III 1H-TOXRUN INTERNATIONAL CONGRESS 2024

No Boundaries for Toxicology: One Health, One Society, One Planet

The Big Challenges of the 21st Century

2-3 May 2024 | Porto, Portugal

SCIENTIFIC LETTERS SL

BOOK OF ABSTRACTS

Volume 1 Supplement 1 (2024)

ISSN 2795-5117

CESPU INSTITUTO UNIVERSITÁRIO DE CIÊNCIAS DA SAÚDE UNIVERSITY INSTITUTE OF HEALTH SCIENCES

TOX RUN

IUCS-CESPU Publishing

https://publicacoes.cespu.pt/index.php/sl

EDITORIAL OFFICE

IUCS-CESPU Publishing
Rua Central de Gandra, 1317
4585-116, Gandra PRD
Portugal

ADMINISTRATIVE EDITOR

Rui Azevedo

https://doi.org/10.48797/sl.2024.261

For citation purposes, cite each abstract independently as indicated on the abstract page at https://publicacoes.cespu.pt/index.php/sl/issue/view/8.

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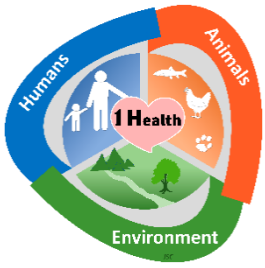

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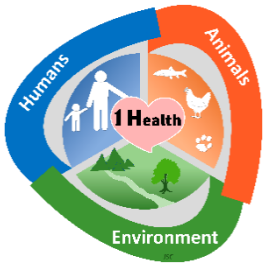

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POSTERS

Poster 52

Short-term and long-term effects of gadolinium and gadoteric acid exposure on rat kidney and liver functions

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,*]

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https://doi.org/10.48797/sl.2024.229

Abstract

Background: There are currently concerns about the safety of gadolinium-based contrast agents (GBCA), as they can release gadolinium [Gd (III)], known to be toxic. Free Gd (III) deposition at different organs, as kidney and liver, has been reported [1,2]. We found that Gd (III) promotes inflammation and fibrosis in proximal tubular cells [3]. GBCA with macrocyclic structure, as gadoteric acid (Gd-DOTA), are considered more stable. **Objective:** To evaluate the short-term and the long-term effects of Gd (III) and Gd-DOTA exposure on biomarkers of renal and hepatic functions, using an animal model. **Methods:** In both short-term (48h) and long-term (20 weeks) studies, eight weeks-old male Wistar rats were divided in 3 groups (*n*=10 each) exposed to: a single dose (0.1 mmol/kg) of Gd (III), of Gd-DOTA (0.1 mmol/kg) or vehicle (control). At the end of protocols, blood was collected and the levels of creatinine, urea, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were evaluated using routine automated assays; cystatin C was measured by ELISA. **Results:** In the short-term study (48h), Gd (III) group presented significantly higher values of AST and ALT, and lower urea levels than the control group; Gd-DOTA group presented higher AST values, compared to the control group. Twenty-weeks after exposure, higher values of AST, ALT, and creatinine, than Gd-DOTA and control groups and, lower cystatin levels, compared to the control group, were found for the Gd (III) group. **Conclusions:** Single exposure to free Gd (III) induced short-term and long-term changes in liver biomarkers; the exposure to Gd-DOTA was associated with fewer short-term disturbances in transaminases, and with no long-term influence in their values. Exposure to Gd-DOTA had little influence in traditional kidney biomarkers. Despite the significantly safer profile for Gd-DOTA, further studies are necessary, testing other biomarkers, to clarify the short-term and the long-term impact of this GBCA.

Keywords: enantioselectivity; dietary supplements; chromatographic; nephrotoxicity; hepatotoxicity

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.

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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,*]

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https://doi.org/10.48797/sl.2024.227

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.

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