ± SE (% IA)	26.2 ± 1.8	29.5 ± 4.6	46.5 ± 7.0	43.3 ± 5.9	NA	77.9 ± 12.0	90.4 ± 2.8
Pu retention ± SE (% IA)	74.9 ± 1.8	46.9 ± 11.1	53.2 ± 3.9	12.8 ± 4.6	NA	11.7 ± 3.6	12.1 ± 3.0

No DTPA pharmacokinetics were assessed in the "Control" group.
The effects of two different DTPA dosages on Pu decorporation were assessed in the "Free DTPA" experiments.
Pu retention was estimated as the Pu content in liver + skeleton + spleen.
AUC_{tot} Total area under plasma concentration curve, $t_{1/2}$ beta elimination half-life, MRT mean residence time, V_d volume of distribution, *Cl* clearance, NA data not available, $n = 3$ rats per group in pharmacokinetic studies and $n = 5$ in decorporation studies, ^{238}Pu-phytate and ^{239}Pu-phytate injected activity was 12 kBq/rat.

complex once formed in extracellular fluids or released from tissues to the bloodstream is excreted by the kidneys like any other drug administered intravenously, following a first-order process mainly due to physiological glomerular clearance. Hence, urinary excretion rate can be represented by a mono-exponential decay and described by the following equation (11):

$$\frac{dQ_U}{dt} = (K_R . Q_0) . e^{-K_E \cdot t}$$

where dQ_U/dt is the urinary excretion rate (expressed in percentage of Pu injected activity excreted by day), K_R represents the renal excretion rate constant of the Pu–DTPA complex or Pu alone (in day^{-1}), Q_0 represents the initial injected Pu activity ($Q_0 = 100\%$ if Q_U is a percentage of this value), K_E is the global elimination rate constant of Pu–DTPA (in days^{-1}) and t is the time elapsed after treatment (in days). $K_R \cdot Q_0$ can be determined graphically in semi-log representation by extrapolation of the curve to the origin. The major advantage of this simple model is that the maximal quantity of an injected drug which can be excreted in urine after a theoretical infinite time (practically seven times the elimination half-life of the considered drug) can be assessed by the relation:

$$\frac{Q_{U\infty}}{Q_0} = \frac{K_R}{K_E} \Longleftrightarrow Q_{U\infty} = \frac{(K_R . Q_0)}{K_E}$$

where $Q_{U\infty}$ represents this theoretical maximal amount of Pu–DTPA which can be excreted in urine (in % of initial activity). Thus, if this model proved to fit the data of urinary excretion of Pu–DTPA, useful parameters such as the elimination constant K_E (or the elimination half-life ($t_{1/2}$) of Pu–DTPA as $t_{1/2} = Ln2 / K_E$) and the quantity $Q_{U\infty}$ could be readily determined and calculated to evaluate the efficiency of the treatment. All data are presented as means ± standard error. Sets of data were compared with Student's *t*-test and differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

In order to assess to what extent the pharmacokinetic parameters of the DTPA formulations influence their effectiveness in increasing Pu elimination from the body,

Table II. Pharmacokinetic Estimates Derived from the Analysis of Urine Data

		Control		Free DTPA		S-MLV		SL-100 nm	
DTPA Dose (μmol kg^{-1})		0		30.0		21.9		3.2	
Interval Time (d)	Mean Time (d)	Pu ± SE (% IA)	Rate (% IA d^{-1})	Pu ± SE (% IA)	Rate (% IA d^{-1})	Pu ± SE (% IA)	Rate (% IA d^{-1})	Pu ± SE (% IA)	Rate (% IA d^{-1})
0–2	1	2.2 ± 0.4	1.12	12.5 ± 4.9	6.27	32.0 ± 5.7	15.99	26.3 ± 5.0	13.14
2–3	2.5	2.4 ± 0.3	0.78	12.2 ± 3.2	3.51	31.0 ± 4.3	9.05	31.7 ± 3.1	11.78
3–6	4.5	3.6 ± 0.2	0.39	18.5 ± 4.4	2.13	48.2 ± 4.0	5.74	52.2 ± 3.6	6.85
6–8	7	4.3 ± 0.2	0.36	21.8 ± 5.0	1.61	57.5 ± 4.7	4.65	62.2 ± 3.6	4.99
8–10	9	4.8 ± 0.2	0.26	24.1 ± 5.3	1.19	64.4 ± 4.5	3.45	69.8 ± 2.6	3.81
10–13	11.5	5.4 ± 0.2	0.18	26.4 ± 5.4	0.74	72.7 ± 505	2.75	77.2 ± 2.4	2.70
13–16	14.5	5.8 ± 0.2	0.15	27.3 ± 5.5	0.32	76.5 ± 6.6	1.29	82.9 ± 2.8	1.66

