

Medicines Adverse Reactions Committee

Meeting date	8 June 2017	Agenda item	3.2.4
Title	Gadolinium based contrast agents and accumulation in brain tissue		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active constituent	GBCA Type	Brand names	Sponsors
Gadoteric acid	macrocyclic	Dotarem	Obex
Gadobutrol	macrocyclic	Gadovist	Bayer
Gadopentetate	linear -ionic	Magnevist	Bayer
Gadobenate dimeglumine	linear -ionic	Multihance	Regional Health
Gadodiamide	linear non-ionic	Omniscan	GE Healthcare
Gadoxetate	linear di-ionic	Primovist	Bayer
Funding	All these agents are funded on the hospital medicines list		
Previous MARC meetings	The safety of gadolinium containing contrast agents has not been discussed previously		
International action	FDA has published several communications on this topic Health Canada has required updates to product information The PRAC have recommended suspension of some GBCAs		
Prescriber Update	www.medsafe.govt.nz/profs/PUArticles/GadoliniumSept2011.htm Gadolinium based contrast agents and nephrogenic systemic fibrosis		
Schedule	General sale medicine		
Usage data	Not available		
Advice sought	<p>The Committee is asked to advise whether:</p> <ul style="list-style-type: none"> – the available evidence shows that gadolinium is deposited in the brain after administration of all of the available GBCAs OR is there evidence to support a difference between the GBCAs – there is evidence of harm resulting from deposition of gadolinium in the brain – any regulatory action is required – any communication or advice to healthcare professionals is required 		

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1.0 PURPOSE

Gadolinium based contrast agents (GBCA) are diagnostic agents that may be given to patients before or during MRI scans to help obtain better images of organs and tissues. After administration, gadolinium agents are mostly eliminated via the kidneys but studies indicate that deposits can build up in some body tissues, including in the liver, kidney, muscle, skin and bone.

Recently concerns have been expressed regarding deposits of gadolinium in the brain (see below). Whether these deposits are toxic remains to be fully elucidated.

The purpose of this paper is to review the available information on the extent to which gadolinium is deposited in the brain, possible mechanisms, the potential toxicity which may be expected to result from these brain deposits and if there are any risk factors which predispose patients to brain deposits.

2.0 BACKGROUND

2.1 Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a medical imaging technique. MRI scanners use a magnetic field, radio waves and field gradients rather than x-rays to generate images. MRI can be used as an alternative to computed tomography scanning (which does use x-rays). MRI generally yields different information to CT scans. The disadvantages of MRI for the patient are that it generally takes more time, is louder and usually requires that the patient goes into a narrow tube. Some people with medical implants or other metal inside the body may not be able to undergo an MRI. This is due to the strong magnetic fields generated which can lead to heating or movement of the metal.

MRI is used in numerous applications such as imaging cancers, demyelinating disease, dementia, cerebrovascular disease, epilepsy or spinal and joint disease. Functional MRI is used to measure how different parts of the brain respond to stimuli. Phase contrast MRI is used to measure flow velocities in the body.

MRI scans are dependent on the physics of the hydrogen atom, which is abundant since the body is mostly made up of water and fat. These atoms are randomly spinning, or precessing, on their axis, like a child's top. All of the atoms are going in various directions, but when placed in a magnetic field, the atoms line up in the direction of the field (Figure 1).

Since the magnetic field runs straight down the centre of the machine, the hydrogen protons line up so that they're pointing to either the patient's feet or the head. About half go each way, so that the vast majority of the protons cancel each other out -- that is, for each atom lined up toward the feet, one is lined up toward the head. Only a couple of protons out of every million aren't cancelled out.

Next, the MRI machine applies a radio frequency (RF) pulse that is specific only to hydrogen. The system directs the pulse toward the area of the body to be examined. When the pulse is applied, the unmatched protons absorb the energy and spin again in a different direction. This is the "resonance" part of MRI. The RF pulse forces them to spin at a particular frequency, in a particular direction. The specific frequency of resonance is called the Larmour frequency and is calculated based on the particular tissue being imaged and the strength of the main magnetic field.

At approximately the same time, the three gradient magnets are also used. They are arranged in such a manner inside the main magnet that when they're turned on and off rapidly in a specific manner, they alter the main magnetic field on a local level. What this means is that the area to be imaged can be precisely located; this area is referred to as the "slice". Slices can be taken of any part of the body in any direction.

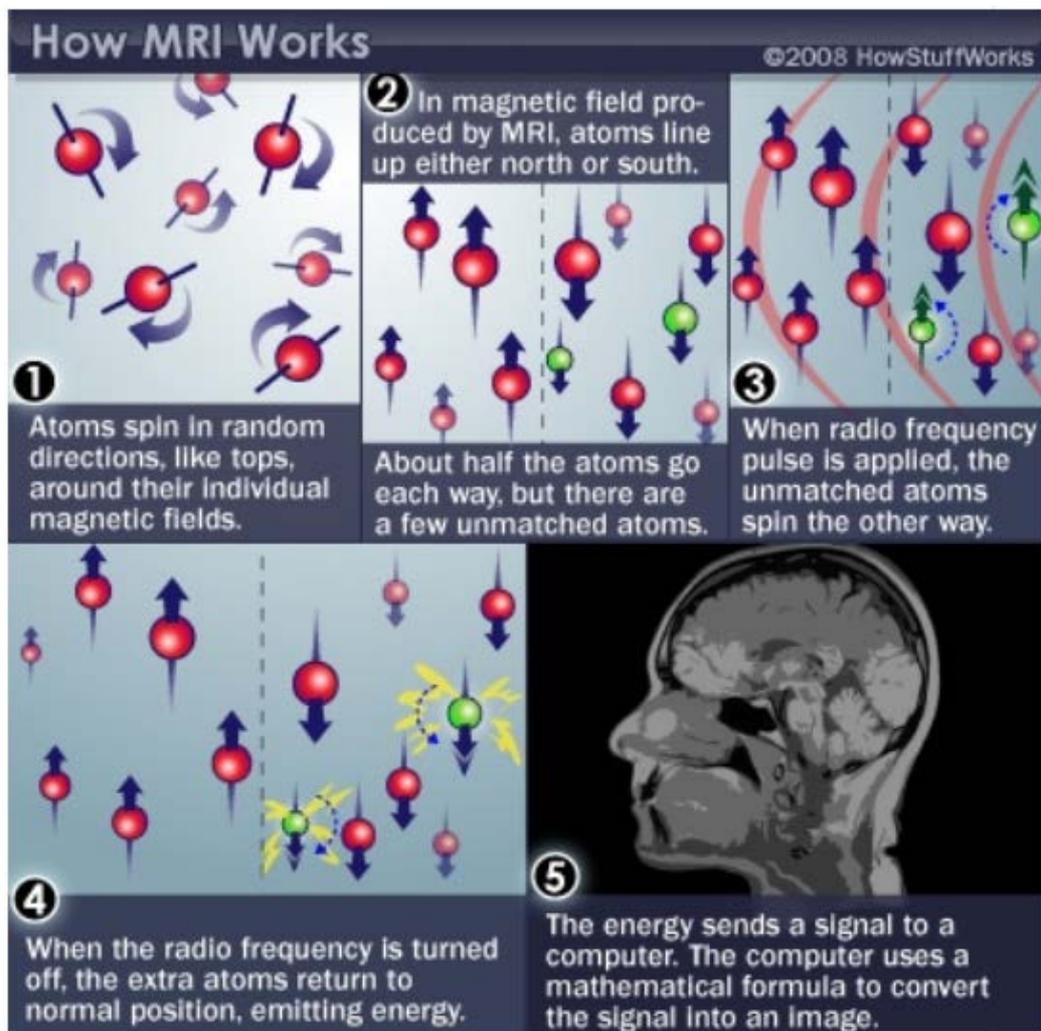


Figure 1: Info-graphic summarising how MRI works

When the RF pulse is turned off, the hydrogen protons slowly return to their natural alignment within the magnetic field and release the energy absorbed from the RF pulses. When they do this, they give off a signal that the coils pick up and send to the computer system. The system goes through the patient's body point by point, building up a map of tissue types. It then integrates all of this information to create 2-D images or 3-D models with a mathematical formula known as the Fourier transform. The computer receives the signal from the spinning protons as mathematical data; the data is converted into a picture.

T1 process is the way in which the excited protons lose energy to the surrounding molecules (spin energy loss to the environment). The rate of energy loss changes in different environments (for example adding contrast agents) which allows differentiation of different tissues.

2.2 Gadolinium based contrast agents (GBCAs)

Contrast agents are used to improve the visibility of the structures in MRI. These agents shorten the relaxation times of nearby water protons altering the contrast in the image.

Gadolinium contrast agents contain gadolinium as the following active substances: gadobenic acid, gadobutrol, gadodiamide, gadopentetic acid, gadoteric acid, gadoteridol, gadoversetamide and gadoxetic acid. Gadoteric acid, gadoteridol and gadobutrol are macrocyclic structures. The other GBCAs are linear structures (See Front Page and Table 1). In all cases the gadolinium is chelated into the structure.

2.3 Data sheets

Data sheets for the New Zealand approved products are published on the Medsafe website, although they are not mandated for general sales medicines.

All the data sheets include a statement consistent with:

'<GBCA> ion does not cross the intact blood-brain barrier and, therefore, does not accumulate in normal brain or in lesions that have a normal blood-brain barrier. However, disruption of the blood-brain barrier or abnormal vascularity allows <GBCA> ion penetration into the lesion.'

Or

'In rats it has been demonstrated that <GBCA> does not penetrate the intact blood-brain barrier.'

There are no warnings or adverse reactions associated with brain deposits included in data sheets. The type of GBCA and indications are summarised in Table 1.

Table 1: GBCAs available in New Zealand and the approved indications

Active	Brand name	Chelation type
Gadodiamide	Omniscan	Linear non-ionic
Indications		
Contrast medium for cranial and spinal resonance imaging (MRI) and for general MRI of the body after intravenous administration. Provides contrast enhancement and facilitates visualisation of abnormal structures or lesions in various parts of the body including the CNS.		
Gadobenic acid	Multihance	Linear ionic
Indications		
Imaging (MRI) of the liver and Central Nervous System (CNS)- the detection of focal liver lesions in patients with known or suspected primary liver cancer (eg. hepatocellular carcinoma) or metastatic disease. the detection of lesions and provides diagnostic information additional to that obtained with unenhanced MRI.		
Contrast enhance Magnetic Resonance Angiography to improve the diagnostic accuracy of detecting clinical significant steno-occlusive vascular diseases in patients with known vascular diseases of the abdominal, supra-aortic or peripheral arteries.		
Gadopentetic acid	Magnevist	Linear ionic
Indications		
Cranial and Spinal Magnetic Resonance Imaging (MRI)		
In particular for the demonstration of tumours and for further differential-diagnostic clarification in suspected meningioma, (acoustic) neurinoma, invasive tumours (e.g. glioma) and metastases; for the demonstration of small and/or isointense tumours; in suspected recurrence after surgery or radiotherapy; for the differentiated demonstration of rare neoplasms such as haemangioblastomas, ependymomas and small pituitary adenomas; for improved determination of the spread of tumours not of cerebral origin.		
Additionally in spinal MRI: Differentiation of intra- and extramedullary tumours; demonstration of solid tumour areas in known syrinx; determination of intramedullary tumour spread.		
Whole Body MRI		
Including the facial skull, the neck region, the thoracic and abdominal space, the female breast, the pelvis and the active and passive locomotive apparatus and imaging of vessels throughout the body.		
In particular, Magnevist permits diagnostic information:		
<ul style="list-style-type: none"> – For the demonstration or exclusion of tumours, inflammation and vascular lesions; – For determination of the spread and demarcation of these lesions; – For the differentiation of the internal structure of lesions; – For assessment of the circulatory situation of normal and pathologically changed tissues; – For the differentiation of tumour and scar tissue after therapy; – For the recognition of recurrent prolapse of a disk after surgery. – For the semi-quantitative evaluation of the renal function combined with anatomical organ diagnosis. 		

Gadoxetic acid	Primovist	Linear – di-ionic
Indications Primovist is indicated for use in adults for the enhancement of magnetic resonance imaging (MRI) of focal liver lesions.		
Gadobutrol	Gadovist	Macrocyclic
Indications In adults and children of all ages including full-term newborns for: contrast enhancement in cranial and spinal magnetic resonance imaging (MRI). This includes: Differentiation of intra- and extramedullary tumours, demonstration of solid tumour areas in known syrinx, determination of intramedullary tumour spread. Gadovist 1.0 is especially suited for high dose indications, such as cases where the exclusion or demonstration of additional foci may influence the therapy or patient management, for detection of very small lesions and for visualisation of lesions that do not readily take up contrast media. Gadovist 1.0 is also indicated for perfusion studies such as the diagnosis of stroke, the detection of focal cerebral ischaemia and tumour perfusion. Contrast enhancement in whole body MRI including head and neck region, thoracic space, breast, abdomen (pancreas, liver and spleen), pelvis (prostate, bladder and uterus), retroperitoneal space (kidney), extremities and musculoskeletal system. Contrast enhancement in magnetic resonance angiography (CE MRA). Contrast enhancement in cardiac MRI including assessment of rest and pharmacological stress perfusion and delayed enhancement.		
Gadoteric acid	Dotarem	Macrocyclic
Indications Magnetic resonance imaging for: – cerebral and spinal disease, – diseases of the vertebral column, – and other whole body pathologies (including angiography of the non-coronary arteries).		

Comments

The indications vary across the different GBCAs.

2.4 Actions taken by international regulators

2.4.1 FDA

The FDA has publicly stated that:

“The U.S. Food and Drug Administration (FDA) is investigating the risk of brain deposits following repeated use of gadolinium-based contrast agents (GBCAs) for magnetic resonance imaging (MRI). MRIs help detect abnormalities of body organs, blood vessels, and other tissues. Recent publications in the medical literature have reported that deposits of GBCAs remain in the brains of some patients who undergo four or more contrast MRI scans, long after the last administration. It is unknown whether these gadolinium deposits are harmful or can lead to adverse health effects.

FDA, including its National Center for Toxicological Research (NCTR), will study this possible safety risk further. We are working with the research community and industry to understand the mechanism of gadolinium retention and to determine if there are any potential adverse health effects. Based on the need for additional information, at this time, we are not requiring manufacturers to make changes to the labels of GBCA products.

To reduce the potential for gadolinium accumulation, health care professionals should consider limiting GBCA use to clinical circumstances in which the additional information provided by the contrast is necessary. Health care professionals are also urged to reassess the necessity of repetitive GBCA MRIs in established treatment protocols.

In published studies, investigators reviewed noncontrast magnetic resonance imaging (MRI) scans of patients who had received several gadolinium-based contrast agent (GBCA) MRIs as part of

management for cancer, multiple sclerosis, or other illnesses. The noncontrast MRIs demonstrated findings highly suggestive that gadolinium contrast was retained in various structures in the brain. To date, no signs or symptoms of adverse health effects and no pathological changes have been associated with these gadolinium deposits in the brain. In some of these studies, examination of brain tissue at autopsy confirmed the presence of gadolinium deposits. In these studies, researchers found that GBCAs more prone to dissociation into free gadolinium, which is when gadolinium separates from the molecule it is bound to, demonstrated greater brain deposition than GBCAs less prone to dissociation. A study in rats performed by a GBCA manufacturer showed greater gadolinium deposition throughout the brain in rats given a linear GBCA that is known to have greater dissociation of gadolinium, compared to a macrocyclic GBCA. No histopathological changes were observed in the animal brains. Gadolinium may also deposit in other body structures such as bone and skin.”

[REDACTED]

On 23 May the FDA stated:

“An FDA review to date has not identified adverse health effects from gadolinium retained in the brain after the use of gadolinium-based contrast agents (GBCAs) for magnetic resonance imaging (MRI). All GBCAs may be associated with some gadolinium retention in the brain and other body tissues. However, because FDA identified no evidence to date that gadolinium retention in the brain from any of the GBCAs, including GBCAs associated with higher retention of gadolinium, is harmful, restricting GBCA use is not warranted at this time. FDA will continue to assess the safety of GBCAs and plan to have a public meeting to discuss this issue in the future.

FDA evaluated scientific publications and adverse event reports submitted to FDA. Some human and animal studies looked at GBCA use over periods longer than a year. These publications and reports show that gadolinium is retained in organs such as the brain, bones, and skin. The publications show that linear GBCAs retain more gadolinium in the brain than macrocyclic GBCAs. However, the review did not identify adverse health effects related to this brain retention.

FDA continues to assess the safety of GBCAs. FDA’s National Center for Toxicological Research is conducting a study on brain retention of GBCAs in rats. Other research is also being conducted about how gadolinium is retained in the body. FDA will update the public when new information becomes available and we plan to have a public meeting to discuss this issue in the future”.

2.4.2 Health Canada

Health Canada has stated that:

“Health Canada has conducted a safety review of gadolinium-based contrast agents (GBCAs) due to growing scientific evidence that gadolinium may accumulate in the brain following multiple contrast-enhanced magnetic resonance imaging (MRI) scans.

Although no health consequences have been identified with gadolinium accumulation in the brain, Health Canada will be working with Canadian manufacturers to update the labelling of GBCAs to include this new information.

Health professionals are advised to:

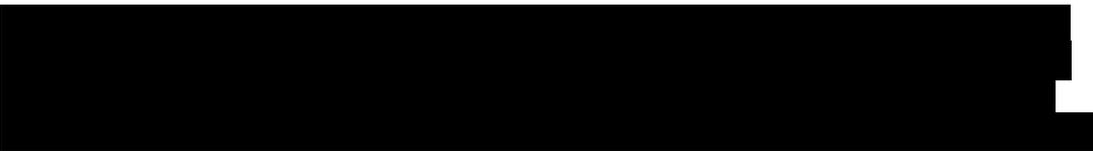
- limit the use of GBCAs to situations where the contrast agent is considered necessary
- use the lowest effective dose, and
- assess the benefits and any potential risks to individual patients before administering repeated doses of GBCAs.

[Redacted]

[Redacted]

[Redacted]

- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]

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2.4.3 EMA

The European Medicines Agency (EMA) have stated:

“EMA’s Pharmacovigilance and Risk Assessment Committee (PRAC) has recommended the suspension of the marketing authorisations for four linear gadolinium contrast agents because of evidence that small amounts of the gadolinium they contain are deposited in the brain.

The agents concerned are intravenous injections of gadobenic acid, gadodiamide, gadopentetic acid and gadoversetamide, which are given to patients to enhance images from magnetic resonance imaging (MRI) body scans.

The PRAC’s review of gadolinium agents found convincing evidence of accumulation of gadolinium in the brain from studies directly measuring gadolinium in brain tissues and areas of increased signal intensity seen on MRI scan images many months after the last injection of a GBCA.

Although no symptoms or diseases linked to gadolinium in the brain have been reported, the PRAC took a precautionary approach, noting that data on the long-term effects in the brain are limited. Deposition of gadolinium in other organs and tissues has been associated with rare side effects of skin plaques and nephrogenic systemic fibrosis, a scarring condition in patients with kidney impairment. Furthermore, non-clinical laboratory studies have shown that gadolinium can be harmful to tissues.

The four agents recommended for suspension are referred to as linear agents. Linear agents have a structure more likely to release gadolinium, which can build up in body tissues. Other agents, known as macrocyclic agents, are more stable and have a much lower propensity to release gadolinium. The PRAC recommends that macrocyclic agents be used at the lowest dose that enhances images sufficiently to make diagnoses and only when unenhanced body scans are not suitable.

Some linear agents will remain available: gadoxetic acid (Primovist), a linear agent used at a low dose for liver scans, can remain on the market as it meets an important diagnostic need in patients with few alternatives. In addition, a formulation of gadopentetic acid (Magnevist) injected directly into joints is to remain available because its gadolinium concentration is very low – around 200 times lower than those of intravenous products. Both agents should be used at the lowest dose that enhances images sufficiently to make diagnoses and only if unenhanced scans are not suitable.

For those marketing authorisations recommended for suspension, the suspensions can be lifted if the respective companies provide evidence of new benefits in an identified patient group that outweigh its risks or show that their product (modified or not) does not release gadolinium significantly (dechelation) or lead to its retention in tissues.”

Comments

All the agents recommended for suspension in the EU are available in New Zealand. The decision has been appealed. The outcome of the re-review is due in July 2017.

2.5 Australian and New Zealand radiologists guidance

The Royal Australian and New Zealand College of Radiologists have produced a guideline on the use of GBCAs in patients with renal impairment.

The guideline is aimed at preventing cases of nephrogenic systemic fibrosis (there is currently no guideline in reducing brain deposition). A copy is attached at Annex 1.

The guideline states:

Consider whether any other imaging modality – including non-contrast MRI, CT, or ultrasound – could provide the required diagnostic information at less risk.

No patient should be denied any imaging investigation that is critical to clinical management.

In high risk patients:

- (a) The minimum adequate dose of gadolinium is used.
- (b) Consider immediate post-scan haemodialysis
- (c) Use a contrast agent with the lowest theoretical risk.

The College also provided information in their September 2015 newsletter (Annex 1). They concluded that it would be prudent to limit the use of gadolinium-based chelates to cases in which the potential benefit justifies the (likely very small) risk associated with administration. In some conditions it has become common practice to conduct repeat gadolinium-enhanced MRI studies at regular intervals over long periods. In light of the possibility that the risks of this strategy may be higher than previously thought, it may be appropriate to consider whether:

- a) The frequency of scanning could be reduced, or
- b) A non-contrast protocol might be sufficient, at least as an initial screen.

Practices may also wish to review their policies on gadolinium chelate choice and use in light of the recent findings.

3.0 SCIENTIFIC INFORMATION

This section contains a summary of the scientific literature, data provided by the companies and CARM reports.

3.1 Published literature

This section is split into four parts. The first part contains an overview of review articles in which various investigators provide their summary and opinion on this safety concern. This is followed by the published systematic reviews. The third part describes pre-clinical studies which may help to understand this issue. The fourth part describes some of the retrospective case series demonstrating gadolinium brain deposition in patients.

In addition, a presentation given by Professor Radbruch to Medsafe providing an overview of this safety concern is available at Annex 2.

Not all of the current literature is included, for brevity and particularly as new papers are being published very quickly.

3.1.1 Overview of Reviews of the current evidence

3.1.1.1 History of use [1, 2]

Since their introduction into clinical practice in the United States in 1988, gadolinium-based contrast agents (GBCAs) have had a tremendous impact on magnetic resonance imaging (MRI). MRI is accompanied by the intravenous administration of a gadolinium based contrast agent in roughly 30% to 45% of all clinical US MR studies. It is estimated that about 30 million MRI scans are performed each year in the US.

Gadolinium, a lanthanide heavy metal, is highly paramagnetic and is the metal of choice for MR contrast agents. However, the free ion is highly toxic and slowly excreted. Therefore, to minimize interaction with endogenous ligands, increase solubility, encourage elimination, and decrease toxicity, gadolinium is bound to an organic chelating agent.

Until 2006, the main discussions regarding safety for all GBCA were related to short term adverse reactions. Adverse reactions to GBCA can be broadly divided into two main categories, allergic and physiologic reactions (coldness, warmth, or pain at the injection site, nausea with or without vomiting, headache, paresthesias, and dizziness).

GBCA-related allergic types of adverse reactions are identical in nature to iodinated contrast agents, and include such adverse events (AEs) as sneezing, hives, and anaphylaxis/anaphylactoid reactions. Allergic-like reactions are uncommon and occur in around 0.04% of patients (lower than the incidence for iodinated contrast media used for CT scans [0.2%]). The incidence of adverse reactions is higher in patients with a history of asthma and in patients who report a prior adverse reaction to the administration of an iodinated contrast agent. The incidence is substantially higher (roughly 20%) in patients who experienced AEs to prior GBCA administration.

Serious AEs are even more uncommon, being observed in very roughly 0.01–0.03% of patients receiving GBCA. Severe life-threatening anaphylactic and fatal reactions do occur, but are exceedingly rare (0.001% to 0.01%), 40 deaths were reported in 51 million GBCA doses administered between 2004 and 2009. The incidence of severe allergic reactions is lower for GBCAs than iodinated contrast agents.

Just as importantly, no significant difference has been observed in the short term AE rate associated with the various CNS indication GBCAs. Thus, many of these agents with similar relaxivities were treated as essentially interchangeable (from a diagnostic point of view), with similar safety and efficacy profiles.

Only after 18 years of use were the first serious adverse effects reported, when nephrologists connected the administration of GBCAs to nephrogenic systemic fibrosis (NSF). Consequently, NSF has almost been completely eliminated by effective screening of patients with renal disease and by avoiding GBCAs in patients with substantial renal disease or by utilizing more stable GBCA associated with extremely few or no cases of NSF.

3.1.1.2 Nephrogenic Systemic Fibrosis [2]

The beginning of 2006 brought with it the landmark observation by Grobner connecting the administration of GBCA to the eventual development of (NSF) in patients with significant renal function impairment.

At this point it is broadly recognized and generally agreed that:

- 1) the vast majority of, if not all, patients with a diagnosis of NSF have significant impaired renal function and have received a GBCA
- 2) confirmed diagnoses of NSF have only been observed following the prior unconfounded administration of gadodiamide (Omniscan), gadopentetate (Magnevist), and gadoversetamide, with apparently three cases reported after the prior unconfounded administration of gadobutrol (Gadovist)
- 3) there do not seem to be any confirmed cases of NSF following the prior unconfounded administration of gadoterate (Dotarem), gadobenate (Multihance), or gadoteridol (Prohance)
- 4) the worse the renal function at the time of GBCA administration the greater the chance of contracting NSF. The vast majority of patients with chronic renal failure who contracted NSF following GBCA administration were stage 5 chronic kidney disease (CKD), and most were already on dialysis
- 5) there do not seem to be any confirmed cases of NSF in dialysis patients who underwent dialysis immediately (ie, within an hour or two) following GBCA administration
- 6) multiple haemodialysis treatments would be required in order to remove the vast majority of an administered intravenous GBCA dose, while peritoneal dialysis appears comparatively quite inefficient at removing intravenously administered GBCA
- 7) the greater the total dose of administered GBCA the greater the likelihood of contracting NSF and possibly the severity of NSF if/ when contracted
- 8) a significant percentage of all NSF patients had received a GBCA while in acute renal failure
- 9) for reasons that are still unknown, the vast majority of patients who receive a GBCA, even those with severe renal disease and even those who receive a GBCA most associated with NSF, do NOT seem to contract NSF.

NSF appears to be mediated almost exclusively by the weaker chelated GBCAs. Even with the weakest of the chelates, Omniscan, only 3% of patients with stage 5 renal failure develop NSF. This suggests that even in this circumstance the host response is not absolute for all individuals, but varies based on the host immune system, where perhaps 3% of the population then have this immune system variation. Beyond this consideration, it seems that the most stable GBCAs do not result in NSF from observational experience in several tens of millions of subjects.

As a direct result of the nearly universal changes in the approach to GBCA administration, there have been few to no newly diagnosed cases of NSF internationally since the 2009 or 2010 time frame.

Comments

GBCAs were not removed from the market following the identification of NSF. The risk can be managed by avoiding use of linear agents in patients with renal failure.

3.1.1.3 Technical issues [3, 4]

Some critical methodological issues have not been adequately standardized in a number of studies investigating deposition of GBCAs in the brain. Some of these issues are highlighted here and need to be considered when evaluating the pre-clinical and clinical studies outlined below.

One major limitation of MRI human studies reporting gadolinium deposition is its retrospective nature. This unavoidable study design explains in part the variability of the MR imaging protocols used, which may change according to the pathology that is being studied and among different institutions.

The influence of MR field strength in quantitative and qualitative evaluation of T1 signal intensity of DN or other brain structures is presently unknown. It seems reasonable to assume that signal intensity will differ between 1.5 T and 3 T, but so far no studies have addressed this question.

In most of the published studies, the authors have used T1-weighted spin echo (SE) to evaluate the DN and/or GP signal intensity and signal changes over time. However, in some quantitative, and qualitative studies, different T1-weighted sequences have been interchangeably used. Recognizing this potential confounding factor, Radbruch *et al.* performed a subgroup analysis to examine whether the two different T1-weighted sequences applied (MPRAGE and SE) had an influence on the signal intensity ratio difference. The authors found no statistically significant influence.

In contrast, Ramalho *et al.* performed an intra-individual qualitative and quantitative comparison between T1 SE and T1 3D MPRAGE in patients who had multiple exposures to gadodiamide (Omniscan) and found that both sequences cannot be used interchangeably for qualitative or quantitative analysis of signal intensity in the DN. It should be recognized that it is virtually impossible to exclude some variability even when using the same imaging sequence, especially if performed on different machines and at different institutions. Significant variations in the sequence parameters and technique over time are expected to provide significant variation of the signal intensity measurements.

Different ratios have been used for quantitative measurements including DN-to-pons, DN-to-middle cerebellar peduncle, DN-to-cerebellar white matter, DN-to-CSF, DN-to-corporum callosum genu (CC), GP-to-Th, GP-to-CSF, GP-to-CC, Th-to-CC, and Caudate nucleus-to-CC. Up to the present time, no dedicated study has focused on comparing these ratios in their entirety, although Radbruch *et al.* compared DN T1 signal intensity with that of pons, CSF, and cerebellum. The authors found comparable results analysing DN-to-pons, DN-to-CSF, and DN-to-cerebellum ratios over time in patients who received gadopentetate (Magnevist) or gadoterate (Dotarem). It is still uncertain what is the best structure to normalize these measurements, or if any is necessary. Further studies are needed to address this.

Studies in mice suggested an LOD (level of detection) by T1 weighted MRI of about 30 micromolar for an unbound commercial Gd(chelate). Protein bound or otherwise immobilized Gd(chelate) can have a relaxivity more than an order of magnitude greater than that of unbound Gd(chelate). Relaxivity is not actually directly proportional to nor necessarily linearly related to detected signal in MRI, but to an order of magnitude approximation, the LOD of Gd(chelate) detected by MRI is likely ~10 micromolar *in vivo*.

Ignoring the tissue water content variables, and assuming a tissue density of 1 g/mL, 6.4 micromolar corresponds to 1 PPM Gd (by mass) in an autopsy sample. That is in the range of published data. McDonald reported 0.3–58.8 ppm in human brain autopsy tissues ([see 3.1.4.4](#)). Precipitated, or isolated in a compartment without or with too limited water, Gd in any form, chelated or not, could have a zero T1 relaxivity.

