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Article

Exposure to actinides: report on Ca-DTPA injections in CEA-AREVA centres

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ABSTRACT **Ca-DTPA was used for the medical treatment of plutonium and americium contaminations in the CEA and AREVA plants from 1970 to 2003. This report is a survey of the administered injections of Ca-DTPA as a chelating molecule. This report will be part of the registration process for Ca-DTPA by intravenous administration, submitted by the *Pharmacie Centrale des Armées*. Out of 1158 injections administered to 469 persons, 548 events of possible or confirmed contaminations were reported. These employees were followed by occupational physicians according to the current regulations. The first part of the report is a summary of the most recent findings. Due to its short biological period and its limited action in the blood, Ca-DTPA does not chelate with plutonium and americium as soon as these elements are deposited in the target organs. This justifies an early treatment, even in cases of suspected contamination, followed by additional injections, if necessary. The second part presents data concerning these 1158 injections (contamination routes, posology, adverse effects, ...). These incidents took place at work, were most often minor, and did not require follow-up treatment. A study concerning the efficacy of the product was conducted on a group of people having received 5 or more injections. These results were compared with the efficacy theoretically estimated. Posologies and therapeutic recommendations were proposed based on these observations. Additional studies are needed to confirm these findings. This document is the first summary in this field. It is the result of the collaboration of the occupational medical departments, the laboratories of the CEA and the AREVA and a working group CEA-AREVA-SPRA.**

Keywords: Ca-DTPA / workers / treatment / overview / occupational physician / incident

RÉSUMÉ **Exposition aux actinides : bilan des injections de Ca-DTPA dans les centres CEA-AREVA.**

Ce document présente le bilan thérapeutique des injections intraveineuses de Ca-DTPA, utilisé comme chélateur du plutonium et de l'américium, réalisées dans les centres du CEA et de AREVA de 1970 à 2003. Ce rapport fait partie du dossier de demande d'autorisation de mise sur le marché du Ca-DTPA par voie intraveineuse, déposée par la *Pharmacie Centrale des Armées*. Le bilan porte sur 1158 injections pratiquées sur 469 personnes, impliquées dans 548 événements de contamination interne potentielle ou avérée. Ces personnes étaient des salariés suivis par la

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médecine du travail selon les réglementations en vigueur. La première partie du document fait la synthèse des données de la littérature. Du fait de sa période biologique courte et de son action limitée au sang, le Ca-DTPA ne chélate pas le plutonium et l'américium dès lors que ceux-ci sont fixés dans les organes de dépôt. Ceci justifie un traitement précoce, sur simple suspicion de contamination, complété, selon les cas, par des injections ultérieures. La seconde partie du document présente les données relatives à ces 1158 injections (mode de contamination, posologie, effets secondaires, ...). Le plus souvent, ces incidents, survenus en milieu de travail, se sont avérés des événements mineurs n'ayant pas nécessité la poursuite du traitement au delà de la première injection. Les cas ayant nécessité 5 injections ou plus ont été isolés et ont fait l'objet d'une étude d'estimation de l'efficacité du produit. Les résultats sont confrontés à l'estimation de l'efficacité développée sur des bases théoriques. Des posologies et schémas thérapeutiques sont proposés à partir de ces observations. Certains points restent à être confortés par des études complémentaires. Il s'agit du premier document de synthèse de ce type. Il est le résultat d'un travail collectif ayant mobilisé les services médicaux du travail, les laboratoires d'analyses médicales CEA et AREVA et les membres d'un groupe de travail CEA-AREVA-SPRA.

1. Context

Ca-DTPA is recommended as a treatment for internal contaminations to *actinides* by the international scientific community since the 1950s (IAEA, 1981). It is used as such in the occupational health services of the CEA and AREVA centres, in any situation of internal contamination deemed as significant by the physician.

In France, up to now, this product has not been registered as a drug (*Autorisation de Mise sur le Marché*).

Upon the request of the Medical Advisor of the CEA, the DECORPO/DTPA work group, made of occupational therapists and biologists, has started to review the use of this product in its intravenous form in the CEA and AREVA centres. With this in mind, a database was established and updated using the information provided by the medical services of the 7 CEA and AREVA centres between 1970 and 2003. In all, 1158 injections were administered (*cf.* Tab. I).

These treatments were given after accidental contaminations (by inhalation or wounds) of plutonium and/or americium, or discovered during a systematic check-up. The employees concerned, working in a controlled area, were under special medical surveillance. They were declared medically apt to work under ionising radiations and under a risk of exposure to contamination by radioelements, according to the regulations in force (Code du travail, 2003).

This document has been used by the scientific expert designated for the clinical study for the registration process concerning Ca-DTPA by intravenous route. This request has been submitted to the "Pharmacie Centrale des Armées", the only manufacturer of Ca-DTPA in France.

TABLE I

General information in Ca-DTPA database.
Bilan global de la base de données Ca-DTPA.

Organizations concerned	CEA and AREVA
Number of centres	7
Centres	- CEA : Cadarache Saclay Valduc Centre Ile de France Fontenay-aux-roses (in part) Marcoule - AREVA La Hague
Duration of study	34 years
Start year	1970
End year	2003
Study criteria	- contamination of an employee - treatment by injection *IV* of Ca-DTPA
Total number of injections	1158
Date of database closure	23 February 2004

2. Literature review of Ca-DTPA in injection form

For over 40 years, the injectable form of Ca-DTPA has been used in the medical treatment of internal contamination after accidental inhalation, cutaneous passage, or more rarely ingestion with transuranians in soluble form (transferable), mainly plutonium, americium and curium. The other transuranians are less frequent and their biological lifetime is much shorter (californium, einsteinium, fermium, mendelevium, and so on). Ca-DTPA enhances the urinary excretion of plutonium, americium and curium. This treatment is not recommended in the case of exposure to uranium or neptunium (Ménétrier *et al.*, 2005).

2.1. Chemical description

Pentatate calcium trisodium is the salt of the sodium of calcic diethylenetriaminepentaacetate. It is also known under the name of trisodium calcium diethylenetriaminepentaacetate and is written Ca-DTPA. Its molecular formula is $Na_3CaC_{14}H_{18}N_3O_{10}$, and its molecular mass of 497.4 Daltons.

2.2. Pharmacological properties

- Ca-DTPA forms stable complexes with metallic ions by exchange with calcic ions.

- Ca-DTPA has a high affinity for some transuranian elements such as plutonium (valence IV), americium (valence III) and curium (valence III).
- Ca-DTPA is thus used to increase their spontaneous excretion. During intoxication by a radionuclide, the complexes thus formed, are eliminated by glomerular filtering in the urine.
- Ca-DTPA is effective for soluble Pu forms (nitrate or chloride). It is less effective for insoluble forms (oxides) or organic complexes (tributylphosphate types).
- Ca-DTPA also complexes transition elements, such as iron, cobalt and zinc.
- By complexation, Ca-DTPA, in biological environments is in competition with endogenous ligands of Pu such as transferrine and organic salts (carbonates, citrates). Because of the pH, the Ca-DTPA has no effect on aggregates that Pu (IV) forms through hydrolysis in the blood and biological media.
- The knowledge obtained results in administering, as early as possible after a contamination, a hight dose of Ca-DTPA to obtain a high concentration in the blood. The aim is to subtract the radioelements from the circulating medium and thus prevent their diffusion to target organs (skeleton and liver).
- During its transfer in the body, Ca-DTPA is not metabolized and is excreted as such (Durbin, 1972).