^{238} Pu-phytate injected activity was 12 kBq/rat; $n = 5$.

each parameter was evaluated separately and the best correlation with the pharmacological effect, i.e., increased Pu excretion, was found with the total area under the plasma concentration curve (AUC_{tot}), as shown in Fig. 1. With the aim of normalising and comparing the formulation in the calculation of the AUC_{tot}, plasma concentrations were expressed as percentages of the DTPA injected dose since the DTPA dose differed from one formulation to another for the same injection volume and the same concentration of lipids injected with liposomes. Thus, the data seem to fit the logistic (or sigmoidal) model where Pu excretion is well correlated with an increase in the AUC_{tot}, with SL-100 nm giving the best results (last plot of the curve). This obviously means that an increase in the body's exposure to DTPA is a precondition for Pu decorporation enhancement and justifies the development of pharmaceutical formulations of DTPA or other chelating agents such as an implantable long-release device which should be able to increase the global availability of the drug *in vivo*. Interestingly, the analysis of another parameter, DTPA total clearance (Cl), would have led to symmetric results as with AUC_{tot} (data not shown) since in our case AUC_{tot} = Dose/Cl = 100/Cl. The present observations were expected in so far as DTPA initially exhibits poor pharmacokinetic properties after parenteral administration. Besides, drug carriers such as sterically stabilised liposomes, which seem to fulfil the kinetic conditions, also display a combined distribution effect since they succeed in targeting and delivering DTPA to specific compartments such as the liver and the skeleton, as previously shown (9,10).

These decorporation experiments coupled to pharmacokinetic experiments often require analysis of many samples (excreta and organs) and must be scheduled in relatively long-term observations (sometimes over several weeks) to assess the lasting effect of a long-term treatment such as liposomes, probably because the elimination half-life or the mean residence time of the carried drug is considerably prolonged (Table I). We therefore wondered whether the analysis of a restricted number of parameters, such as urinary excretion, and the use of a simple and well-known pharmacokinetic model for intravenous drug renal clearance, would

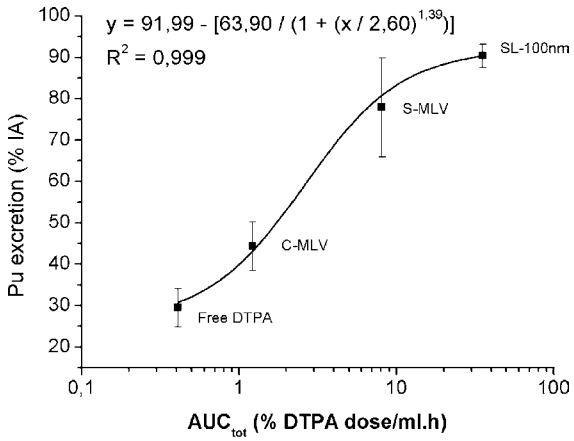

Fig. 1. Relationship between plutonium total cumulated excretion in urine and faeces 16 days after a single decorporation treatment and DTPA body exposure (AUC total) related to different DTPA formulations injected intravenously in rats. ^{238}Pu-phytate injected activity was 12 kBq/rat, $n = 5$ per treatment group.