MRI does not detect all the gadolinium deposits present in human tissues. To date, bone deposition, which is likely the largest repository for gadolinium, is not demonstrable with MRI, and only the DN

and GP exhibit MR visible deposition in the brain despite the gadolinium presence in essentially all brain tissue. It is currently considered that insoluble gadolinium salts, such as phosphate, bicarbonate, and hydroxide, or soluble protein-bound gadolinium should not have a known effect on T1 shortening. As such, MR imaging significantly underestimates how much gadolinium may be retained in human tissues where it is identified on MRI, and is largely invisible in most tissues where it is present.

Gadolinium tissue measurements are also influenced by many factors. Any separation of the gadolinium from the biological matrix in which it resides offers a variable that must be carefully controlled for.

Preparation of brain tissue may remove the water-soluble contrast agent, leaving only gadolinium bound to substances other than the chelate, and this may lead to underestimation of any accumulation. The matrix (solvent mixtures, etc.) used for extraction from human tissues must be validated to determine that it does not alter the analytes in the process. Most experiments involving human tissue also start with formalin fixed tissue, adding the possibility that fixation has altered the gadolinium chemistry in the deposited gadolinium. The importance of the benign nature of the separation, causing no significant change to the tissue or alteration of the gadolinium species extracted, cannot be overemphasized.

Practical, readily available analytical methods for detection of gadolinium at the parts per million concentration include MRI, magnetic resonance dispersion, fluorescence, x-ray fluorescence, electron microscopy with x-ray spectroscopy, neutron diffraction, radioactivity, and mass spectral analysis. Inductively coupled plasma mass spectrometry (ICP-MS) is also a destructive technique in which the tissue sample is incinerated. This means that it is unable to detect the gadolinium species present (chelated, unchelated, and what unchelated may be bound to).

An analytical technology capable of resolving gadolinium (chelate) from dissociated gadolinium is mass spectral analysis, which detects the presence of the gadolinium on the basis of the mass (actually mass to charge ratio, m/z) of its gas phase ionized form. Gadolinium is particularly easy to identify in a mass spectrum due to its isotope pattern arising from the fact that natural gadolinium consists of several stable isotopes in a specific ratio.

MALDI Imaging Mass Spectrometry (MALDI IMS, MALDI is matrix-assisted laser desorption ionization) analysis refers to the creation of gas phase analytes by laser desorption from a surface, combined with mass spectral analysis of the desorbed species. MALDI IMS is capable of sampling a 10 μm thick tissue. The technique results in density maps showing the localization of compounds of specific mass on the tissue surface.

3.1.1.4 Gadolinium chelation [2, 5]

The various GBCA in use today are chelated complexes of gadolinium ions and their unique ligand molecules. The strength of the bond between the gadolinium ion and its chelating ligand molecule differs among the various approved GBCA. This is predominantly due to the various structures and characteristic types of bonds utilized in generating the various GBCA chelated complexes in clinical use today.

These can be broadly summarized as being either:

- a) macrocyclic versus linear in nature, with macrocyclic ones being far more tightly bound than linear ones, the ligands of macrocyclic GBCAs form a rigid cage for the gadolinium
- b) ionic versus non-ionic, with ionic ones being more tightly bound than are non-ionic ones. Ligands of linear GBCAs wrap around the ligand and the formed cage is not fully closed

Thus, the weakest bonds among the GBCA in use today are those that are both linear as well as non-ionic.

The description of gadolinium as “free” is incorrect; gadolinium released from its manufactured ligand should be described as unchelated, dechelated or dissociated. Gadolinium is never free; it is always in some form of bond to some other molecule/chemical. Gadolinium released *in vivo* from its ligand is often rapidly bound to native host molecules, and exists *in vivo* in a number of various chemical entities, including: precipitated oxides, hydroxides, carbonates, or natural biological chelating agents such as citrate, amino acids, peptides or proteins. The term transmetallation is widely used to designate this exchange process.

3.1.1.5 Gadolinium deposition [1, 2, 6]

Peer-reviewed articles on deposition of gadolinium in animals with normal renal function, some illustrating deleterious consequences, were published as early as 1984.

The higher stability of macrocyclic chelators compared with their linear counterparts was established in 1988 with clear differences in bone retention observed. In 1995, the biodistribution of gadolinium after administration of four approved gadolinium chelates (Dotarem, Magnevist, Omniscan, and ProHance) in both mice and rats was evaluated. These studies demonstrated that a measurable fraction of the gadolinium dose is retained in the tissues with the main sites of deposition being the liver, kidneys, and femur in both species. After an additional seven days, the concentration of gadolinium retained by the liver and kidneys continued to fall, whereas those in the femur remained constant. The elimination half-life from bone has been estimated to be 3,500 days for gadolinium, consistent with other metal deposition studies in which elimination is significantly longer than for other tissues.

Early indications that gadolinium retention was occurring in humans can be gleaned from initial pharmacokinetic studies. The urinary excretion of Magnevist after 48 hours was only $91\% \pm 13.0\%$ in patients with normal renal function. This study provided an early insight into the potential for incomplete elimination of gadolinium.

Bone

One of the earliest major studies that showed direct evidence of gadolinium deposition in humans with normal renal function was an article published by Gibby *et al.* in 2004. Gadolinium was shown to be deposited in the resected femoral heads of patients who had previously undergone gadolinium chelate-enhanced MRI studies with either Omniscan or ProHance, and then subsequently underwent femoral head replacement surgery. They found gadolinium deposition in the bone specimens and reported that 2.5 times more gadolinium was deposited with Omniscan than with ProHance.

Darrah *et al.* also analyzed the deposition in bone tissue obtained from femoral head specimens collected at the time of hip replacement. Gadolinium was measured in patients with histories of GBCA exposure to Omniscan, ProHance, and controls who had not received gadolinium. Their results showed gadolinium deposition in exposed patients to be 2–3 orders of magnitude higher than in controls without gadolinium exposure and they also documented higher levels of gadolinium in trabecular (spongy) bone than in cortical bone. They found no correlation between elapsed time between gadolinium exposure and surgical removal of the femoral head and that gadolinium deposited in bone is retained for >8 years in their observed patient population. In addition, Darrah showed lower levels of gadolinium in a group of patients with fractures and secondary osteoporosis compared with higher levels among patients with osteoarthritis suggesting that increased mineral loss may release gadolinium previously stored in bone.

Skin

All GBCAs resulted in gadolinium retention in the skin of rats for up to 35 days after injection. At later time points, however, the gadolinium retained after administration of macrocyclic GBCAs returned to untreated levels. This is in distinction to the linear agents, which exhibited high levels of gadolinium retention even one year after injection.

In a recent case report, Roberts *et al.* measured high levels of gadolinium deposition in the skin of a 30-year-old brain tumour patient with normal renal function who had received 61 doses of GBCAs, mostly Magnevist and MultiHance that resulted in extremely high cumulative doses and marked increase T1 SI on non-enhanced T1 images in GP and DN. Following an episode of cholecystitis and subsequent cholecystectomy the patient developed severe progressive generalized contractures not explained by his unilateral tumour or prior treatments. Although no external skin changes of NSF were present and the patient's renal function was normal he underwent skin biopsy that revealed no increased fibrosis, increased numbers of fibrocytes or macrophages. Staining of skin sections with antibodies against CD34, however, showed increased CD34 immunoreactivity in the septations of the adipose connective tissue. ICP-MS analysis of skin showed a gadolinium deposition level of 14.5 µg/g which is compatible with levels described in the NSF patients analyzed. Although not definitive, this case suggests a possible link between very high levels of tissue gadolinium and gadolinium associated disease in patients that is not NSF.

Brain [2, 6-8]

In 2014, the association of unusual brain MRI findings in patients with a history of GBCA administration was reported.

Increased signal intensity in the dentate nucleus (DN) and globus pallidus (GP) on unenhanced T1-weighted images (T1WI) showed a positive correlation with previous exposure to linear chelate type GBCAs (gadopentetate or gadodiamide), even in patients with normal renal function (Figure 2). Previously, high signal intensity in the dentate nucleus on T1WI had been attributed to a secondary progressive subtype of multiple sclerosis or a history of irradiation. High signal intensity in the globus pallidus has been associated with hepatic dysfunction, Wilson disease, Rendu-Osler-Weber disease, manganese toxicity, calcification, haemodialysis, total parenteral nutrition, and neurofibromatosis type 1.

Additional MR studies by Kanda *et al* and, independently, by Radbruch *et al* analyzed T1 signal within GP and DN among patients receiving the macrocyclic agents ProHance and Dotarem (gadoterate), respectively. They did not observe similar SI changes suggesting that these macrocyclic agents either do not deposit Gd in normal brain tissues or do so at a markedly lower level.

Six studies have exclusively assessed serial injections of macrocyclic GBCAs (Prohance, Dotarem, Gadovist) (Table 2). Five of these studies did not present any SI increase after serial injections of macrocyclic GBCAs. Only the study by Stojanov *et al.* reported an SI increase after 4.74 ± 0.72 injections of Gadovist. In contrast, Radbruch *et al.* assessed 7.3 ± 3.1 and Cao *et al.* 7.8 ± 2.4 injections of Gadovist and did not find any SI increase in the DN. Moreover, the study of Stojanov *et al.* has been criticized for the published image that did not display obvious subjective SI increase after serial injections of Gadovist.

Similar findings were reported in paediatric patients. Hu *et al.* analysed 21 children who had received GBCA more than five times: all 21 patients had increased signal intensity in the dentate nucleus and globus pallidus.

McDonald *et al.* first confirmed finding gadolinium in the brains of autopsy patients who had received multiple prior doses of gadodiamide (3.1.4.4). They evaluated gadolinium concentrations in four brain regions from 23 autopsy subjects. The brain tissue from the non-GBCA group demonstrated undetectable levels of gadolinium, whereas brain tissues from the GBCA group contained 0.1–58.8 mg gadolinium per gram of tissue. Despite direct evidence of gadolinium deposition within neuronal tissues, no histologic change of neural tissues was detected. McDonald *et al.*, and demonstrated that the signal intensity/T1 shortening magnitude scaled with the amount of measured gadolinium intracranially and with the dose of GBCA.

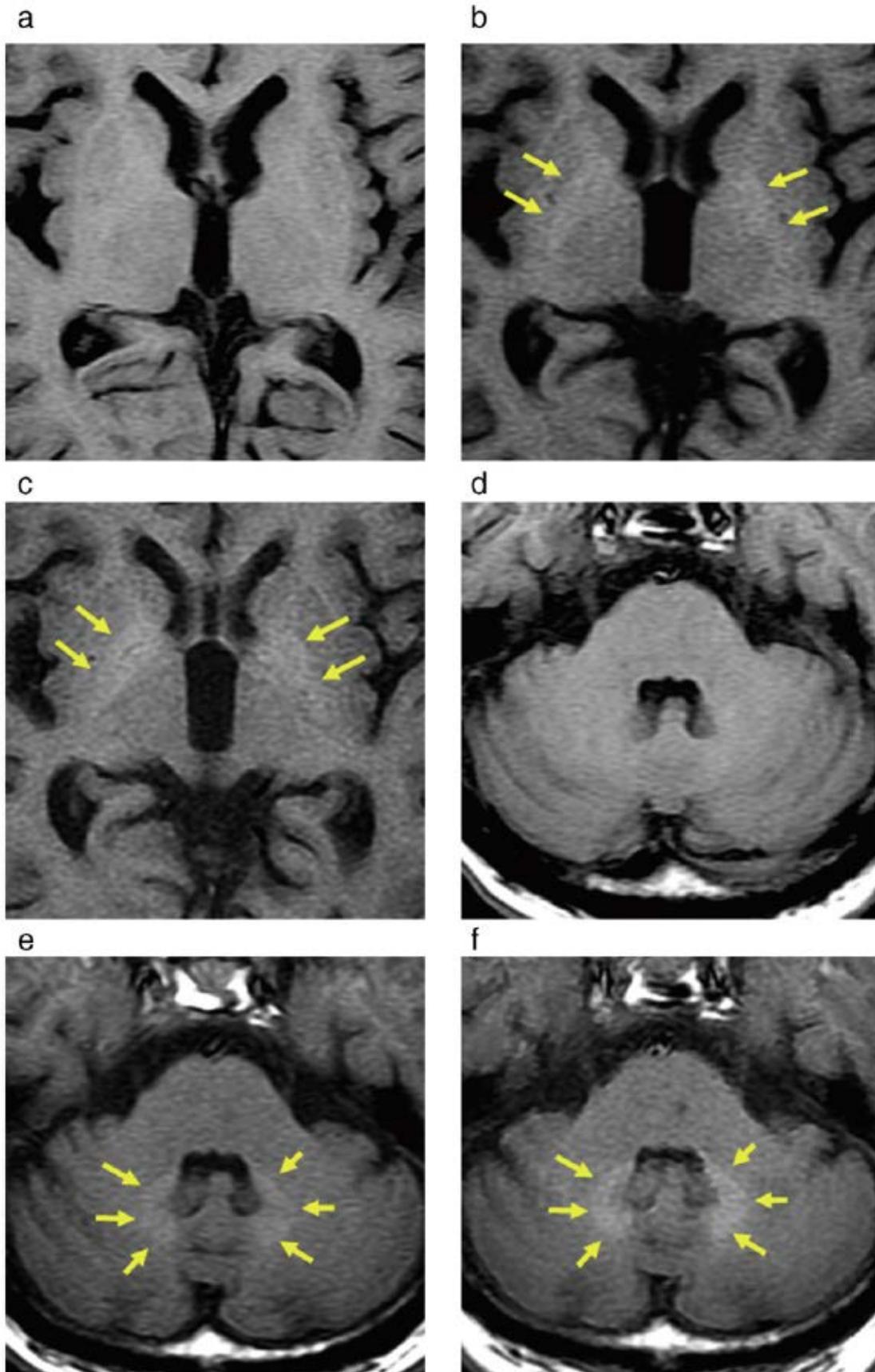


Figure 2: Progressive increase in signal in the dentate nucleus and globus pallidus in patients with a history of lung cancer. Axial unenhanced T1WI of the first (a, d), fifth (b, e), and 9th (c, f) gadolinium-enhanced MRI exams. The signal intensity of the globus pallidus (a–c) and dentate nucleus (d–f) is gradually increasing.

Other results revealed that Gd is also deposited in human brain tissues with the macrocyclic agents Gadavist (gadobutrol) and ProHance (gadoteridol) and with the two linear protein interacting agents MultiHance (gadobenate) and Eovist (gadoxetate). Similar to previous autopsy brain tissue reports and MR T1 SI reports the levels of Gd in brain tissue were highest in GP and DN but Gd was also present in all other brain tissues sampled, although at much lower concentrations (these preliminary results are discussed in more detail in the section on clinical information [3.1.4.6](#)).

These studies showed that gadolinium was far more widely distributed throughout the brain than merely the locations at which T1 shortening was detected on unenhanced MRI. Further, studies have now shown that it is almost certain that each of the GBCA, regardless of structure or ionicity, is associated with some level of residual or accumulated intracranial gadolinium, although there may be markedly different magnitudes and/ or rates of this effect seen among the different GBCA in clinical use today.

Table 2: Retrospective patient studies that assessed serial injections of specific GBCAs[2]

Study (journal)	Study design	Linear GBCAs				Macrocyclic GBCAs		
		Omniscan	Magnevist	Multihance	Omniscan/ Magnevist	Omniscan/ Multihance/ Magnevist	Prohance	Gadovist
1. Kanda I (Radiology)	19 patients ≥6 inj. Omniscan/Magnevist 16 patients ≥6 scans without GBCA	-	-	-	YES	-	-	-
2. Errante (Invest Radiol)	38 patients Multiple Sclerosis ≥2 inj. Omniscan 37 patients brain mets ≥2 inj. Omniscan	YES	-	-	-	-	-	-
3. Quattrocchi (Invest Radiol)	10 patients 1 Inj. Omniscan – no SI increase 28 patients 1–5 inj. Omniscan –no SI Increase 8 patients ≥6 inj. Omniscan –SI increase	YES	-	-	-	-	-	-
4. Kanda II (Radiology)	23 patients (median 2, max 11 inj.) Magnevist 36 patients (median 2, max 15 inj.) Prohance	-	YES	-	-	NO	-	-
5. Radbruch I (Radiology)	50 patients (6.06 ± 1.20 inj.) Dotarem 50 patients (6.32 ± 1.83 inj.) Magnevist	-	YES	-	-	-	-	NO
6. McDonald (Radiology)	13 patients (4–29 inj.) Omniscan 10 patients without GBCAs	YES	-	-	-	-	-	-
7. Ramalho I et al. (Radiology)	23 patients (5.0 ± 2.4 inj.) Omniscan 46 patients (4.6 ± 2.2 inj.) Multihance	YES	-	tendency (p < .013)	-	-	-	-
8. Weberling (Invest Radiol)	50 patients (7.7 ± 3.2 inj.) Multihance	-	-	YES	-	-	-	-
9. Stojanov (Eur Radiol)	58 patients multiple sclerosis (4.74 ± 0.72 inj.) Gadovist	-	-	-	-	-	YES*	-
10. Radbruch II (Invest Radiol)	30 patients (7.3 ± 3.1 inj.) Gadovist	-	-	-	-	-	NO	-
11. Cao et al. (AJR)	25 patients (7.8 ± 2.4 inj.) Gadovist 25 patients (12.1 ± 5.2 inj.) Magnevist	-	YES	-	-	-	NO	-
12. Ramalho II et al. (Eur Radiol)	18 patients (5.9 ± 2.3) Omniscan subsequently (5.5 ± 1.9) Multihance; 44 Pat (4.5 ± 2.0) Multihance	**	-	NO**	-	-	-	-
13. Tedeschi et al. (Eur Radiol)	35 patients (6.3 ± 4.1 Inj.) Magnevist	-	YES	-	-	-	-	-
14. Hu et al. (Ped Radiol)	21 patients (children) (range: 5–37 injections)	-	YES	-	-	-	-	-
15. Flood et al. (Radiology)	46 patients (children) ≥ 3 inj. Magnevist	-	YES	-	-	-	-	-
16. Radbruch III et al. (Invest Radiol)	35 patients ≥5 inj Magnevist subsequent ≥5 in. Gadovist, subsequent ≥5 inj. Dotarem (in 12 Pat)	-	YES	-	-	-	NO	NO
17. Zhang et al. (Radiology)	13 patients with 39–59 linear GBCA inj.	-	-	-	-	YES	-	-

The studies are ordered chronologically.

* The study by Stojanov et al. was criticized because the reported SI increase could not be demonstrated in the published images.

** The study by Ramalho II et al. assessed 2 patient groups with serial Multihance injections: 5.5 ± 1.9 injections in group 1 and 4.5 ± 2.0 injections in group 2. Group 1 received 5.9 ± 2.7 prior injections of Omniscan while group 2 did not have any prior GBCA injections. A significant SI increase could be shown only in group 1.

Three animal studies have been conducted to evaluate gadolinium deposition following serial injections of different GBCAs. All three studies did not find any signal intensity increase in the deep cerebellar nuclei (DCN) after the injection of saline or macrocyclic GBCAs. In contrast, all studies reported significant signal intensity increase in the DCN after injection of linear GBCAs. Notably, the highest signal intensity increase among the linear GBCAs was found for the non-ionic linear GBCA (Omniscan).

The most compelling result from one of the first autopsy analyses was that the cumulative dose was significantly associated with amount of gadolinium deposition, but not time since the last dose; thus, at this point there is no evidence to suggest clearance from the brain occurs (Figure 3).

In summary, the retrospective patient studies provide evidence that

1. linear GBCAs are correlated with an signal intensity increase in the DN if a certain number of injections (probably 5–6 injections) is exceeded
2. the non-ionic linear GBCA Omniscan causes a stronger signal intensity increase than the ionic linear GBCA Multihance
3. macrocyclic GBCAs cause an signal intensity increase to a lesser degree than linear GBCAs.

Notably, no visible signal intensity increase after serial injections of macrocyclic GBCAs is documented yet.

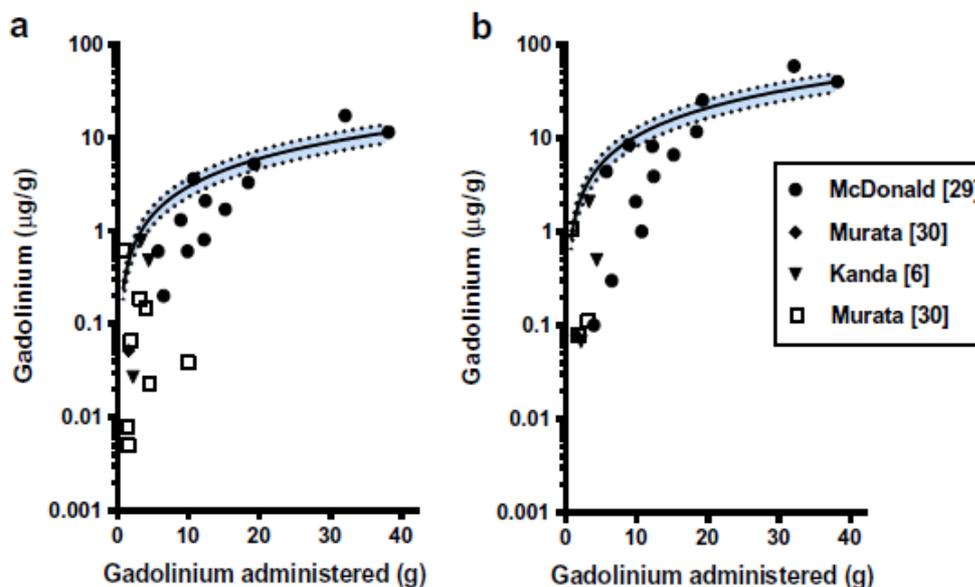


Figure 3: Meta-regression plot of gadolinium concentration in the globus pallidus (a) and dentate nucleus (b) following multiple administrations of gadolinium-based contrast agents. Linear contrast agents are represented by closed markers, while macrocyclic contrast agents are open markers. The solid line represents the linear regression best fit, and the dashed lines represent the 95% confidence band.

The major limitation of these studies is that the form of the gadolinium as either chelated or dechelated remains unknown. A conference abstract from Pietsch *et al.* showed that 24 days after the last injection of the respective GBCA, 30% of the tissue-gadolinium bound to macro-molecules in the brain in the Omniscan-group, while no gadolinium bound to macromolecules was found in the Gadovist-group. Thus the current hypothesis is that the gadolinium bound to macro-molecules is the origin of the signal intensity increase after serial injections of linear GBCAs. The less stable the GBCA, the more gadolinium dissociates from the complex and becomes visible when bound to a macromolecule in the DN. However, more research is certainly needed to prove this hypothesis.

Comments

Although many of the reviews consider that gadolinium brain deposition occurs with all GBCAs the evidence discussed in the pre-clinical and clinical information suggests that this may not be correct.

3.1.1.6 Proposed mechanism of deposition [2, 9, 10]

Although there is now definitive proof that gadolinium delivered as GBCAs forms deposits in the brain, questions remain:

1. through what mechanism is gadolinium entering and remaining in the brain
2. if dechelation is necessary for uptake, what factors contribute to GBCA stability in vivo
3. what form of gadolinium is in brain deposits of patients with normal renal function?

The proposed mechanisms of gadolinium deposition are shown in Figure 4 and discussed below.

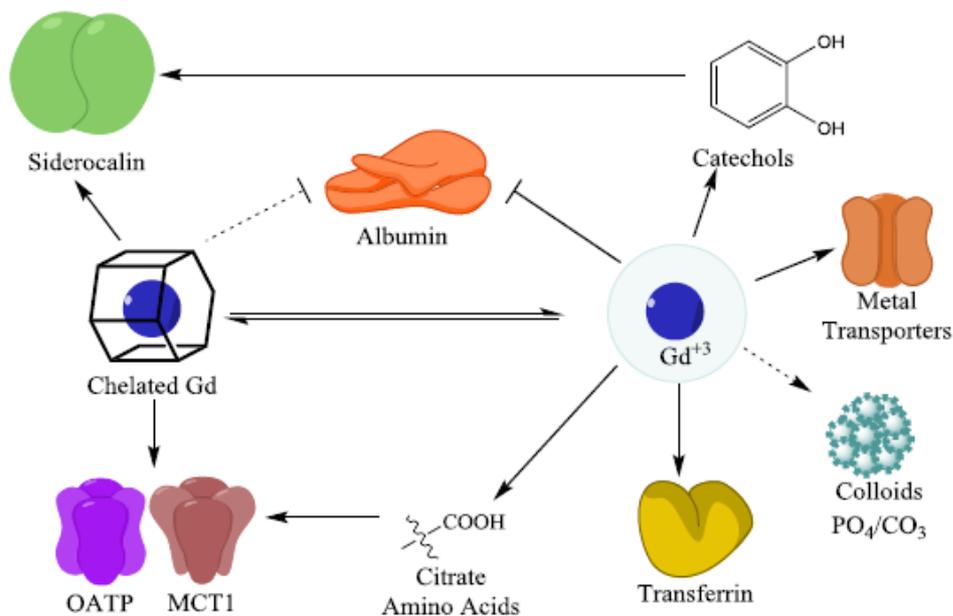


Figure 4: Proposed mechanisms for gadolinium or gadolinium-based contrast agent uptake into the brain. Each illustrated target is associated with processes that result in delivery of metals to the central nervous system, or has been proposed as an uptake mechanism. Binding targets of gadolinium or chelated gadolinium associated with uptake are indicated by an arrow, and processes that limit uptake (i.e., binding to albumin) are denoted by a bar. Since all gadolinium-based contrast agents do not bind albumin, and evidence exists supporting both increased and decreased uptake of colloids, those lines are dashed. Abbreviations: CO₃, carbonate; Gd, gadolinium; MCT1, monocarboxylate transporter 1; OATP, organic anion-transporting polypeptide; PO₄, phosphate.

Transmetallation

Transmetallation is also known as the dechelation or dissociation theory. The theory of transmetallation suggests that with prolongation of the biologic half-life that accompanies significant renal dysfunction, a greater percentage of the administered GBCA dose will dissociate from its ligand molecule while still within the recipient's body. Endogenous metals such as iron and zinc attract the ligand to release gadolinium that deposits in the tissue as gadolinium phosphate. Lower thermodynamic stability of the GBCM will facilitate easier transmetallation with endogenous metals such as iron or zinc. The gadolinium may then biodistribute based on the form and structure of the molecule to which the gadolinium ion had coupled. In the case of gadolinium phosphate, the newly formed molecule might then biodistribute to the bony skeleton. Here it might remain for months or years as an inadvertent "reservoir" in the body from which it might be able to interact with other molecules.

In support of the transmetallation theory is the fact that the weakest bonds would be expected to be those associated with the two linear non-ionic agents, gadodiamide and gadoversetamide. There is a relatively strong association of NSF and the prior unconfounded administration of these two GBCA. Also in support of the transmetallation theory is that there is a very low, near zero incidence of the development of NSF following the prior unconfounded administration of any macrocyclic GBCA.

There remain, however, some observations which are clearly not adequately explained by the theory of transmetallation. For example, there are no cases of NSF being diagnosed following the prior unconfounded administration of the linear ionic agent gadobenate. However, there are roughly 100 cases of confirmed NSF following the prior unconfounded administration of gadopentetate, also a linear ionic agent. Further, there seem to be three cases of NSF following the prior unconfounded administration of gadobutrol, a macrocyclic agent. Although this number is exceedingly small, the fact remains that as a macrocyclic agent, it is not clear why the incidence is not zero, as it is with the other two macrocyclic agents, gadoterate and gadoteridol.

Glymphatic system

The glymphatic system is a newly described paravascular pathway for CSF and ISF (interstitial fluid) exchange in the brain. In the classical model, the CSF is thought to be secreted by the choroid plexus, transverses the ventricular system, reaching the subarachnoid space, and is reabsorbed into the vascular system, either by the arachnoid granulations or eliminated through the cervical lymphatics. With the glymphatic concept, it is accepted that a large proportion of subarachnoid CSF recirculates into the brain parenchyma along paravascular spaces and exchanges with the ISF. This fluid movement facilitates the efficient clearance of interstitial solutes from the brain parenchyma.

The glymphatic system may also transport GBCA to the brain. Brain MRI was performed on 27 subjects who had been administered GBCA four hours before. On post contrast FLAIR image, the subarachnoid space and perivascular space showed increased signal intensity, and GBCA transfer to the subarachnoid space and perivascular space. These results demonstrated that even in patients with normal renal function, intravenously administered GBCA can be transported through the glymphatic system and reach the brain. However, the association between the hyper-intensity of the DN and the GBCA transported through the glymphatic system is still unclear.

Uptake by iron trafficking mechanisms

Iron transport and regulation processes are well understood. With a sophisticated system evolved to tightly regulate the distribution in the body, it is not surprising that investigations on the toxicokinetics of non-endogenous or trace metals often consider parallels to iron physiology.

It is of interest that the brain grey matter structures where gadolinium deposits are intrinsically iron-rich and are specifically affected by neurodegenerative disorders with brain iron and manganese accumulation.

GBCAs are known to reduce iron-binding capacity and increase serum ferritin without any impact on serum iron in patients with end-stage renal disease. In a retrospective analysis, transferrin saturation and serum ferritin levels were higher in end stage kidney disease patients with established NSF than in control end stage kidney disease patients.

Omniscan facilitates the differentiation of peripheral blood mononuclear cells (PBMCs) into CD163+ macrophages. These cells are pro-fibrotic and express high levels of iron recycling and storage proteins: transferrin receptor (Tfr1), HO-1, H-ferritin and ferroportin. In patients with NSF, pro-fibrotic CD163+ ferroportin+ macrophages were shown to infiltrate the dermis, subcutaneous tissue, myocardium and vascular tissues of patients who died with NSF.

Another study demonstrated that gadolinium delivered as the chloride or as a GBCA enhanced iron uptake in cell cultures from four different tissues, while iron did not impact gadolinium uptake.