2.3. Pharmacokinetic properties

2.3.1. Plutonium biokinetic properties

The distribution to target organs has recently been revised (Leggett, 2003) with 60% for the liver and 30% for the skeleton. The plasmatic Pu availability rapidly decreases according to a sum of exponentials. The distribution to target organs takes biological periods of 20 minutes and 24 hours. The chelation is all the more effective since it starts as soon as possible after contamination by the radionuclide, before the latter is fixed in target organs.

A small fraction of plutonium is constantly transferred from the deposition organs to the systemic compartment. It can then be accessible to treatment by Ca-DTPA. This justifies, in the case of a significant contamination, that the treatment be continued after the incident.

2.3.2. Ca-DTPA pharmacokinetic properties

Ca-DTPA is only slightly absorbed orally. In animals, the intestinal absorption is around 5% (FDA, 2004). It is rapidly distributed in the extracellular fluids and does not go through cellular membranes. Chelation mainly occurs in blood.

The Ca-DTPA biological period is short. Over 95% of the quantity injected is excreted in less than 6 hours (Durbin and Schmidt, 1989). It is nearly completely excreted 12 hours after its administration (Gusev *et al*., 2001; REAC/TS, 2002). A study on two healthy volunteers evidenced that in 24 hours, 99% of the Ca-DTPA injected was excreted in the urines and that less than 0.5% remained in the plasma (Stather *et al*., 1983).

In this last study, the plasma retention of ^{14}C-DTPA is monitored up to 7 hours after intravenous injection. It is described as the sum of 3 exponentials whose biological periods are respectively 1.4 minutes, 14.3 minutes and 95 minutes. The fractions concerned correspond to 60%, 20% and 20% of the initially injected quantity.

Ca-DTPA pharmacokinetic model

The Ca-DTPA behaviour in the body, after intravenous injection, can be described by the following compartmental model.

From human data (Stather *et al*., 1983), the modelling results in plasma transfer rates to extra cellular fluids (ECF) (K1) extracellular fluids and from ECF to plasma (K2). These are very short with respective biological periods of 2.5 and 6.3 minutes. The Ca-DTPA plasma clearance rate (K3) towards urine is of about 19 minutes, similar to that of inuline (17 minutes) which indicates an excretion by glomerular filtering (Fig. 1).

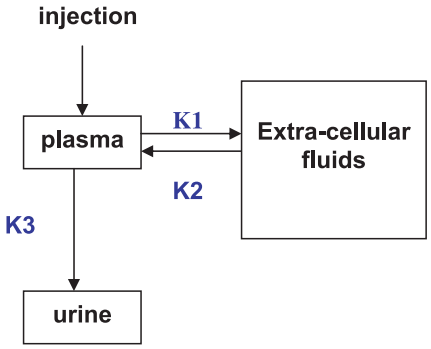

Figure 1 – ***Compartmental model of ^{14}C-DTPA behaviour after injection IV.***
Modèle compartimental du comportement du ^{14}C-DTPA après injection IV.

Figure 2 gives the expected Ca-DTPA levels (in percentages of the injected activity) in the plasma, the extracellular fluids (ECF) and urine of K1, K2 and K3 *versus* time. These values are in agreement with those experimentally measured, in other words in the plasma and urine.

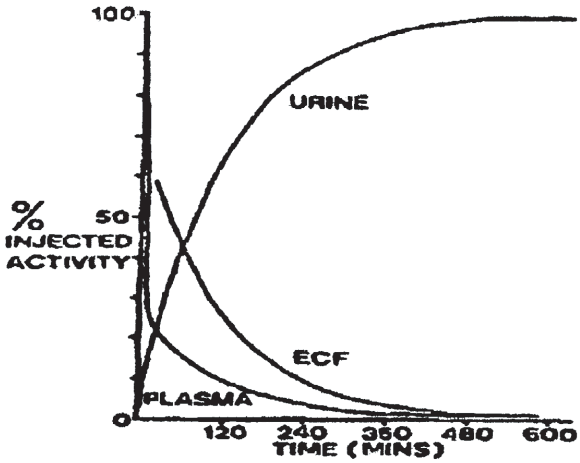

Figure 2 – ***Levels of ^{14}C-DTPA in the body and cumulated excretion after injection IV calculated using K1, K2 and K3 (Stather et al., 1983).***
Niveaux de ^{14}C-DTPA dans l'organisme et excrétion cumulée après injection IV calculés à partir de K1, K2 et K3 (Stather et al., 1983).

In the first hours, the removal of Ca-DTPA from plasma is the reflection of urinary excretion. It indicates a significant transfer of plasma towards extracellular fluids (FDA, 2004).

2.3.3. Biokinetic properties of the Pu-DTPA complex

The urinary elimination of the Pu-DTPA complex seems to occur in a two-phase way. A rapid phase for 25% of the quantity produced with a biological period of 12 hours, and a slow phase for the residual quantity with a period of 7 days (Jolly Jr *et al.*, 1972). This kinetic is in agreement with that described by Schofield (Schofield *et al.*, 1974) indicating a period of roughly 5 days.

Brief summary: the short biological period of Ca-DTPA and its action limited to the transfer compartment do not allow it to chelate plutonium after it has been fixed in deposition organs.

This justifies a therapeutic administration in two steps:
- an administration as early as possible after the event, prior to the fixation of the contaminating agent in the deposition organs,
- an administration after the incident to trap the residual circulating fraction.

2.4. Conditions of use in literature

2.4.1. Dosage

The most recommended dosage for adults for administration IV is 1 g (30 µmol kg^{-1}) non-fractioned. This dosage can be administered in the days after.

In children under 12, a single dose of 14 mg kg^{-1} by intravenous, is recommended without exceeding 1 g (FDA, 2004).

2.4.2. Contra-indications

No cases known according to FDA (2004), WHO (1984), and IAEA (1981).

2.4.3. Precautions of use

- Ca-DTPA can also chelate endogenous metallic ions such as those of Zn, Mn or Mg. The treatment can cause a depletion of these ions thus requiring a supplement in oligoelements.
- Ca-DTPA is not recommended in the case of pregnancy or breast feeding.
- No studies on benefit-risk have been undertaken for children. The dose administered in a child must be adjusted to their weight.
- The people with kidney problems must be specially monitored.

2.4.4. Interactions with other medications

No satisfactory study has been carried out for humans.

2.4.5. Side effects

The early side effects most often described (FDA, 2004) are nausea, vomiting, diarrhoea, fever, rashes, muscle cramps. These symptoms would lessen despite treatment prolongation.

Later side effects are seemingly minor and only slightly described in specialized literature. The FDA mentions a possible deficiency in metallic oligoelements (zinc, manganese, magnesium), during a prolonged treatment.

