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LIPOSOMAL FORMULATIONS OF BISPHOSPHONATE MOLECULES FOR THE TREATMENT OF INTERNAL STRONTIUM/COBALT CONTAMINATION

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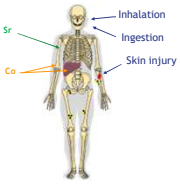
CONTEXT

The situations of exposure

- Nuclear accident
- Decommissioning site, maintenance operation
- Nuclear medicine
- Research activities
- Malevolent act

➔ Civilian population, military responders and nuclear industry workers

The health risks



Potential chemical and radiological toxicities

The patient care process

Emergency medical treatment recommended (ASN 2008):

- ⁶⁰Co: DTPA calcium salt (first intention) and cobalt gluconate
- ⁹⁰Sr: Ammonium chloride or calcium gluconate

- Modest effectiveness
- Lack of specificity (except for DTPA)

STRONTIUM-90

- Alkaline earth metal
- Fission product
- β emitter
- T_{1/2} ~ 29 years

COBALT-60

- Transition metal
- Activation product
- β emitter
- T_{1/2} ~ 5 years

⁹⁰Sr

- Bone tumours (Clarke 1970)
- Haematopoietic disorders (White 1993)

⁶⁰Co

- Respiratory effects (Yoshihisa 2012)
- Skin effects (Adams 2017)
- Potential carcinogenic (Karagas 2022)

OBJECTIVES

To propose a more effective pharmacological treatment for decorporation with the use of:

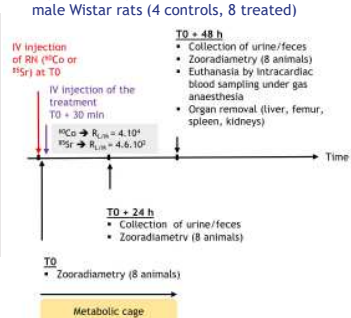
- A molecule from bisphosphonate series** (Landon 2023)
 - Bone tropism (Cremers 2011)
 - Molecular modeling data favourable (Burgada 2007)
 - Confirmed affinity between Co and etidronate (EHPB) (Scheglova 2019)
- Stealth liposomes formulation**
 - Protect active substances (Niu 2012)
 - Prevent chelation of endogenous cations
 - Target major retention organs (skeleton, liver)
 - Delay their elimination from the body (Allen 1995)

MATERIAL & METHODS

Decorporation experiments

- 1. Biokinetic / efficiency study (free EHPB) - 24 h
 - 2. Efficiency study - 48 h
 - DTPA
 - Free EHPB
 - EHPB liposomes
 - 1. Efficiency study - 48 h
 - Ca gluconate
 - Free EHPB
 - EHPB liposomes
 - 2. Efficiency study (EHPB liposomes) - 6 days
- Measurements
- Animal: zooramdiometry
 - Biological samples: gamma counting

Experimental protocol: catheterized adult male Wistar rats (4 controls, 8 treated)

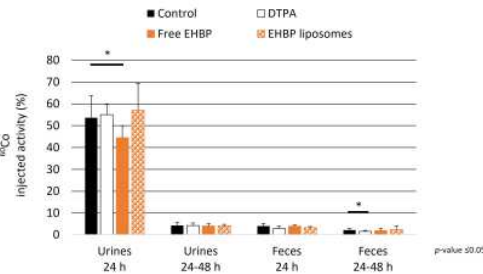


RESULTS & DISCUSSION

Cobalt decorporation experiments

Efficiency study of 48 hours

Total elimination of ⁶⁰Co on day 1 and between day 1 and day 2



Tissue distribution of ⁶⁰Co at day 2 as function of treatments (% of injected activity, mean ± standard deviation)

	Control n=12	DTPA n=8	Free EHPB n=6	EHPB liposomes n=7
Liver	3.9 ± 1.0	3.0 ^a ± 0.7	4.3 ± 1.4	4.0 ± 1.0
Kidneys	0.8 ± 0.1	0.7 ^b ± 0.1	1.1 ± 0.5	0.9 ± 0.1
Skeleton	0.7 ± 0.1	0.5 ^c ± 0.1	0.8 ± 0.2	0.8 ± 0.1
Blood	0.28 ± 0.05	0.17 ^c ± 0.02	0.29 ± 0.09	0.34 ^d ± 0.07
Spleen	0.049 ± 0.010	0.035 ^e ± 0.005	0.045 ± 0.014	0.066 ^f ± 0.016

