Gadolinium deposition: the current scientific situation and the different regulatory approaches in the US and Europe

By Dr Alexander Radbruch

The significance of the finding of gadolinium depositions in the brain following serial injections of gadolinium based contrast agents (GBCAs) is the subject of on-going active scientific research and debate, which are being carried out against the background of different regulatory actions being adopted in the United States and in Europe.

In November 2017 the European Commission decided to withdraw — with a few minor exceptions — all GBCAs of linear chemical structure from the market. In contrast, the US Food and Drug Administration merely issued a directive in December 2017, requiring manufacturers to add a new label warning to all GBCAs (of both linear and macrocylic structural categories) that are currently on the U.S. market. The new class warning specified simply that patients could retain gadolinium in their body long after an injection of GBCAs.

This review summarizes the scientific background to the gadolinium deposition debate and discusses the different approaches of the two regulatory agencies.

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INTRODUCTION:

Over the last three years, the significance of the finding of gadolinium deposits in patients' brains following serial injections of gadolinium based contrast agents (GBCAs) has been one of the top issues hotly debated in radiological science.

The debate was triggered unintentionally in early 2014 when Tomonori Kanda, a young Japanese radiologist, found increased hyperintensities in the dentate nucleus and the globus pallidus on non-enhanced T1-weighted images. The hyperintensities correlated with the number of previous GBCA injections that the patient had received [1]. Further research showed that gadolinium in the brain tissue was indeed the source of the hyperintensities and that other parts of the brain were also affected, with the dentate nucleus showing the highest amounts of gadolinium [2, 3}. Subsequently, Kanda *et al.* [4] and Radbruch *et al.* [5] independently reported that hyperintensities in the dentate nucleus were exclusively found after the injection of linear GBCAs, but not after injection of macrocyclic GBCAs. Ever since these findings, many preclinical and clinical studies have been published, with the aim of assessing the propensity of currently marketed GBCAs to cause hyperintensities or gadolinium deposition in the brain or in other parts of the body [6, 7].

Coincidentally, this debate on the significance of gadolinium deposition in the brain started just as the

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issue of nephrogenic systemic fibrosis (NSF) caused by the administration of GBCAs was being resolved. The first report of a correlation between NSF and the injection of GBCAs in renally impaired patients was published in 2006 by Grobner *et al* [8]. However, over the subsequent years NSF has been effectively eliminated [9], due to the widespread adoption of strict guidelines [10] that include the prohibition of the use of GBCAs in renally impaired patients.

Part of the fervor of the current debate on gadolinium deposition is thus understandable against the background of the previous NSF debate.

However, it needs to be highlighted that, so far at least, there have been no reports of clinically significant consequences correlating with the recent findings of gadolinium deposition in the brain. This is a clear difference with the earlier issue of GBCA-related NSF.

The intense scientific debate on gadolinium depositions was temporarily halted in 2017 with different regulatory actions being adopted on either side of the Atlantic.

The EU decided to remove all linear GBCAs (with a few minor exceptions) from the market, based on the application of the "Precautionary Principle". In contrast, in the United States, the FDA issued a class warning for all marketed GBCAs [Table 1].

The remainder of this article will summarize the current status of scientific knowledge of the mechanism involved in the deposition of gadolinium in the brain. Subsequently, the different approaches of the FDA and the EU will be discussed.

CHEMICAL STRUCTURES OF GBCAs

Since free gadolinium is toxic it needs to be bound to a chelating ligand, [11] Depending on the chemical structure of the ligand, GBCAs can be categorized as being either linear or macrocyclic. Whereas the ligands of macrocyclic GBCAs form a rigid cage with a pre-organized cavity into which the gadolinium ion fits, ligands in linear GBCAs merely wrap around the gadolinium ion, so forming a more flexible cage that is not fully closed [11]. The different structure of these chelates results in the GBCAs having different chemical stabilities, with consequent differences in their propensity to release gadolinium.