3. Methodology

The employees involved in a potential or real contamination incident with plutonium and americium are treated by the radioprotection service and the occupational medical service of each centre (Blanchin *et al*., 2004). The

circumstances of the incident and the measures taken (decontamination, treatment, prescription of examinations) are written up in a "decontamination block logbook" identical for all centres. When the medical advisors of the CEA and AREVA decided to retrospectively study the use of intravenous Ca-DTPA, the description of Ca-DTPA injections in these logbooks was used. The files selected are those, for which, depending on the circumstances, the initial treatment resulted in the intravenous injection of Ca-DTPA, preceded or not by a respiratory intake (turbo-inhalation).

The GT-DTPA work group created a database. Table II summarizes the main criteria used in this study.

TABLE II

Criteria selected for acquisition of a case in the database.
Critères retenus pour la saisie d'un cas dans la base de données.

Criterion	Accuracy of selected criterion
Recording in logbook	Compulsory
Ca-DTPA treatment by injection or infusion	Compulsory
Medical file	Need to have a medical file that can be used
Exposure to transuranians	Exposure to plutonium (Pu), americium (Am) or curium (Cm) isotopes
Population of the study	Employees with special medical surveillance
Contamination mode	Inhalation, ingestion, wound and percutaneous
Posology	All posology used taken into account

3.1. Description of study

All the centres have input their data from the block logbooks or medical files in the database (*cf.* screens below). This information was centralized in the service of the CEA medical advisor and controlled by the sole database manager. A confidentiality number is given to each file. Several meetings validated all the information and the entire database. The final validation is dated 23 February 2004.

This database can be used starting with an event, an individual, or the type of treatment administered. The event is defined as a post-accidental contamination or discovered during a systematic examination, having required treatment by intravenous injection.

This indicator only concerns one person for one or several injections. This person can be involved in several different events.

TABLE III

Number of people and events.
Nombre de personnes et d'évènements.

Number of people	Number of events
409	1
48	2
7	3
4	4
1	6
Total 469	Total 548

Table III shows the total number of people involved in the study (463 men and 6 women) distributed according to the number of events having been undergone by each of them over the study period. The same person can be involved in different events over the period. All of the report is based on the number of events rather than on the number of persons.

3.2. Post-incidental radiotoxilogical survey

Among the examinations practised by the Medical Laboratories to evaluate the level of internal exposure, some provide immediate results:
- measurements on nasal mucus,
- direct or indirect (swabs) measurements on contaminated wound,
- lung monitoring.

Others require a longer retrieval and analysis time:
- urine analysis,
- faecal analysis,
- blood test.

3.3. Treatment efficacy

The efficacy of Ca-DTPA is estimated using the evolutions of urinary excretions significantly increased compared to spontaneous excretion. The standard efficacy factor is of about 50 knowing that a fluctuation of 25 to 100 can be admissible because of the results observed after treatment. This fluctuation is real among different people and can vary for the same person.

3.4. Biological surveillance

In animals, the administration of Ca-DTPA at very high doses can induce renal alterations. In man, only one renal problem was recorded, after the administration

of high doses of Ca-DTPA during a prolonged treatment. Among the biological examinations prescribed every year in preventive medicine for all employees of CEA and AREVA centres, azotemia and creatinine measurements, depending on the years and centres, were used. These two indicators of renal function were collated in the year prior to and following the injection of Ca-DTPA.

3.5. Triage of cases and group distribution

The database includes 1158 injections for 548 events. This data was distributed over different groups depending on the number of injections made for a same event, as detailed in Table IV.

TABLE IV

Classification of data.

Classification des données.

Group	Type of group
1	Number of people having received a single injection after a single event classified "nothing else".
1bis	Number of people having received several times a single injection per distinct event and classified "sans suite".
2	Number of people having received 2, 3, 4 injections after the same event.
3	Number of people having received 5 injections or more after the same event.

The average time to obtain a result for radiotoxicological examinations with a dosimetric aim is of about 1 week. A treatment, which goes beyond this, concerns contaminations which could lead to a significant irradiation dose. This classification is the result of medical practice in the management of an incident.

4. Results

4.1. All groups

According to the methodology presented above, 548 events entailed 1158 injections during the period of observation. 542 events involved a man and 6 a woman. The average age is 34.

- 83% of events were treated with 1 single injection of Ca-DTPA,
- 1 single event was treated with 245 injections over 4 years (see Fig. 3).

The contamination mode by transuranians varies according to the groups. If inhalation is predominant for groups 1 and 1 bis, the percutaneous passage (wound and transcutaneous) is predominant in groups 2 and 3.

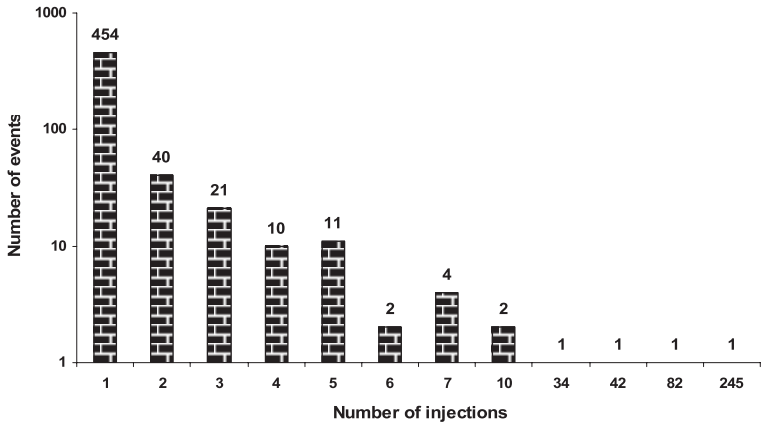

Figure 3 – ***Distribution of number of injections and number of associated events.***
Répartition du nombre d'injections et nombre d'évènements associés.

Posology

The injection posology of Ca-DTPA varied **from 100 mg to 1000 mg**, depending on international feedback (Lafuma, 1963), and on national medical recommendations or recommendations from each centre. The posology most often used was of 500 mg (67% of cases). 8% of the injections were of 1000 mg.

Administration

- Direct Intravenous (*IV*) for 93% of injections.
- Increase of treatment by rapid infusion starting in 2002.

4.2. Group 1

Group 1 corresponds to the number of people having received a single injection after a single event without radiological consequences. The number of people involved is 332 (70.8% of the total). The total number of injections for this group was 340. Eight people involved in another event having required several injections are accounted for in groups of higher index (2 or 3).

Circumstances of events

- Route of exposure: inhalation 44.3%, wound 37.6%, transcutaneous 3.1%, inhalation + ingestion 0.9%, inhalation + transcutaneous 4.6%, inhalation + wound 4.3%, ingestion + transcutaneous 0.3%, transcutaneous + wound 4.3%, inhalation + ingestion + transcutaneous 0.3%, inhalation + ingestion + wound 0.3%.

- Radionuclides: different actinides (1 to 4 radionuclides per event).

Physical form		
Known	170	50%
Dust	149	87.6%
Solution	20	11.8%
Dust + solution	1	0.6%

Chemical form		
Known	135	39.7%
Nitrate	9	6.7%
Oxide	94	69.6%
Oxalate	16	11.9%
Metal	7	5.2%
Oxide + metal	1	0.7%
Pu-TBP	0	0%
Solvent phase	5	3.7%
Other chemical form	3	2.2%

Dosage and administration mode of treatment

- Most injections were made *IV* of 0.5 g (191 for 323 known, in other terms 59.1%).
- Time between incident and start of treatment: known in 92.8% of cases. The time is short: less than 1 hour (52.7%) and less than 2 hours (92.6%).
- Duration of treatment: one single injection (definition of group 1).