Transferrin receptor has been implicated in the brain deposition of many metals because it contains two potential metal binding sites and is the primary carrier of iron into the brain. While transferrin receptor does bind gadolinium, it does so only at one site, with relatively poor affinity ($\log K_A = 6.8$). Since it has been observed that GBCAs reduce iron binding capacity (a measure of transferrin receptor saturation) in patients without changing serum iron levels, it appears that evidence already exists that gadolinium binds transferrin receptor *in vivo* when delivered as a GBCA. However, since the binding affinity of gadolinium to the chelates in GBCAs is at least 10⁹-fold higher than the binding affinity to transferrin receptor, it is still uncertain why there would be a detectable amount of gadolinium exchanged from GBCAs to transferrin receptor.

Other transporters

Lipocalins are a diverse family of proteins that preferentially bind intact complexes of iron and polyaromatic chelators. Siderocalin, a human lipocalin, is present at low basal levels, but is upregulated during inflammation, including in renal injury, and its putative receptors are present on

the blood–brain barrier, indicating a potential alternative mechanism for gadolinium uptake into the brain.

Three approved GBCAs are known to bind to albumin, which helps keep them in the blood pool rather than traverse to extracellular fluid. Albumin also has 23 sites that bind calcium and four sites that bind transition metals. Using bovine serum albumin as a model, the four metal-binding sites all bind gadolinium with millimolar affinity. Under normal conditions, gadolinium binding to albumin would therefore have a limiting effect on brain deposition of gadolinium in most patients.

If a significant amount of gadolinium released from GBCAs is present as unchelated gadolinium, then it is available for uptake by metal transporters. Gadolinium is a potent, non-competitive inhibitor of calcium channels, a feature often attributed to the similar ionic radii of gadolinium³⁺ and Ca²⁺. However, because gadolinium is not a substrate of these channels, it is unlikely that they are relevant to gadolinium uptake into the brain.

Other metal transporters relevant to CNS uptake include a zinc transporter (ZnT10), transient potential melastatin-7 (TRPM7) and a divalent metal transporter (DMT1). To date, there seem to be no studies that have investigated the potential for these to transport gadolinium. Given the available evidence, it seems unlikely that metal transporters are responsible for the uptake of gadolinium into the brain, at least not as a substrate.

There has been an extensive body of work investigating the function of organic ion transporters and citrate salts of metals. When administered with a specific inhibitor for the monocarboxylic acid transporter (MCT1), Al-citrate uptake into the CNS is significantly reduced. Since GBCAs present structural moieties similar to Al-citrate, and the ionic agents (eg, gadopentetate) are essentially metallo-organic anions, the possibility of MCT1- or OATP-mediated uptake of intact complexes must be considered. Further, the binding affinities of citric acid for aluminium and gadolinium are similar.

Efficacy of chelation therapy

The use of chelation therapy to remove gadolinium from the body has been proposed. Since excess chelate is known to improve the stability of GBCA complexes in plasma, it is reasonable to expect that a simple chelator like DTPA or ester prodrugs of DTPA would be able to bind gadolinium remaining in the body.

There are however several limitations in assuming complete chelate formation upon introduction of a chelator:

1. the binding affinity of the chelator for gadolinium is reduced by the medium
2. sufficient chelator concentrations may not be achievable in all compartments where gadolinium deposits
3. it is unknown precisely how much chelator is necessary to safely and effectively remove all gadolinium from the body
4. other metals such as iron may be preferentially removed.

3.1.1.7 Toxicity [5, 6, 11]

It has been assumed that unchelated gadolinium is highly toxic, based on very high dose exposures. In reality, experience with millions of humans who have received linear GBCA agents, shows that the presence of gadolinium deposited in bones is largely asymptomatic. Histologic evidence of this inertness is at present based on limited experience in autopsy series in which the examination of brain specimens showed gadolinium in brain tissue, with no evidence of a histologic reaction.

However, subjects who report symptomatic disease may exhibit a relatively marked response in tissues, similar to what has been histologically shown in NSF.

Autopsy studies have not identified any gross histologic tissue changes comparing exposed and control brain tissues using hemotoxylin and eosin stains.

Individual case reports have described a variety of toxic occurrences from GBCAs (published reports are summarised in Annex 3).

- Gadolinium neurotoxicity was described in two case reports of presumed gadolinium induced encephalopathy, by Maramattom *et al.* and Hui *et al.*
- Miller *et al.* recently described the MRI changes occurring in the brain of a male patient who received 35 GBCA doses of a linear agent (gadopentetate) when he was between the ages of eight and 20 years. This individual was diagnosed at age five years with a rhabdomyosarcoma of the left orbit. His medical history is notable for several intercurrents. However at 21 years old, he had no intracranial lesion on MRI, visible treatment-related intracranial structural abnormality. Recent neuropsychological testing, suggested difficulties with executive functioning, visual memory and reasoning, reading comprehension, and math abilities.

The proposed mechanisms for gadolinium toxicity are summarized in Table 3.

Table 3: Summary of potential mechanisms of gadolinium toxicity

Mechanisms	Study type	Test subjects/cells	Reference
Release of chemokines and subsequent attraction of CD34 + fibrocytes leading to fibrosis	In vitro	Human macrophages	Idee et al. (2014) Del Galdo et al. (2010)
Stimulation of the expression and release of the cytokines involved in tissue fibrosis development	In vitro	Human monocytes	Newton and Jimenez (2009)
Induction of expression of a profibrotic chemokines and cytokines: IL-4, IL-6, IL-13, and VEGF in monocytes and type I and II collagen in fibroblasts	In vitro	Human monocytes Human fibroblasts	Wermuth and Jimenez (2014)
Inhibition of stretch-activated and voltage-gated calcium channels	In vitro	Rat and human cells Isolated rat atrium	Mlinar and Enyeart (1993) Laine et al. (1994)
Blockage of Ca ²⁺ -dependent enzymes such S-transferases, dehydrogenases, kinases, ATPase, and glutathione		Rat cortical neurons	Xia et al. (2011)
Disruption of Ca ²⁺ homeostasis			
Induction of fibronectin expression, apoptosis, and necrosis in fibroblasts	In vitro In vivo	Human foreskin fibroblasts Rats	Do et al. (2014)
Induction of fibrocyte markers (CD34 and procollagen type I)			
Mobilization of iron and the differentiation of peripheral blood mononuclear cells into ferroportin-expressing fibrocytic cells	In vivo	Mice	Bose et al. (2015)
Apoptosis	In vitro	Alveolar macrophages Rat cortical neurons Hepatocytes	Mizgerd et al. (1996) Xia et al. (2011) Liu et al. (2003)
Elevation of reactive oxygen species	In vitro	Rat cortical neurons Mitochondria	Xia et al. (2011) Liu et al. (2003)
Blockage of ATP and ADP hydrolysis via stimulation of angiotensin II AT1 receptors	In vitro	Rat aortic rings	Angeli et al. (2011)
Effects on ACE activity via transmetallation with zinc	In vitro In vivo	Rabbit lung ACE Rats	Corot et al. (1998)

Comments

The number of case reports of adverse occurrences other than NSF is very low considering the extensive use of these agents. In addition, the cases are generally confounded as multiple administrations of GBCA are generally associated with monitoring of a severe underlying condition.

3.1.1.8 'Gadolinium deposition disease' [5, 11]

Gadolinium deposition disease (GDD) is a newly recognized disease. For at least several years, various members of the larger health care community have recognized gadolinium toxicity in patients with normal renal function. Unfortunately for these sufferers, because they did not have renal failure, the medical establishment downplayed and misunderstood their symptoms. As the medical establishment dismissed them, sufferers often sought help from nonconventional healthcare practitioners.

GDD represents symptoms in patients with normal renal function who have received a GBCA agent (see also [3.1.4.14](#)). The main difference between gadolinium storage condition and GDD is that in gadolinium storage condition gadolinium is presumably inert in the tissues, while in GDD the presence of gadolinium generates considerable symptomatology. In order for GDD to occur, it is hypothesised that the host generates an immunologic response that is host-destructive. Therefore there are two components that the authors consider to be essential in GDD:

1. the presence of gadolinium in the body
2. the host response to its presence.

The recognition of both of these components will become essential, as appropriate therapy will most likely involve addressing both.

The principal symptoms reported by patients included:

- bone pain (peripheral but also central)
- skin and subcutaneous tissue burning pain (peripheral arm and leg [glove and sock] but also central)
- progressive thickening and discoloration of the skin and subcutaneous tissue of the distal arms and legs occurs
- disoriented mentation that is frequently described by sufferers, which can be disabling to the point that the person may be unable to continue their normal employment.

The great majority of these individuals are European-origin white, and many are female. This may represent a selection bias, as these are volunteers from online advocacy groups. These patients appear well educated, have access to information on the Internet, and have motivation and intellectual curiosity sufficient to look for a reason for their symptoms; and this stereotype may influence our current thinking on epidemiology. However, the authors' opinion is that it may represent a genetic susceptibility. As it appears to be a condition of difficulty with metal metabolism, the condition is reminiscent of another disease of metal handling, genetic hemochromatosis, which is a gene-based disease that occurs in white individuals of Celtic origin.

3.1.1.9 Ongoing questions [2]

Authors of these review articles consider that there are several pressing questions. Among others, these include the following questions.

- 1) What is the molecular form(s) or structure(s) of the residual or retained gadolinium within the various tissues in which it is found?
- 2) Precisely in what compartment or location is the gadolinium found? In other words, is it intracellular, or extracellular, or both?

3) How did gadolinium find its way to the other side of the intact blood brain barrier? In no studies to date has there been any damage identified to the brain parenchyma adjacent to the detected residual gadolinium, suggesting that the physically associated blood brain barrier in this region is still intact.

4) Is there any clinical significance to these observations of residual intracranial – or “intra-body” – gadolinium?

In a discussion on this issue Reeder *et al.* made the following points.

Unlike NSF, gadolinium deposition, although concerning, lacks paired evidence of adverse neurologic or biologic outcomes. Therefore, which, if any, practical recommendations are appropriate at this stage. Caution should be taken in concluding that gadolinium retention is “dependent on the class of contrast agent”, as additional work evaluating all agents is needed. Is it prudent to switch preferentially to a class of pharmaceutical agents, some of which are expensive, purely on the basis of imaging observations? This is fraught with potential for abuse from pharmaceutical companies and legal firms to seize on this controversy to their financial benefit.

In response, Kanal has noted that common sense demands that we decrease that concern by means of reasonable and readily implementable steps, such as prescribing agents that seem to accumulate less intracranially per administered dose. Withholding gadolinium or promoting macrocyclic agents is premature, but withholding gadolinium if it is not truly indicated will benefit everyone and prescribing agents that (all else being equal) accumulate less gadolinium in the body are practical, reasonable, common sense, and easily implementable recommendations until further information becomes available.

In response, Radbruch concurs that the entirety of the marketed GBCAs has to be assessed in order to conclude that a signal intensity increase in the deep nuclei is dependent on the class of contrast agent. The hypothesis that the differentiation in macrocyclic and linear GBCAs is most likely the crucial factor when looking at causes for a potential signal intensity increase in the deep nuclei, is not proven yet.

It is true that gadolinium deposition in the deep nuclei “lacks paired evidence of adverse neurologic or biologic outcomes”. However, it should also be mentioned that clinically relevant sequelae of gadolinium retention in the brain cannot be excluded and — given the fact that there is histologically proved accumulation in the brain, it is important to prove that there is no clinical damage rather than to prove that there is damage.

3.1.2 Systematic reviews

Two systematic reviews were identified and are discussed below.

3.1.2.1 Pharmacokinetics [12]

The aim of this meta-analysis was to ascertain the existence of a deep compartment for gadolinium storage in the body and to assess whether all the GBCAs present the same toxicokinetic profile. The authors applied a systematic literature search methodology, all clinical and preclinical studies reporting time-dependent plasma concentrations and renal excretion data of gadolinium from 1980 to 2015 were identified and analysed.

Since the individual data were not available, the analysis focused on the average values per groups of subjects or animals, which had received a given GBCA at a given dose. The rate constants of the distribution phase (α), rapid elimination phase (β), and residual excretion phase (γ) of gadolinium were determined in each group from the plasma concentration (C_p) time curve and the relative urinary excretion rate (rER) time curves, taking the 2-hour time point as a reference.

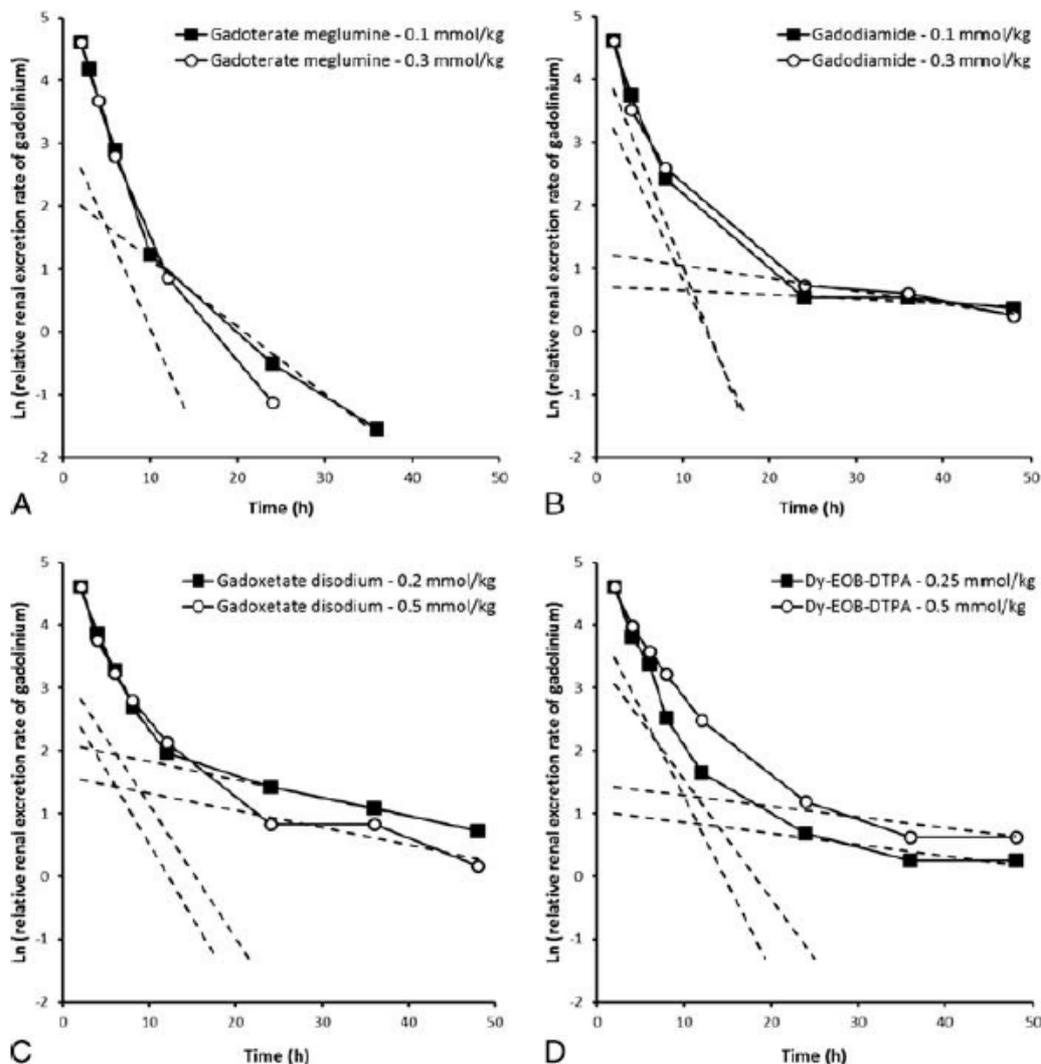


Figure 5: Linearized time curves of the relative urinary excretion rates (rER) of gadolinium after injection of gadoterate (A), gadodiamide (B), or gadoxetate (C), and of dysprosium after injection of Dy-EOB-DTPA (D) in healthy volunteers. The slow-slope one is the trend line of the second phase data points. The fast-slope one is the result of the subtraction between the Y-coordinates of the first phase data points and the Y-coordinates of the slow-slope construction line. In the group who received 0.3mmol/kg of gadoterate, the number of time points was not sufficient to assess the slope of the second phase.

Moreover, as bone may represent a reservoir for long-term gadolinium accumulation and slow release into the blood stream, the time curves of the relative concentration in the bone of ^{153}Gd -labeled GBCAs in mice or rats were analyzed taking day 1 concentrations as a reference. The ratio of gadolinium concentrations in the bone marrow as compared with the bone was also calculated.

The relative urinary excretion rate (rER) plots (Figure 5) revealed a prolonged residual excretion phase of gadolinium in healthy volunteers, consistent with the existence of a deep compartment of distribution for the GBCAs. The rate constant γ of gadoterate (0.107 hour^{-1}) is five times higher than that of the linear agents ($0.020 \pm 0.008 \text{ hour}^{-1}$), indicating a much faster blood clearance for the macrocyclic GBCA. Similar results were obtained in the preclinical studies. A strong correlation was shown between the γ values of the different products and their respective thermodynamic stability constants (K_{therm}). Greater clearance rates of ^{153}Gd from murine bone were also found after gadoterate or gadoteridol injection ($0.131\text{--}0.184, \text{ day}^{-1}$) than after administration of the linear agents ($0.004\text{--}0.067, \text{ day}^{-1}$). The concentrations of ^{153}Gd in the bone marrow from animals exposed to either gadoterate or gadodiamide are higher than those in the bone for at least 24 hours (Table 4).

Moreover, the ratio of concentrations (bone marrow/bone) at four hours is significantly lower with the former agent than the latter (1.9 vs 6.5, respectively).

Table 4: Bone Clearance Rate Constants (k) and Corresponding Half-Lives (T_{1/2}) of ¹⁵³Gd-Labeled GBCAs and ¹⁴C-Gadodiamide in Groups of Mice or Rats

Product Categories	Product Chemical Names	No. Groups	Rate Constants k, day ⁻¹	Half-Lives T _{1/2} , day
Linear ¹⁵³ Gd-GBCA	Gadodiamide	5	0.0044	158
	Gadopentetate dimeglumine	4	0.0156	44
	Gadoxetate disodium	1	0.0330	21
	Gadobenate dimeglumine	2	0.0673	10
Macrocytic ¹⁵³ Gd-GBCA	Gd-DO3A	1	0.0540	13
	Gadoterate meglumine	4	0.1306	5
	Gadoteridol	3	0.1838	4
Linear ¹⁴ C-GBCA	¹⁴ C-gadodiamide	1	0.2083	3

Data are presented as means of k and T_{1/2} values measured in each group. k is the slope of the time curve of the relative concentrations in the bone versus day 1 (rCB = CB_t/CB₁), or versus day 3 for gadoxetate disodium (rCB = CB_t/CB₃).

GBCA indicates gadolinium-based contrast agent.

This analysis showed that gadolinium distribution pharmacokinetics differ between cortical bone, trabecular bone, and bone marrow. Thus, as proposed for lead deposition in the bone, it is possible that different pools of gadolinium exist, which are more or less available for exchange with the blood compartment. The bone marrow might represent a labile pool, whereas the mineral bone would contain firmly bound gadolinium ions, which must await osteoclastic turnover to be released.

The present work bears some limitations. The analysis was performed on the average values from different groups of subjects or animals and not on the individual data, preventing the authors from applying statistical analyses. However, this approach showed the consistency of the data between the different studies despite the large variability in the design (species, number of individuals, injected doses and analytical techniques).

Another limitation is the lack of available data for some GBCAs. The sigma-minus method could not be applied to groups of healthy volunteers who had received gadoteridol, gadobutrol, gadopentetate, or gadobenate. Fortunately, some preclinical studies provided supportive data about ¹⁴C-gadoterate, ¹⁴C-gadopentetate, and ¹⁴C-gadobenate, which reinforce the demarcation between macrocyclic and linear GBCAs in terms of residual excretion. As for the deep compartment, information is lacking about the pharmacokinetic profiles of the GBCAs in human bone.

In conclusion using a nonconventional pharmacokinetic approach, it was shown that gadoterate undergoes a much faster residual excretion from the body than the linear GBCAs, a process that seems related to the thermodynamic stability of the different chelates.

3.1.2.2 Systematic review of gadolinium deposition in the brain [13]

The aim of this systematic review was to investigate the association between increased signal intensity in the DN and GP in the brain and repeated administrations of GBCAs.

Primary outcomes included the presence of increased signal intensity within the DN and GP on unenhanced T1-weighted MR images in patients following administrations of GBCAs.

25 publications satisfied the inclusion criteria (19 magnetic resonance images analyses, 3 case reports; 3 autopsy studies) (Table 5). The authors were unable to perform a meta-analysis, therefore no overall conclusions were possible. The authors provided a descriptive review of the papers.

The authors concluded that it seems that some researchers report incompatible findings due to unintended limitations in their studies.

Table 5: Publications included in the systematic review

Study	Study groups	Administrations of GBCA	Contrast agent	Remarks	
Original studies					
1	Adin et al. 2015 [42]	<ul style="list-style-type: none"> Control = 54 Increased SI = 103 	<ul style="list-style-type: none"> • 0 • 2–60; median 18 	Predominance of gadopentetate dimeglumine (Magnevist)	No significant difference in SI between Magnevist and non-Magnevist group
2	Cao et al I 2016 [37]	<ul style="list-style-type: none"> • On hemodialysis = 25 • Control on hemodialysis = 13 • Near-normal renal function = 25 • Control near normal renal function = 13 	<ul style="list-style-type: none"> • 1.8 ± 1 • 0 • 1.8 ± 1 • 0 	linear GBCA	The percentage of patients with increased SI in DN post-GBCA was significantly greater in relation to pre-GBCA only in the group on hemodialysis.
3	Cao et al II 2016 [10]	<ul style="list-style-type: none"> • Gadobutrol group = 25 • Gadopentetate dimeglumine = 25 	<ul style="list-style-type: none"> • 7.8 ± 2.4 (6–16) • 12.1 ± 5.2 (6–23) 	gadobutrol and gadopentetate dimeglumine	Significant increase in SI in gadopentetate dimeglumine group and insignificant in gadobutrol group.
4	Errante 2014 [30]	<ul style="list-style-type: none"> • MS group = 38 • Brain metastases group = 37 	<ul style="list-style-type: none"> • 2–14 • 2–21 	gadodiamide (Omniscan)	DNP were significantly higher between the first and the last scan in both study groups in patient with 6 or more examinations.
5	Flood 2016 [25]	<ul style="list-style-type: none"> • GBCA-naive control subjects = 57 • GBCA-exposed patients = 30 • Pre- and post-GBCA comparison = 16 	<ul style="list-style-type: none"> • 0 • 5.9 ± 2.7 • 5.8 ± 2.1 	gadopentetate dimeglumine (Magnevist)	SI in DN was significantly higher in the GBCA-exposed group than the GBCA-naive group.
6	Hu 2016 [19]	<ul style="list-style-type: none"> • Control group = 21 • GBCA group = 21 	<ul style="list-style-type: none"> • 0 • 5–37 	gadopentetate dimeglumine (Magnevist)	Significant increase in the ND-to- corpus callosum genu ratio and the GP-to- corpus callosum genu ratio between the first and most recent GBCA exam.
7	Kanda 2014 [2]	<ul style="list-style-type: none"> • contrast-enhanced MR subgroup = 19 • unenhanced MR subgroup = 16 	<ul style="list-style-type: none"> • 7.1 (6–12) • 0 	gadopentetate dimeglumine (Magnevist) gadodiamide (Omniscan)	DNP and GPT ratio was correlated with the number of previous contrast-enhanced MR scan.
8	Kanda 2015 [9]	<ul style="list-style-type: none"> • Magnevist group = 23 • ProHance group = 36 • Both agenst = 14 • Control = 54 	<ul style="list-style-type: none"> • median 2; max 11 • median 2; max 15 • median 2; max 5 • 0 	gadopentetate dimeglumine (Magnevist) gadoteridol (ProHance)	Only the DN-to-cerebellum ratio was significantly associated with linear GBCA.
9	Kromrey 2016 [18]	<ul style="list-style-type: none"> • Gadobutrol group = 271 • Control group = 116 	<ul style="list-style-type: none"> • 1 • 0 	gadobutrol	After 5-year follow-up, no significant differences in SI were observed between gadobutrol group and controls as well as between baseline and follow-up measurement.
10	Quattrocchi 2015 [14]	<ul style="list-style-type: none"> • group A = 10 • group B = 28 • group C = 8 	<ul style="list-style-type: none"> • 1 • 1–5 • >6 	gadodiamide	A significant increase of DNP was between the first and the last MRI in group C.
11	Radbruch I 2015 [12]	study group = 30	7.3 ± 3.1	gadobutrol	No SI increase in the DN and GP was found after serial applications gadobutrol.
12	Radbruch II 2015 [3]	<ul style="list-style-type: none"> • Magnevist group = 50 • Dotarem group = 50 	<ul style="list-style-type: none"> • 7.32 ± 1.83 • 7.06 ± 1.20 	gadopentetate dimeglumine (Magnevist), gadoterate meglumine (Dotarem)	In the linear GBCA group, the mean difference in SI of DNP between the last and first examinations was significantly larger than 0, while in the macrocyclic GBCA group was not significant.
13	Ramvalho I 2015 [17]	<ul style="list-style-type: none"> • Omniscan group = 23 • MultiHance group = 46 	<ul style="list-style-type: none"> • 5.0 ± 2.4 (3–11) • 4.6 ± 2.1 (3–11) 	gadodiamide (Omniscan) gadobenate dimeglumine (MultiHance)	GPT and DN-to- middle cerebellar peduncle ratio increased significantly over time with multiple administrations of a linear nonionic GBCA (gadodiamide) but did not increase with serial applications of a linear ionic GBCA (gadobenate dimeglumine).
14	Ramvalho II 2016 [21]	<ul style="list-style-type: none"> • gadobenate dimeglumine = 44 • previous gadodiamide and current gadobenate dimeglumine = 18 	<ul style="list-style-type: none"> • 4.5 ± 2.0 (3–11) • 5.9 ± 2.7 (3–11) • 5.5 ± 1.9 (3–10) 	gadodiamide (Omniscan) gadobenate dimeglumine (MultiHance)	Significant increase in DN-to- middle cerebellar peduncle ratio appeared after gadodiamide injections. It was insignificantly higher in the group receiving both GBCAs.

Study	Study groups	Administrations of GBCA	Contrast agent	Remarks
15 Ramalho II 2016 [44]	T1-weighted spin-echo and 3D MPRAGE = 18	4.78 ± 2.51 (2–10)	gadodiamide (Omniscan)	The differences in DN-to- middle cerebellar peduncle ratio between the 2 sequences for both baseline and last examination were statistically significant, but the change in ratio with time was not.
16 Stojanov 2015 [31]	relapsing-remitting MS group = 58	4.74±0.72 (4–6)	gadobutrol (Gadovist)	DNP, but not GPT, showed a significant correlation with the number of administered doses of GBCA.
17 Tanaka 2016 [45]	• MS group = 21 • neuromyelitis optica spectrum disorder group = 6	at least 10	linear	Number of GBCA doses correlated positively with signal intensity increase in 81% of MS patients and in 33.3% of NMOsd patients.
18 Tedeschi 2016 [15]	relapsing-remitting MS group = 74	6.0 ± 3.8 (1–15)	gadopentetate dimeglumine, gadobutrol	Previous gadolinium administrations correlate with DN T1 relaxometry and are linked to linear gadolinium chelates.
19 Weberling 2015 [11]	study group = 50	7.7 ± 3.2 (5/15)	gadobenate dimeglumine	The DNP and DN-to-cerebrospinal fluid ratio difference between the first and the last MRI was significantly larger than 0.
Case reports				
20 Barbieri 2016 [38]	3 cases patients with impaired renal function and vascular calcification; two of them had NSF.		Gadoteridol, Gadodiamide	Increased SI within DN and GP after exposure to relatively low doses of linear GBCAs
21 Roberts 2016 [24]	A patient with a clival chordoma.		gadopentetate dimeglumine (Magnevist)	Subtle hyperintensity within DN appeared after 4 doses of MRI contrast and after sixth dose hyperintensity was noted within both DN and GP bilaterally.
22 Miller 2015 [46]	A pediatric patient.	35	Linear GBCA	Progressive increases were the most evident in DN, DP, and the thalamus.
Autopsy examinations				
23 McDonald 2015 [20]	• GBCA group = 13 • Control group = 10	At least 4	gadodiamide	DN was associated with the greatest dose-dependent change in T1-weighted signal intensity, whereas the pons demonstrated the lowest overall absolute change in T1-weighted signal intensity with gadolinium. All patients exposed to multiple doses of a GBCA had elevated levels of elemental gadolinium in the four prescribed neuroanatomic regions.
24 Kanda 2015 [27]	• GBCA group = 5 • Non-GBCA group = 5	At least 2	• gadopentetate dimeglumine (Magnevist) • gadodiamide (Omniscan) • gadoteridol (ProHance)	Gadolinium was detected in all specimens in the GBCA group and in some specimens in the non-GBCA group; however, the gadolinium concentration was significantly higher in the GBCA group in each region.
25 Murata 2016 [28]	• gadoteridol group = 5 • gadobutrol group = 2 • gadobenate group = 1 • gadoxetate group = 1 • control group = 9		• gadoteridol (ProHance) • gadobutrol (Gadovist) • gadobenate (MultiHance) • gadoxetate (Eovist)	Gadolinium deposition in normal brain and bone tissue occurred with macrocyclic and linear GBCAs in patients with normal renal function.

Legend: SI, signal intensity; GBCA, gadolinium based contrast agent; DN, dentate nucleus; GB, globus pallidus; DNP, dentate nucleus-to-pons ratio; GPT, globus pallidus-to-thalamus ratio; MS, multiple sclerosis; NMOsd, neuromyelitis optica spectrum disorder group

3.1.3 Pre-clinical information

3.1.3.1 Frenzel *et al.* [14]

The aim of this study was to assess the complex stability and gadolinium dissociation rate of all marketed GBCAs in human serum at pH 7.4 and 37°C.

The kinetic profiles of gadolinium dissociation of GBCAs were determined by incubation for 15 days in human serum from healthy volunteers at a concentration of 1 mmol/L, pH 7.4, and 37°C. The initial rates of gadolinium release and the amounts of gadolinium released after 15 days were established by HPLC-ICP-MS analysis.

In an attempt to simulate the situation in patients with end-stage renal disease who often have elevated serum phosphate levels, the influence of 10 mmol/L phosphate on gadolinium dissociation was also investigated.

The GBCAs were grouped and ranked in the following order according to their stabilities in native human serum at pH 7.4 and 37°C [%gadolinium release after 15 days and initial rate (%/d) (95% confidence interval) in brackets].

