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Short-term effects of gadolinium and gadoteric acid on kidney — impact on inflammation

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Background and Aims: The nephrotoxicity of free gadolinium [Gd (III)] has been reported, raising concerns about the safety of gadolinium-based contrast agents (GBCA), widely used in magnetic resonance imaging. The GBCA with macrocyclic structure, such as gadoteric acid (Gd-DOTA), appear as more stable. Using human proximal tubular cells cultures, we found that free Gd (III) triggers death by apoptosis and necrosis, and increases the expression of modulators of inflammation, hypoxia and fibrosis, which are known as major risk factors for the development and worsening of kidney disease.

Our aim was, using animal models, to evaluate the short-term effects of Gd (III) and of gadoteric acid on inflammatory biomarkers, at blood and renal tissue levels.

Method: Wistar rats were exposed to a single dose of Gd (III) or Gd-DOTA (groups A and B, respectively); a control group was also included (C). After 48h, blood and kidney samples were collected. The plasma levels of interleukin (IL)6 and transforming growth factor (TGF) beta 1 were assessed by ELISA; the kidney gene expression of IL6 (*il6*), TGF beta 1 (*tgbf1*) and nuclear factor-kappa B (*nfkb1*) was determined through qPCR.

Results: Gd (III) group (A) presented higher circulating IL6 levels ($P = 0.001$) and increased kidney gene expression of *il6* ($P = 0.013$), *tgbf1* ($P = 0.006$) and *nfkb1* ($P = 0.011$) than the control group (C); compared to Gd-DOTA group (B), the IL6 plasma concentration ($P = 0.005$) and *tgbf1* mRNA levels were also higher ($P = 0.004$). The Gd-DOTA group (B) presented increased gene expression of *il6* ($P = 0.006$) than the control group (C).

Conclusion: Short-term exposition to free Gd (III) induced an inflammatory response, shown by the increase in circulating IL6, and in kidney gene expression of *il6*, *tgbf1* and *nfkb1*. The exposition to Gd-DOTA was associated with a lower inflammatory response, showing only increased kidney gene expression of *il6*. Despite the much safer profile for Gd-DOTA, further studies are warranted, evaluating other biomarkers, to clarify the short-term, and even the long-term effects, of these compounds.

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