1 injection for 1 event	
Quantity injected (g)	Number of events
0.25	85
0.5	191
1	46
1.25	1
2	1
Not known	16

IV

IV (g)	*Number of files*	*%*
0.25	86 *	26.7
0.50	188	58.1
1	35	10.9

Infusion

Infusion (g)	*Number of files*	*%*
0.25	0	
0.50	3	0.9
1	13 *	4

* 2 cases (0.25+1) and (1 et 1)

Post-incidental monitoring

The bioassay monitoring is known for 271 events.

Side effects

Cutaneous allergy: rashes, urticary lesions of face and chest in the minutes after injection. Confirmation was brought by allergy tests (Prick tests and Intra-dermic reaction).

Monitoring of biological parameters

The people involved were under yearly medical surveillance within the framework of occupational medical services, including a blood analysis. For 59.7% cases in group 1, we have the azotemia and creatinine for the year prior to and the year after the injection. There is no significant modification in the results:

- creatinine:
  creatinine prior to: from 7 to 14.4 mg L^{-1},
  creatinine after: from 7 to 15.8 mg L^{-1}.

- azotemia:
  azotemia prior to: 0.11 to 0.51 g L^{-1},
  azotemia after: 0.15 to 0.52 g L^{-1}.

4.3. Group 1 bis

Group 1 bis corresponds to the number of people having received several times a single injection per distinct event not requiring medical follow up. The number of people involved is 46 (9.8%) for 114 events which represents 114 injections.

Circumstances of events

- Route of exposure: inhalation 52.3%, wound 34.2%, transcutaneous 1.8%, inhalation + ingestion 2.7%, inhalation + transcutaneous 1.8%, inhalation + wound 7.2%.
- Radionuclides: 1 to 3 radionuclides per event.

Physical form		
Known	77	67.5%
Dust	70	90.9%
Solution	6	7.8%
Dust and solution	1	1.3%

Chemical form		
Known	57	50%
Nitrate	0	0%
Oxide	55	96.5%
Oxalate	0	0%
Metal	1	1.8%
Pu-TBP	0	0%
Solvent phase	0	0%
Other	1	1.8%

Dosage and mode of administration of treatment

- Most injections were made of 0.5 g (64 for 106 known, in other terms 60.4%). All these injections were made by *IV*.
- Time between incident and start of treatment: known in 92.5% of cases. The time is short: less than 1 hour (45.9%) and less than 2 hours (92.9%).
- Duration of treatment: one single injection per event (definition of group 1 bis).

Injected quantity (g)	Number of events
0.25	38
0.5	64
1	4
Not known	8

Post-incidental monitoring

The bioassay monitoring is known for 111 events.

Side effects

No side effects were detected in group 1 bis.

Monitoring of biological parameters

The people involved were under yearly medical surveillance within the framework of occupational medical recommendations, including a blood analysis. For 43.9% cases in group 1 bis, we have the creatinine and azotemia for the year prior to and the year after the injection. There is no significant modification in the results:

- creatinine:
  creatinine prior to: from 8 to 13.7 mg L^{-1},
  creatinine after: from 9 to 13.7 mg L^{-1};
- azotemia:
  azotemia prior to: 0.19 to 0.46 g L^{-1},
  azotemia after: 0.20 to 0.46 g L^{-1}.

4.4. Group 2

Group 2 corresponds to the number of people having received 2, 3, or 4 injections after the same event. The number of people involved is 68 (14.5%) for 71 events. Three people involved in another event having required more than four injections are accounted for in group 3. The total number of injections for this group is 184.

Circumstances of events

- Route of exposure: wound 32.4%, inhalation 30.9%, transcutaneous 11.8%, inhalation + ingestion 4.4%, inhalation + transcutaneous 4.4%, inhalation + wound 7.4% transcutaneous + wound 8.8%.
- Radionuclides: different actinides (1 to 5 radionuclides per event).

Physical form		
Known	42	59.2%
Dust	31	73.8%
Solution	11	26.2%

Chemical form		
Known	36	50.7%
Nitrate	7	19.4%
Oxide	27	75%
Oxalate	0	0%
Metal	0	0%
Pu-TBP	0	0%
Solvent phase	0	0%
Other	1	2.8%
Nitrate and other	1	2.8%

Dosage and mode of administration of treatment

- Most first injections were made of 0.5 g (77.6%) by *IV* (92.5%).
- Time between incident and start of treatment: known in 98.5% of cases. The time is short: less than 1 hour (40.9%) and less than 2 hours (62.1%).
- Duration of treatment: from several days to less than 1 year (225 days).

Quantity injected (g)	*Number of events*
0.1*	1
0.5	2
1	28
1.5	21
2	13
3	1
4	2
Not known	3

* second injection not known

Post-incidental monitoring

The bioassay monitoring is known for all events.

Side effects

No immediate side effects were detected in group 2.

Delayed side effects noted: one case of headache and one case of asthenia with loss of weight without any link established with the DTPA treatment.

Monitoring of biological parameters

The people involved were under yearly medical supervision within the framework of occupational medical recommendations, including a blood analysis. For 59.1% cases in group 1 bis, we have the creatinines and azotemia data for the year prior to and the year after the injection. There is no significant modification in the results:

- creatinine:
  creatinine prior to: from 7.2 to 14.1 mg L^{-1},
  creatinine after: from 6.8 to 14.1 mg L^{-1};
- azotemia:
  azotemia prior to: 0.23 to 0.44 g L^{-1},
  azotemia after: 0.2 to 0.58 g L^{-1}.

4.5. Group 3

Group 3 corresponds to the number of people having received 5 injections or more after the same event. The number of people involved, 23 (4.9%) is equal to the number of events. The number of injections for this group is 518 (45% of all the injections in the study). The distribution is very widespread (78% of injections in group 3 only concern 4 subjects).

Number of events	*Number of IV + infusions*
11	5
2	6
4	7
2	10
1	34
1	42
1	82
1	245

Circumstances of incidents

- Route of exposure: wound 47.9%, Inhalation 30.4%, inhalation + wound 4.3%, transcutaneous + wound 17.4%
- Radionuclides: different actinides (1–5 radionuclides per event).

Physical form		
Known	14	60.9%
Dust	9	64.3%
Solution	4	28.6%
Dust and solution	1	7.1%

Chemical form		
Known	13	56.5%
Nitrate	3	23.1%
Oxide	8	61.5%
Oxalate	0	0%
Metal	1	7.7%
Solvent phase	0	0%
Other chemical form	1	7.7%

Dosage and administration mode

- Most first injections (69.6%) were of 0.5 g. Different dosages were used after the same event.
- Time between incident and start of treatment: known in 95.6% of cases. It is short: less than 1 hour (54.5%) and less than 2 hours (86.4%).
- Total injected quantity 1.25 to 121.5 g
- Duration of treatment from 7 days to 1934 days.

Post-incidental monitoring

Bioassay data were collected from everyone.

Side effects

No side effects in group 3.

Surgical treatment

In case of a contaminated wound, a surgical intervention was performed (as a reminder, a wound was involved in 70% of events):

- 68.8% were surgically treated (11/16),

- interval between wound and intervention: among the 11 known, 54.5% were operated on in less than 24 hours and all of them before 22 days.