In vitro experiments have shown that, after incubation at 37 degrees in human serum for 15 days, 20% of the original gadolinium was released from non-ionic linear GBCAs. For ionic linear GBCAs, only 2 % of the gadolinium was released while no detectable levels of released gadolinium were found with macrocyclic GBCAs [11].

Animal studies provided evidence that similar levels of the intact form of all GBCAs currently on the market — no matter whether the GBCA was linear or macrocyclic — could be found in the cerebrospinal fluid 4 hours after injection. The route of entry to the CSF is most probably via the choroid plexus. Twenty four hours after injection, similar levels of intact GBCAs could be found in the brain [12]. However, it was found, again in experimental animal models, that four weeks after injection, residual free gadolinium was almost exclusively found with linear GBCAs, while none at all was detected with macrocyclic GBCAs [13, 14].

Further animal studies provided additional evidence as to how this finding might be explained. Whereas macrocyclic GBCAs are mostly completely washed out of the brain over time in an intact form, a small proportion of the injected linear GBCAs dechelates, with the gadolinium so released then binding to macromolecules or precipitating and remaining in the brain [15]. Such gadolinium bound to macromolecules is most likely the basis for the hyperintensity that is observed on non-enhanced T1-weighted images.

Combining the results from the *in vitro* studies and the animal studies described above, the hypothesis can be proposed that the propensity of any particular type of GBCA to cause "dechelated" gadolinium deposition in the brain (i.e. becoming visible as T1 hyperintensity in the dentate nucleus) correlates with its specific chemical stability of the GBCA, as quantitated in the *in vitro* experiments summarized above [6].

It is thus important to differentiate such "dechelated" gadolinium deposition from the presence of the intact chelate in the brain since the intact chelate is washed out over time and remains only temporarily in the brain [16].

Product	Type (formulation)	EU Regulations	FDA Regulations
Artirem / Dotarem (*gadoteric acid*)	macrocyclic (i.v.)	maintain	maintain
Artirem / Dotarem (*gadoteric acid*)	macrocyclic (intra-articular)	maintain	maintain
Gadovist (*gadobutrol*)	macrocyclic (i.v.)	maintain	maintain
Magnevist (*gadopentetic acid*)	linear (intra-articular)	maintain	maintain
Magnevist (*gadopentetic acid*)	linear (i.v.)	**suspend**	maintain
Multihance (*gadobenic acid*)	linear (i.v.)	**restrict use to liver scans**	maintain
Omniscan (*gadodiamide*)	linear (i.v.)	**suspend**	maintain
Optimark (*gadoversetamide*)	linear (i.v.)	**suspend**	maintain
Primovist (*gadoxeticacid*)	linear (i.v.)	maintain	maintain
Prohance (*gadoteridol*)	macrocyclic (i.v.)	maintain	maintain

Table 1: Overview of GBCAs currently on the European and US markets and the respective decisions of the EU and the FDA regulatory authorities.

Finally, it should be noted that gadolinium deposition will most likely occur not only in the brain but anywhere in the human body where there is an environment that is suitable for the transmetallation and dechelation process [17]. Hence, any increase in signal intensity in the dentate nucleus of the brain might be regarded as an indicator or marker of gadolinium release throughout the whole body.

DIFFERENT APPROACHES OF THE FDA AND THE EU

The FDA acknowledged in its class warning of 17th December 2017 that "*linear GBCAs result in greater retention — and retention for a longer time — than macrocyclic GBCAs. Gadolinium levels remaining in the body are higher after administration of ... non-ionic linear GBCAs than after ionic linear GBCAs*" [18]. However, the FDA limited itself to issuing a class warning for all marketed (linear and macrocyclic) GBCAs, and recommended healthcare professionals to "*consider the retention characteristics of each agent when choosing a GBCA for patients who may be at higher risk for gadolinium retention*" [18]

In contrast, the EU pulled all linear GBCAs (with the exception of Multihance and Primovist for liver imaging and Magnevist for intrarticular use) from the European market.