Nonionic Linear GBCAs:

- Optimark [21 (19–22) %, 0.44 (0.40–0.51) %/d]
- Omniscan [20 (17–20) %, 0.16 (0.15– 0.17) %/d].

Ionic Linear GBCAs:

- Magnevist [1.9 (1.2–2.0) %, 0.16 (0.12–0.36) %/d],
- Multihance [1.9 (1.3–2.1) %, 0.18 (0.13– 0.38) %/d],
- Vasovist [1.8 (1.4–1.9) %, 0.12 (0.11– 0.18) %/d],
- Primovist [1.1 (0.76–1.2) %, 0.07 (0.05– 0.08) %/d].

Macrocyclic GBCAs: Gadovist, Prohance, and Dotarem (all [limit of quantification of 0.1%, <0.007%/d]).

In the presence of additional 10 mmol/L phosphate in serum, the initial gadolinium release rates of the nonionic linear GBCAs, Omniscan, and Optimark increased about 100-fold, and, after 15 days, the amount of gadolinium released from these agents was more than 75% higher than in native serum. The initial rates found for the ionic linear GBCAs increased about 12- to 30-fold, but, despite this, increase in the initial rate, the amount of gadolinium released after 15 days was comparable to that in native serum. The elevated phosphate level did not lead to any measurable release of gadolinium from the three macrocyclic GBCAs (Figure 7).

The dissociation of gadolinium from its ligand is an equilibrium process. It is defined by two distinct and independent parameters, kinetics and thermodynamic stability.

The kinetic inertia of a gadolinium complex is characterized by its dissociation rate, which expresses how fast the equilibrium is reached and thus how fast gadolinium is released from a gadolinium complex. To understand the importance of the dissociation rate for the stability of a gadolinium complex in a patient, it must be compared with its elimination rate from the body. If the kinetic inertia is high (ie, the dissociation rate is much slower than the elimination rate) release of gadolinium becomes negligible during the residence time of the gadolinium complex in the body, irrespective of its (in-)stability as expressed by the stability constant.

If kinetic inertia is low and thus dissociation is fast relative to the elimination, thermodynamic stability becomes the determining parameter. The complex stability constant, K_{therm} , describes the dissociation equilibrium of the deprotonated gadolinium complex. At physiological pH 7.4, partial protonation of the ligand competes with the complexation of gadolinium reducing the stability of the gadolinium complex. Complex stability is enhanced by the number of charged carboxylates in the coordination sphere of the gadolinium ion. Each negatively charged oxygen atom binds more strongly to gadolinium than an uncharged amide or alcoholic oxygen thereby achieving a greater thermodynamic stability. This is reflected by the stability constants, which are generally several orders of magnitude lower for nonionic than for ionic chelates from the same class.

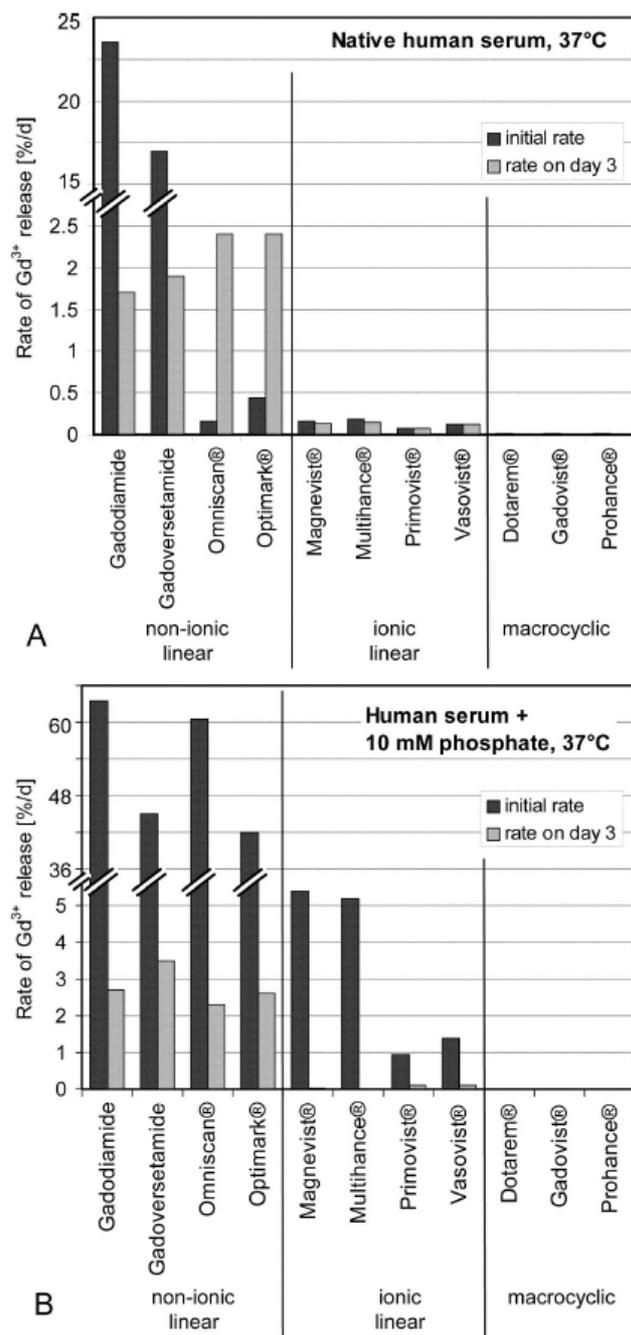


Figure 6: Comparison of the rates of Gd release for 1 mmol/L solutions of all GBCAs in native human serum from healthy volunteers at 37°C (A) and in the same serum with 10 mmol/L phosphate added (B). Dark bars show initial rates light bars show rates on day 3.

The conditional stability constants of the marketed GBCAs are in the range of 10^{15} to 10^{19} . This means that a solution containing 1 mmol GBCA/L contains about 3 nmol/L to 10 pmol/L of free gadolinium at equilibrium.

All three macrocyclic GBCAs appeared stable in human serum at 37°C for 15 days, both under physiological conditions and in the presence of elevated phosphate levels. The amounts of gadolinium released into the serum from all linear gadolinium complexes were several orders of magnitude greater than predicted by the conditional stability constants. After 15 days, the release of gadolinium from the non-ionic linear GBCAs was about 10 times higher than that from the ionic GBCAs. Excess ligand in the formulations of Optimark and Omniscan stabilized the non-ionic linear gadolinium complexes for a limited period of time, but after three days, the release of gadolinium

from these formulations was much faster than from the ionic linear GBCAs. The acceleration of gadolinium release in the presence of elevated serum phosphate levels was also much greater for the non-ionic than for the ionic linear GBCAs.

The study confirmed the hypothesis that under physiological conditions, all GBCAs can be divided into three distinct stability classes, the nonionic linear, ionic linear, and macrocyclic GBCAs (listed in order from lower to higher stability).

3.1.3.2 Robert *et al.* [15]

The aim of this study was to prospectively compare in healthy rats the effect of multiple injections of macrocyclic (gadoterate) and linear (gadodiamide) GBCAs on T1-weighted signal intensity in the deep cerebellar nuclei (DCN), including the DN.



Figure 7: Injection and MRI scheme. Four injections of 0.6 mmol of Gd per kilogram per week were performed for 5 weeks.

The study was conducted as described in Figure 8. Gadolinium concentrations were measured with inductively coupled plasma mass spectrometry in plasma and brain. Blinded qualitative and quantitative evaluations of the T1 signal intensity in DCN were performed, as well as a statistical analysis on quantitative data. Figure 9 shows the regions of interest.

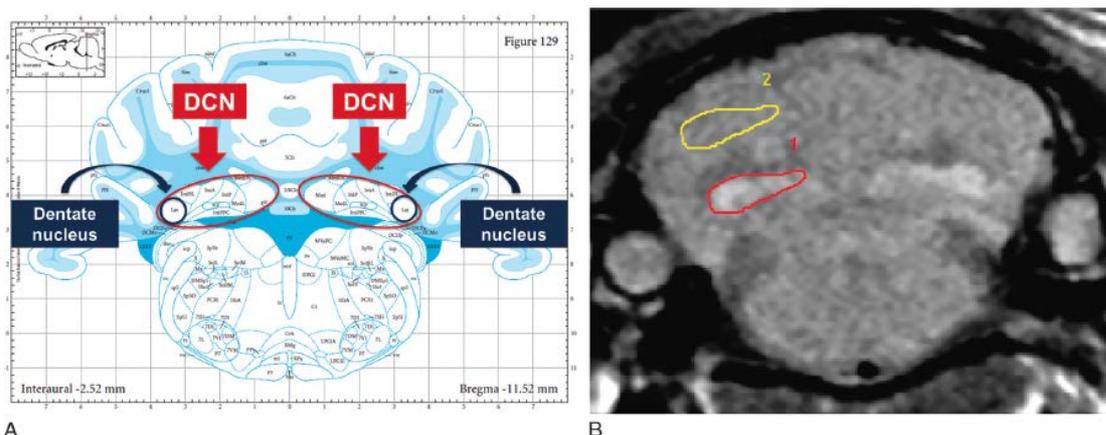


Figure 8: A, Anatomy of rat brain: localization of the deep cerebellar nuclei (DCN) and dentate nucleus. B, Regions of interest (ROI) positioning for quantitative analysis. Signal intensity ratio was calculated as the ratio of DCN signal to adjacent cerebellum signal (ROI-1/ROI-2).

A significant and persistent T1 signal hyperintensity in DCN was observed only in gadodiamide-treated rats.

The DCN-to-cerebellar cortex signal ratio was significantly increased from the 12th injection of gadodiamide (1.070 ± 0.024) compared to the gadoterate group (1.000 ± 0.033 ; $P < 0.001$) and control group (1.019 ± 0.022 ; $P < 0.001$) and did not significantly decrease during the treatment free period.

Total gadolinium concentrations in the gadodiamide group were significantly higher in the cerebellum (3.66 ± 0.91 nmol/g) compared with the gadoterate (0.26 ± 0.12 nmol/g; $P < 0.05$) and control (0.06 ± 0.10 nmol/g; $P < 0.05$) groups (Figure 10).

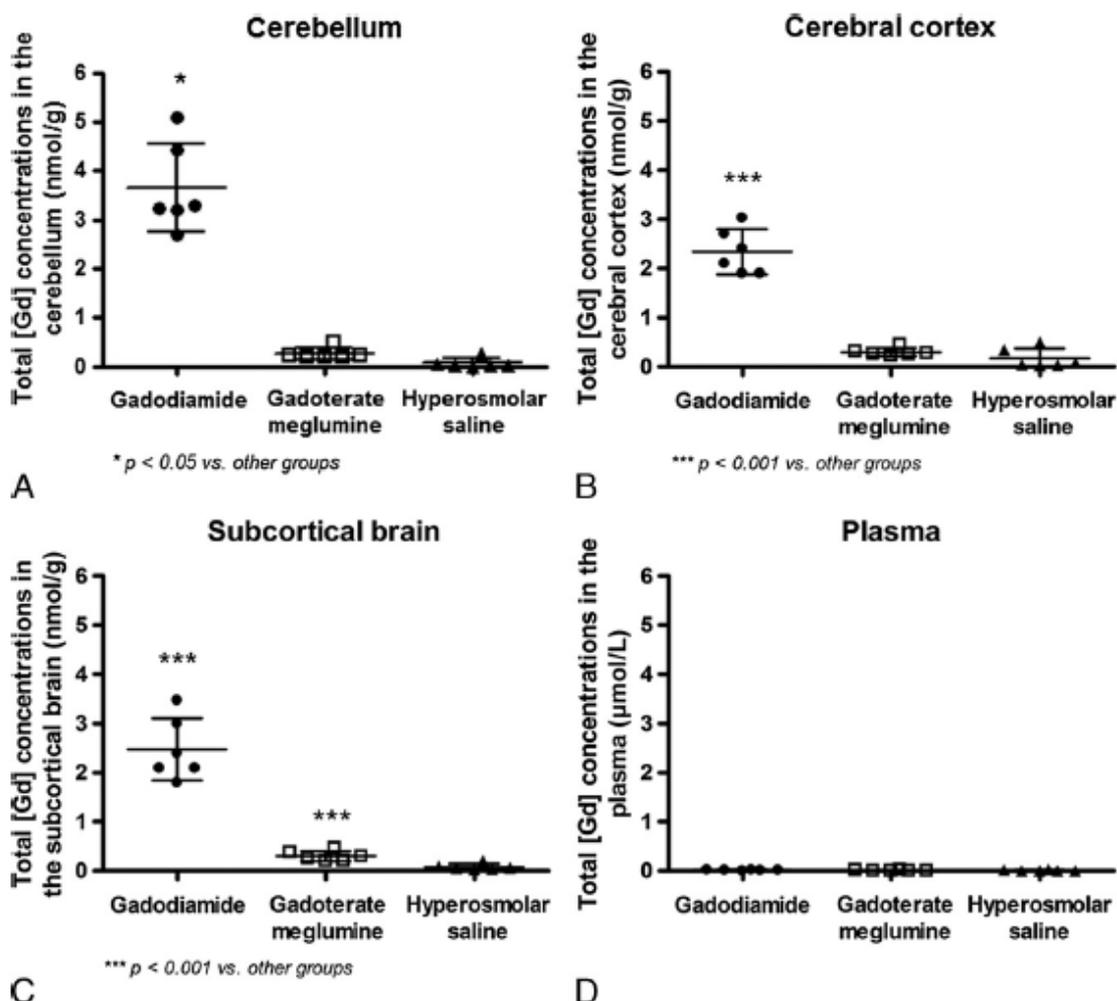


Figure 9: Total gadolinium concentrations in the cerebellum (A), cerebral cortex (B), subcortical brain (C), and plasma (D) at completion of the treatment-free period (week 10). Individual values, mean, and SD are given.

The authors note that the present study in healthy rats demonstrates, for the first time, a progressive and persistent brain T1w signal hyperintensity in the DCN, including DN, after repeated administrations of the linear GBCA gadodiamide.

Interestingly, this effect was qualitatively observed in this animal model from the eighth injection of gadodiamide, which is close to the threshold of six injections reported in humans to observe signal hyperintensity in the DN. Quantitatively, compared to gadoterate, this signal hyperintensity in DCN was significantly increased from the 12th injection of gadodiamide.

Signal hyperintensity in the DCN did not resolve during the 5-week treatment-free period, suggesting no washout effect and the persistence of this phenomenon after the last administration of gadodiamide. No signal hyperintensity was observed in the DCN with the macrocyclic gadoterate.

The authors concluded that repeated administrations of the linear GBCA gadodiamide to healthy rats was associated with progressive and persistent T1 signal hyperintensity in the DCN, with gadolinium deposition in the cerebellum in contrast with the macrocyclic GBCA gadoterate for which no effect was observed.

Comments

This study was partly performed to test whether the rat was a useful model for the observed effects in humans. The results showed that the model replicated effects seen in humans.

3.1.3.3 Robert *et al.* [16]

The aim of this study was to evaluate gadolinium retention in the DCN of linear GBCAs compared with a macrocyclic contrast agent.

The brain tissue retention of gadolinium of three linear GBCAs (gadobenate, gadopentetate, and gadodiamide) and a macrocyclic GBCA (gadoterate) was compared in healthy rats that received 20 intravenous injections of 0.6 mmol Gd/kg. An additional control group with saline was included. T1-weighted magnetic resonance imaging was performed as per the schema shown in Figure 11.

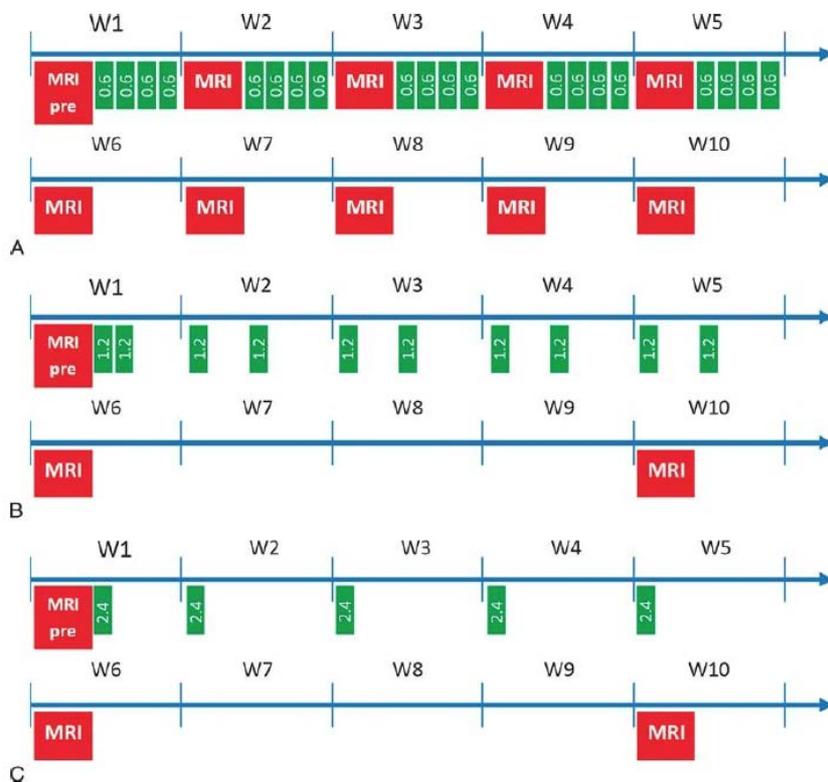


Figure 10: Injection and MRI schemes. A, Comparative study with 5 groups of n = 8 rats and 4 injections of 0.6mmol of Gd per kilogram per week over a period of 5 weeks. B and C, Simplified injection protocols (n = 4 gadodiamide-treated rats/group): 2 injections of 1.2mmol of Gd per kilogram per week for 5 weeks (B) and 1 injection of 2.4 mmol of Gd per kilogram per week for 5 weeks (C).

Total gadolinium concentration was measured with inductively coupled plasma mass spectrometry. Blinded qualitative and quantitative evaluations of the T1 signal intensity in DCN were performed, as well as a statistical analysis on quantitative data.

At completion of the injection period, all the linear contrast agents (gadobenate, gadopentetate, and gadodiamide) induced a significant increase in signal intensity in DCN, unlike the macrocyclic GBCA (gadoterate) or saline (Figure 12).

Total gadolinium concentrations for the three linear GBCAs groups at week 10 were significantly higher in the cerebellum (1.21 ± 0.48 , 1.67 ± 0.17 , and 3.75 ± 0.18 nmol/g for gadobenate, gadopentetate, and gadodiamide, respectively) than with the gadoterate (0.27 ± 0.16 nmol/g, $P < 0.05$) and saline (0.09 ± 0.12 nmol/g, $P < 0.05$). No significant difference was observed between the macrocyclic agent and saline.

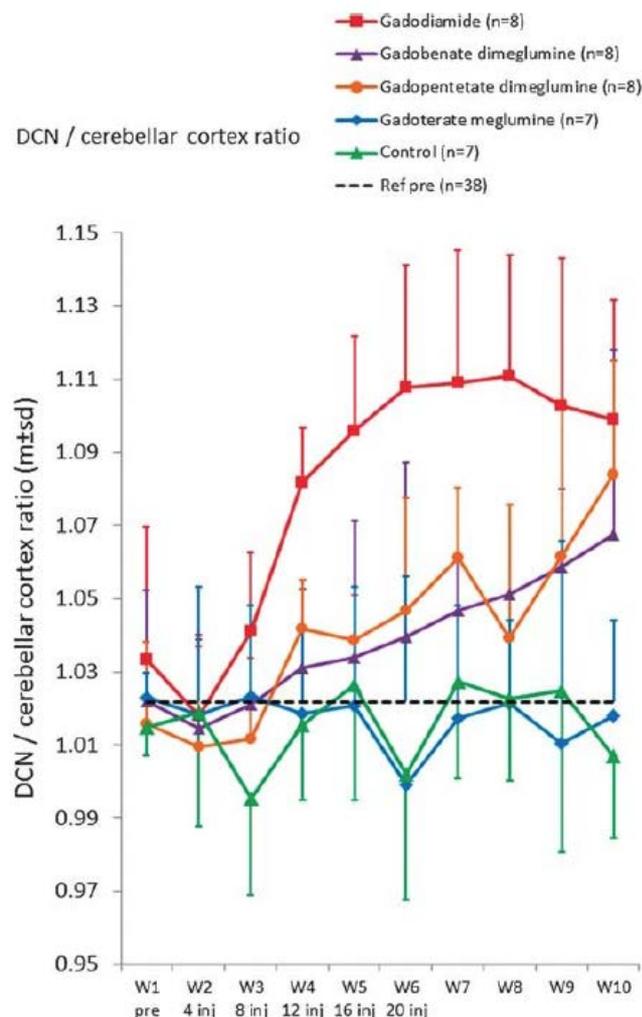


Figure 11: Quantitative analysis. Temporal changes in DCN/cerebellar cortex T1-weighted signal ratio (mean ± SD). The dashed line corresponds to the mean ratio pre-injection for all rats (n = 38).

The total gadolinium concentration in the cerebellum was 4 to 14 times higher after linear chelate injections compared with gadoterate, and 13 to 42 times higher compared with the control group (Figure. 13).

In the cerebellum, the concentration of Gd from highest to lowest were:

- Gadodiamide- 3.75 ± 0.18 nmol/g
- Gadopentetate- 1.67 ± 0.17 nmol/g
- Gadobenate- 1.21 ± 0.48 nmol/g
- Gadoterate- 0.27 ± 0.16 nmol/g
- Saline- 0.09 ± 0.12 nmol/g.

The cerebellar total Gd concentration of all linear contrast agents was significantly greater than that measured in the gadoterate and saline groups. No significant difference was observed between the macrocyclic agent and saline.

Total plasma concentrations were very low and inferior to the limit of quantification for all GBCAs except for gadodiamide with a concentration of 0.04 ± 0.02 nmol/mL. Only the total plasma concentration of Gd after gadodiamide was significantly different from saline (P<0.05).

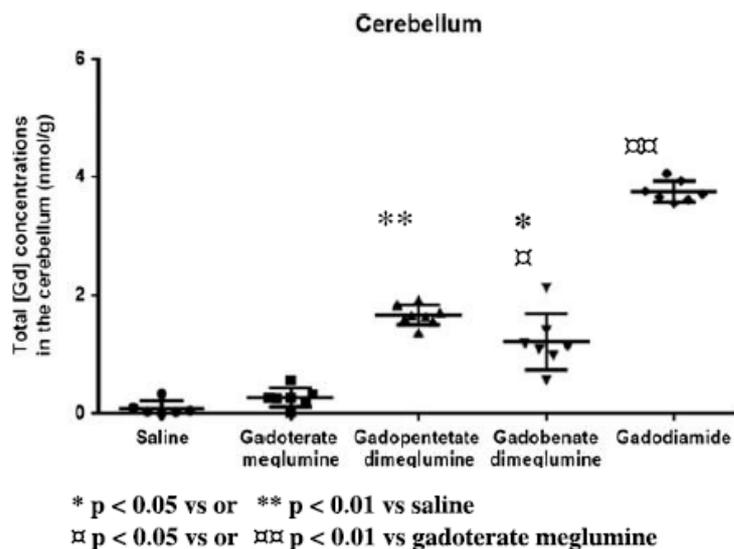


Figure 12: Total gadolinium concentration in nanomole gadolinium per gram of tissue for cerebellum

The T1 signal intensity measured after administration of gadobenate and gadopentetate progressively increased during the 10 weeks of follow-up, not only during the injection period (W1–W5) but also during the five subsequent treatment-free weeks (W6–W10). Two hypotheses might explain this prolonged increase of T1 contrast. The first hypothesis could be that the increase in signal intensity is due to a progressive change of the gadolinium form, from a low-relaxivity (eg, gadolinium under a chelated form) to a high-relaxivity molecule (eg, dissociated gadolinium bound to a macromolecule). A second hypothesis is that some organs, such as bones, can be a reservoir for gadolinium and may slowly release enough metal back into extracellular space to gradually reach the brain.

No obvious behavioural abnormalities were detected in rats, regardless of the GBCA administered. It is likely that if gadolinium accumulation in the DCN has toxicological or functional consequences, these will be subtle and may occur at a later time point. Lesions of DN (including from iatrogenic origin) are typically associated with ataxia, which needs highly sensitive nonclinical models to be detected. They may also lead to dysarthria, which, of course, cannot be explored in this experimental model. Dedicated experimental models are therefore needed for in-depth analysis of the potential deleterious consequences of gadolinium accumulation in the DN.

The authors concluded that repeated administrations of the linear GBCAs gadodiamide, gadobenate, and gadopentetate to healthy rats were associated with progressive and significant T1 signal hyperintensity in the DCN, along with gadolinium deposition in the cerebellum. This is in contrast with the macrocyclic GBCA gadoterate for which no effect was observed.

Comments

This study confirmed the difference in potential for GD brain deposition between linear and macrocyclic agents in a rat model. The form of gadolinium found in the brain was not determined. No gadolinium was found after administration of the macrocyclic GBCA five weeks after the last administration.

3.1.3.4 Jost *et al.* [17]

The authors evaluated T1-weighted signal intensity in the DCN and globus pallidus (GP) up to 24 days after repeated administration of linear and macrocyclic GBCAs in rats. In a second part of the study, CSF spaces were evaluated for contrast enhancement by fluid-attenuated MRI.

Sixty adult male Wistar-Han rats were randomly divided into a control and five GBCA groups ($n = 10$ per group) (Figure 14). The administered GBCAs were gadodiamide, gadopentetate, and gadobenate

(linear GBCAs) as well as gadobutrol and gadoterate (macrocylic GBCAs) and saline (control). The ratios of signal intensities in deep CN to pons (CN/Po) and GP to thalamus (GP/Th) were determined.

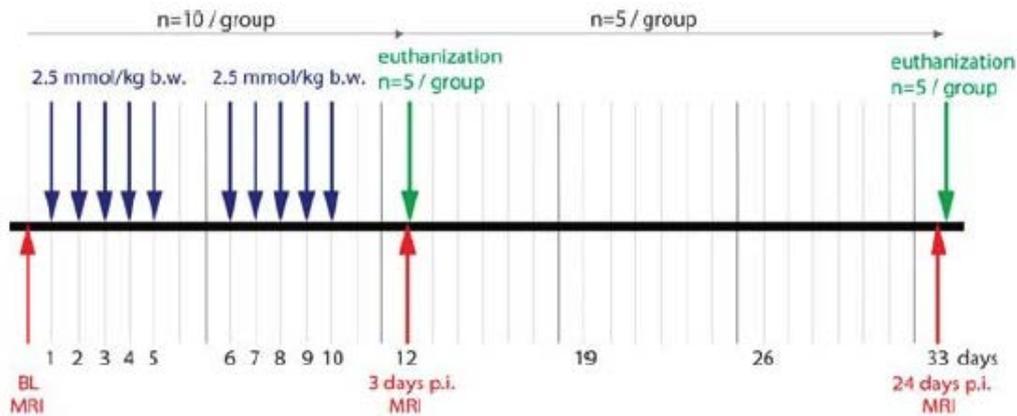


Figure 13: Study setup and application scheme for GBCAs.

For the evaluation of the CSF spaces, 18 additional rats were randomly divided into six groups (n = 3 per group) that received the same GBCAs as in the first part of the study. After MR cisternography for anatomical reference, a fluid-attenuated inversion recovery sequence was performed before and one minute after intravenous injection of a dose of 1 mmol Gd/kg body weight GBCA or saline.

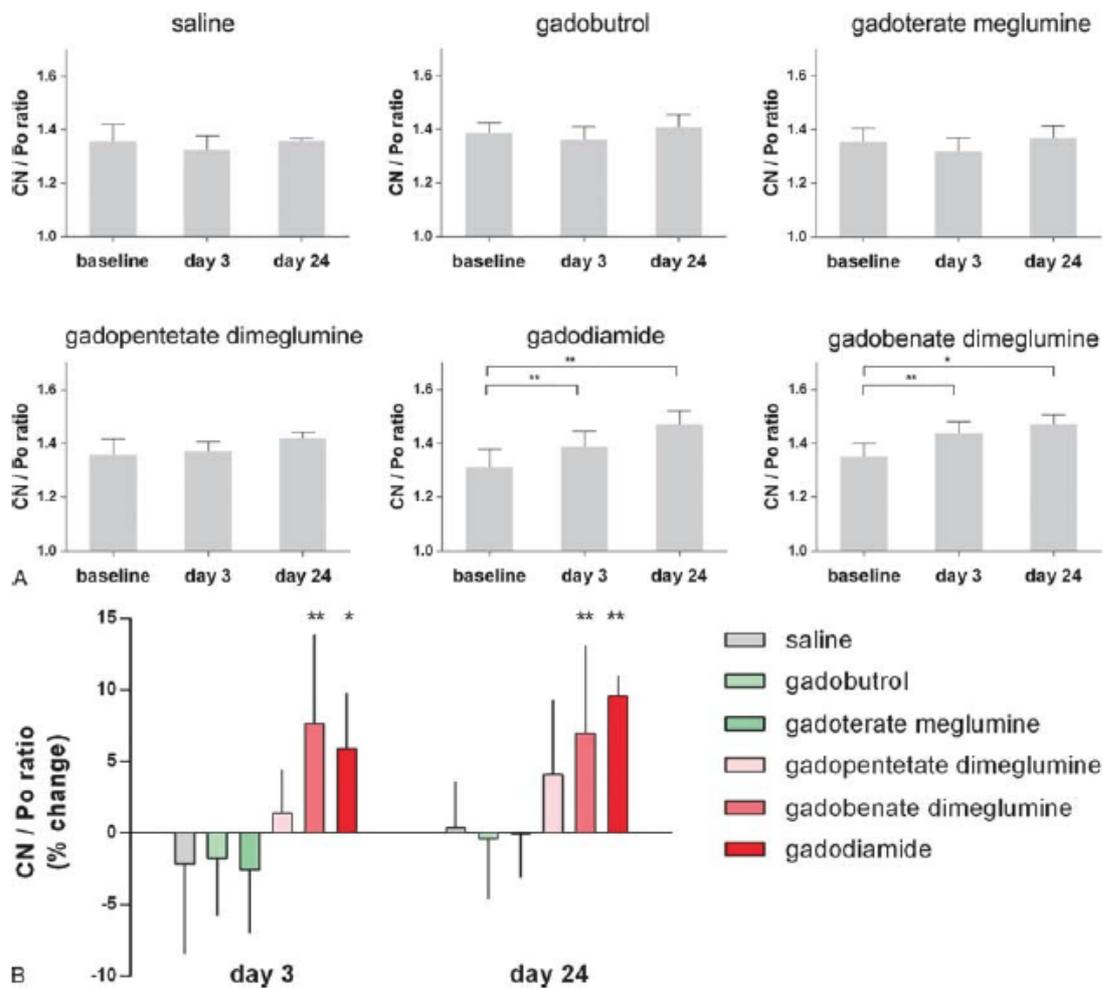


Figure 14: Change over time for signal intensity ratios between deep CN and pons (CN/Po) compared with baseline after injection of saline and GBCA

A significantly increased signal intensity ratio of CN/Po was observed three and 24 days after the last injection of gadodiamide and gadobenate (Figure 15). No significant changes were observed between the two time points. Gadopentetate injection led to a moderately elevated but statistically not significant CN/Po signal intensity ratio. No increased CN/Po signal intensity ratios were determined in the MRI scans of rats that received macrocyclic GBCAs gadobutrol and gadoterate or saline. The ratio of signal intensity in GP/Th was not elevated in any group injected with GBCAs or saline. Enhanced signal intensities of CSF spaces were observed in the post contrast fluid-attenuated inversion recovery images of all animals receiving GBCAs but not for saline (Figure 16).