Interval between wound and surgery

Interval	*Number of files*	*Observations*
0-1 day	6	
2-7 days	3	
> 7 days	2	19-22 days

Administration modes of Ca-DTPA with reference to surgery

	Ca-DTPA local			*IV*			*Infusion*		
	before	during	after	before	during	after	before	during	after
Number	8	5	0	10	1	8	0	3	1

Vital status of group 3

- 17 people were alive at the end of the study,
- 5 were no longer to be found,
- 1 person died ten years after the incident from a coronary disease.

Monitoring of biological parameters

The people involved were under yearly medical supervision within the framework of occupational medical recommendations, including a blood analysis. For 83% cases in group 3, we have the creatinine and azotemia data for the year prior to and the year after the injection. There is no significant modification in the results:

- creatinine:
  creatinine prior to: from 8.0 to 11.97 mg L^{-1},
  creatinine after: from 8.0 to 12.3 mg L^{-1};
- azotemia:
  azotemia prior to: 0.17 to 0.45 g L^{-1},
  azotemia after: 0.12 to 0.60 g L^{-1}.

5. Interpretation of results

5.1. Efficacy of Ca-DTPA by injection IV

5.1.1. Theoretical bases

Plutonium is distributed from the systemic compartment to the liver (60%) and to the skeleton (30%). The plasma availability of Pu decreases rapidly according to a

sum of exponentials with biological periods of 20 minutes and 24 hours. The chelation is all the more effective if it is started early after contamination, before the radionuclide is distributed in the target tissues. The spontaneous excretion of plutonium is very low versus the accumulation in the organs.

The injected Ca-DTPA is quickly distributed throughout extracellular fluids. It does not go through cell membranes. Its biological period is short: 12 hours after its administration it is nearly completely excreted. Over 95% of the quantity injected is excreted in less than 6 hours.

The chelation of plutonium mainly occurs in the blood. The urinary excretion of the Pu-DTPA complex occurs in a two-phase way: a rapid phase for 25% with a biological period of 12 hours and a slow phase for the remaining quantity with a biological period of about 7 days. This kinetic is on the whole in agreement with a single period of 5 days.

The short biological period of Ca-DTPA and its action limited to the blood compartment, does not allow plutonium to be chelated once it is distributed in its deposition organs. This justifies early therapy prior to the deposition of the radionuclide in the target organs and then possible further injections to trap the circulating fraction of the radionuclide.

The efficacy of the treatment by injected Ca-DTPA is estimated from the urinary excretion of the radionuclide.

5.1.2. Quantification of Ca-DTPA efficacy

Principle

The urinary excretion of plutonium depends on the systemic activity and more specifically on the quantity of plutonium present in the blood and extra-cellular fluids. By increasing the urinary excretion of plutonium, the Ca-DTPA participates in the decrease of the systemic activity and thus reduces the irradiation dose. To estimate the efficacy of the therapy, the individual curve of urinary excretion under Ca-DTPA treatment is compared to the excretion curve expected without treatment. The dosimetric benefit is then evaluated versus the absence of therapy (Piechowski *et al*., 1992).

Nominal values

Action of Ca-DTPA

The efficacy *on the day of the injection* is evaluated by the factor of increase in urinary excretion, which varies from 25 to 100. A nominal factor of 50 is retained.

The *total efficacy after injection* integrates the action of the Ca-DTPA over the following days, *i.e*. the effect of the remaining Ca-DTPA. This late component has a some days half-time and corresponds to a fraction of injected DTPA of a few percent whereas the initial short component has a less than 0.1 d half-time with a fraction close to 1. The integrated increase of plutonium excretion after DTPA injection is thus of the order of:

$$50\left(1 + \frac{some\ days \times few\ \%}{0.1 \times 1}\right) \approx 50\left(1 + \frac{\approx 0.2}{0.1}\right) \approx 150$$

Consequently, one must make the difference between the effect observed per *day* (increase of urinary excretion by a factor of 50 the first day) and the *total* effect after injection with an exponential decrease the following days (increase of urinary excretion by a factor of 150).

For a nominal pharmacological action of Ca-DTPA thus defined, in other words a factor of 150 per injection, a minimum of roughly 20 days is needed between 2 injections. This time results from the remaining action of the chelator and from the time needed to renew the plutonium circulating in the extra-cellular compartment accessible to Ca-DTPA.

Reference urinary excretion curve

This depends on the routes of intake and on physico-chemical parameters. The evaluation presented below is based on the curves provided in ICRP publication 78. The calculation is made for plutonium-239 after wound or inhalation of compounds of type M (fairly soluble compounds – moderate absorption) and type S (insoluble compounds – slow absorption). The time of follow up considered is of 1 000 days.

Evaluation of the efficacy and dosimetric benefit

The order of magnitude of the plutonium-239 excretion, without Ca-DTPA action, is shown in Table V, based on the curves from ICRP publication 78.

TABLE V

Daily urinary excretion without Ca-DTPA as fraction of the intake.
Excrétion urinaire journalière hors Ca-DTPA en fraction de la quantité incorporée.

Successive phases / Exposure routes	# 10 days	# 300 days	# 700 days
Wound	10^{-3}	10^{-4}	10^{-5}
Inhalation of a type M compound	10^{-4}	10^{-5}	10^{-6}
Inhalation of a type S compound	10^{-6}	10^{-7}	

An isolated injection of Ca-DTPA during one of these successive phases produces a dosimetric benefit which is evaluated by multiplying the excretion without Ca-DTPA by the nominal efficacy of #150. The dosimetric benefit represents the percentage of dose avoided thanks to the therapeutic action *versus* the irradiation dose which would have been received without treatment. The values of the dosimetric benefit are shown in Table VI.

TABLE VI

Dosimetric benefit of an injection of Ca-DTPA.
Gain dosimétrique pour une injection de Ca-DTPA.

Successive phases / Exposure routes	# 10 days	# 300 days	# 700 days
Wound	15%	1.5%	0.15%
Inhalation of type M compound	1.5%	0.15%	0.015%
Inhalation of type S compound	0.015%	0.0015%	

These different levels of dosimetric benefit show the effectiveness of early injections at short intervals, then a significantly lower efficacy for delayed treatment. If we now consider, a repeated and systematic treatment during different post-incident phases, assuming a time interval of 20 days between two completely effective injections, we obtain the results shown in Table VII. They correspond to a number of completely effective injections of 1 during the initial phase of 10 days, of 15 (= 300/20) during the following phase of 300 days and of 35 (=700/20) during the last phase of 700 days.

TABLE VII

Total dosimetric benefit from a systematic long term treatment.
Gain dosimétrique total pour un traitement systématique au long cours.

Successive phases / Exposure routes	# 10 days [(a)]	# 300 days [(b)]	# 700 days [(c)]
Wound	15%	22.5%	5.25%
Inhalation of type M compound	1.5%	2.25%	0.525%
Inhalation of type S compound	0.015%	0.075%	

(a), (b), (c) = respectively 1, 15 and 35 injections with maximum effect.

The advantage of an early treatment is even more obvious. Of note is the variability of the Ca-DTPA action depending on the type of contamination and the validation of the therapy consisting of administering a sustained treatment in the first weeks or months after the incident, then to space them out or stop the injections.