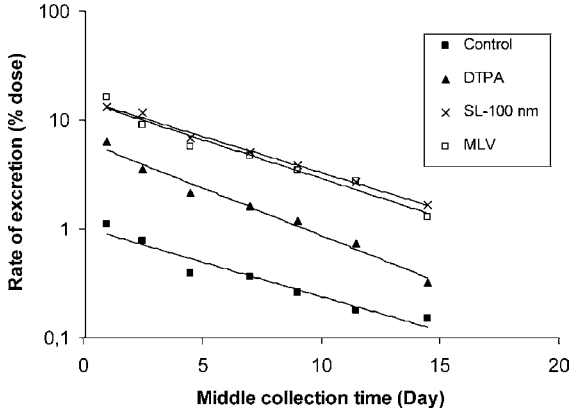

Fig. 2. Pu urinary elimination rate decrease as a function of time after a single decorporation treatment. ^{238}Pu-phytate injected activity was 12 kBq/rat and DTPA dose was 30, 21.9 or 3.2 μmol kg^{-1} when rats were injected with free DTPA solution, S-MLV liposomes or SL-100 nm liposomes, respectively. $n = 5$.

help to predict the whole pharmacological effect of a decorporation treatment within a short experimental time. Towards this end, Pu–DTPA complex was considered as any drug excreted in urine and excretion rates were calculated from cumulated excretion data compiled in Table II and tested for fitting to the mono-exponential model described in the Materials and Methods section. The representations of Pu excretion rates induced by different selected DTPA formulations, shown in Fig. 2, demonstrate that the excretion of the complex can be reasonably well modelled by this equation. This behaviour is not surprising as our results are in accordance with those of other authors who have empirically demonstrated from experimental data in treated humans, and without particular pharmacokinetic considerations, that Pu urinary elimination rates induced by DTPA therapy exponentially decrease with time after each administration (12,13). It was also proposed that Pu elimination rates or the day of DTPA administration can be fractionated into a sum of two exponential decay functions, but that globally the rates tend to be described by a power function of time elapsed after one treatment and for longer periods of observation over 100 days (14). This was originally described by Langham *et al.* who reported that Pu excretion data in treated human subjects for long periods after DTPA administration can be expressed more conveniently by power functions. They proposed the following expression for the urinary elimination (15):

$$E_u = I_0 \cdot A \cdot t^{-0.74}$$

in which E_u is the percent of injected dose excreted per day, I_0 the Pu initially deposited, A is the fraction excreted in urine during the first day, and t (>1) the number of days between injection and sample collection. Lastly, Hall *et al.* derived Langham's function and proposed a sophisticated sum of at least two exponential decay functions to model Pu excretion rate, but only to make early assessments of the systemic body burden and determine optimal treatment schedules (16). It is worth noting that such power functions were later used to describe the heterogeneous distribution of calcium and drugs (17–19). As far as Pu faecal elimination is

Table III. Interpretation of the Urinary Elimination Rate Graphs

	Control	Free DTPA	S-MLV	SL-100 nm
DTPA Dose (μmol kg^{-1})	0	30.0	21.9	3.2
$K_R \cdot Q_0$ (% IA d^{-1}) (data from 0–16 days)	1.0343	6.4493	15.078	15.373
K_E (% IA d^{-1}) (data from 0–16 days)	0.1459	0.1998	0.1646	0.1543
$t_{1/2}$ of DTPA–Pu excretion (d) (data from 0–16 days)	4.8	3.5	4.2	4.5
$7 \times t_{1/2}$ DTPA–Pu (d) (data from 0–16 days)	33.3	25	29	32
Q_U 16 days (% IA)	5.8	27.3	76.5	82.9
$Q_{U\infty}$ (extrapolated data from 0–16 days) (% IA)	7.1	32.3 [a]	91.6 [a,b]	99.6 [a,b,c]
$Q_{U\infty}$ (extrapolated from 0–6 days) (ratio with $Q_{U\infty}$)	5.2 (73%)	26.7 (83%)	70.3 (77%)	88.9 (89%)

[238] Pu-phytate injected activity was 12 kBq/rat; $n = 5$.
$K_R \cdot Q_0$ Extrapolated initial Pu urinary elimination rate (K_R renal elimination rate constant, Q_0 initial Pu contamination activity), K_E elimination rate constant, $Q_{U\infty}$ theoretical cumulated Pu urinary excretion after infinite time, $t_{1/2}$ excretion Pu or Pu–DTPA complex elimination half-life.
[a] Significantly different ($p < 0.05$) from control group.
[b] Significantly different ($p < 0.05$) from free DTPA treated group.
[c] Significantly different ($p < 0.05$) from S-MLV treated group.