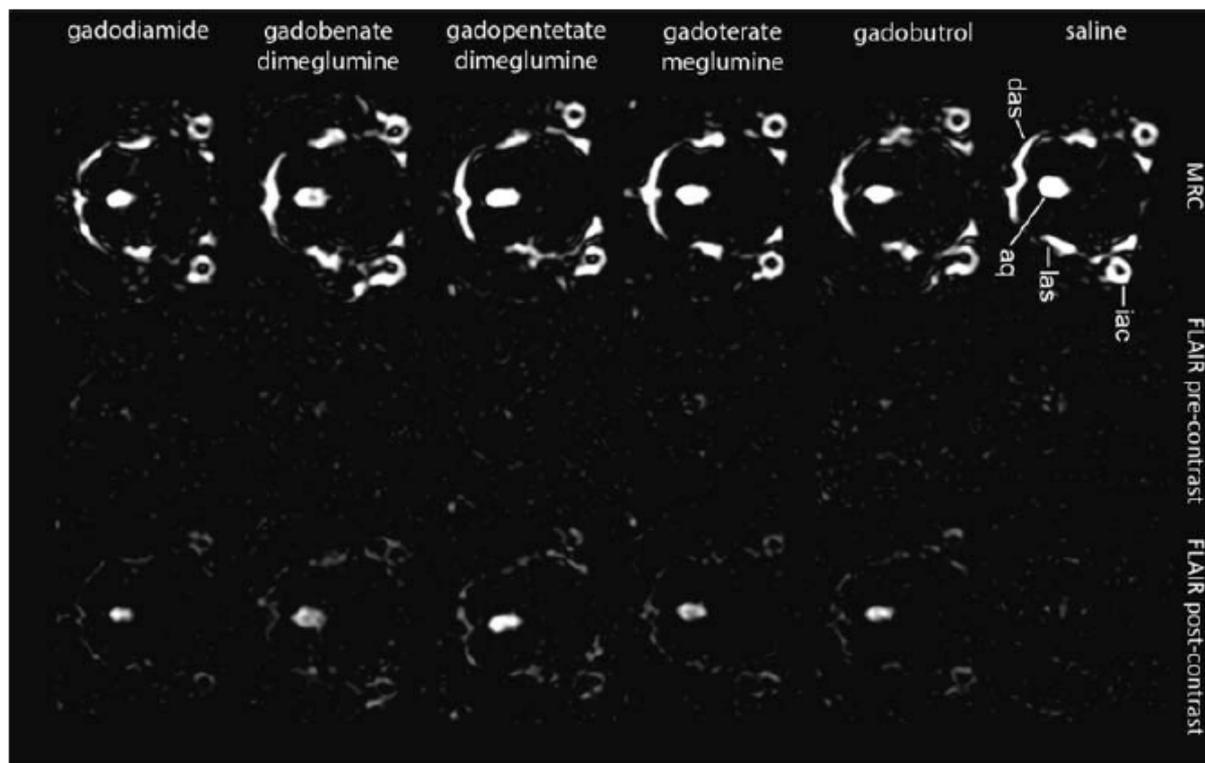


Figure 15: Representative transversally acquired MRCs (left column) of the rat brains at a level showing the dorsal (das) and lateral arachnoid space (las) as well as the aqueduct (aq) and inner auditory canal (iac). The middle column illustrates the respective slices acquired with FLAIR before GBCA administration. The right column represents FLAIR images acquired 1 minute p.i. of saline, gadobutrol, gadoterate, gadopentetate, gadobenate, and gadodiamide

In this animal study in rats, increased signal intensity in the CN was found up to 24 days after multiple, extended doses of linear GBCAs. However, in contrast to clinical reports, the signal enhancement in the GP was not reproduced, demonstrating the limitations of this animal experiment. The elevated signal intensities remained persistent over the entire observation period. In contrast, no changes of signal intensities in either the CN or the GP were observed for macrocyclic GBCAs.

All GBCAs investigated were able to pass the blood-CSF barrier in rats to a certain, not yet quantified extent.

Comments

This study shows that all GBCAs enter the brain, but a persistent change in signal intensity on MRI was only seen with two GBCAs (both linear).

3.1.3.5 Jost *et al.* [18]

The aim of this study was to evaluate the infiltration and distribution of GBCA in the CSF as a potential initial pathway of GBCA entry into the brain of rats.

The study was performed in two parts: First, an MRI-based evaluation of GBCA infiltration and distribution within the CSF up to four hours after the administration, and second, the quantification of CSF, blood, cerebellum and pons gadolinium concentration 24 hours post injection.

Ninety-six rats were randomly divided into a control and seven GBCA groups ($n = 12$ each), and an additional six rats were used to monitor quantitative changes of signal intensity after a necessary service of the MRI system. For the two study parts, each group was divided into two subgroups ($n = 6$ each). The first subgroup underwent MR cisternography (MRC) and FLAIR MRI up to four hours after GBCA administration. Subsequently, a CSF and blood sample was obtained for ICP-MS-based gadolinium quantification. Animals from the second subgroup underwent CSF and blood sampling 24 hours after GBCA injection and samples from the cerebellum and pons were also taken.

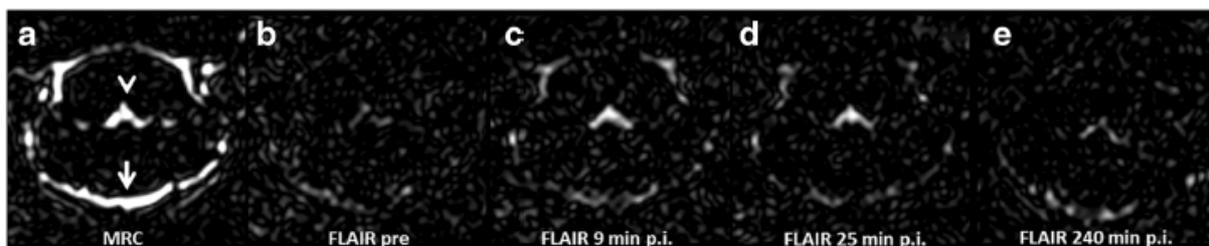


Figure 16: Representative images. The CSF spaces were visualised by MR cisternography (MRC), for example the fourth ventricle (arrowhead) and the subarachnoid space (arrow) (a). In the fluid-attenuated (FLAIR) images before GBCA injection the respective CSF signal is almost completely attenuated (b). After GBCA administration a clear signal enhancement of the CSF spaces was found in the FLAIR images up to 240 min post injection (p.i.) (c–e)

Signal enhancement of the CSF spaces was observed in all FLAIR images after GBCA administration. Figure 17 shows representative images of the brain at the level of the fourth ventricle. The cavity fluid spaces are visualized by MRC to determine the anatomical location and are almost completely attenuated in the baseline FLAIR scan (Fig. 17b). A clearly visible signal enhancement indicating the presence of GBCA in the fluid spaces was demonstrated by FLAIR imaging after 9 min, 25 min and 240 min post injection (Fig. 17c–e). The FLAIR imaging throughout the brain depicted GBCA-induced signal enhancement in all ventricles and the subarachnoid space.

CSF signal enhancement was detected for all GBCAs at comparable levels. A rapid signal enhancement was found immediately after administration in the inner CSF cavities (third and fourth ventricle, aqueduct), which was followed by successively declining CSF signals. After 240 min the signal intensity reached almost baseline level. By comparison, the CSF signal in the subarachnoid space (spinal cord, lateral and cerebral location) increased at a slower rate with a peak at 25 min post injection. Subsequently, decreasing signal intensities were observed until 240 min post injection, declining more rapidly and rigorously at the level of the spinal cord than on the lateral and cerebral level.

Analytical determinations of the gadolinium concentrations in the CSF and blood were conducted 4.5 and 24 hours post GBCA injection by ICP-MS (Figure 18). At 4.5 h, the CSF gadolinium concentrations for the marketed GBCAs were in the range of 18.8 ± 7.7 nmol/ml (gadobutrol) to 27.4 ± 12.7 nmol/ml (gadoterate).

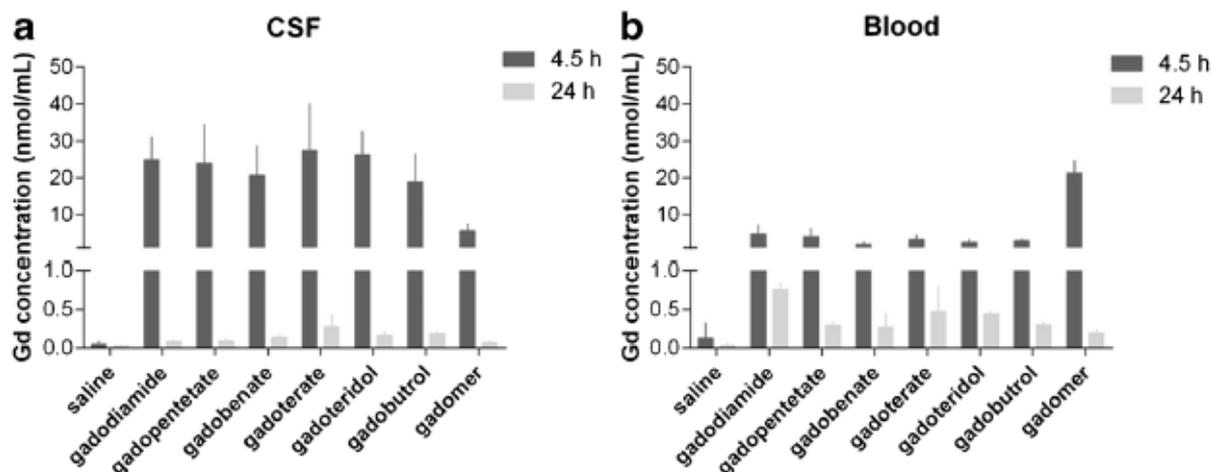


Figure 17: Gadolinium (Gd) concentrations in CSF and blood. The gadolinium concentration determined in the CSF (a) and blood (b) samples obtained at 4.5 h and 24 h, respectively

The gadolinium concentrations measured in the cerebellum and pons obtained 24 h post injection were higher than those in the CSF and blood. In the cerebellum, the concentrations for the marketed GBCAs were in the range of 0.63 ± 0.05 nmol/g (gadoteridol) to 1.06 ± 0.05 nmol/g (gadodiamide). In the pons, slightly lower gadolinium concentrations were detected (Figure 19).

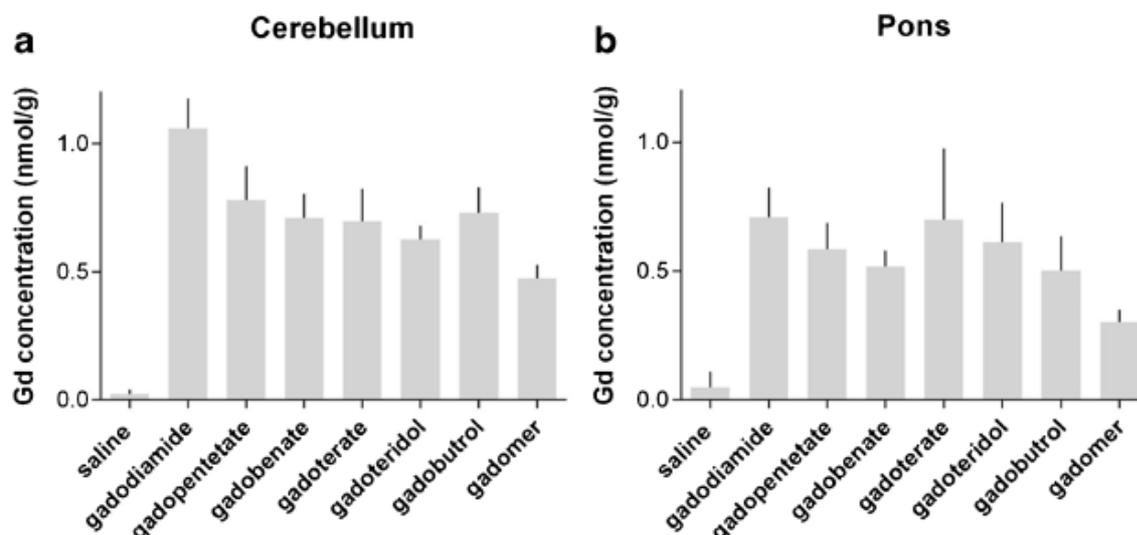


Figure 18: Gadolinium (Gd) concentrations in the cerebellum and pons. The gadolinium concentration per gram tissue determined in the cerebellum (a) and pons (b) 24 h after administration

The kinetics of signal enhancement differs between the inner CSF cavities (ventricles and aqueduct) and subarachnoid space. The faster signal increase in the inner cavities demonstrates that the primary location of GBCA infiltration is most likely the choroid plexus located in the ventricles. The fenestrated capillaries of the choroid plexus are relatively permeable to smaller substances, such as GBCAs, which can pass into the choroid plexus interstitium.

The choroid plexus continuously secretes CSF, and the choroid plexus epithelium forms the blood-CSF barrier. Importantly, the blood-CSF barrier is known to be physiologically more leaky than the BBB.

This study demonstrated that all marketed GBCAs cross the blood-CSF barrier in rats to an almost identical extent. However, the ability to cross this barrier seems to depend on the molecular size as demonstrated by the considerably lower CSF gadolinium concentration for the experimental gadomer which is significantly larger (17 kDa) than the marketed GBCAs (<1 kDa). In contrast to the

analytical gadolinium quantification, the reduction was not observed with FLAIR MRI as the r_1 relaxivity of gadomer is about a factor of five higher than that of the other GBCAs. After penetrating the blood-CSF barrier, further GBCA distribution within the CSF is driven by diffusion, convection and CSF flow that are directed through the ventricles to the subarachnoid space of the cortex and spinal cord. The delayed MRI signal increase observed in the subarachnoid space represents this distribution process.

For the marketed GBCAs, the averaged CSF gadolinium concentrations are about a factor of 7.4 higher than the respective blood concentrations at 4.5 h post injection. However, after 24 h GBCAs are almost completely cleared from the CSF, and the respective gadolinium concentrations are much lower than those in the blood. This is in contrast to gadolinium concentrations in the cerebellum and pons that are higher than those in the CSF and blood at 24 h post injection (Figure 19). This demonstrates that all GBCAs can be found in the brains of rats 24 h after the administration.

Slight quantitative differences between the agents seem to exist. In the cerebellum of animals administered gadodiamide, the gadolinium concentration was higher than that of the other GBCAs. The finding of this study (ie, the fact that all GBCAs independently of their chemical structure initially reach the cerebellum and pons) leads to the hypothesis that the GBCA complex stability plays a role during further elimination from this brain structures.

Although it was demonstrated that the infiltration and distribution of GBCAs into the CSF occurs, the further GBCA distribution into the brain parenchyma is not conclusive. Assuming that the GBCA in the CSF represents the source of the gadolinium found in the cerebellum and pons, different pathways of distribution might exist.

In summary, this study shows that GBCAs can penetrate from blood into the CSF independent of their chemical structure or physicochemical properties. Only the molecular size seems to be an important parameter as demonstrated by a lower CSF gadolinium concentration after administration of the macromolecular agent gadomer. Dynamic FLAIR MRI demonstrates a kinetic from the inner CSF spaces to the subarachnoid space and suggests a passive distribution and washout driven by convection and CSF flow. Twenty-four hours after injection, GBCA clearance from the CSF was almost complete, whereas slightly higher gadolinium concentrations were found in the cerebellum and pons, suggesting delayed excretion from these structures. To date, the mechanism of final distribution from the CSF into the brain and specifically to the DN and the GP could not be evaluated in this experiment and needs further study.

Comments

This study again shows that all GBCAs pass into the brain via the CSF in rats. The timing of the locations identified on MRC was suggestive of an origin in the choroid plexus. There appeared to be an accumulation of GBCA in the cerebellum and pons following the initial distribution.

3.1.3.6 Rasschaert et al. [19]

The purpose of this preclinical study was to investigate whether moderate chronic kidney disease is a factor in potentiating gadolinium uptake in the brain. The study was performed on renally impaired (subtotal nephrectomy) rats versus rats with normal renal function.

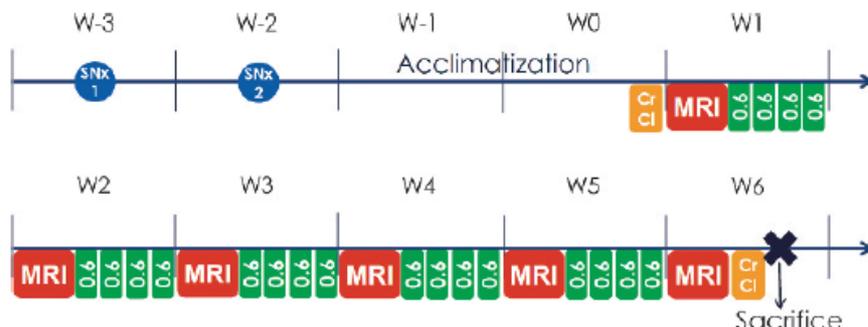


Figure 19: Protocol scheme of the study. SNx, subtotal nephrectomy of the 5/6 or sham operation; SNx 1 indicates first part of the surgery; SNx 2, second part of the surgery. MRI was performed before the first injection, and then once a week (W). Twenty injections of gadodiamide, 0.6 mmol Gd/kg/injection, were distributed over 5 weeks, leading to a cumulative dose of 12 mmol Gd/kg. Sacrifice was performed 6 days after the last injection

The animals received four daily injections of 0.6 mmol gadolinium/kg a week for five weeks (cumulative dose of 12 mmol Gd/kg) of gadodiamide or saline solution as per the schedule in Figure 20. The MR signal enhancement in the DCN was monitored by weekly magnetic resonance imaging examinations. One week after the final injection, the total gadolinium concentration was determined by inductively coupled plasma mass spectrometry in different regions of the brain including the cerebellum, plasma, cerebrospinal fluid, parietal bone, and femur.

Endogenous creatinine clearance (CrCl) was calculated at the beginning (ie, three days before the first administration) and end of the study (ie, five days after the last injection) (Figure 21).

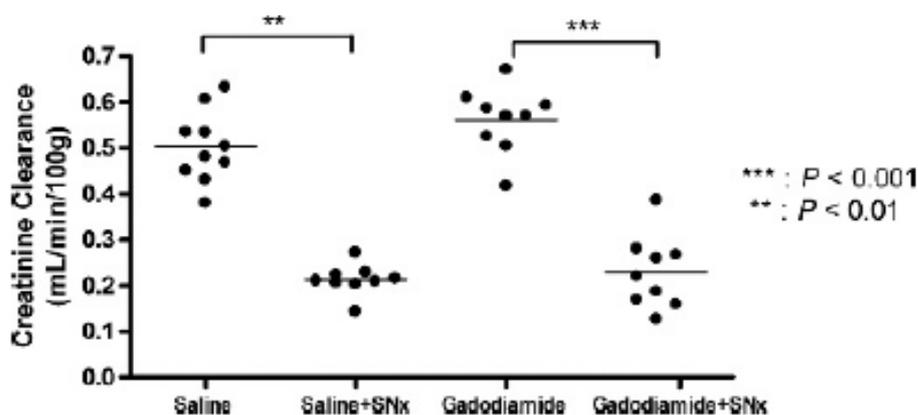


Figure 20 Individual CrCl values for the four different groups

Total gadolinium concentrations in the cortical brain, subcortical brain, cerebellar parenchyma, DCN, brain stem, CSF, plasma, femur, and parietal bone were determined by ICP-MS (inductively coupled plasma mass spectrometry). The lower limit of quantification (LLOQ) of gadolinium was 0.02 nmol/mL in plasma and CSF, 0.02 nmol/g in brain matrix, and 0.10 nmol/g in bone matrix.

After the administration of gadodiamide, the subtotal nephrectomy group presented a significantly higher T1 signal enhancement in the deep cerebellar nuclei (Figures 22 and 23) and a major increase in the total gadolinium concentration in all the studied structures, compared with the normal renal function group receiving the same linear GBCA (gadodiamide).

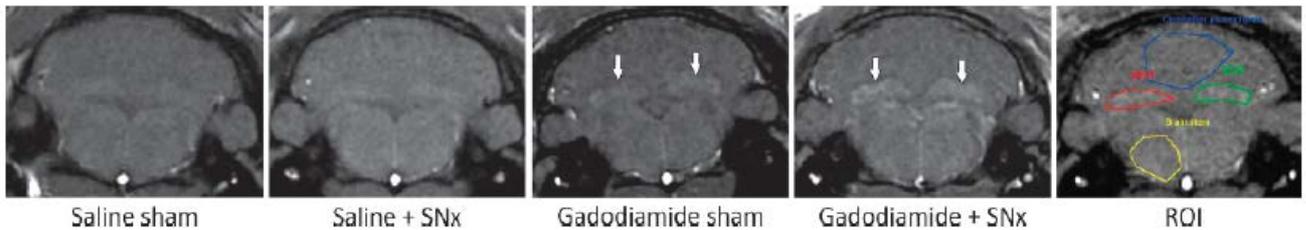


Figure 21: Typical T1wMR images obtained at week 6 (1 rat per group). DCN T1 hypersignal was observed in the two gadodiamide groups (white arrows). ROI refer to DCN (green and red), cerebellar parenchyma (blue), and brain stem (yellow)

Those potentiated animals also showed a pronounced hypersignal in the choroid plexus, still persistent six days after the last injection, whereas low concentration of gadolinium was found in the cerebrospinal fluid (<0.05 µmol/L) at this time point. Plasma gadolinium concentration was then around 1 µmol/L. Plasma gadolinium was predominantly in a dissociated and soluble form (around 90% of total gadolinium). Total gadolinium concentrations in the brain, cerebellum, plasma, and bones correlated with creatinine clearance in both the gadodiamide-treated groups (Figure 24).

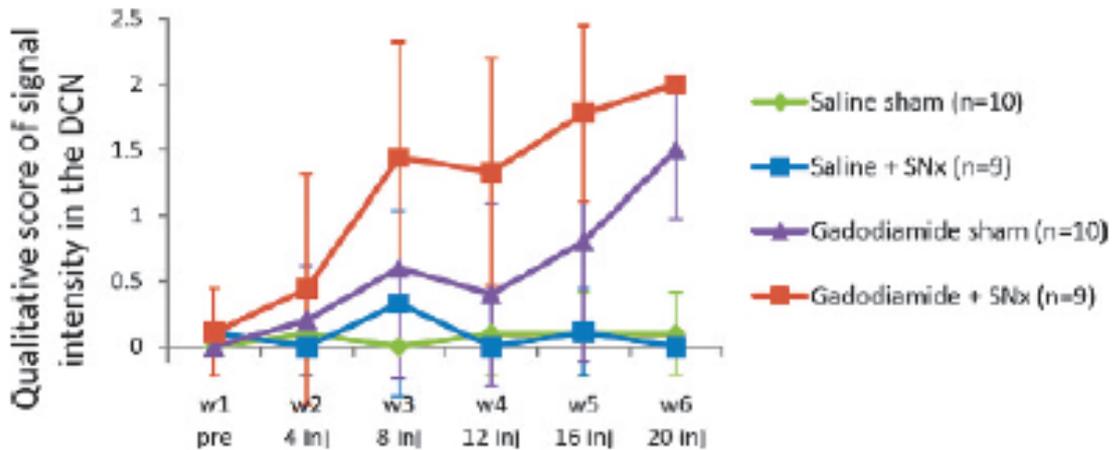


Figure 22: Typical qualitative blinded evaluation: temporal changes in T1w signal enhancement between the DCN and surrounding cerebellar parenchyma, over the course of the injections (week 1: before the first injection; week 6: after 20 injections) (values are mean ± SD)

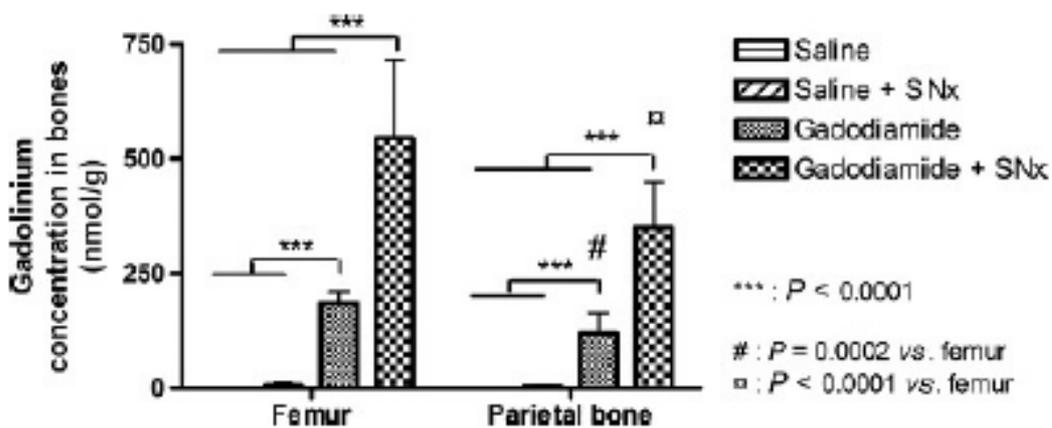


Figure 23: Gadolinium concentration in two different bones (mean ± SD)

The authors comment that the relevance of the T1 DCN ratio versus the cerebellar parenchyma or the brain stem could be disputed owing to the non-negligible concentrations of total Gd found in these areas. However, none of the measured tissues was found to be gadolinium-free, therefore there was no rigorous reference structure. Under these conditions, a slightly higher increase in the

T1 signal was observed in both gadodiamide-treated groups over time in the cerebellar parenchyma compared with the brain stem). Therefore, the DCN-brain stem and CP-brain stem ratios may be more reliable.

Interestingly, circulating gadolinium was still found six days after the last administration, notably in the renally impaired group. It is worth noting that almost all circulating gadolinium was in dissociated form, which supports the hypothesis of *in vivo* dissociation of the non-ionic Linear-GBCA gadodiamide (Figure 25).

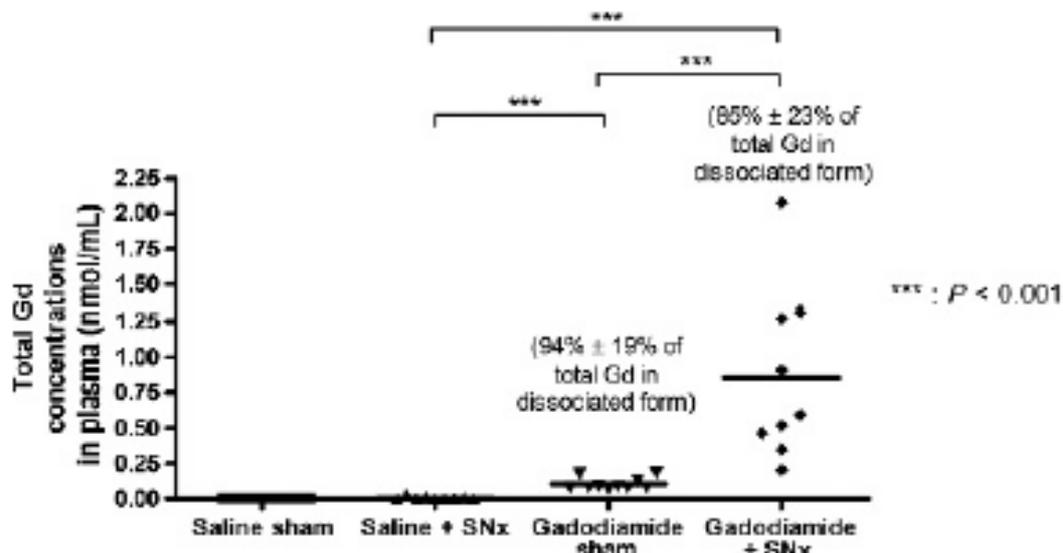


Figure 24: Total gadolinium concentration determined by ICP-MS in plasma collected six days after the last injection. Percentages (\pm SD) represent the proportion of dissociated gadolinium, determined by liquid chromatography inductively coupled plasma mass spectrometry

In this study, total gadolinium concentrations in the cerebellar parenchyma were 4.7 ± 0.5 nmol/g and 10.0 ± 2.8 nmol/g in the sham and SNx gadodiamide-treated groups, respectively. However, no T1 enhancement was observed, unlike in the DCN. This may suggest that intra tissue gadolinium is sequestered in the cerebellar parenchyma in a different form, without associated T1 effect.

Gadolinium may also be trapped in the choroid plexus, in a form that leads to a T1 effect. This tissue is well known for sequestering toxic heavy metals and metalloid ions. It is therefore assumed that gadolinium can cross the blood-cerebrospinal barrier, which would represent a passageway to the adjacent interstitium, as seen for “general toxicants” such as mercury, cadmium, or arsenic. Indeed, tight junctions of the blood-CSF barrier are more permeable than those of the blood-brain barrier.

