OPEN ACCESS

Scientific Letters

III 1H-TOXRUN
International Congress 2024
02-03 May, 2024 | Porto, Portugal

Poster 54

Gadolinium and gadoteric acid exposure induce long-term down-regulation in erythroid-related genes

Susana Coimbra [1,2,3,*], Susana Rocha [1,2], Sofia D. Viana [4,5,6], Rute Rebelo [1,2], Petronila Rocha-Pereira [1,7], Maria João Valente [8], Cristina Catarino [1,2], Elsa Bronze-Da-Rocha [1,2], Luís Belo [1,2], Flávio Reis [4,5] and Alice Santos-Silva [1,2,*]

[1] UCIBIO—Applied Molecular Biosciences Unit, Department of Biological Sciences, Faculdade de Farmácia, Universidade do Porto, Porto, Portugal
[2] Associate Laboratory i4HB, Institute for Health and Bioeconomy, Faculdade de Farmácia, Universidade do Porto, Porto, Portugal
[3] 1H-TOXRUN—One Health Toxicology Research Unit, University Institute of Health Sciences, CESPU, CRL, Gandra, Portugal
[4] Institute of Pharmacology & Experimental Therapeutics, & Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, University of Coimbra, Coimbra, Portugal
[5] Center for Innovative Biomedicine and Biotechnology (CIBB), University of Coimbra, Coimbra
[6] Polytechnic Institute of Coimbra, ESTESC-Coimbra Health School, Pharmacy, Coimbra, Portugal
[7] Health Science Research Centre, University of Beira Interior, Covilhã, Portugal
[8] National Food Institute, Technical University of Denmark, Kgs Lyngby, Denmark

* Correspondence: carla.coimbra@ipsn.cespu.pt (SC); assilva@ff.up.pt (ASS)

Abstract

Background: Gadolinium-based contrast agents (GBCA) differ in their potential to release gadolinium [Gd (III)], known to be toxic. Gadoteric acid (Gd-DOTA) is a macrocyclic GBCA, with a more stable structure. After GBCA exposure, Gd (III) retention in red blood cells (RBC) and kidney has been reported [1,2]. Nephrogenic systemic fibrosis, a severe condition found in renal disease patients exposed to GBCA, is associated with decreased hemoglobin (Hb) levels [3]. **Objective:** To evaluate the long-term effects of Gd (III) and Gd-DOTA exposure on erythropoietic function, using an animal model. **Methods:** In a long-term study (20 weeks after exposure), male Wistar rats were divided in 3 groups *(n*=10 each): exposure to a single dose (0.1 mmol/kg) of Gd (III), of Gd-DOTA or vehicle (control). At the end of the protocol, blood and renal tissue were collected; erythrogram was determined, and next-generation sequencing analysis was employed to evaluate differential gene expression of kidney tissue transcriptome. **Results:** Gd (III) group presented significantly lower RBC and hematocrit values, and higher mean *cell hemoglobin concentration (MCHC) and a trend towards lower Hb levels*; Gd-DOTA group presented trends to similar changes, without reaching statistical significance. In both groups, down-regulation of *HBA1* (encodes Hb subunit alpha 1), *HBB* (encodes Hb subunit beta) and *SLC4A1* (encodes band 3, a transmembrane chloride/bicarbonate anion exchanger1, found in RBC and kidney) genes was observed. **Conclusions:** Single exposure to free Gd (III) induced long-term down-regulation in erythroid-related genes that may underly erythropoietic and erythrocyte disturbances, as suggested by less RBC and increased MCHC. Although only alteration tendencies in these biomarkers were observed, exposure to Gd-DOTA showed the same genes downregulation. Further studies are necessary to confirm gene expression data through qPCR, to better understand the interplay between Gd (III) and erythropoiesis, and to evaluate Gd-DOTA safety.

Keywords: gadolinium; Gd-DOTA; RBC; gene expression

Acknowledgments

This work received financial support by FCT through National Funds for the project 2022.08400.PTDC. This work was supported by FCT through the project UIDP/04378/2020 and UIDB/04378/2020 of the Research Unit

on Applied Molecular Biosciences—UCIBIO and the project LA/P/0140/2020 of the Associate Laboratory Institute for Health and Bioeconomy—i4HB.

References

1. Richter, H., Bucker, P., Martin, L.F., Dunker, C., Fingerhut, S., Xia, A., Karol, A., Sperling, M., Karst, U., Radbruch, A., Jeibmann, A. Gadolinium Tissue Distribution in a Large-Animal Model after a Single Dose of Gadolinium-based Contrast Agents. Radiology (2021), 301, 637-642.
2. Di Gregorio, E., Furlan, C., Atlante, S., Stefania, R., Gianolio, E., Aime, S. Gadolinium Retention in Erythrocytes and Leukocytes From Human and Murine Blood Upon Treatment With Gadolinium-Based Contrast Agents for Magnetic Resonance Imaging. Invest Radiol (2020), 55, 30-37.
3. Wiginton, C.D., Kelly, B., Oto, A., Jesse, M., Aristimuno, P., Ernst, R., Chaljub, G. Gadolinium-Based Contrast Exposure, Nephrogenic Systemic Fibrosis, and Gadolinium Detection in Tissue. Am J Roentgenol (2008), 190, 1060-1068.