concerned, after DTPA treatments the faecal output depends on the DTPA formulation but was always lower than the urinary output as it accounted for 41, 7.8 and 8.7% of total excretion after the administration of free DTPA, S-MLV or SL-100 nm, respectively, (10). So, this urinary excretion rate model should give good approximations to the main elimination pathway of Pu after different treatments. Besides, Pu faecal excretion rate after DTPA treatment did not seem to decrease exponentially with time (data not shown), presumably because the biliary or metabolic clearance of the Pu–DTPA complex is a much more complicated process than the first-order urinary filtration. Table III presents the derived parameters calculated from our adapted model. All selected DTPA formulations clearly increase Pu excretion rate in urine, with the greatest initial rate $K_R \cdot Q_0$ being achieved with the large S-MLV and SL-100 nm liposomes (a 15 and two-fold increase compared to control and free DTPA, respectively). The rates seem to decrease identically with the two liposomal formulations as attested by the half-life of elimination. Hence, the theoretical maximum amount of Pu that could be excreted in urine in an infinite time and the time required to reach 99% of this maximum amount (i.e., around seven times the half-life of elimination) were calculated and the results lead us to the following interpretations: 1) a maximum amount of excreted $Q_{U\infty}$ of only 7.1% of injected Pu should be expected without treatment and no further significant excretion in urine should occur after 33 days, which is in agreement with the long retention behaviour of systemic Pu described so far and due to Pu fixation in target tissues and very low exchanges with the bloodstream at times remote from systemic contamination (20,21); 2) a $Q_{U\infty}$ value of 27.3% of Pu excreted in urine could be expected after 25 days with free DTPA at the therapeutic dose of 30 μmol kg^{-1} in these experimental conditions; 3) $Q_{U\infty}$ values of 91.6 and 99.6% of Pu excreted in urine could be expected after treatment with DTPA liposomal formulations whereas excretion over 16 days was 76.5 and 82.9% for S-MLV and SL-100 nm, respectively. It is also worth noting that a multiple dosing regimen could be undertaken, and given the $t_{1/2}$ of elimination a weekly dosing appears to be appropriate.

In addition, from a practical point of view, one value of this fitting lies in the fact that it can predict the long-term effectiveness of a given DTPA formulation by using the Pu elimination rate or conversely the elimination half-life when these kinetic parameters are available, or by determining them with just a few urine samples at defined times soon after treatment administration. A limited sampling strategy was checked using samples collected over the 16-day period (see Table III). When using urine samples taken from 0–13, 0–10 or 0–8 days, the calculated $Q_{U\infty}$ is very close (difference less than 7% for the control and between 96 and 102% for the liposomal formulations) to the $Q_{U\infty}$ calculated from the 1–16 day samples. For the two liposomal formulations, $Q_{U\infty}$ calculated from urine samples collected only on days 0–8 is still very accurate (higher than 91%). This means that the plan to optimise treatment schedules of pharmaceutical formulations of DTPA can be applied using both the plasma pharmacokinetic parameters of the encapsulated DTPA formulation (such as the AUC_{tot} or $t_{1/2}$ of elimination) but also the urinary excretion collected over only 8 days.

CONCLUSION

This study demonstrates that the correlation between a modified pharmacokinetic parameter and the induced pharmacological effect of DTPA formulations is a good illustration of the usefulness of such a pharmaceutical approach in designing further investigations or developments aimed at enhancing Pu or other radionuclide decorporation by a chelating agent *in vivo*. To illustrate, a molecule can be selective and have affinity for a radionuclide *in vitro* but may display *in vivo* toxicity or exhibit an unfavourable fate or pharmacokinetics after administration, which is the case of the distribution of DTPA which does not match the biokinetics of Pu. Our pharmacokinetic interpretation method adapted to plutonium excreted as Pu–DTPA complex may help to provide sound arguments when planning simpler and faster decorporation protocols, which would require a limited number of urine samples and collection times since animal experiments that evaluate a candidate

treatment are often long (several weeks or months) and hence expensive.