The cerebellum is an important target for many toxicants, including metals. No overt behavioural abnormalities were observed under our experimental conditions. It is worth noting that no in-depth neurocognitive investigation was performed in this study and that the animals were killed shortly after the last administration. Because total gadolinium measurements were performed in the brain areas, no tissue was available for histological analysis. In-depth neurotoxicological studies are therefore warranted to investigate the risk associated with brain GBCA uptake

The authors conclude that, renal insufficiency in rats potentiates gadolinium uptake in the cerebellum, brain, and bones.

Comments

Renal impairment had a significant effect on the amount of gadolinium found in the brain and in a dissociated state. The result is consistent with the *in vitro* stability studies performed by Frenzel *et al.* (3.1.3.1).

3.1.3.7 Lohrke et al. [20]

The aim of this preclinical study was to systematically examine differences between linear and macrocyclic GBCAs in their potential to induce changes in brain and skin histology.

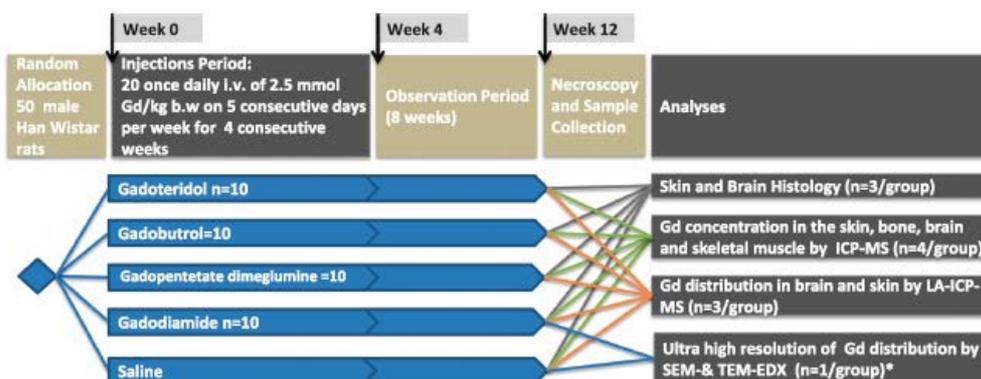


Figure 25: Schematic illustration of the study design. Healthy male Wistar-Han rats were randomly allocated into 1 control and 4 GBCA groups n = 10. Each animal received 20 daily intravenous injections at a dose of 2.5mmol Gd/kg body weight. Eight weeks after the last application, the animals were killed

Fifty male Wistar-Han rats were randomly allocated into control (saline, n = 10 rats) and four GBCA groups as per the schema in Figure 26. No histopathological changes in the brain could be detected. There were no differences between animals administered any GBCAs compared to controls (Figure 27).

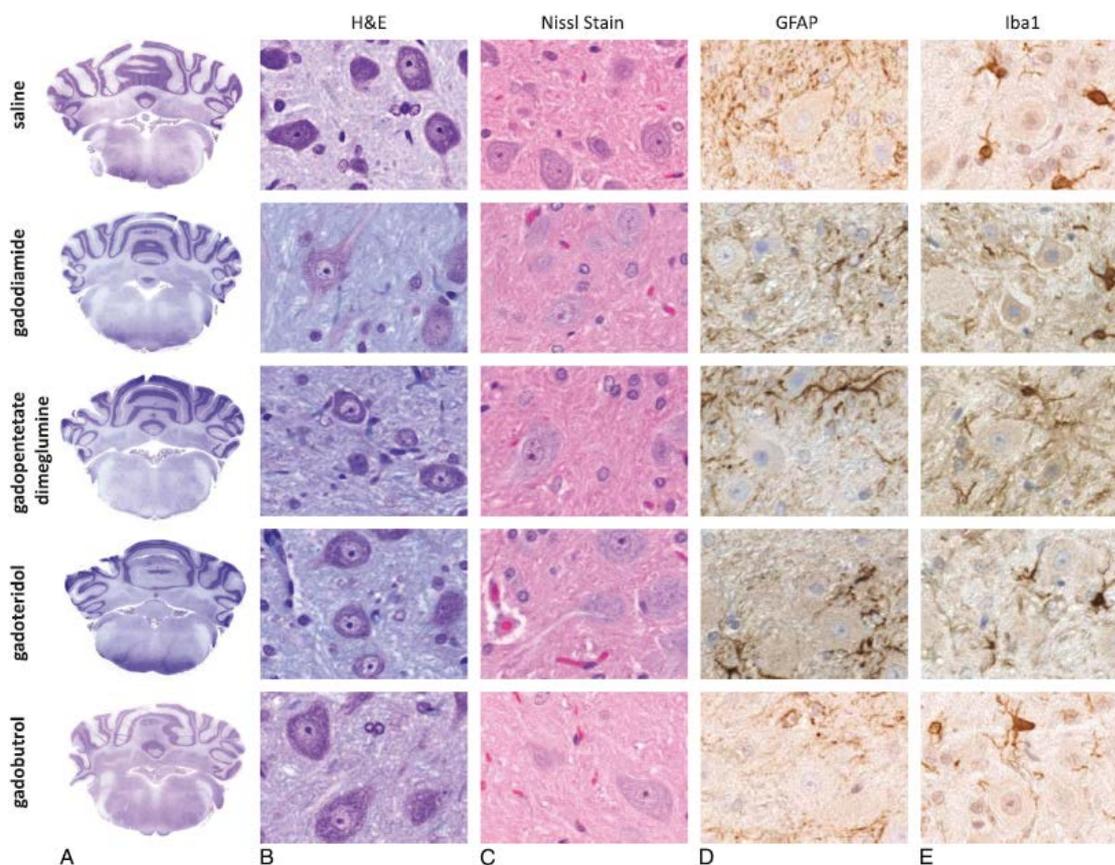


Figure 26: Histopathological microscopic examination of rat brain. Slides stained with (A and B) H&E or (C) cresyl violet (Nissl stain). Immunohistochemistry using (D) GFAP to assess the astrocyte number and (E) morphology, and a microglial marker (Iba1)

The gadolinium concentration in the skin, bone, brain, and skeletal muscle samples were analyzed using inductively coupled plasma mass spectroscopy (ICP-MS, n = 4). The spatial gadolinium distribution in the brain and skin samples was analyzed in cryosections using laser ablation coupled with ICP-MS (LA-ICP-MS, n = 3). For the ultra-high resolution of gadolinium distribution, brain sections of rats injected with gadodiamide or saline (n = 1) were assessed by scanning electron microscopy coupled to energy dispersive x-ray spectroscopy and transmission electron microscopy, respectively.

The gadolinium concentrations observed in the skin/brain samples (in nanomole gadolinium per gram of tissue) for each agent were as follows:

- gadodiamide: $1472 \pm 115/11.1 \pm 5.1$
- gadopentetate dimeglumine: $80.8 \pm 6.2/13.1 \pm 7.3$
- gadobutrol: $1.1 \pm 0.5/0.7 \pm 0.4$
- gadoteridol: $1.7 \pm 0.8/0.5 \pm 0.2$.

The average detected residual gadolinium concentration in the brain was approximately 15-fold higher for linear than for macrocyclic GBCAs. The highest amounts of gadolinium found in brain corresponded to less than 0.0002% of the injected dose per gram of tissue.

Using LA-ICP-MS, high gadolinium concentrations in the DCN and in the granular layer of the cerebellar cortex were detected only for gadodiamide and gadopentetate. The energy dispersive x-ray spectroscopy analysis revealed gadolinium-containing spots in the skin of animals administered gadodiamide and gadopentetate.

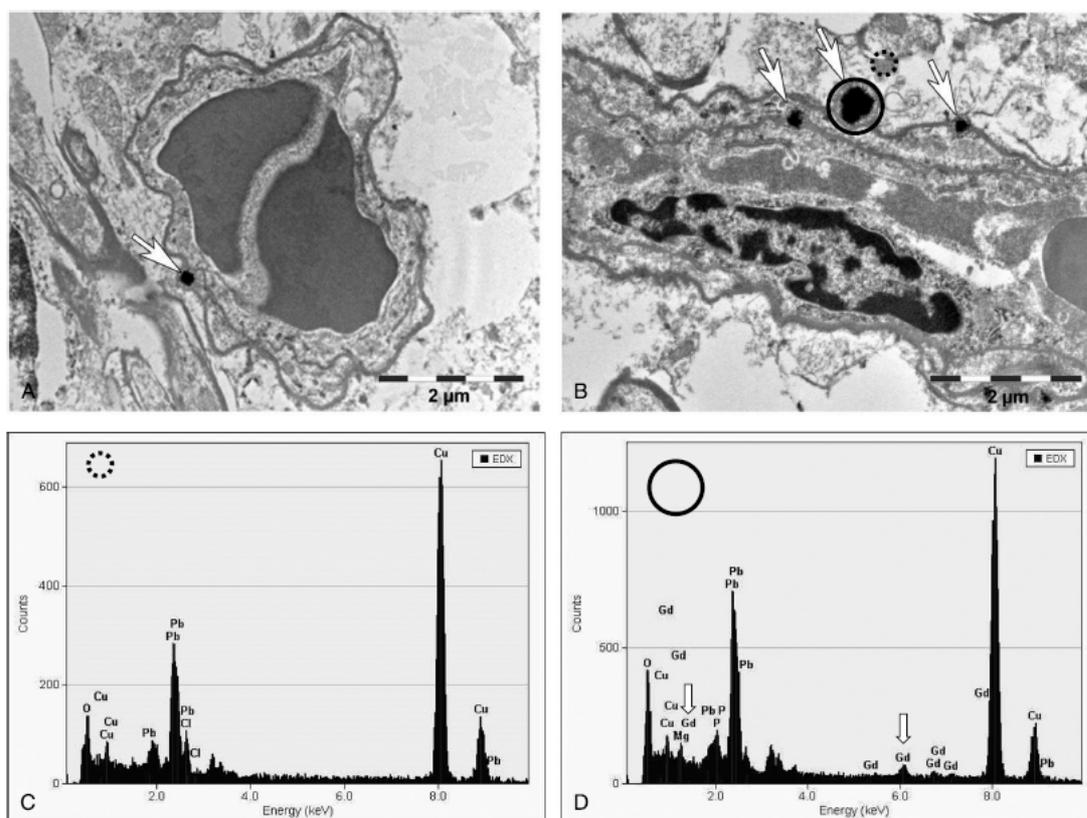


Figure 27: Transmission electron microscopy tissue localization of Gd-containing spots in the region of the lateral (dentate) cerebellar nuclei in the brain after the repeated high-dose application of gadodiamide. (A) 1 single focus (original magnification, x18,900) and (B) several electron-dense signals occurring as multiple roundish nodules with variable diameter (original magnification, x18,800). The location indicates intracellular deposition within endothelial cell of blood vessels; 1 signal appeared to be adjacent to an endothelial cell on the adluminal side. The EDX analysis showed, compared with the control area (C), Gd-positive signals (D, arrows). No positive signals could be detected in neurons or in the neutrophil.

Transmission electronmicroscopy revealed several Gd-containing spots in the region of the dentate nuclei in the brain of 1 animal injected with gadodiamide (Figure 28). The Gd positive high electron-dense structures in TEM could only be detected in the endothelial wall of several microvessels in the brain of 1 gadodiamide administered rat and not in neurons, neutrophil, or other glial cells, raising the possibility that Gd may not have passed the BBB. This finding has to be further examined on more samples and animals, as well as after the administration of other GBCAs than gadodiamide.

Consistent with previously published preclinical NSF studies, some of the animals injected with gadodiamide but none of the other groups showed macroscopically and histologically NSF-like skin lesions. Despite the limitations of animal models in general, these findings suggest that the preclinical studies in the rat reliably mimic effects, at least in the skin, that appear to be associated with GBCA.

In summary, the detected low gadolinium concentrations in the skin and brain were well correlated with the higher kinetic stability of macrocyclic GBCA.

Comments

In this study gadolinium deposits were only detected in animals administered gadodiamide. It was not clear that the gadolinium had cross the BBB as the deposits appeared to be in the capillary wall. Other metals were also found in these deposits.

3.1.3.8 Frenzel *et al.* [21]

The authors conducted a bioanalytical study in rat brain tissue to investigate whether the residual gadolinium is present as intact GBCA or other chemical forms.

Rats were divided randomly in six groups of 10 animals each. They received 10 daily injections of 2.5 mmol/kg bodyweight of one of five different GBCAs: linear GBCAs such as gadodiamide (Omniscan), gadopentetate (Magnevist), or gadobenate (Multihance) and macrocyclic GBCAs such as gadobutrol (Gadovist) and gadoterate (Dotarem) or saline. On days 3 and 24 after the last injection (post injection), five randomly chosen animals of each group were killed by exsanguination, and their brains were excised and divided into cerebrum, pons, and cerebellum.

The brain sections were homogenized by sonication in ice-cold buffer at pH 7.4. Soluble and insoluble fractions were separated by centrifugation, and the soluble fractions were further separated by gel permeation chromatography (GPC) which separates based on weight. The gadolinium concentration in all tissue fractions and in the GPC eluate was measured by inductively coupled plasma–mass spectrometry. In a recovery control experiment, all GBCAs were spiked to blank brain tissue and more than 94% recovery of gadolinium in the tissue fractions was demonstrated.

Only traces of the administered gadolinium were found in the rat brain tissue on day 3 and day 24 post injection (Figure 29). In the animals treated with macrocyclic GBCAs, gadolinium was found only in the soluble brain fraction and was present solely as low molecular weight molecules, most likely the intact GBCA. In the animals treated with linear GBCAs gadolinium was found to a large extent in the insoluble tissue fraction. The gadolinium concentration in the soluble fraction was comparable to the macrocyclic agents. According to GPC analysis, a smaller portion of the gadolinium in the soluble fraction of the linear GBCAs groups was bound to macromolecules larger than 250 to 300 kDa.

The nature of the gadolinium-containing macromolecules and the insoluble species were not determined, but they appeared to be saturable with gadolinium.

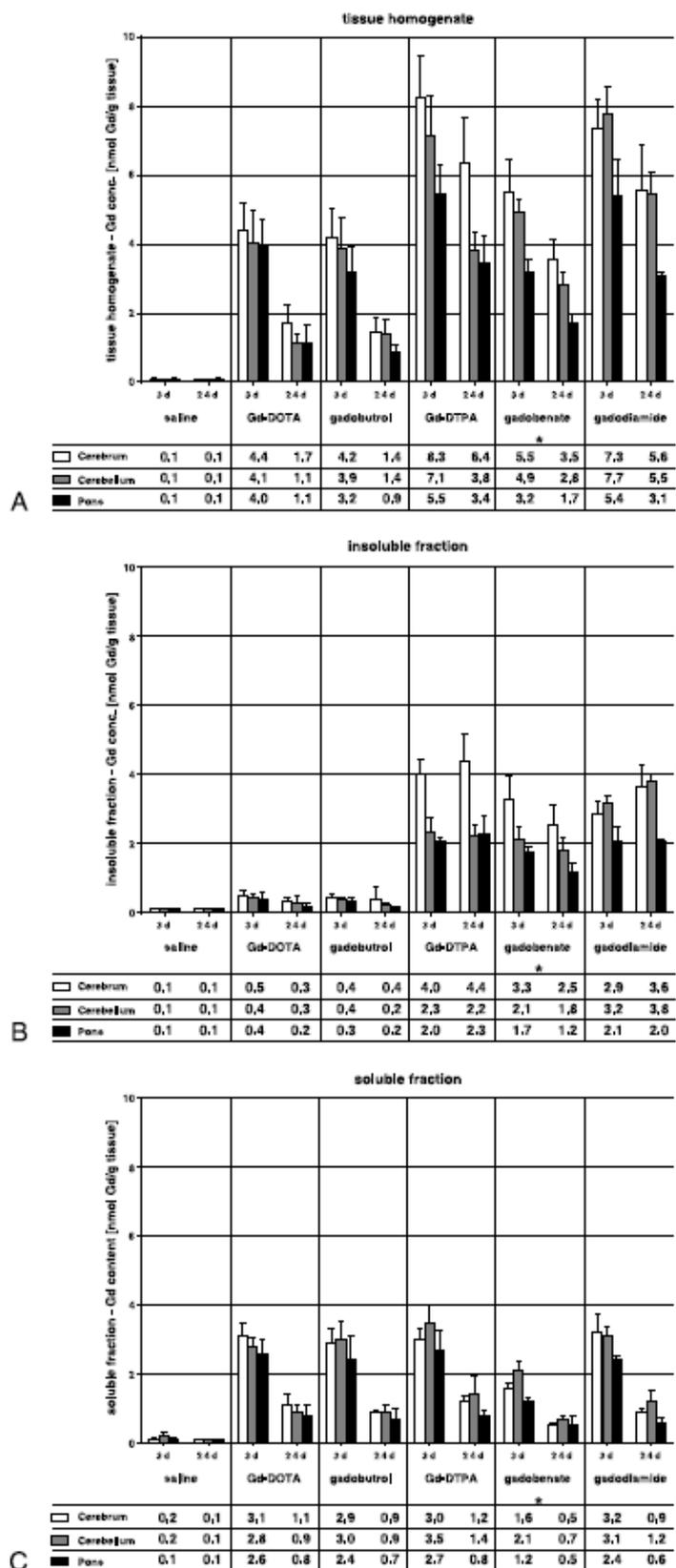


Figure 28: Total gadolinium concentrations (nmol Gd/g tissue) in the tissue homogenates (A) of the three brain sections cerebrum, cerebellum and pons measured 3 and 24 days after the last injection and in the insoluble (B) and soluble (C) fractions. Data is the mean of five animals with SD. *indicates faster elimination of gadobenate is likely due to additional hepatobiliary excretion of ~50% in rats which accounts for only ~5% in humans

The excretion of the soluble gadolinium species in the linear and macrocyclic GBCA groups was still ongoing between days 3 and 24 post injection. This was also observed for the macromolecular gadolinium species in the linear GBCA groups, but at a slower rate.

The residual gadolinium found in the rat brain after repeated administration of all three linear GBCAs was present in at least three distinctive forms—soluble small molecules, including the intact GBCA, soluble macromolecules, and to a large extent in insoluble form. The latter two are most likely responsible for the prolonged signal intensity enhancement in brain structures observed in MRI. No relevant differences between the three linear GBCAs were observed.

The repeated injection of kinetically inert macrocyclic or kinetically less restricted linear GBCAs at very high dosages into rats resulted in very low gadolinium concentrations in brain tissues and in some remarkable differences in the observed chemical gadolinium species.

The authors concluded that the gadolinium concentrations in the brain after administration of macrocyclic GBCAs are lower, and the gadolinium is only present in soluble small molecules, which were slowly excreted. This underlines the crucial importance of the kinetic inertness of macrocyclic agents in the prevention of potential retention of gadolinium in the brain compared with the three linear, kinetically less restricted GBCAs.

Comments

This study also shows that all GBCAs enter the brain of rats after administration and are slowly cleared (takes more than 24 days). There was a significant difference between the linear and macrocyclic GBCA; insoluble gadolinium was only found with the linear GBCAs.

3.1.3.9 Smith *et al.* [22]

The aim of this study was to measure the levels of gadolinium present in the rat brain 1 and 20 weeks after dosing with contrast agent and to determine if there are any histopathologic sequelae.

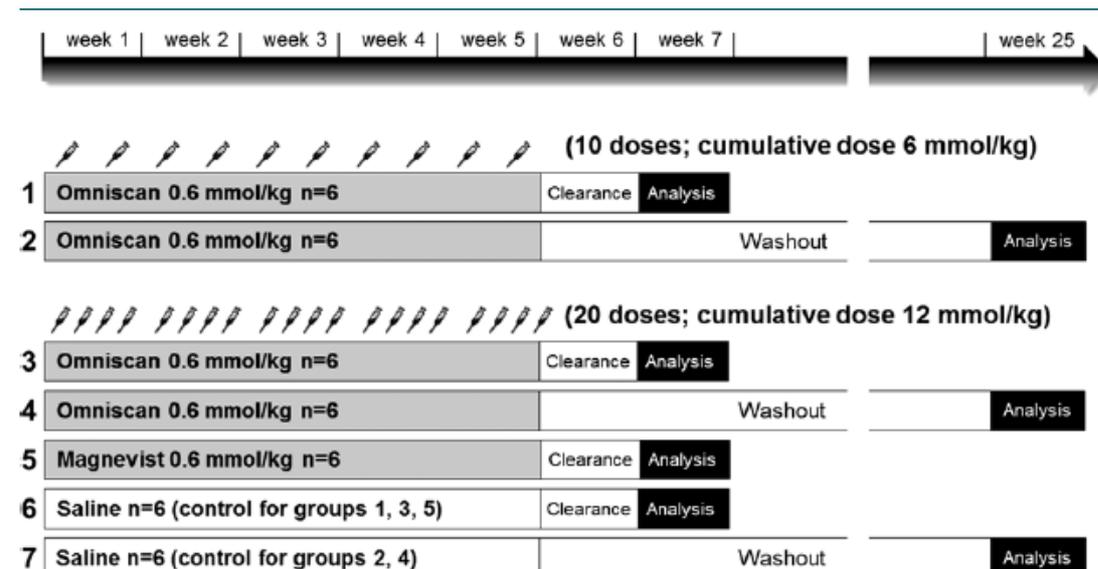


Figure 29: Schematic of the study design, including all dosing regimens and the two time points, at week 7 (1 week after dosing) and week 25 (20 weeks after dosing). Note that the high and low cumulative dose groups were administered identical daily doses but at different frequencies per week. Each dose administered (0.6 mmol per kilogram of body weight) is equivalent to a human dose of 0.1 mmol per kilogram of body weight, adjusted for allometric scaling

Absolute gadolinium levels were quantified in the blood and brains of rats one week after dosing and 20 weeks after dosing with up to 20 repeat doses of gadodiamide (cumulative dose, 12 mmol per kilogram of body weight) by using inductively coupled plasma–mass spectrometry.

Treatment groups (n = 6 rats per group) included low-dosage and high-dosage gadodiamide and osmolality-matched saline controls. Brain sections were submitted (blinded) for standard toxicology assessment per Registry of Industrial Toxicology Animal data guidelines. Analysis of variance and Mann-Whitney U tests with post hoc correction were used to assess differences in absolute gadolinium levels and percentage of injected dose, respectively.

Dose-dependent low levels of gadolinium were detected in the brain, a mean \pm standard deviation of 2.49 nmol per gram of brain tissue \pm 0.30 or 0.00019% of the injected dose one week after dosing (Figure 31). This diminished by approximately 50% (to 1.38 nmol per gram of brain tissue \pm 0.10 or 0.00011% of the injected dose) 20 weeks after dosing. As a percentage of injected dose, the levels of gadolinium measured were comparable between different doses, indicating that mechanisms of uptake and elimination were not saturated at the tested doses. There were no histopathologic findings associated with the levels of gadolinium measured.

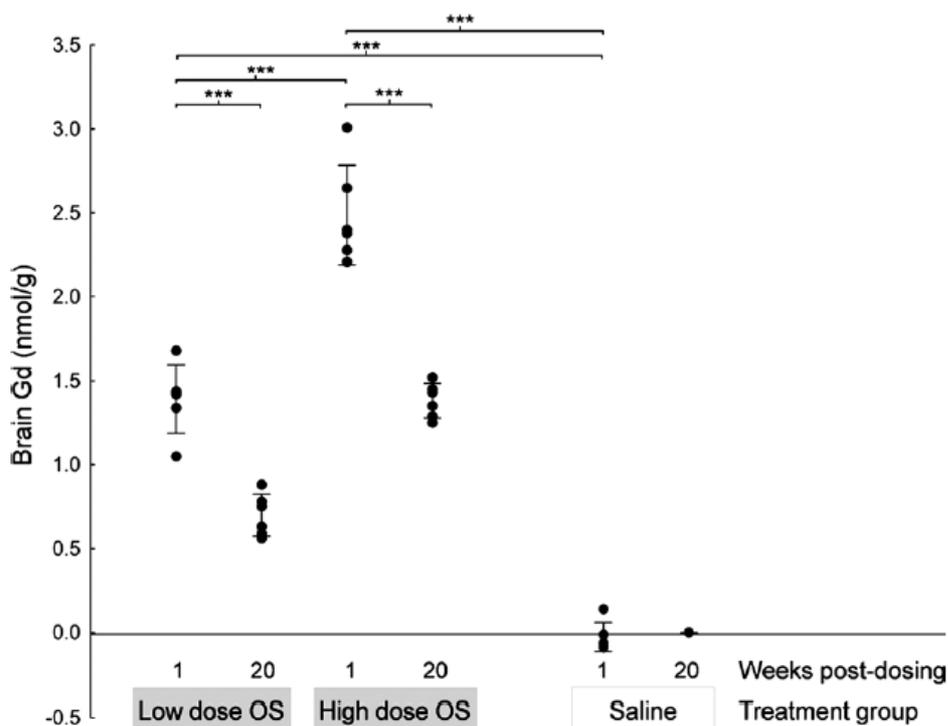


Figure 30: Plot shows that gadolinium levels measured in the brain with ICP-MS were dose dependent and decreased with time. Error bars represent 61 standard deviation of the mean. *** = P , .0001 according to ANOVA for pairwise comparison. OS = Omniscan

This study confirms the presence of small amounts of gadolinium (approximately 1/1 000 000th of the injected dose) in the brain after repeated dosing of gadodiamide in healthy rats and demonstrates partial clearance over 20 weeks. Toxicology evaluation showed no evidence of treatment-related histopathologic findings.

Low levels of gadolinium are present in the brain after repeat dosing with gadodiamide, which is partially cleared over 20 weeks with no detectable neurotoxicity.

Comments

The decrease in brain gadolinium one week to 20 weeks post administration is expected and consistent with the studies above which showed that clearance of soluble gadolinium took longer than one week. It should be noted that a significant quantity of gadolinium was detected at 20 weeks and not all the gadolinium had been cleared. It is likely that the gadolinium remaining at 20 weeks represents insoluble gadolinium, although this study did not investigate the form of gadolinium.

3.1.3.10 Comments on the pre-clinical information

These studies in rats were able to replicate the brain deposition of gadolinium found in humans (see clinical information below). They are therefore considered to provide a useful model for investigating this issue.

All GBCAs were found in the brain after administration. The flow of the GBCAs through the brain structures indicated that they passed through the choroid plexus into the CSF and from there into the cerebellum and pons.

The presence of GBCA in the brain does not necessarily correlate to deposition of gadolinium in the brain. The rat studies found a clear difference in the amount of gadolinium in the brain, identified by MRI several weeks after administration. Insoluble gadolinium species with deposition and high intensity signal on MRI were found with linear GBCAs but not macrocyclic GBCAs. This is consistent with the stability of these agents assessed *in vitro* using human serum. Therefore it is assumed, since all agents pass into the CSF and then the brain, that the amount of deposition is then due to the stability of the GBCA. Stability may be important as it appeared to take more than one month for all the administered GBCA to clear from the rat.

Areas of the brain noted to show high intensity signal on non-contrast MRI were consistent with human studies (see below). However, it was also noted that other brain areas contained gadolinium when this was measured with other techniques. MRI does not therefore identify all the gadolinium deposited in the brain (as already noted for bone deposits).

There was no evidence of any gadolinium deposition from macrocyclic agents, so far. The current evidence is insufficient to determine if there is a difference between different linear agents, although Omniscan appears to cause most deposition.

Renal impairment increased gadolinium deposition in the brain associated with Omniscan, other GBCAs were not investigated.

The amount of gadolinium found in the rat brains was at most around 0.00019% of the injected dose. That is a very small quantity.

The clearance of insoluble gadolinium deposited in the brain was looked at for short periods after GBCA was administered. Where gadolinium deposits were detected, clearance was low to none up to the end of the study period.

No histopathologic changes were found associated with the gadolinium brain deposition. In the study where transmission electronmicroscopy was used the gadolinium was found in blood vessel endothelial cells. Of note, other metals were also detected in these deposits.

No obvious behavioural abnormalities were noted in these studies, but this was not an outcome the studies were designed to detect.

3.1.4 Clinical information

3.1.4.1 Kanda *et al.* [23]

The aim of this study was to explore any correlation between the number of previous linear gadolinium- based contrast material administrations and high signal intensity in the DN and GP on unenhanced T1-weighted MRI images.

A group of 381 consecutive patients who had undergone brain MR imaging was identified for cross-sectional analysis. For longitudinal analysis, 19 patients who had undergone at least six contrast-enhanced examinations were compared with 16 patients who had undergone at least six unenhanced examinations (Table 6).

Table 6: Summary of patient characteristics

Parameter	Consecutive Patient Group (n = 381)	Contrast-enhanced Examination Subgroup (n = 19)	Unenhanced Examination Subgroup (n = 16)
Age (y)*	67.4 ± 11.2	67.7 ± 9.6	73.5 ± 8.6
Sex			
M	229	10	6
F	152	9	10
Brain radiation therapy			
Whole brain	31	0	0
Partial or gamma knife	46	0	0
Tumor anywhere in body	222	11	9
Brain tumor	104	0	0
Chemotherapy	200	16	9
Platinum-based chemotherapy	134	11	8
Molecularly targeted therapy	48	3	3
Abnormal liver function	30	0	0
Abnormal renal function			
eGFR between 30 and 60 mL/min/m ²	36	0	3
eGFR < 30 mL/min/m ²	2	0	0

Note.—Except where indicated, data are numbers of patients.
* Data are means ± standard deviations.

The mean signal intensities of the DN, pons, GP, and thalamus were measured on unenhanced T1-weighted images.

The DN-to-pons signal intensity ratio was calculated by dividing the signal intensity in the DN by that in the pons, and the GP-to-thalamus signal intensity ratio was calculated by dividing the signal intensity in the GP by that in the thalamus. Stepwise regression analysis was undertaken in the consecutive patient group to detect any relationship between the DN-to-pons or GP-to-thalamus signal intensity ratio and previous gadolinium-based contrast material administration or other factors. A random coefficient model was used to evaluate for longitudinal analysis.

The DN-to-pons signal intensity ratio showed a significant correlation with the number of previous gadolinium-based contrast material administrations ($P < .001$; regression coefficient, 0.010; 95% confidence interval [CI]: 0.009, 0.011; standardized regression coefficient, 0.695) (Table 7).

