Tuning of the Radium Biodistribution by Dietary Supplements in a CD1 Mice Model

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Summary

- Current status of $^{223}$Ra
- Physical and chemical properties of Radium
- Study design
- Animal experiment protocols
- Results
- Conclusion
Current status of Ra-223

First EMA & FDA approved alpha-emitter „in vivo generator“ introduced by Bayer.

+ simple formulation of radium chloride, Ra and Pb self-targeted to bone tissue
- other organs accumulation, not fully known interactions, cost/effectiveness
  (1 dose ≈ 4000 € in comparison with <500 € for $^{18}$F-FDG and <100 € for $^{99m}$Tc)

Since 2017 - Bayer and EMA informed on increased risk of death and fractures with Zytiga and prednisone /prednisolone - significant limit in the use of $^{223}$Ra
Physical and chemical properties of Ra

Alkaline earth element
- complex chemistry (no chelator available)
- favorable decay properties
- self targeting to bone tissue
- total decay energy of $\approx 27$ MeV
  - $4x \alpha$
  - $2x \beta$
- nuclear recoil effect is not always an issue

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Study design

Attempt to modify Ra biodistribution in vivo by application of dietary supplements - Ca\textsuperscript{2+} / vitamin D\textsubscript{3} or co-treatment with zoledronic acid

Basic premises:

1. Ra metabolism should follow Ca
2. Increase of Ca\textsuperscript{2+} concentration should normally promote Ra elimination
3. commercially available and Pharma grade preparates should be tested

Radium chloride stock prepared from \textsuperscript{227}Ac/\textsuperscript{227}Th/\textsuperscript{223}Ra generator (Guseva 2004)
CaCl\textsubscript{2}, vitamin D\textsubscript{3}, zoledronic acid – commercial & pharma grade

Animals: healthy outbred CD1-Foxn\textsuperscript{1nu} ♀ (Charles River)

All experiments were performed according to the animal protection act No.:246/1992. and were approved by the ethical committee of the Ministry of Health No.46/2014.

5 animals per group, individually caged, 12h light /dark regime, 26-28°C controled atmosphere, 1 day starving before Ra application
sterile conditions
Animal experiment protocols

10 mice premedicated with CaCl\(_2\) (1.11 g/L). The solution was offered as drinking water *ad-libitum*

15 mice premedicated with vitamin D\(_3\), 125 IU/mouse (0.02 ml solution on a biscuit, 3x a week).

5 mice refused intake of vitamin-doped biscuit - excluded from the study

10 mice premedicated with zolendronic acid (0.1 mL solution/mouse of 4 mg/100 ml subcutaneous injection twice a week

10 mice as control group without any additional treatment

Premedication was performed for one week prior to Ra application

\(^{223}\)Radium chloride (200 kBq/animal in 0.05 mL phys. saline applied into *vena caudalis*)

½ sacrificed at 24 h, second half at 96 h timepoint - major organs were analyzed
Results: $^{223}\text{RaCl}_2 + \text{CaCl}_2 \text{ – 24 h.}$

(one-way ANOVA, *P = 0.05; **P = 0.01; n = 5)
Results: $^{223}\text{RaCl}_2 + \text{CaCl}_2$ – 96 h.

(one-way ANOVA, *P = 0.05; **P = 0.01; n = 5)
Results: Vitamin D$_3$ – 24h.

No statistically significant difference.
Results: Vitamin D₃ – 96 h.

(one-way ANOVA, *P = 0.05; **P = 0.01; n = 5)
Results: Zoledronic acid – 24 h.

(one-way ANOVA, *P = 0.05; **P = 0.01; n = 5)
Results: Zoledronic acid – 96 h.

(one-way ANOVA, *P = 0.05; **P = 0.01; n = 5)
Ra excretion

U – urine, F – feces
Conclusions – take home message

- Radium metabolism can be significantly affected by dietary supplements and other compounds related to Calcium metabolism.

- Calcium at applied concentration did not cause increased elimination of Radium.

- Further studies are needed - slight improvement in Ra biodistribution could possibly be further improved by optimizing the pre-treatment protocols.

- Thus, $^{223}$RaCl$_2$ is „not dead“, but we should better understand its metabolic pathways and interactions to further improve bone lesions treatment.

Disclosure – Authors filed an EU patent application.
Thank you for attention!

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