The values are given more in order to advise on a therapeutic approach and to underline its efficacy than to be considered as an absolute reference. Nevertheless, they should be used carefully to explain the therapy and its advantage to the patient and to those in charge of the facility.

Moreover, this evaluation does not take into account some specific aspects as it is impossible to systematize in a simple way all the different cases:

- some chemical forms are only slightly if at all accessible to Ca-DTPA; these can be very refractory oxidized compounds (absence of solubilization) or stable complexes greatly soluble in a biological environment (rapid urinary elimination independently of Ca-DTPA);
- the first injection of Ca-DTPA done as soon as possible in case of a wound is assumed to purge the body of the circulating plutonium which is not yet fixed. This initial part of the kinetic is not shown on the curves and concerns a large fraction of the plutonium absorbed if the treatment is done very early. In this case, Ca-DTPA immediately removes, before any metabolization process, part of the incorporated plutonium. Since the evaluation of the efficacy (normally high, about half of the plutonium absorbed), must be made apart, the standard excretion curve for the wound cannot *de facto* be used with this objective in mind.

5.1.3. Analysis of cases in group 3

Group 3 corresponds to the number of people having received 5 injections or more after the same event. This group was particularly analysed since it is the most documented. The number of people involved is 23 (4.9% of events). The number of injections for this group is 518 (45% of total injections in the study).

The exposure routes found are:

- wound = 11 files (47.9%),
- inhalation = 7 files (30.4%),
- mixed exposure = 5 files (21.7%).

The efficacy assessment is based on the ratio of amplitude between the urinary measurements without treatment, sometimes visualized by a representative curve and those after treatment. The injections selected are those for which the urinary measurements were made in the days following the treatment.

The analysis of data from group 3 is divided into two different parts depending on the route of intake of the radionuclides; for contaminations due to wound then inhalation. In each part, the analysis focused on a general study of all the files and, due to the variability of the circumstances and of the type of material incriminated, on a case-by-case study.

The files selected for the study on efficacy are those in which a pre- or post Ca-DTPA injection urinary excretion follow-up was found (Piechowski *et al.*, 2003).

5.1.3.1. Contamination from a wound

In the case of a wound, the radionuclide can be directly incorporated. A treatment is quickly started, completed by a decontamination of the skin, direct activity measurements on the wound and the prescription of urine analyses. These can be completed by faecal analyses and a measurement of the body burden by Whole Body Counting (WBC).

General study of all cases

Table VIII shows the distribution of the estimations of efficacy, by quantification of the amplitude of urinary excretion. This distribution is very wide (*cf.* Fig. 4).

This distribution results from the differences in incident circumstances, of the physico-chemical type and time between two injections.

Figure 5 shows that this distribution of efficacy is log normal with a median value of 11.

TABLE VIII

General study of the efficacy on the contamination.

Étude générale de l'efficacité pour la contamination.

Number of files allowing an estimation of efficacy	11
Number of injections allowing an estimation of efficacy	171
Minimum efficacy	0.1
Maximum efficacy	137
Average efficacy	21
Efficacy (geometrical average)	7.7
Efficacy (median)	10.9
Observed standard deviation	26.4

Case by case study

Types of wounds and materials are rather different from one case to another. Table IX and Figure 6 present the distribution case by case of efficacy assessments.

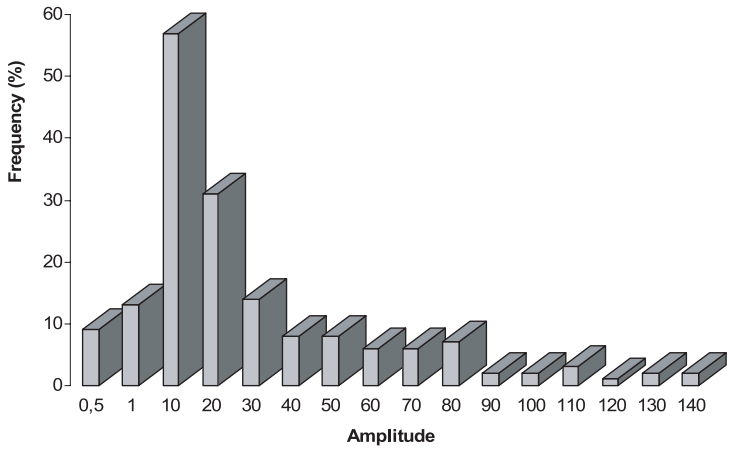

Figure 4 – ***Diagram of Ca-DTPA efficacy in case of wound.***
Diagramme de l'efficacité du Ca-DTPA de tous les cas de blessure.

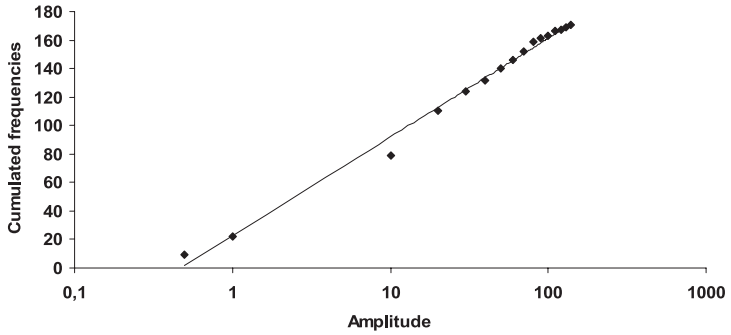

Figure 5 – ***Cumulated frequency of Ca-DTPA efficacy in all cases of wound.***
Fréquence cumulée de l'efficacité du Ca-DTPA de tous les cas de blessure.

For each case, we can note dispersion in the values of the amplitude. These amplitudes represent the efficacy of the action of a Ca-DTPA injection only for those injections at least 20 days after the previous one (spaced out by 20 days). Ca-DTPA increases the spontaneous elimination of Pu after formation of the stable Pu-DTPA complex. The amplitude observed after injection is the ratio between the excretion of Pu-DTPA complex and the spontaneous excretion level of Pu without treatment. To evaluate this amplitude, it is necessary to consider the injections spaced out by 20 days, so as to avoid the interference due to the remaining action of the chelating agent.

TABLE IX

Case by case study of the efficacy on contamination.
Étude de l'efficacité cas par cas pour la contamination.