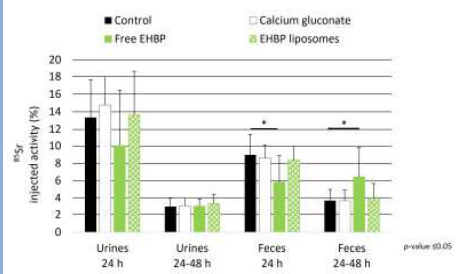
Treatments were administered by IV, at 30 μmol.kg⁻¹, 30 min after IV injection of 9 kBq ⁶⁰Co. n, number of animals. Significantly different from the control group: ^a p-value <0.05, ^b p-value <0.05, ^c p-value <0.01, ^d p-value <0.001.

- ⁶⁰Co is excreted mainly in the urine and rapidly within 24 hours
- The liver is the main storage organ for ⁶⁰Co
- Low decorporation efficacy of reference medical treatment (DTPA)
- EHPB liposomes treatment ⇒ delayed action
- Blood: release of EHPB from liposomes after prolonged circulation
- Spleen (organ of the reticuloendothelial system): chelation of ⁶⁰Co by EHPB molecules release from liposomes

Strontium decorporation experiments

Efficiency study of 48 hours

Total elimination of ⁸⁵Sr on day 1 and between day 1 and day 2



Tissue distribution of ⁸⁵Sr at day 2 as function of treatments (% of injected activity, mean ± standard deviation)

	Control n=12	Calcium gluconate n=8	Free EHPB n=8	EHPB liposomes n=8
Skeleton	59.1 ± 7.0	59.3 ± 7.3	64.9 ± 11.4	61.2 ± 9.8
Blood	0.12 ± 0.03	0.12 ± 0.02	0.16 ± 0.07	0.11 ± 0.03
Liver	0.03 ± 0.01	0.03 ± 0.01	0.03 ± 0.01	0.03 ± 0.01
Kidneys	0.02 ± 0.004	0.02 ± 0.004	0.03 ± 0.01	0.02 ± 0.003
Spleen	0.003 ± 0.001	0.003 ± 0.001	0.004 ± 0.002	0.003 ± 0.001

Treatments were administered by IV, at 30 μmol.kg⁻¹, 30 min after IV injection of 56 kBq ⁸⁵Sr. n, number of animals.

- Elimination ⁸⁵Sr slower (urinary and fecal route)
- Preferential retention organ: skeleton
- Absence of efficacy of calcium gluconate (reference medical treatment)
- Absence of efficacy of EHPB-based treatments (free and liposomal form)

Efficiency study after 6 days

Tissue distribution of ⁸⁵Sr at day 6 as function of treatments (% of injected activity, mean ± standard deviation)

	Control n=4	EHPB liposomes n=6 ^a
Skeleton	46.3 ± 18.3	38.8 ± 10.5
Blood	0.03 ± 0.01	0.03 ± 0.006
Liver	0.007 ± 0.002	0.006 ± 0.001
Kidneys	0.006 ± 0.002	0.005 ± 0.002
Spleen	0.001 ± 0.0003	0.001 ± 0.0001

Treatment was administered by IV at 30 μmol.kg⁻¹ immediately after IV injection of 56 kBq ⁸⁵Sr. n, number of animals. ^a Except for the spleen (n=7).

Longer-term decorporation study under more optimal conditions (no delay between injections):

- At T0 + 6 days, the skeleton retains most of the ⁸⁵Sr
- Following the use of EHPB liposomes, encouraging 16% reduction in ⁸⁵Sr content in the skeleton (result not significant)

Hypothesis for these results

- Low molar ratio ($R_{L/M} = 4.6 \cdot 10^2$)
- Strong competition with endogenous Ca²⁺
- Short plasma half-life of Sr (~ 1 h). When injections are delayed by 30 min, the kinetics of Sr and EHPB do not coincide.

CONCLUSIONS & PERSPECTIVES

Conclusions

- EHPB-based treatments did not show an expected efficacy under the conditions of administration (dosage and time) defined in our studies
- The results obtained with the reference treatments (DTPA salts and Ca gluconate) show little or no efficacy
- ➔ questions about their use in the event of internal contamination

Perspectives

- Use more suitable decorporation conditions ➔ increase the $R_{L/M}$ after EHPB toxicity studies
- Evaluate the effectiveness of decorporation over the longer term (more than 6 days) ➔ small stealth liposomes having a delayed action
- Increase the capabilities of the galenic formulation ➔ development of active stealth liposomes

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