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REFERENCES

1. W. D. Norwood. Therapeutic removal of plutonium in humans. *Health Phys.* **8**:747–750 (1962).
2. R. Wood, C. Sharp, P. Gourmelon, B. Le Guen, G. N. Stradling, D. M. Taylor, and M.-H. Hengé-Napoli. Decorporation treatment—medical overview. *Radiat. Prot. Dosim.* **87**:51–57 (2000).
3. D. M. Taylor, G. N. Stradling, and M.-H. Hengé-Napoli. The scientific background to decorporation. *Radiat. Prot. Dosim.* **87**:11–17 (2000).
4. P. W. Durbin, B. Kullgren, J. Xu, and K. N. Raymond. Development of decorporation agents for the actinides. *Radiat. Prot. Dosim.* **79**:433–443 (1998).
5. F. E. H. Crawley and J. W. Haines. The dosimetry of carbon-14 labelled compounds: the metabolism of diethylenetriamine pentaacetic acid (DTPA) in the rat. *Int. J. Nucl. Med. Biol.* **6**:9–15 (1979).
6. W. Stevens, F. W. Bruenger, and D. R. Atherton. The retention and distribution of 241Am and 65Zn, given as DTPA chelates in rats and of [^{14}C]DTPA in rats and beagles. *Radiat. Res.* **75**:397–409 (1978).
7. J. W. Stather, H. Smith, and M. R. Bailey. The retention of ^{14}C-DPTA in human volunteers after inhalation or intravenous injection. *Health Phys.* **44**:45–52 (1983).
8. Y. E. Rahman, M. W. Rosenthal, and E. A. Cerny. Intracellular plutonium: removal by liposome-encapsulated chelating agent. *Science* **180**:300–302 (1973).
9. G. Phan, B. Ramounet-Le Gall, J. Manceau, M. Fanet, H. Benech, P. Fritsch, E. Fattal, and J.-R. Deverre. Targeting of diethylene triamine pentaacetic acid encapsulated in liposomes to rat liver: an effective strategy to prevent bone deposition and increase urine elimination of plutonium in rats. *Int. J. Radiat. Biol.* **80**:413–422 (2004).
10. G. Phan, A. Herbet, S. Cholet, H. Benech, J.-R. Deverre, and E. Fattal. Pharmacokinetics of DTPA entrapped in conventional and long-circulating liposomes of different size for plutonium decorporation. *J. Control. Release* **110**:177–188 (2005).
11. J. P. Labaune. *Pharmacocinétique. Principes fondamentaux* 2nd edn. Masson, Paris, 1988.
12. G. B. Schofield and J. C. Lynn. A measure of the effectiveness of DTPA chelation therapy in cases of plutonium inhalation and plutonium wounds. *Health Phys.* **24**:317–326 (1973).
13. G. B. Schofield, H. Howells, and F. Ward. Assessment and management of a plutonium contaminated wound case. *Health Phys.* **26**:541–554 (1974).
14. L. Jolly Jr., H. A. McClearen, G. A. Poda, and W. P. Walke. Treatment and evaluation of a plutonium-238 nitrate contaminated puncture wound. A two-year case history. *Health Phys.* **23**:333–341 (1972).
15. W. H. Langham, J. N. P. Lawrence, J. McClelland, and L. H. Hempelmann. The Los Alamos Scientific Laboratory's experience with plutonium in mans. *Health Phys.* **8**:753–760 (1962).
16. R. M. Hall, G. A. Poda, R. R. Fleming, and J. A. Smith. A mathematical model for estimation of plutonium in the human body from urine data influenced by DTPA therapy. *Health Phys.* **34**:419–431 (1978).
17. M. E. Wise. Negative power functions of time in pharmacokinetics and their implications. *J. Pharmacokinet. Biopharm.* **13**:309–346 (1985).
18. M. E. Wise and G. J. J. M. Borsboom. Two exceptional sets of physiological clearance curves and their mathematical form: test cases? *Bull. Math. Biol.* **51**:579–596 (1989).
19. P. Macheras. A fractal approach to heterogeneous drug distribution: calcium pharmacokinetics. *Pharm. Res.* **13**:663–670 (1996).
20. R. W. Leggett. A model of the retention, translocation and excretion of systemic Pu. *Health Phys.* **49**:1115–1137 (1985).
21. The metabolism of plutonium and related elements. International Commission on Radiological Protection. A report of a Task Group of Committee 2. Annals of the ICRP 16: i–vi, 1–98 (1986).