Case n°	Number of injections allowing an estimate of efficacy	Minimum efficacy	Maximum efficacy	Average	Geometrical average	Median
100063	4	3.0	13.8	8.8	7.7	9.2
100166	13	0.2	34.1	3.8	1.0	0.6
100239	18	0.1	60.7	16.9	2.4	0.9
100331	5	0.2	93.8	21.0	3.5	4.1
100429	7	0.3	35.1	8.0	2.9	2.2
100432	14	2.2	49.0	14.5	9.9	12.6
100439	6	19.0	75.0	42.3	37.6	42.5
100459	44	2.5	75.0	24.1	18.0	19.9
100477	17	0.1	70.3	14.5	4.3	5.3
100526	36	0.6	137.5	34.4	16.0	18.3
100527	7	0.9	23.5	5.2	2.8	2.4

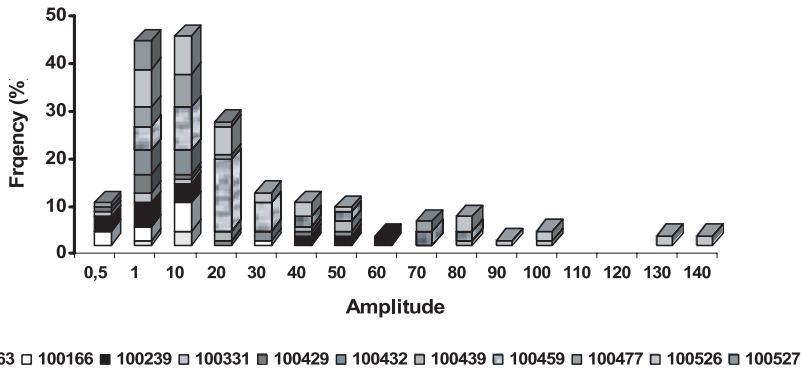

Figure 6 – ***Ca-DTPA efficacy diagram from case by case study of wounds.***
Diagramme de l'efficacité du Ca-DTPA de l'étude cas par cas pour les blessures.

The numerical values in Table X confirm that in the case of wounds:

- if the injections are repeated in the first days after contamination, the remanence of Ca-DTPA complicates the estimation of efficacy. Efficacy must be estimated case by case for the entire duration of the treatment;

TABLE X

Study of the efficacy *versus* time between two injections in the case of wounds.
Étude de l'efficacité en fonction de l'espacement entre deux injections dans le cas des blessures.

	Time between 2 injections less than 20 days	Time between 2 injections more than 20 days
Number of injections allowing an estimation of efficacy	133	38
Minimum efficacy	0.1	2.2
Maximum efficacy	88.3	137.5
Average efficacy	15.3	41.0
Efficacy (geometrical average)	5.7	23.5
Efficacy (median)	9.1	29.3
Observed standard deviation	18.8	37.7

- if the injections are spaced out (by more than 20 days), the average efficacy observed is close to 40, which confirms the validity of the nominal factor of 50, commonly mentioned in publications and used in Chapter 5.1.

The conclusions on the theoretical modelling are verified in the case of contaminations by wound. The results confirm the values of dosimetric benefit provided in Tables VII and VIII.

5.1.3.2. Inhalation intake

The circumstances of files from group 3 are very different after incorporation by inhalation. This variability especially depends on the physico-chemical form of the radionuclide, on the quantities inhaled and the duration of exposure. The industrial conditions of actinide manipulation, using glove boxes and wearing individual protective material leads to the fact that the level of severity in these inhalation cases is generally low and only very rarely leads to the prescription of an intravenous treatment.

General study of all cases

Table XI and Figure 7 show the distribution of the efficacy estimates for all the files in group 3.

Figure 8 reveals that this distribution of efficacy is log normal with a median value of 3.

Case by case study

Only 2 files were studied, one with 16 injections allowing an estimation of efficacy according to the criteria selected and the other involving a single such injection (*cf.* Tab. XII).

TABLE XI

General study of efficacy after inhalation.
Étude générale de l'efficacité pour l'inhalation.

Number of files allowing estimate of efficacy	2
Number of injections allowing estimate of efficacy	17
Minimum efficacy	0.7
Maximum efficacy	30
Average efficacy	6.9
Efficacy (geometrical average)	3.9
Efficacy (median)	3.1
Observed standard deviation	8.4

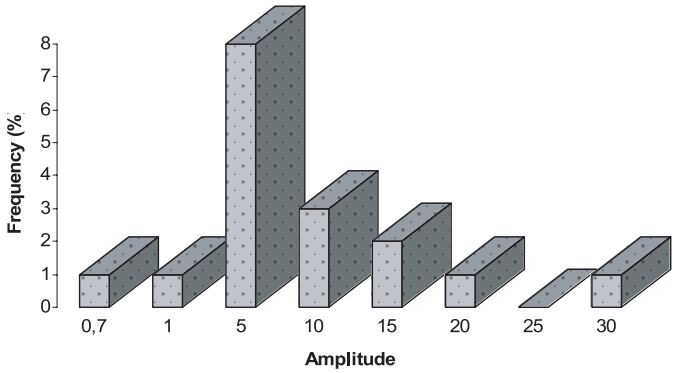

Figure 7 – ***Diagram of Ca-DTPA efficacy in all inhalation cases.***
Diagramme de l'efficacité du Ca-DTPA de tous les cas d'inhalation.

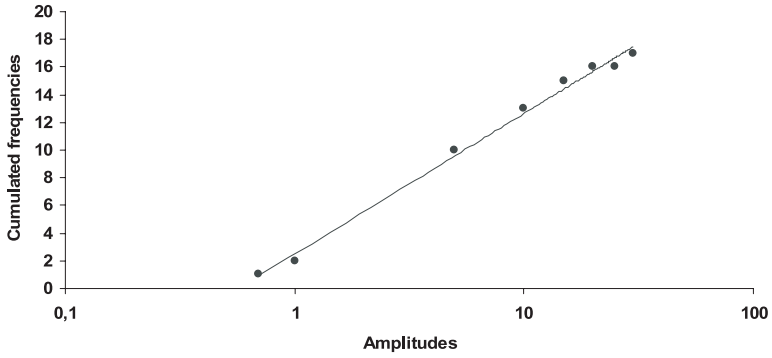

Figure 8 – ***Cumulated frequency of Ca-DTPA efficacy in all inhalation cases.***
Fréquence cumulée de l'efficacité du Ca-DTPA de tous les cas d'inhalation

TABLE XII
Case by case study of the efficacy after inhalation.
Étude de l'efficacité cas par cas pour l'inhalation.

Case number	Number of injections allowing an estimation of efficacy	Minimum efficacy	Maximum efficacy	Average	Geometrical average	Median
100387	16	0.7	23.9	5.6	3.5	2.8
100500	1	30.0	30.0	30.0	30.0	30.0

The number of files in group 3 resulting from incorporation by inhalation is too low to allow a conclusion. The nominal efficacy is however lower than in the case of wounds.

5.2. Tolerance to Ca-DTPA

Among the 1158 injections performed on 469 patients, only one undesirable effect was recorded. This was an immediate allergic cutaneous reaction, diagnosed by an allergologic prick test, reaction which was quickly treated with no consequences. Because of the nephrotoxicity observed in animals at massive doses, the selected biological parameters were related to renal functions (creatinine and azotemia).

Since the beginning of Ca-DTPA use in the CEA AREVA centres, the prescribing physicians have been careful as to the appearance of secondary effects in the short term or during multiple injections. No secondary effect was observed in patients having received several injections. The people concerned continued and are still continuing (for the younger ones and those still in the company) to be biologically and clinically tested within the framework of routine monitoring.

5.3. Estimation of the benefit risk ratio

The good tolerance to this treatment, known in the literature, is also found in the observations. The cohort exclusively includes "healthy workers" under regular medical supervision.

The benefit comes from the reduction of the body burden of plutonium and americium. This causes a dosimetric benefit which correlatively reduces the probability of cancer due to ionizing radiations (*cf.* Chap. 5.1).

The ICPR assumes that all doses produce effects. Therefore, it recommends, through its optimisation principle, to undergo any appropriate action aiming at reducing the dose. This antidote is thus concerned by this principle and the Ca-DTPA is, in the opinion of the authors, medically justified.

