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Gadolinium-bound Contrast Agents: No Evidence-based Data to Support a Relationship Between Structure and Hypersensitivity Reactions

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Sir,

We came across a recent article[[1](#)] concerning nephrogenic systemic fibrosis, where the discussion on the structure-toxicity relationship of gadolinium-bound contrast agents (GBCAs) included the assertion that the patently lower thermodynamic and kinetic stability of nonionic and linear GBCAs “does not necessarily reflect overall risk for individual patients because nonionic contrast agents have fewer serious allergic-type adverse events and fewer deaths (see FDA AERS database)”. We believe that this allegation is not evidence-based and can be confusing.

To support their statement, Zou and Ma quote three articles. The first one[[2](#)] refers to the retrospective analysis of hypersensitivity reactions in patients who received a nonionic, linear agent (gadodiamide), an ionic and linear agent (gadopentetate) or a nonionic, macrocyclic GBCA (gadoteridol) (53 responses to a questionnaire, from 105 centers). As stressed by the authors of the article, “high usage of a particular agent by an institution that carefully records reactions could bias the comparison with another agent commonly employed at other institutions that record reactions less meticulously”. [[2](#)] The second article[[3](#)] is a single case report involving gadobenate. It seems quite difficult to draw general conclusions from such a report. The third article[[4](#)] refers to a large-scale, prospective study concerning first-generation, high-osmolality ionic, and second generation, low osmolality and nonionic iodinated contrast agents. Extrapolating the general conclusions from this study to GBCAs (based, as we assume, on the ‘ionicity’ of the molecules and the fact that there are contrast agents in both cases) makes no sense.

The currently published prospective, controlled, double-blind clinical trials confirm that all marketed GBCAs cannot be differentiated with respect to hypersensitivity reactions. In our opinion, the retrospective analysis of databases (where several GBCAs such as gadobutrol or gadoterate may not be taken into account) can be subjected to many potential biases and should be performed with extreme caution.

Hypersensitivity reactions to GBCAs do occur, and they can be very serious, but their nature (allergic or non-allergic) remains a topic of debate. Should there be allergic hypersensitivity reactions, polysensitization between GBCAs is not always found and the notion of class allergy is debated.[[5](#)] However, suggesting a higher incidence for some molecular category of GBCA is scientifically groundless. Even as a structure-activity relationship seems plausible with regard to the mechanism of nephrogenic systemic fibrosis, as indicated by Zou and Ma, there are no rigorous data to support any structure-activity relationship concerning GBCA-induced hypersensitivity reactions so far. Furthermore, there is definitely no link between these two categories of adverse reactions to GBCAs. In our opinion, permitting unsubstantiated rumors to circulate regarding a supposedly higher rate of adverse reactions with one or another category of GBCAs can be misleading in daily practice.

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