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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

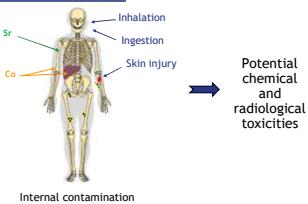
STRONTIUM-90

- Alkaline earth metal
- Fission product
- β^- emitter
- $T_{1/2} \sim 29$ years

COBALT-60

- Transition metal
- Activation product
- β^- emitter
- $T_{1/2} \sim 5$ years

The health risks



- Potential chemical and radiological toxicities
- ^{90}Sr : Bone tumours (Clarke 1970)
- ^{59}Co : Respiratory effects (Yoshikawa 2012)
- Skin effects (Adams 2017)
- Haematopoietic disorders (White 1993)
- Potential carcinogenic (Karagas 2022)

The patient care process

Emergency medical treatment recommended (ASN 2008):

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

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

OBJECTIVES

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

1 A molecule from bisphosphonate series (Landon 2023)

- Bone tropism (Cremers 2011)
- Molecular modeling data favourable (Burgada 2007)
- Confirmed affinity between Co and etidronate (EHBP) (Scheglova 2019)

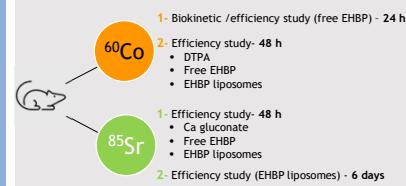
2 Stealth liposomes formulation

- Protect active substances (Niu 2012)
- Prevent chelation of endogenous cations
- Target major retention organs (skeleton, liver)
- Delay their elimination from the body (Allen 1995)



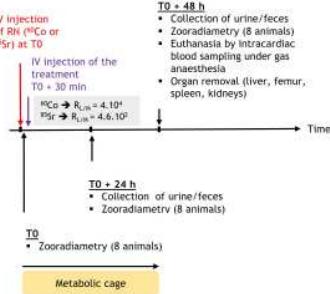
MATERIAL & METHODS

Decorporation experiments



- Measurements
 - Animal: zooradiometry
 - Biological samples: gamma counting

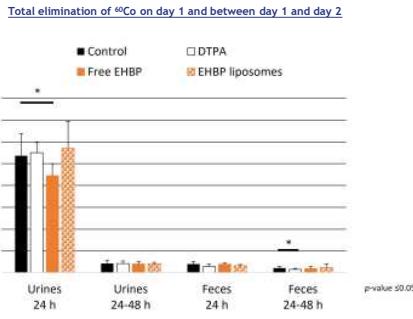
- Experimental protocol: catheterized adult male Wistar rats (4 controls, 8 treated)



RESULTS & DISCUSSION

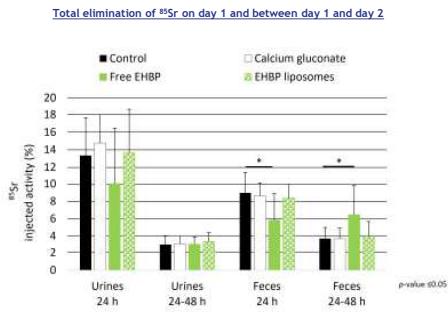
Cobalt decorporation experiments (Landon 2024)

Efficiency study of 48 hours



Strontium decorporation experiments (Landon 2024)

Efficiency study of 48 hours



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

	Control n=4	EHBP liposomes n=8
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 $\mu\text{mol kg}^{-1}$ immediately after IV injection of 56 kBq ^{85}Sr . n, number of animals.

* 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 ^{85}Sr
- Following the use of EHBP liposomes, encouraging 16% reduction in ^{85}Sr content in the skeleton (result not significant)

CONCLUSIONS & PERSPECTIVES

Conclusions

- EHBP-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_{LM} after EHBP 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

Hypothesis for these results

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

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