5.4. Treatment protocol

5.4.1. Indications

These depend on:

- The type of incorporation (*cf.* Chap. 5.1)
  The main indication of the treatment is the contaminated wound, as this can be considered as a medical emergency. The treatment must be immediately started since the plutonium and americium rapidly pass through the blood to the target organs where they remain. In case of wounds, the radio nuclide is to be found immediately in the blood and Ca-DTPA must then be given as quickly as possible to limit deposition by means of its chelating effect.
  After inhalation, the efficacy is lesser and more inconsistent. The absorption from the respiratory tract to the blood reduces the notion of emergency. However after significant inhalation, which level can be defined according to several criteria (air concentration, sampling of nasal mucus, and circumstances of the incident) the initial treatment needs to be started.
- Physico-chemical form
  Some materials are less accessible to treatment either because they are less soluble, as oxidized compounds, or because they have been complexed under a stable form which can easily be eliminated in the urines. In the absence of certainty on the solubility of the compound, the initial treatment must however be started.

In conclusion, the main indication of the treatment is that of the contaminated wound, especially by transferable materials. However, in an emergency situation, the information in terms of types of compound, exposure level, and incorporation are rarely known from the start. The indication of the initial treatment must then be extended to all the situations in which there is a risk of transcutaneous absorption, and to situations of significant inhalation, whatever the compound involved.

5.4.2. Dosage

In most bibliographical references, the dosage is of 1 gram per injection or per day; the CEA-AREVA physicians generally give 500 mg: 67% of our injections.

The 1 gram dosage is extrapolated from the dose used in animals (30 micromoles g^{-1} so for man 30 micromoles kg^{-1}) and from the dosage of the EDTA, the chelator used in the treatment of contaminations by actinides before the Ca-DTPA. No further justification was found for this dose among those recommending it. The FDA did not answer on this point.

The dosage in zinc form recommended in the literature, for prolonged treatments, is also of 1 gram per injection or per day and its lesser efficacy did not result in modifying it. This form is not used in France.

No recommendations on dosage modulation according to the importance of the incident, of the route of exposure of the chemical form of the radionuclide and of the duration of the treatment were found. In most files, the dosage remained the same for the different injections. In the case where it was changed, the results do not allow a comparison between the efficacies of the different dosages.

The only known observation (Lafuma, 1963) presenting comparisons of dosages from 1 g to 100 mg relates to a contamination incident which occurred in 1962 at Fontenay-aux-roses. The observation of a chelating effect at doses much lower than 1 gram is why the CEA centres use a dosage of 250 and 500 mg, in other words, 1/4 or 1/2 of a 4 ml 25% ampoule.

Dosages lower than 250 mg were not used much for practical reasons of fractioning. This compound also seemed well tolerated at these dosages, which explains why they were not reduced.

The evolution of dosage over times in CEA and AREVA centres shows:

- a predominance of dosage of 250 mg in the observations after 1962 which demonstrated the efficacy of Ca-DTPA at this dose;
- an "increase" to 500 mg in the 80s, which could be linked to:
  - the publication of the Handford accident (Breitenstein Jr *et al.*, 1990) with the case of a person having received 432 injections of 1 gram without any noticeable secondary effects;
  - how easy the preparation was to use (half of an ampoule);
- a recent use of the 1 gram dosage in the some plants, followed IRSN recommendations (IRSN, 2002). This dosage is recommended recurrently in literature without any critical analysis on its quantitative aspects.

The theoretical approaches show the need for a sufficient quantity of Ca-DTPA, which is the case in this range of dosage, but does not allow the choice between 0.5 and 1 gram per day.

Comparative clinical studies are necessary for similar physico-chemical forms of radionuclides and contamination routes.

In conclusion:

- the response to the treatment seems mostly related to the physico-chemical form of the radionuclide,

- the dosage from 250 mg to 1 g does not seem to be a determining factor.

It seems reasonable to propose for the first injections:
- in general, a dosage of 0.5 gram in other words half an ampoule,
- in the case of a wound with a contamination which seems significant or which cannot be evaluated (very contaminated cutting object, large wound in glove box, blast by contaminated particles, ...) a dosage of 1 gram, in other words, 1 ampoule.

5.4.3. Administration

The administration is strictly intravenous, by slow direct injection or by infusion (about 1/4 hour).

The infusion allows maintaining access in case there is to be an associated medical treatment. It is important to underline that the setting up of an infusion must not delay the treatment, especially in the case of a wound, since the time between contamination and treatment must be as short as possible.

Local administration, by washing with a solution of Ca-DTPA at 25%, can be associated in case of wounds

5.4.4. Continuing or stopping the treatment

The decision to continue or stop the treatment depends on:
- first, the additional information provided on the circumstances of the accident,
- second, the evolution of the results of urine analysis results,
- after the initial injection, the first elements provided by the analysis of the circumstances of the accident will help to decide on whether to continue the injections over the first days:
  - contamination by wound: controls by a detector (α or X), confirmation of contamination by cutting object,
  - contamination by inhalation: measurement of the air activity of the room, analysis of nasal mucus, Whole Body Counting (WBC).

The therapeutic program used nowadays is:
– 1 injection per day for 3 to 5 days,
– 2 to 3 injections per week for 3 weeks,
– 1 injection per week for 3 months.

Depending on the levels observed, the first urinary bioassay results will indicate whether or not to pursue the treatment. When the treatment must be stopped, except for specific cases, one should refer to the general data on dosimetric benefit in Chapter 5.1 (Tabs. VI and VII).

6. Conclusions

This document presents the therapeutic results of injections of Ca-DTPA, used as a plutonium and americium chelating agent, performed in the CEA and AREVA centres from 1970 to 2003. The report (Grappin *et al.*, 2006) is part of the file requesting the Authorization to Market the Ca-DTPA by intravenous means. This report describes 1158 injections made on 469 people, involved in 548 events of potential or actual internal contamination. These people were employees under regular medical surveillance by the occupational medical services in compliance with the regulations applied.

The first part of the document summarizes the data found in literature. Because of its short biological period and of its action limited to blood, Ca-DTPA does not chelate plutonium and americium if these are fixed in the deposition organs. This means providing early treatment based on a simple suspicion, endorsed after confirmation of contamination, and providing the subsequent injections.

The second part of this document presents the data related to these 1158 injections (contamination type, posology, secondary effects, ...). Most often, these incidents having occurred in the work-place, were proven to have been minor events with no need to continue the treatment beyond the first injection.

A group of cases having been treated with 5 injections or more was isolated and a study was undertaken on the estimation of the product efficacy. The results were then compared to the estimation of efficacy developed on a theoretical basis. Posologies and therapeutic programs are proposed based on these observations, even though some points remain to be confirmed by additional studies.

This is the first summary-type document of its kind. It is the result of a collective effort involving the CEA and AREVA occupational medical services, the medical analyses laboratories and the members of the work group from the CEA-AREVA-SPRA.

This report was written under the authority of J.-M. Giraud, medical advisor to the CEA, and of B. Quesne, medical advisor to the AREVA group. The authors thank P. Raynaud, F. Pic, F. Salle, A. Florin, T. Desse and D. Schoulz for their cooperation.

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