The GP-to-thalamus signal intensity ratio showed a significant correlation with the number of previous gadolinium-based contrast material administrations ($P < .001$; regression coefficient, 0.004; 95% CI: 0.002, 0.006; standardized regression coefficient, 0.288), radiation therapy ($P = .009$; regression coefficient, -0.014; 95% CI: -0.025, -0.004; standardized regression coefficient, -0.151), and liver function ($P = .031$; regression coefficient, 0.023; 95% CI: 0.002, 0.044; standardized regression coefficient, 0.107) (Table 7).

Table 7: Correlations of dependent variables to DN to pons and GP to thalamus signal intensity ratios in 381 patients

Parameter	Regression Coefficient	95% CI	Standardized Regression Coefficient	P Value
Analysis for dentate nucleus–to-pons ratio				
First step of analysis				
Sex	−0.007	−0.015, 0.002	−0.057	.145
Age	−0.000	0.000, 0.000	−0.004	.921
No. of previous contrast material administrations	0.009	0.008, 0.011	0.671	<.001
Brain radiation therapy	0.000	−0.010, 0.010	0.001	.990
Tumor anywhere in body	−0.007	−0.017, 0.004	−0.060	.200
Brain tumor	0.000	−0.013, 0.014	0.004	.942
Chemotherapy	0.006	−0.008, 0.019	0.050	.416
Abnormal liver function	0.003	−0.010, 0.016	0.024	.678
Platinum-based chemotherapy	0.007	−0.008, 0.022	0.040	.376
Molecularly targeted therapy	0.000	−0.016, 0.015	−0.001	.980
Abnormal renal function	0.002	−0.011, 0.015	0.014	.712
Final step of analysis				
No. of previous contrast material administrations	0.010	0.011, 0.009	0.695	<.001
Analysis for globus pallidus–to-thalamus ratio				
First step of analysis				
Sex	0.001	−0.011, 0.013	0.006	.911
Age	0.000	0.000, 0.001	0.008	.874
No. of previous contrast material administrations	0.004	0.002, 0.006	0.285	<.001
Brain radiation therapy	−0.012	−0.025, 0.002	−0.125	.084
Tumor anywhere in body	−0.003	−0.017, 0.011	−0.025	.686
Brain tumor	−0.010	−0.029, 0.008	−0.082	.264
Chemotherapy	−0.008	−0.027, 0.011	−0.069	.398
Platinum-based chemotherapy	0.014	−0.004, 0.032	0.117	.125
Molecularly targeted therapy	0.019	−0.002, 0.039	0.107	.076
Abnormal liver function	0.021	−0.001, 0.042	0.096	.056
Abnormal renal function	0.007	−0.011, 0.024	0.037	.463
Final step of analysis				
No. of previous contrast material administrations	0.004	0.002, 0.006	0.288	<.001
Brain radiation therapy	−0.014	−0.025, −0.004	−0.151	.009
Liver abnormality	0.023	0.002, 0.044	0.107	.031

Note.—The R^2 for the dentate nucleus–to-pons signal intensity ratio was 0.491 for the first step of analysis and 0.483 for the final step of analysis; the R^2 for the globus pallidus–to-thalamus signal intensity ratio was 0.092 for the first step of analysis and 0.075 for the final step of analysis.

Scatterplots of the DN– to-pons and GP–to-thalamus ratios according to number of previous gadolinium-based contrast material administrations are shown in Figure 32 and indicate a positive correlation between the number of previous gadolinium based contrast material administrations and the dentate nucleus–to-pons ratio.

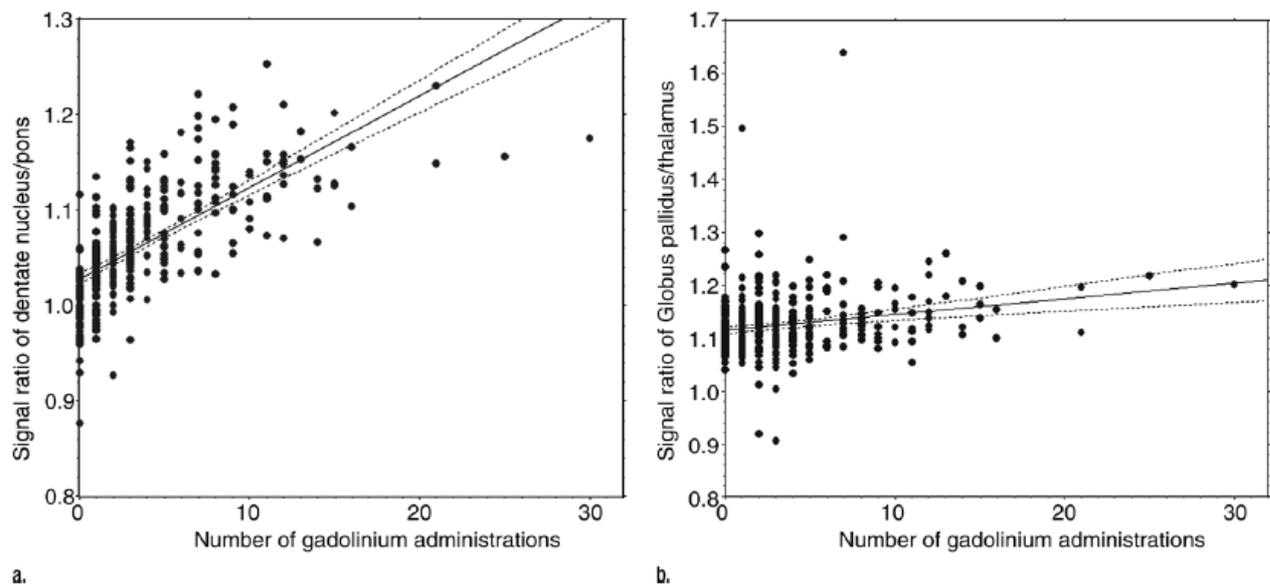


Figure 31: (a) Scatterplot of dentate nucleus–to–pons signal intensity ratio versus number of previous gadolinium-based contrast material administrations. (b) Scatterplot of globus pallidus–to–thalamus signal intensity ratio versus number of previous gadolinium-based contrast material administrations. In each plot, solid line represents linear regression and dashed lines indicate 95% confidence limits.

The DN–to–pons and GP–to–thalamus signal intensity ratios in patients who had undergone contrast-enhanced examinations were significantly greater than those of patients who had undergone unenhanced examinations ($P < .001$ for both).

This study has several limitations, noted by the authors. The hospital at which the study was based tends to transfer patients with end-stage disease to other hospitals and autopsy is seldom performed, making pathologic correlation with imaging findings impossible. In addition, the authors could not check all the imaging histories in other hospitals for each patient before admission to their institution.

The number of exposures to gadolinium-based contrast material may have been underestimated.

The authors found no correlation between renal function and GP or DN signal intensities, which might have been a consequence of patients with impaired renal function tending not to undergo contrast-enhanced studies.

The administered dose of gadolinium-based contrast material was not calculated according to patient weight, and so the authors could not measure the gadolinium-based contrast material doses as millimolars per kilogram.

The study was retrospective, and, despite the large number of patients available for cross-sectional analysis, the sample size of control subjects in the subgroups was small.

Finally, because the signal intensity change is very small after a single administration of gadolinium-based contrast material, it could not be quantified after a single dose.

The authors conclude that high signal intensity in the DN and GP on unenhanced T1-weighted images may be a consequence of the number of previous gadolinium-based contrast material administrations.

3.1.4.2 Kanda *et al.* [24]

The aim of this study was to assess whether an association exists between hyperintensity in the DN on unenhanced T1-weighted MRI and previous administration of GBCAs that contain different types of gadolinium chelates.

Evaluated were 127 cases among 360 consecutive patients who underwent contrast agent-enhanced brain MR imaging. Two radiologists conducted visual evaluation and quantitative analysis on unenhanced T1-weighted MR images by using regions of interest.

DN-to-cerebellum (DN/cerebellum) signal intensity ratios were calculated and the relationship between DN/ cerebellum and several factors was evaluated, including the number of previous linear chelate and/or macrocyclic GBCA administrations by using a generalized additive model. The Akaike information criterion was used in model selection. Interobserver correlation was evaluated with paired t tests and the Lin concordance correlation coefficient.

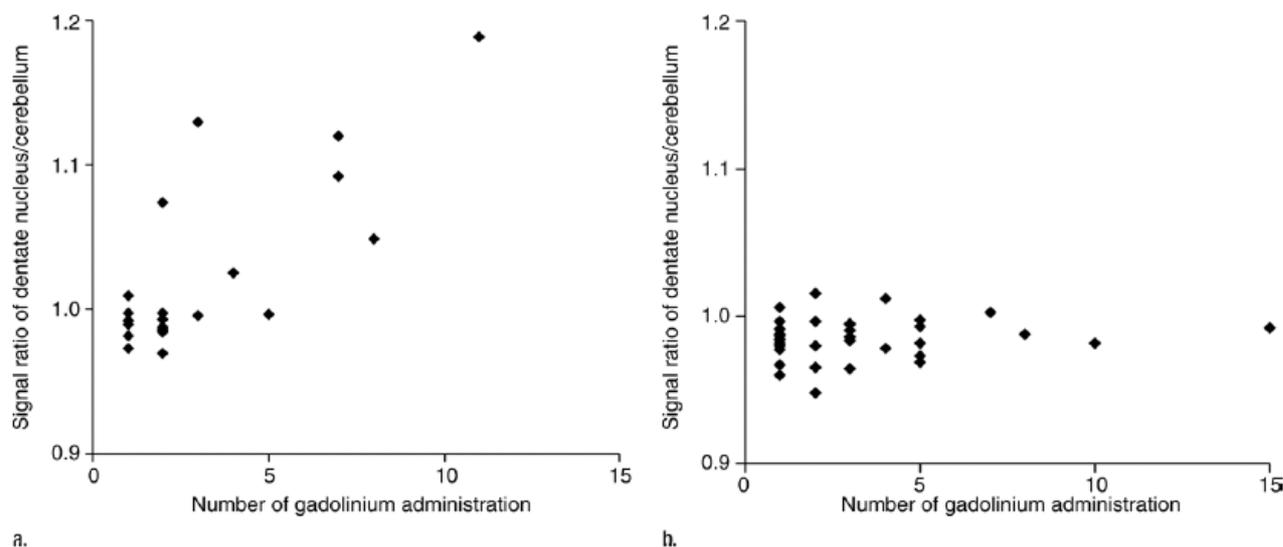


Figure 32: Scatterplots show (a) DN-to-pons signal intensity ratio versus number of previous GBCA administrations for 23 patients who had only linear GBCA administration and (b) DN-to-pons signal intensity ratio versus number of previous macrocyclic chelate GBCA administrations for 36 patients who had only macrocyclic GBCA administration

The images of nine patients (7.1%) showed hyperintensity in the DN. Twenty-three patients (18.1%) received linear GBCAs, 36 patients (28.3%) received macrocyclic GBCAs, 14 patients (11.0%) received both types of GBCA (linear and macrocyclic), and 54 patients (42.5%) had no history of administration of gadolinium chelate. Inter-observer correlation was almost perfect (0.992 [95% confidence interval: 0.990, 0.994]). The DN/ cerebellum ratio was associated with linear GBCA ($P < .001$), but not with macrocyclic GBCA exposure ($P = .875$).

According to the Akaike information criterion, only linear GBCA was selected for the final model, and the DN/cerebellum ratio had strong association only with linear GBCA. Hyperintensity in the DN on unenhanced T1-weighted MR images is associated with previous administration of linear GBCA, while the previous administration of macrocyclic GBCAs showed no such association.

3.1.4.3 Radbruch *et al.* [25]

The aim of this study was to compare changes in signal intensity ratios of the DN and the GP to those of other structures on unenhanced T1-weighted MRI between linear and macrocyclic GBCAs.

Two groups of 50 patients who underwent at least six consecutive MR imaging examinations with the exclusive use of either a linear GBCA (gadopentetate) or a macrocyclic GBCA (gadoterate) were analysed retrospectively (Table 8).

Exclusion criteria were

(a) an estimated glomerular filtration rate (eGFR) lower than 60 mL/min per 1.73 m² in a blood sample recent to the date of the last MR imaging examination

- (b) a history of brain haemorrhage, stroke, or brain ischemia
- (c) oedema, tumour, or other lesions located in the cerebellum or pons
- (d) history of intracranial infection, such as meningitis or encephalitis
- (e) missing or unsatisfactory unenhanced T1-weighted MR images (eg, largely varying MR parameters) from the first or last MR imaging examination performed with linear GBCAs or macrocyclic GBCAs
- (f) missing documentation of the contrast agent applied.

Table 8: Patient characteristics

Parameter	Macrocyclic GBCA Group	Linear GBCA Group
Total no. of patients	50	50
Age (y)*	49.98 ± 14.09	46.78 ± 15.18
Mean interval between GBCA administrations (wk)*	11.28 ± 2.47	14.00 ± 6.19
Patient sex		
No. of men	27	30
No. of women	23	20
No. of contrast-enhanced MR imaging examinations*	7.06 ± 1.20	7.32 ± 1.83
Accumulated dose*	162.41 ± 45.20	124.22 ± 39.31
History of surgery	37	37
History of chemotherapy	46	41
Molecularly targeted therapy	12	12
Alkylating antineoplastic agent	46	37
Other therapy	16	20
Underwent radiation therapy	44	32
Whole brain	2	2
Tumor selective	42	31
Diagnosis		
Glioblastoma	16	13
Glioma World Health Organization grade I–III	31	27
Tumor other than glioma	2	8
No tumor	1	2
eGFR		
60–90 mL/min per 1.73 m ²	12	9
>90 mL/min per 1.73 m ²	38	41
Abnormal liver function	12	15

Note.—Data are numbers of patients, unless indicated otherwise.
* Data are means ± standard deviations.

The difference in mean signal intensity ratios of DN to pons and GP to thalamus on unenhanced T1-weighted images from the last and first examinations was calculated.

One-sample and independent-sample t tests were used to assess the difference in signal intensity ratios for both groups, and regression analysis was performed to account for potential confounders.

The signal intensity ratio difference in the linear group was greater than 0 (mean DN difference ± standard deviation, 0.0407 ± 0.0398 [P < .001]; GP, 0.0287 ± 0.0275 [P < .001]) and significantly larger (DN, < , .001 and standardized difference of 1.16; GP, <P , .001 and standardized difference of 0.81) than that in the macrocyclic group, which did not differ from 0 (DN, 0.0016 ± 0.0266 [P = .680]; GP, 0.0031 ± 0.0354 [P = .538]) (Figure 34). The signal intensity ratio difference between the last and first examinations for the DN remained significantly different between the two groups in the regression analysis (P < .001).

Limitations of the current study are mostly caused by its retrospective design. Since patients were not randomly assigned to the different contrast agents, it cannot be ruled out that other confounding variables can explain the difference between the contrast agent groups; however, even when controlling for a large number of potentially confounding variables, the effect of the contrast agent group remained significant. A further limitation of the study is that only two of the nine available GBCAs on the market have been analyzed. This approach was chosen because of the applied GBCAs in the author's department. Finally, the fact that other properties of the assessed

GBCAs besides the classification as either linear or macrocyclic contribute to the difference in signal intensity increase cannot be excluded.

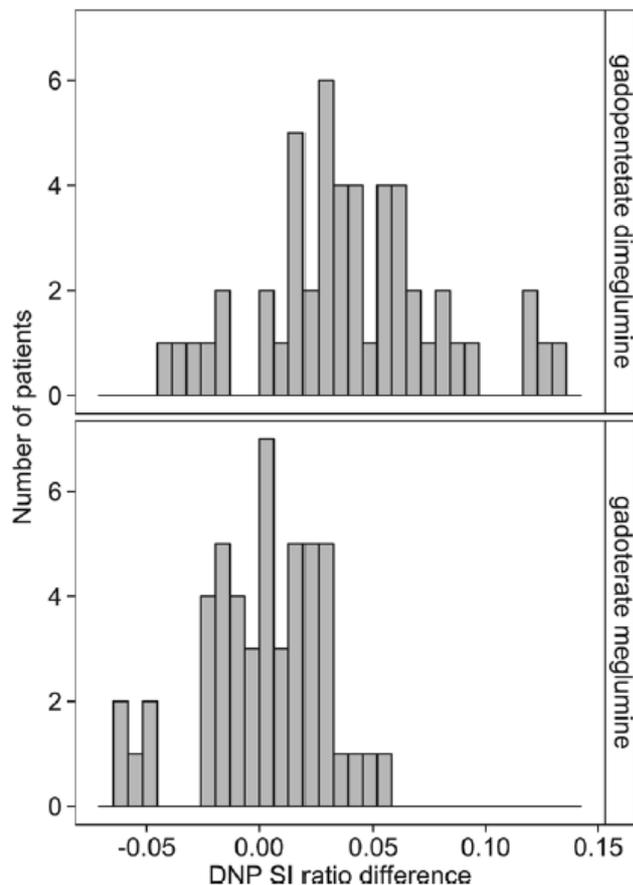


Figure 33: Graphs of the distribution of DN-to-pons (DNP) signal intensity ratio differences between the last and first MR imaging examinations for the two patient groups.

This study indicates that a signal intensity increase in the DN and GP on T1-weighted images is caused by serial application of the linear GBCA gadopentetate but not by the macrocyclic GBCA gadoterate. Clinical implications of this observation remain unclear.

3.1.4.4 McDonald *et al.* [26]

In this single-centre study, signal intensities from T1-weighted MRI and postmortem neuronal tissue samples from 13 patients who underwent at least four GBCA (Omniscan)-enhanced brain MR examinations between 2000 and 2014 (contrast group) were compared with those from 10 patients who did not receive GBCA (control group). Antemortem consent was obtained from all study participants (Table 9).

Exclusion criteria included patients younger than 18 years, neoplastic involvement of the prescribed regions of interest in the CNS, clinical documentation or MR evidence of post treatment and/or post radiation changes to the prescribed CNS regions, history of multiple sclerosis history of metabolic disease, history of metal toxicity, history of previous intravenous or intra-articular gadolinium exposure (control group only), or patients lacking precontrast axial T1-weighted MR images.

Neuronal tissues from the DN, pons, GP, and thalamus of these 23 deceased patients were harvested and analyzed with inductively coupled plasma mass spectrometry (ICP-MS), transmission electron microscopy, and light microscopy to quantify, localize, and assess the effects of gadolinium deposition. Associations between cumulative gadolinium dose, changes in T1-weighted MR signal intensity, and ICP-MS-derived tissue gadolinium concentrations were examined by using the Spearman rank correlation coefficient.

Table 9: Demographic and clinical characteristics of study population

Group and Patient No.	Age at Death (y)	Examination Indication*	No. of MR Examinations	Gadolinium Dose (mL) [†]	Interval between Imaging and Death (d)	eGFR (mL/min/1.73 m ²) [‡]	Alkaline Phosphatase Level (U/L) [§]	Aspartate Aminotransferase Level (U/L) [§]	Total Bilirubin Level (mg/dL) [§]
Contrast group									
1	22	Encephalitis	4	52	18–84	94 (62–125)	86 (37–114)	29 (14–39)	0.4 (0.4–0.5)
2	50	CNS metastases	5	75	13–311	74 (59–89)	71 (53–80)	29 (17–49)	0.5 (0.4–1.2)
3	47	CNS metastases	6	85	86–520	54 (49–59)	57 (39–75)	42 (22–253)	0.4 (0.3–1.8)
4	62	GBM	7	129	29–338	78 (58–98)	84 (63–91)	18 (13–28)	0.7 (0.4–1.1)
5	46	CNS metastases	8	140	511–1610	108 (92–123)	83 (60–94)	25 (18–35)	0.5 (0.3–0.9)
6	72	Subependymoma	9	160	197–1266	103 (95–111)	78 (51–88)	28 (20–30)	0.5 (0.4–0.7)
7	51	GBM	10	162	44–427	81 (71–90)	60 (31–90)	22 (15–54)	0.6 (0.4–1.0)
8	61	CNS metastases	11	117	623–1169	88 (73–102)	85 (65–113)	34 (23–64)	0.6 (0.3–1.0)
9	60	GBM	11	199	20–403	96 (77–115)	158 (75–397)	50 (22–76)	1.1 (0.4–1.6)
10	69	Pituitary adenoma	14	241	17–3532	76 (67–84)	56 (38–81)	24 (17–39)	0.7 (0.6–0.8)
11	40	Oligodendroglioma	17	252	53–1059	105 (84–126)	51 (35–79)	26 (24–28)	0.5 (0.4–0.6)
12	61	GBM	28	500	62–983	83 (69–96)	58 (40–111)	27 (19–45)	0.6 (0.4–0.7)
13	40	GBM	29	420	106–2195	122 (95–149)	122 (106–131)	27 (18–106)	0.5 (0.4–0.6)
Control group									
1	84	TBI	1	...	3189	47 (47–47)	136 (78–298)	38 (27–86)	1.2 (0.5–2.0)
2	86	Dementia	2	...	3	62 (59–65)	190 (118–474)	60 (27–548)	0.5 (0.3–2.7)
3	62	Lymphoma	1	...	516	44 (41–49)	113 (95–155)	30 (19–85)	0.2 (0.1–0.2)
4	91	TIA	1	...	2	64 (51–72)	85 (71–544)	25 (14–62)	0.6 (0.5–3.0)
5	74	Dementia	1	...	791	40 (34–60)	66 (59–85)	18 (16–19)	0.7 (0.6–0.8)
6	56	Seizure	3	...	663	10 (8–11)	173 (109–457)	39 (20–87)	0.7 (0.3–1.2)
7	83	TIA	6	...	2032	62 (53–70)	103 (75–373)	41 (24–107)	0.7 (0.4–1.0)
8	92	Hydrocephalus	1	...	5008	43 (43–43)	150 (99–643)	21 (14–146)	0.6 (0.6–0.6)
9	89	Lymphoma	1	...	8	29 (18–37)	50 (38–72)	18 (18–18)	0.1 (0.1–0.1)
10	60	ICH	1	...	2359	104 (81–109)	62 (62–62)	32 (27–36)	0.7 (0.6–0.9)

* GBM = glioblastoma multiforme, ICH = intracranial hemorrhage, TBI = traumatic brain injury, TIA = transient ischemic attack.
[†] Cumulative gadolinium dose from all intravenous gadolinium-enhanced MR examinations. Gadodiamide concentration = 287 mg/mL.
[‡] Data are medians, with range in parentheses.
[§] Normal laboratory ranges for assays are as follows: alkaline phosphatase level, 45–142 U/L; aspartate aminotransferase level, 8–48 U/L; total bilirubin level, 0.1–1.0 mg/dL.

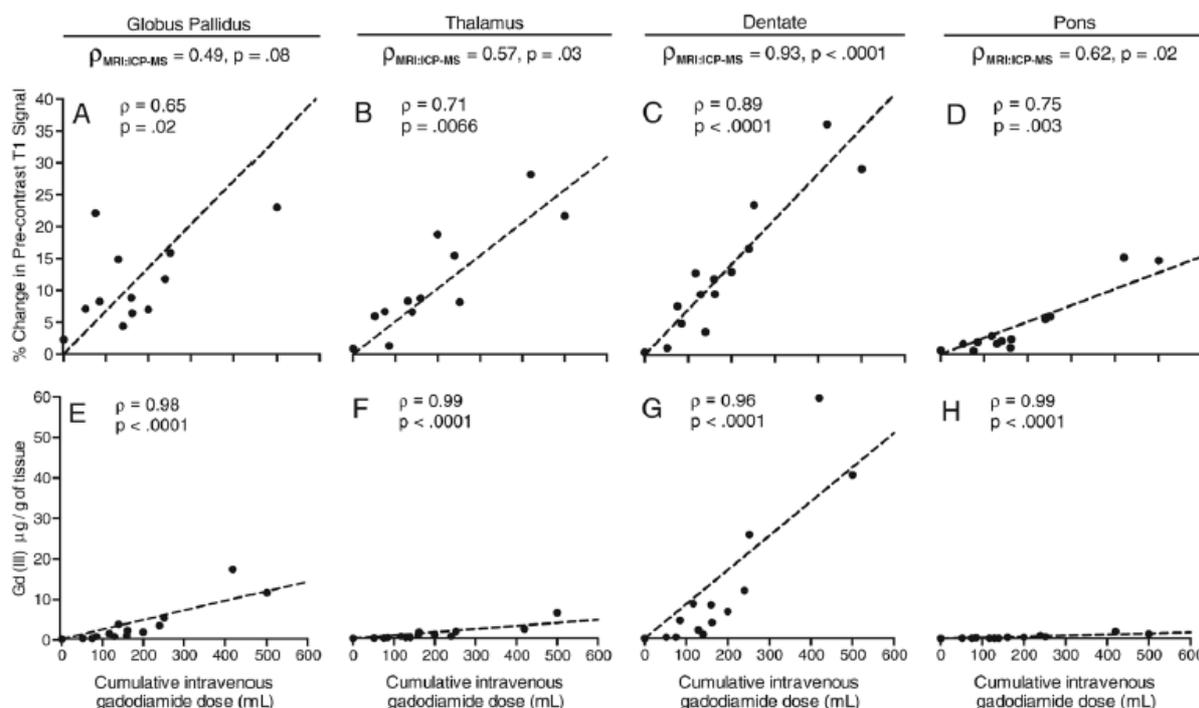


Figure 34: Gadolinium detection with mass spectrometry of cadaveric tissues and quantification of MR signal intensity changes. A–D, Changes in T1-weighted signal intensities in globus pallidus, thalamus, dentate, and pons are plotted against cumulative intravenous gadolinium exposure. E–H, Changes in gadolinium ion signal detected with mass spectrometry are plotted against cumulative intravenous gadolinium exposure. The strength of association between signal intensity changes and dose, gadolinium ion signal intensity and dose, and signal intensity changes and gadolinium ion signal intensity are shown with Spearman rank correlation coefficient (r) and associated P value.

Compared with neuronal tissues of control patients, all of which demonstrated undetectable levels of gadolinium, neuronal tissues of patients from the contrast group contained 0.1–58.8 mg gadolinium per gram of tissue, in a significant dose-dependent relationship that correlated with signal intensity changes on precontrast T1-weighted MR images ($r = 0.49$ – 0.93) (Figure 35). All patients in the contrast group had relatively normal renal function at the time of MR examination. Gadolinium deposition in the capillary endothelium and neural interstitium was observed only in the contrast group.

Unlike control group patients, where gadolinium accumulation was not detected with transmission electron microscopy, x-ray microanalysis confirmed the presence of extensive gadolinium deposits within neuronal tissues of patients exposed to gadolinium. Among gadolinium-exposed samples, gadolinium was prominently clustered in large foci within the endothelial wall (Figure 36, B); however, densitometry performed with wider field views suggested that 18%–42% of gadolinium appears to have crossed the blood-brain barrier and been deposited into the neural tissue interstitium (the space among neural cells and capillaries which connects the vascular system to neural networks).

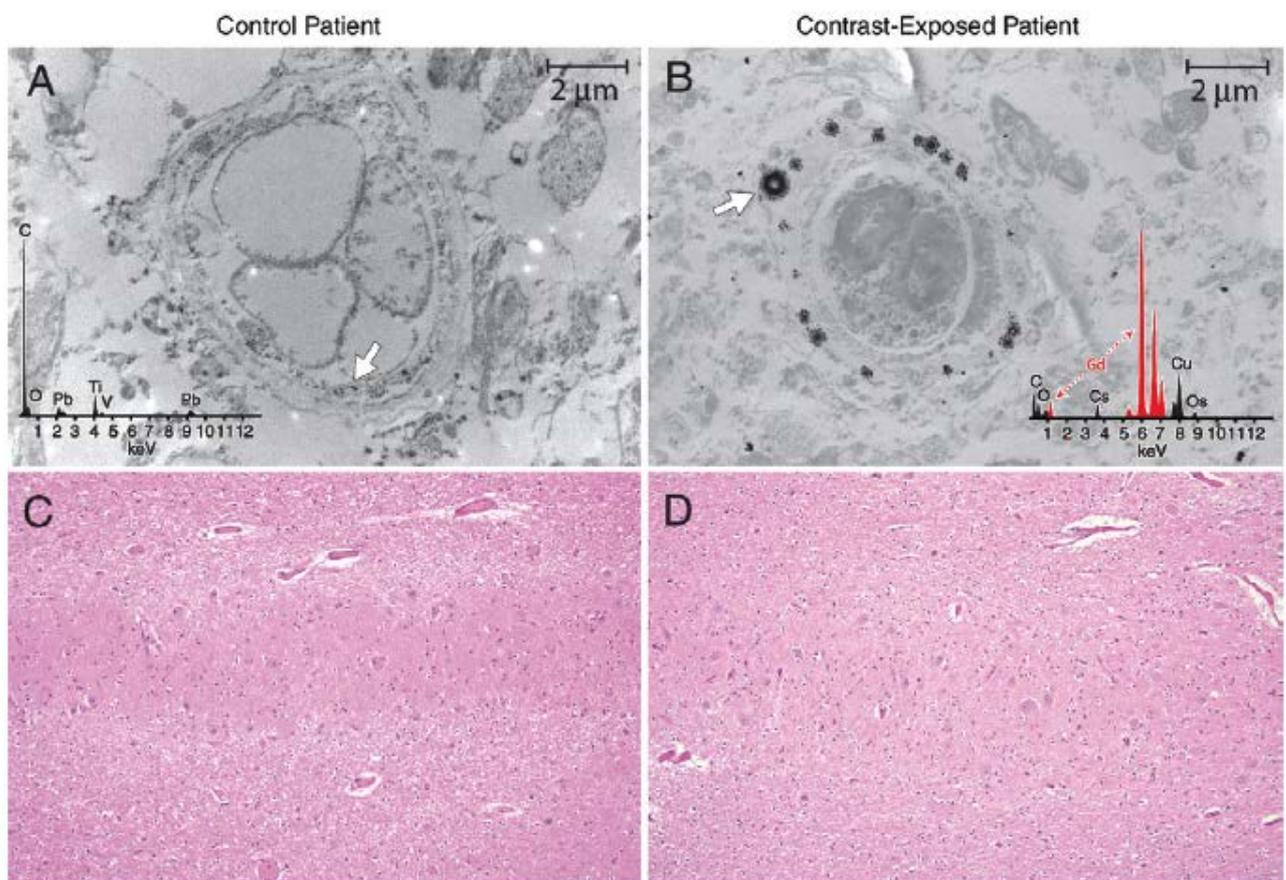


Figure 35: Tissue localization and cellular response to gadolinium deposition. A, B, Transmission electron micrographs (0.2% lead citrate stain; original magnification, 310 000) of dentate nuclei tissue samples of, A, control patient 4 and, B, contrast group patient 13. X-ray spectra are also shown for selected electron-dense foci (arrow); gadolinium peaks in spectra are indicated by red overlay. C = carbon, Cs = caesium, Cu = copper, Gd = gadolinium, O = oxygen, Os = osmium, Pb = lead, Ti = titanium, V = vanadium. C, D, Photomicrographs from light microscopy (hematoxylin-eosin stain; original magnification, 3100) of dentate nuclei from, C, control patient 4 and, D, contrast group patient 13.

