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## **Histopathologic assessment of neurotoxicity after repeated administration of gadodiamide in healthy rats**

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Currently, no consensus on the exact implementation of kinetic modeling of subtle BBB leakage has been reached and in vivo validation remains difficult. Some of the suggested corrections would influence the numerical values, but the group effects and conclusion of increased BBB leakage in Alzheimer disease will remain the same, which is confirmed by another research site (10).

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## Histopathologic Assessment of Neurotoxicity after Repeated Administration of Gadodiamide in Healthy Rats

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## Editor:

We read with great interest the article by Dr Smith and colleagues on accumulation and partial clearance of gadolinium from the brain after repeated administration of gadodiamide in a rodent model with intact blood-brain barrier, which was recently published online in *Radiology* (1). The authors state that there was no “detectable neurotoxicity” and no “histopathologic consequence” after up to 20 doses of intravenously administered gadodiamide with a cumulative dose of up to 12 mmol/kg. While it is certainly encouraging that the authors could not detect any extensive tissue damage, we are concerned that the histopathologic assessment limits such conclusions.

First, contrary to guidelines for toxicologic histopathology, pathologists were not made aware of the different treatment groups, as is recommended for evaluations where a known toxic syndrome with a defined spectrum of lesions does not exist (2,3).

Second, and more importantly, neurotoxicity assessments were not specified, making comparison with independent studies impossible. Stereological evaluation would allow quantification of neuronal cell number and volume (4). Furthermore, only standard hematoxylin-eosin (H-E) stains were mentioned, which have limited sensitivity in detecting subtle changes associated with potential gadolinium-related neurotoxicity such as impaired mitochondrial function (5). Assessment of pathologic changes on this level would require methods such as lactate dehydrogenase immunoreactivity or electron microscopy. In addition, it is known that glial cells react to neurotoxic events (6), and previous studies found gadolinium to be deposited mostly within or in close proximity to the endothelial wall (7). Therefore, a critical evaluation of potential gadodiamide-related neurotoxicity should include quantitative measures of reactive astrogliosis and microglial activation. While not strictly required for toxicologic assessments according to current guidelines (3), we believe that a statement like the one made by Dr Smith and colleagues would need to be based on appropriate evaluation and quantification of neuronal function.

In addition, gadolinium is regularly used in conditions with an impaired blood-brain barrier, leading to a different risk profile for gadolinium accumulation. For example, we and other investigators recently provided evidence of gadolinium deposition in patients with multiple sclerosis within routine clinical care (8). In conclusion, we do not believe that the shown representative normal appearing H-E images alone exclude gadolinium-related neurotoxicity, especially in conditions with potentially increased gadolinium uptake in the brain.

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## Response

From

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We thank Dr Schlemm and colleagues for their interest in our article and acknowledge the points they raise. We acknowledge that the current lack of reported neurotoxicity associated with brain gadolinium levels reported to date in both clinical and nonclinical studies is not definitive proof of absence of neurotoxicity and that if there are neurologic effects of gadolinium at the low levels measured they could be subtle in nature. We also acknowledge there are limitations with a standard H-E toxicologic assessment of central nervous system tissue but considered that it is an important first step, as is the case in standard drug development, to conduct a study of this type in the controlled setting of a nonclinical model with superior tissue preservation and morphology afforded by the methods employed. We also recognize the benefits and risks of blinded histopathologic assessments. For clarity, the independent histopathologic assessment was conducted masked to individual animal group assignment to avoid bias in our small cohort, but not to the agents used. The pathologist was then unmasked to groupings to enable interpretation and reporting.

We concur that it is important to systematically assess the potential risk of gadolinium presence in the central nervous system and are undertaking further studies to detect potential subtle lesions or functional deficits that may have no overt histologic footprint. Such studies will include more detailed tissue examination, such as ultrastructure with transmission electron microscopy, detailed behavioral assessments, and other analytic techniques as appropriate. Proving a potentially negative finding requires a high standard of rigor with a weight of evidence approach and multiple studies and/or techniques may be required. Considering gadolinium has been detected in the brain postmortem following administration of all types of contrast

agent (both linear and macrocyclic) (1–3), it is important that all agents are assessed in a systematic way for potential impact.

We also acknowledge that a healthy animal with an intact blood-brain barrier cannot replicate the varied co-morbidities and underlying conditions of the clinic but is likely to be an invaluable tool in elucidating mechanisms of transport into the brain and action of any potential toxicity free of confounding underlying disease states.

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