The EU justifies the withdrawal of the linear GBCAs on the basis of its application of the precautionary principle. One inevitable outcome of using this approach is that, even if there are no known clinical consequences correlated to any gadolinium deposition, nevertheless the very possibility of any gadolinium release in patients should be avoided or at least kept to a minimum This is particularly relevant given the earlier debate over NSF which showed that gadolinium release can potentially be a trigger of, or result in severe adverse effects or disease [19].

It is important to note that, apart from the potential risk of gadolinium deposition, there are several other aspects that must be included in the general risk/benefit evaluation that should always be undertaken prior to the injection of any particular GBCA. These additional aspects include possible allergic reactions as well as the overall diagnostic potential and clinical necessity/advantage of GBCA administration.

" ... there have been no reports of clinically significant consequences correlating with the recent findings of gadolinium deposition..."

In the specific case of liver imaging, the EU decided that the linear GBCAs (Multihance and Primovist) fulfilled an important diagnostic need which could not be achieved with macrocylic GBCAs. Consequently, the EU made an exception for these two agents for liver imaging. Moreover, the EU maintained Magnevist for intra-articular usage "because the dose of gadolinium that is required for these scans is very low " [20].

However, apart from these exceptions the EU has not identified any other significant advantages of linear GBCAs that could justify the increased risk of gadolinium deposition in the risk /benefit assessment.

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Despite the differences between the regulations on GBCAs in the US and Europe, it is important to point out that the international radiology and scientific communities agree on most of the significant points in the gadolinium deposition debate.

First and foremost, it needs to be repeated that no adverse clinical consequences correlating with GBCA administration have been reported, nor have any pathologic tissue changes been identified as being associated with, or the result of the gadolinium deposit [21].

For the radiologist it is crucial to communicate this message to patients and to avoid in all cases any risk of unnecessarily alarming the patient.

Moreover, there is a broad agreement that GBCAs are an indispensable part of the overall clinical decision making process, that they should only be used if clinically indicated and that in any case only the lowest possible dose that still provides images of acceptable diagnostic reliability should be used.

Finally, one of the biggest threats coming out of the current debate remains an exaggerated and unreasonable decline in the use of GBCAs in clinically indicated situations, due to a growing "phobia" on the part of radiologists to using gadolinium based products. Radiologists should avoid this scenario by proactively addressing the issue and by reassuring concerned patients.

CONCLUSION:

Results from experimental animal models together with those from *in vitro* experiments have provided evidence that a very small proportion of the administered dose of linear Gadolinium based contrast agents dechelate *in vivo* and form high relaxivity complexes that become visible on non-enhanced T1 weighted images in metal-rich regions such as the dentate nucleus. This effect could not be shown for macrocyclic GBCAs that are, over time, mostly washed out of the body in an intact form.

No clinical correlates or adverse histopathological changes caused by the gadolinium deposits have currently ben identified. In their application of the precautionary principle, the EU have suspended all linear GBCAs (with minor exceptions) from the European market while the FDA has issued a general warning for all GBCAs currently on the market.

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DISCLOSURES:

Alexander Radbruch has been on the advisory boards of Bayer, Bracco, GE-Healthcare and Guerbet. He currently holds consultant contracts with Bayer and Guerbet.

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Book Review

Chest Radiology, 7th Edition

Patterns and Differential Diagnoses

By James C. Reed, Published by Elevier, 2017, Book Price €98.09, eBook Price €70.19

Written with the aim of sharpening the reader's skills in chest x-ray interpretation, this trusted clinical resourcce walks the reader through a logical, sequential thought process for the differential diagnoses of 23 radiologic patterns of common chest diseases, using 150 superbly illustrated patient cases. A solid and thorough understanding of how to read and interpret chest x-rays is gained, with expert guidance on common disease patterns, differential diagnoses, narrowing down the diagnoses, and further studies (from additional radiographic exams to CT or to biopsy). Each chapter follows a consistent format: Presenting Case, Questions, Discussion, Top 5 Diagnoses, Summary, and Answer Guide. The book is an ideal resource for mastering this lower-cost modality before considering more complicated and costly procedures and is heavily illustrated with chest radiographs and additional CT, HRCT, and MR correlative images.