Although most of the patients exposed to gadolinium had primary or secondary brain malignancies, the regions of tumour involvement and post radiation changes were located in areas distant from the prescribed neuroanatomic locations.

Despite direct evidence of gadolinium deposition within neuronal tissues, the authors were unable to detect gross histologic changes between contrast and control groups in haematoxylin-eosin–stained tissues samples with visual light microscopy.

Intravenous GBCA exposure is associated with neuronal tissue deposition in the setting of relatively normal renal function. Additional studies are needed to investigate the clinical significance of these findings and the generalizability to other GBCAs.

Comments

Deposits of gadolinium following Omniscan administration were detected in the capillary wall and interstitium but not within neurones. No changes were noted on histopathology. Other metals were also detected in the deposits.

3.1.4.5 Kanda *et al.* [27]

The authors used inductively coupled plasma mass spectroscopy to evaluate gadolinium accumulation in brain tissues, including the DN and GP, in subjects who received a GBCA.

Brain tissues obtained at autopsy in five subjects who received a linear GBCA (GBCA group) and five subjects with no history of GBCA administration (non-GBCA group) were examined with inductively coupled plasma mass spectroscopy. Formalin-fixed DN tissue, the inner segment of the GP, cerebellar white matter, the frontal lobe cortex, and frontal lobe white matter were obtained, and their gadolinium concentrations were measured (Table 10).

None of the subjects had received a diagnosis of severely compromised renal function (estimated glomerular filtration rate, 45 mL/min/1.73 m²) or acute renal failure. Fisher permutation test was used to compare gadolinium concentrations between the two groups and among brain regions.

Gadolinium was detected in all specimens in the GBCA agent group (mean, 0.25 µg per gram of brain tissue ± 0.44 [standard deviation]), with significantly higher concentrations in each region (P = .004 vs the non-GBCA group for all regions). In the GBCA group, the DN and GP showed significantly higher gadolinium concentrations (mean, 0.44 µg/g ± 0.63) than other regions (0.12 µg/g ± 0.16) (P = .029).

Table 10: Calculated sample concentrations for gadolinium in human tissues

Group	DN	GP	Cerebellar White Matter	Frontal Lobe Cortex	Frontal Lobe White Matter
GBCA group					
1	0.5	0.48	0.098	0.14	0.086
2	0.1	0.13	0.05	0.049	0.016
3	2.1	0.78	0.29	0.57	0.39
4	0.067	0.027	0.033	0.039	0.033
5	0.12	0.12	0.034	0.025	0.013
Mean	0.58	0.31	0.10	0.16	0.11
Non- GBCA group					
1	0.0002	0.0004	0.0002	<0.0016	<0.0016
2	<0.0016	<0.0016	0.0067	<0.0016	<0.0016
3	<0.0016	0.0053	<0.0016	<0.0016	<0.0016
4	<0.0016	<0.0016	<0.0016	<0.0016	<0.0016
5	0.0099	0.015	0.018	0.0066	0.0017
Mean	0.0020	0.0041	0.0050	0.0013	0.00034

Note.— Data are gadolinium concentration (measured in micrograms per gram of brain tissue).

The authors concluded that even in subjects without severe renal dysfunction, GBCA administration causes gadolinium accumulation in the brain, especially in the DN and GP.

Comments

The nature of the gadolinium and location within brain structures were not reported.

3.1.4.6 Murata *et al.* [28]

The purpose of this study was to determine whether gadolinium is deposited in brain and bone in patients receiving linear ionic or macrocyclic GBCAs.

Tissue samples were collected from nine decedents undergoing autopsy who had contrast-enhanced MRI with only single agent exposure to a GBCA. Decedents with only non-contrast MRI or no MRI served as controls (Table 11).

Table 11: General information on the decedents

Case ID	Age	Sex	Major Diagnosis	GBCA	No. of CEMRI	Total Dose, mL	Last-First CEMRI Before Death, d	Renal Function (eGFR)
1	26	F	SLE	Gadobutrol (Gadovist)	1	5	5	>60
2	65	F	Liver cirrhosis	Gadobutrol (Gadovist)	2	20	392–441	Recorded only as >30
3	50	M	AML	Gadoteridol (ProHance)	1	24	15	>60
4	31	F	DLBCL	Gadoteridol (ProHance)	11	126	19–318	>60
5	71	M	Gastric cancer	Gadoteridol (ProHance)	3	57	53–818	>60
6	80	F	Bladder cancer	Gadoteridol (ProHance)	1	18	118	>60
7	57	M	AML	Gadoteridol (ProHance)	1	20	90	>60
8	67	M	HCC	Gadoxetate (Eovist)	10	100	90–819	>60
9	50	M	HCC	Gadobenate (MultiHance)	1	20	83	>60
10	79	F	Interstitial pneumonia	Control				>60
11	67	M	AML	Control				>60
12	28	M	Lung tumor	Control				>60
13	54	F	CAD	Control				>60
14	54	F	Myocarditis	Control				23
15	76	M	Interstitial pneumonia	Control				32
16	77	M	Bladder cancer	Control				28
17	19	F	Heart disease	Control				>60
18	68	M	CAD	Control				>60

GBCA indicates gadolinium-based contrast agent; CEMRI, contrast-enhanced magnetic resonance imaging; SLE, systemic lupus erythematosus; AML, acute myelogenous leukemia; DLBCL, diffuse large B-cell lymphoma; HCC, hepatocellular carcinoma; CAD, coronary artery disease.

Multiple brain areas, including GP and DN, as well as bone and skin, were sampled and analyzed for gadolinium using inductively coupled plasma mass spectrometry.

Gadolinium levels were compared between groups of decedents using the Mann-Whitney test and between brain and bone tissues of the same cases using the Wilcoxon signed-rank test. To compare the levels of gadolinium deposition across the various agents studied as well as across the varying administered doses, the gadolinium deposition in the GP, DN, and bone in each study subject was normalized by the cumulative dose of gadolinium injected in each case. This yields a ratio of amount of gadolinium deposited (in micrograms) in 1 g of tissue per millimole of GBCA administered.

Table 12: Level of gadolinium deposition by tissue type

Case ID	GBCA	ICP-MS Results (µg/g tissue)							
		PT	GP	CA	WM	Pons	DN	Skin	Bone
1*	Gadobutrol (Gadovist)	0.216	0.625	0.201	0.205	0.107	1.07	NA	NA
2	Gadobutrol (Gadovist)	0.069	0.188	0.040	0.018	0.005	0.111	NA	5.280
3	Gadoteridol (ProHance)	0.039	0.066	0.019	0.020	0.020	0.078	NA	0.754
4	Gadoteridol (ProHance)	0.013	0.039	0.011	0.023	NA	NA	NA	1.620
5	Gadoteridol (ProHance)	0.011	0.023	0.008	0.006	NA	NA	NA	0.428
6	Gadoteridol (ProHance)	0.008	0.008	<0.004	0.003	<0.004	<0.004	0.005	0.098
7	Gadoteridol (ProHance)	<0.004	<0.005	<0.004	<0.004	<0.003	<0.005	0.002	0.094
8	Gadoxetate (Eovist)	0.067	0.148	0.051	0.013	NA	NA	NA	1.300
9	Gadobenate (MultiHance)	0.028	0.052	0.031	0.010	0.009	0.078	0.057	2.380
10	Control	<0.0006	<0.0005	<0.0005	<0.0003	NA	NA	NA	0.0006
11	Control	<0.0006	0.0008	<0.0005	0.0004	NA	NA	NA	0.0018
12	Control	0.0005	0.0008	<0.0006	0.0003	<0.0010	<0.0010	NA	0.0008
13	Control	<0.0005	<0.0007	<0.0006	<0.0004	NA	NA	NA	0.0009
14	Control	0.0025	0.0005	<0.0005	0.0003	NA	NA	NA	0.0031
15	Control	0.0007	<0.0010	<0.0009	0.0006	NA	NA	NA	0.0046
16	Control	<0.0030	<0.0030	<0.0060	<0.0020	NA	NA	NA	0.0020
17	Control	<0.0007	<0.0008	<0.0004	<0.0004	0.0007	0.0004	NA	0.0023
18	Control	<0.0008	<0.0009	<0.0007	<0.0006	<0.0010	0.0008	NA	0.0067

*Gadobutrol administered only 5 days before death.

Gd indicates gadolinium; GBCA, gadolinium-based contrast agent; ICP-MS, inductively coupled plasma mass spectrometry; PT, putamen; GP, globus pallidus; CA, caudate nucleus; WM, white matter; DN, dentate nucleus; NA, not available).

Gadolinium was found with all agents in all brain areas sampled with highest levels in GP and dentate (Table 12). Bone levels measured 23 times higher (median) than brain levels ($P = 0.008$ for bone vs globus pallidus) and showed a significant correlation ($r = 0.81$, $P = 0.022$). In controls, gadolinium levels in the brain were at or below limits of measurement and were significantly lower compared with study cases ($P = 0.005$ for GP).

The data from this study show that gadolinium is also deposited in tissues with macrocyclic agents (gadobutrol and gadoteridol) and two linear protein interacting agents (gadobenate and gadoxetate). This is important because previous *in vivo* studies of brain T1 SI showed no signal increase with macrocyclic agents such as gadoteridol and gadoterate (Dotarem), suggesting either no deposition or much lower deposition with these agents. This had not been confirmed with much more sensitive brain tissue analysis. Measurable levels of gadolinium were found in all brain areas sampled, including the caudate nucleus, putamen, cerebral white matter, and pons. Gadolinium was also found in the skin of the two gadoteridol cases in which the authors were able to obtain samples.

Although this is a small preliminary study, it is also important to stratify relative levels of deposition among the agents measured. The normalized ratios of deposition measured for the macrocyclic agent gadobutrol were unexpectedly higher, with one decedent (subject 1) measuring much higher than the average gadoteridol ratio and the other lower but still several times higher compared with gadoteridol. One possible explanation for study subject 1 is the fact that this decedent received gadobutrol only five days before death when terminally ill with septic shock and possibly with multiple organ failure. In this case, the gadolinium may also be in a so-called washout phase. Thus, subject 1 is likely an outlier. But the other gadobutrol case (subject 2) received his/her last dose 392 days before death and his/her analysis showed a much lower level of tissue gadolinium. In MRI studies on living patients no signal intensity change in DN and GP was reported with the administration of gadbutrol. In addition, no T1 shortening in cerebellar nuclei was reported in rats receiving gadobutrol. No conclusions can be drawn from this small sample size, and more studies are needed to evaluate this.

In reality, the size of the GP and the DN consists of only a few grams of tissue, and the amount of gadolinium deposited is very small, measuring only a few nanograms per gram of tissue. Thus, the total amount of gadolinium deposited in these cases was extremely small. However, of particular interest is the higher level of bone gadolinium deposition found in our cases.

Limitations of this study include the small number of cases and the retrospective nature of the study. Although all available records were carefully reviewed for each case, it was not possible to be completely certain that a decedent did not receive a CE-MRI with another agent that was not included in their records.

It is not determined from this study whether deposited gadolinium is dissociated or if it remains chelated. It is also not known if the gadolinium is extracellular or if some may be intracellular. Further studies are needed to address these important questions.

The authors conclude that gadolinium deposition in normal brain and bone tissue occurs with macrocyclic and linear protein interacting agents in patients with normal renal function. Deposition of gadolinium in cortical bone occurs at much higher levels compared with brain tissue and shows a notable correlation between the two. Thus, the bone may serve as a surrogate to estimate brain deposition if brain gadolinium were to become a useful clinical or research marker.

Comments

Many of the decedents had had their last GBCA administration within in a month of death. Data from the pre-clinical studies indicated that at least a month was required for the GBCA to wash out. The nature of the gadolinium in the brain was not investigated so it was not clear if this was due to an insoluble deposit or soluble gadolinium. The results appear to be at odds with the other clinical studies and the pre-clinical studies.

3.1.4.7 Quattrocchi *et al.* [29]

The authors conducted a retrospective study on patients with a meningioma who had routinely undergone follow-up enhanced MRI scans with gadodiamide (Omniscan). Across a time interval of 18 months (from January 2013 to July 2014), the authors identified 102 consecutive patients eligible for this study. Of these, to reduce selection bias, patients were included according to these criteria: (1) first brain MRI scan at the author's institution according to information extracted from the digital clinical chart and (2) absence of supratentorial and/or posterior cranial fossa comorbidity, either on brain images or on the archived reports. Enhanced MRI scans were conducted after an intravenous administration of gadodiamide in the authors' institution.

Forty-six patients (40 women, 6 men) in the age range of 46 to 87 years were included in the study. The patients were separated into three groups: Group A with one enhanced MRI scan (n = 10), Group B with one to five enhanced MRI scans (n = 28), and Group C with at least six MRI scans (n = 8). The authors replicated the method of measurement of unenhanced T1 signal intensity of the DN relative to the pons as previously published.

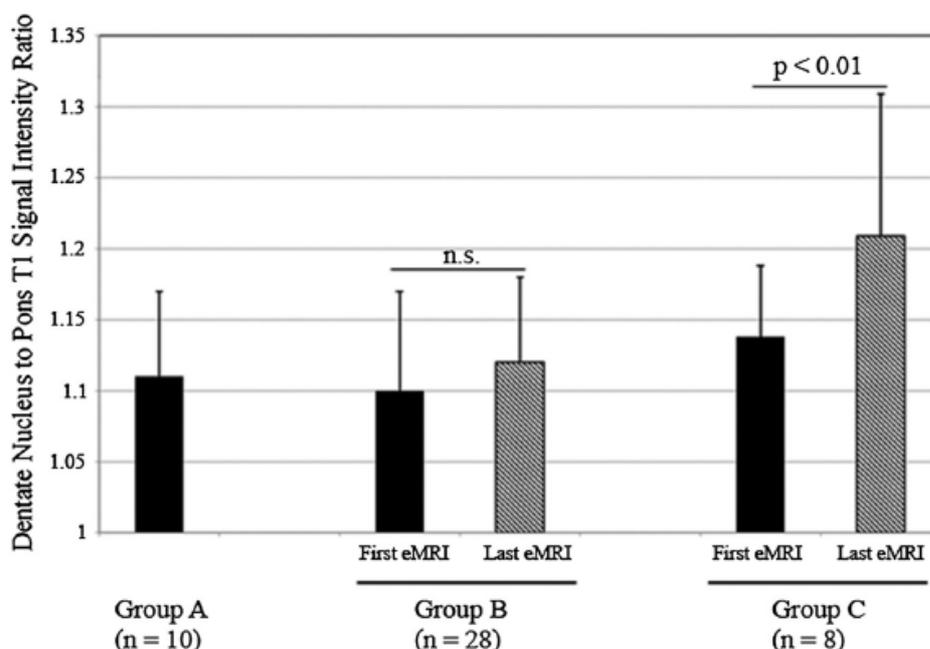


Figure 36: The graph plot shows the average and the standard deviations (error bars) of the dentate nucleus to pons ratios of the first (group A, group B, and group C) and the last (group B and group C) MRI scans in the groups of patients with 1, less than 6, and 6 enhanced MRI scans or more.

A significant increase in T1 hyperintensity of the dentate nuclei of the cerebellum on non-enhanced scans was observed between the first and the last MRI in the group of patients with a history of at least 6 enhanced MRI scans ($P < 0.01$), whereas no differences were observed in the group with 1 to 5 enhanced MRI scans ($P = 0.74$) (Figure 37).

The authors concluded that this analysis conducted on a cohort of consecutive patients with meningioma and with no systemic interval therapy confirms that T1 signal hyperintensity of the DN may be seen on unenhanced T1 images of patients undergoing multiple MRI scans with intravenous administration of gadodiamide.

To date, the authors have not received any report on neurological significant complaints that may be associated with the unenhanced T1 hyperintense DN in their patients. Nevertheless, there is a need to shed light on the mechanism of the T1 hyperintensity as well as to conduct a fine-grained analysis on the histological and microstructural appearance of the DN after multiple intravenous injections of gadodiamide in animal models and/or human studies.

3.1.4.8 Ramalho et al. [30]

The aim of this study was to determine if a correlation exists between the number of previous enhanced MRI examinations and high signal intensity in the GP and DN in patients who received gadodiamide (Omniscan; group 1), a linear non-ionic gadolinium-based contrast agent, and in those who received gadobenate (MultiHance; group 2), a linear ionic contrast agent.

The study population included 69 patients. Two radiologists conducted a quantitative analysis of unenhanced T1-weighted images by using region of interest measurements. The GP-to-thalamus (TH) signal intensity ratio, DN-to-middle cerebellar peduncle (MCP) signal intensity ratio and relative percentage change (R_{change}) between the first and last examinations for each patient were calculated. Relation between the signal intensity ratios and R_{change} and the number of enhanced MR imaging examinations was analyzed by using a generalized additive model. Inter- and intra-observer agreement was evaluated with the Lin concordance correlation coefficient test.

The patient characteristics are shown in Table 13.

Table 13: Demographic and patient characteristics by group

Characteristic	Group 1 (n = 23)	Group 2 (n = 46)
Age (y)	51.1 ± 14.9 (17–76)	60.2 ± 13.9 (29–86)
Sex*		
Female	19	24
Male	4	22
No. of MR imaging examinations	5.0 ± 2.4 (3–11)	4.6 ± 2.1 (3–11)
Interval (d)	1500.1 ± 780.2 (98–3097)	1086.2 ± 582.9 (94–2633)
Diagnoses	Meningioma (n = 13), pituitary lesions (n = 3), stroke (n = 2), posterior reversible encephalopathy syndrome (n = 1), intracranial aneurysm (n = 1), glomus jugular tumor (n = 1), clivus chordoma (n = 1), spinal hemangioblastoma (n = 1)	Pituitary lesions (n = 16), meningioma (n = 7), stroke (n = 11), breast cancer with no brain metastasis (n = 3), vestibular schwannoma (n = 2), clivus chordoma (n = 1), trigeminal mass (n = 1), cerebrospinal fluid leak (n = 1), intraventricular mass (n = 1), trauma (n = 1), acute hematoma (n = 1), epidermoid (n = 1)

Note.—Unless otherwise indicated, data are mean ± standard deviation, with the range in parentheses.
* Data are numbers of patients.

The interval between the first and last examination was 1500.1 days ± 780.2 (range, 98–3097 days) for group 1 and 1086.2 days ± 582.9 (range, 94–2633 days) for group 2. All patients had normal liver and renal function.

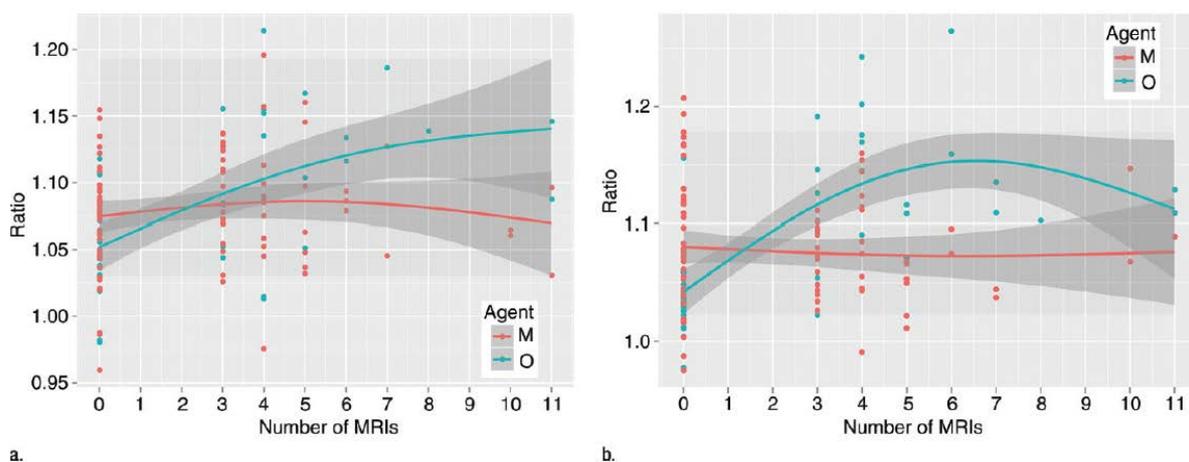


Figure 37: Graphs of the (a) GP:TH and (b) DN:MCP and signal intensity ratio differences between the first and last MR imaging examinations for the gadobenate (MultiHance) (M) group and the gadodiamide (Omniscan) (O) group.

Gadodiamide showed a significant increase in DN:MCP and GP:TH ($P < .001$ for both) and in R_{change} ($P = .001$ for GP:TH, $P < .001$ for DN:MCP). In group 2, there was no significant increase in DN:MCP or GP:TH over time or in R_{change} for GP:TH, but there was a significant trend toward an increase in R_{change}

for DN:MCP ($P = .013$) (Figure 38). Interobserver agreement was almost perfect (0.99; 95% confidence interval: 0.99, 0.99) for all evaluated structures.

The authors state that the study had some limitations. First, the results did not clarify whether gadolinium deposition in neural structures is purely dose dependent or whether it also depends on repeated administration of GBCAs. Another limitation was the lack of a control group of patients who did not receive a GBCA. However, multiple prior reports have shown that control groups composed of patients who did not undergo gadolinium enhancement have no signal intensity changes. An additional limitation was the potential confounding effect of variations between the groups studied, including age, sex, interval between the two examinations, and underlying disease processes. Finally, as with the majority of studies on GBCA use, it was essentially impossible to exclude with absolute certainty the possibility that other agents had been used in these patients.

In conclusion, a significant increase in GP:TH or DN:MCP is associated with multiple gadodiamide-enhanced studies but not with gadobenate-enhanced studies, likely reflecting differences in stability and elimination of both contrast agents. The rate-of-change data indirectly showed a considerable difference in gadolinium accumulation between the two GBCAs studied. However, it also suggested gadolinium deposition with gadobenate in the DN, although this was considerably less than that with gadodiamide.

3.1.4.9 Radbruch *et al.* [31]

The aim of this study was to determine the effect of more than 20 serial injections of macrocyclic GBCAs on the signal intensity of the DN on unenhanced T1-weighted MRI.

33 patients who underwent at least 20 consecutive MR imaging examinations (plus an additional MR imaging for reference) with the exclusive use of macrocyclic GBCAs gadoterate and gadobutrol were analysed (Table 14).

Exclusion criteria were:

- (a) oedema, tumour, or other lesions located in the cerebellum or pons
- (b) missing or unsatisfactory unenhanced T1-weighted MR imaging examination
- (c) widely varying MR imaging parameters between the first and the last MR imaging examination.

Signal intensity ratio differences were calculated for DN-to-pons and DN to-MCP ratios by subtracting the signal intensity ratio at the first MR imaging examination from the signal intensity ratio at the last MR imaging examination. One-sample t tests were used to examine if the signal intensity ratio differences differed from 0, and Bayes factors were calculated to quantify the strength of evidence for each test.

Patients underwent a mean of $23.03 \pm$ (standard deviation) 4.20 GBCA administrations (mean accumulated dose, $491.21 \text{ mL} \pm 87.04$ of a 0.5 M GBCA solution) with an average of $12.09 \text{ weeks} \pm 2.16$ between every administration (Table 14).

Both ratio differences did not differ significantly from 0 (DN-to-pons ratio: 0.0032 ± 0.0154 , $P = .248$; DN-to-MCP ratio: 0.0011 ± 0.0093 , $P = .521$), and one-sided Bayes factors provided substantial to strong evidence against a signal intensity ratio increase (Bayes factor for DN-to pons ratio = 0.09 and that for DN-to-MCP ratio = 0.12) (Table 15).

Table 14: Patient characteristics

Characteristic	Value
Total no. of patients	33
Age at first MR imaging examination (y)*	41.1 ± 10.5
Interval between first and last MR imaging examination (wk)*	273.06 ± 39.27
Mean interval between GBCA administrations (wk)*	12.09 ± 2.16
M/F	18/15
No. of enhanced MR imaging examinations*	23.03 ± 4.20
Cumulative dose (mL of 0.5 M GBCA solution)*	491.21 ± 87.04
Cumulative dose (mmol of gadolinium)*	245.60 ± 43.52
Gadoterate meglumine	174.30 ± 41.02
Gadobutrol	71.30 ± 29.56
Surgery†	28
Prior to measurement	23
During measurement	5
Chemotherapy†	29
Prior to measurement	4
During measurement	25
Received radiation therapy†	32
Prior to measurement	19
During measurement	13
Whole brain	2
Prior to measurement	2
During measurement	0
Tumor selective	27
Prior to measurement	15
During measurement	12
Unknown location	3
Prior to measurement	2
During measurement	1
Diagnosis	
Glioblastoma	8
Glioma World Health Organization grade I-III	23
Choroid plexus papilloma	1
Intramedullary melanotic tumor	1
Estimated glomerular filtration rate	
>90 mL/min per 1.73 m ²	26
50–90 mL/min per 1.73 m ²	6
Unknown	1
Abnormal liver function	11

Note.—Data are number of patients, unless indicated otherwise.

* Data are means ± standard deviation.

† Brain tumors are diagnosed in all patients. Subsections refer to the time of the excision of the tumor, chemotherapy, and radiation therapy relating to the study period.

A sensitivity power analysis showed that the mean difference that this study could have detected with a power of .80 was considerably smaller than the signal intensity ratio increases observed in a previous study with the linear GBCA gadopentetate, in which the identical analysis was applied (and only roughly a quarter of the amount of gadolinium compared with the current study was injected). Potential confounding factors in this study are the slightly varying parameters between the first and last MR imaging examination.

Table 15: Mean, standard deviations and results of the one sample t tests for different groups of patients

Patient Group and Measure	Mean*	Two-tailed PValue	Two-sided Bayes Factor	One-sided Bayes Factor: SI Increase	One-sided Bayes Factor: SI Decrease
All patients (n = 33)					
DN-to-pons ratio	-0.0032 ± 0.0154	.248	0.35	0.09	0.61
DN-to-MCP ratio	-0.0011 ± 0.0093	.521	0.23	0.12	0.33
< 3.5% deviation of TR and TE parameters (n = 17)					
DN-to-pons ratio	-0.0016 ± 0.0159	.683	0.27	0.19	0.35
DN-to-MCP ratio	-0.0024 ± 0.0090	.280	0.43	0.13	0.72
≥ 3.5% deviation of TR/TE parameters (n = 16)					
DN-to-pons ratio	-0.0048 ± 0.0152	.225	0.50	0.13	0.88
DN-to-MCP ratio	0.0004 ± 0.0097	.868	0.26	0.29	0.23
Patients from previously published studies (n = 13)					
DN-to-pons ratio	-0.0050 ± 0.0178	.327	0.43	0.16	0.71
DN-to-MCP ratio	-0.0007 ± 0.0124	.839	0.28	0.24	0.32
Patients not in previously published studies (n = 20)					
DN-to-pons ratio	-0.0019 ± 0.0140	.543	0.28	0.15	0.40
DN-to-MCP ratio	-0.0013 ± 0.0070	.425	0.31	0.14	0.49
Patients with pre-existing hyperintensities (n = 16)					
DN-to-pons ratio	-0.0035 ± 0.0163	.403	0.35	0.15	0.55
DN-to-MCP ratio	-0.0029 ± 0.0096	.237	0.49	0.13	0.84
Patients without pre-existing hyperintensities (n = 17)					
DN-to-pons ratio	-0.0028 ± 0.0150	.448	0.32	0.15	0.50
DN-to-MCP ratio	0.0007 ± 0.0089	.739	0.26	0.33	0.20

Note.—Bayes factors quantify the strength of evidence in favor of the alternative versus the null. All Bayes factors reported are < 1 hence representing at least anecdotal evidence for the null. To interpret Bayes factors, Jeffrey's (1961) classification (30) can be used: anecdotal (originally called "worth no more than a bare mention"), 1–0.33; substantial, 0.33–0.10; strong, 0.10–0.033; very strong, 0.033–0.01; decisive, < 0.01.

* Data are means ± standard deviation.

The authors conclude that this study indicates that 20 or more serial injections of macrocyclic GBCAs administered with on average three months between each injection are not associated with a signal intensity increase in the DN.

3.1.4.10 Oner *et al.* [10]

The authors aimed to present brain MRI changes after intrathecal administration of a linear ionic agent (gadopentetate, Magnevist).

Patients who had any type of contrast-enhanced MRI, before or after an intrathecal contrast-enhanced MR cisternography (CE-MRC) studies performed between 1998 and 2014 were included. Those with altered renal function, transplantation, diabetes, or known malignancies were excluded from the study. Patients who met the inclusion criteria were contacted and evaluated with a non-enhanced control brain MRI after written informed consent (Table 16).

Table 16: Patients demographics and image analysis results

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	
Age, sex	39, Male	49, Male	35, Male	15, Male	74, Male	23, Male	
CE-MRC date-elapsed time, year	2003–12	2004–11	2008–7	2011–4	2012–4	2008–8	
Pathology	CSF rhinorrhea	CSF rhinorrhea	CSF rhinorrhea	Arachnoid cyst	CSF rhinorrhea	CSF rhinorrhea	
Visual score	4	3	2	4	4	3	
Gp/Th	Initial unenhanced MRI	1.068	1.090	1.056	0.980	1.073	1.034
	Initial enhanced MRI	0.972	1.108	1.056	1.001	1.455	1.028
	Control unenhanced MRI	1.182	1.155	1.120	1.230	1.192	1.092
DN/Po	Initial unenhanced MRI	1.010	0.920	1.008	0.914	1.090	1.012
	Initial enhanced MRI	0.983	0.790	1.008	1.126	1.763	1.016
	Control unenhanced MRI	1.102	1.060	1.103	0.998	1.192	1.104

Comparison of the demographics and clinical characteristics together with image analysis.
CE-MRC indicates intrathecal contrast-enhanced MRI; Gp/Th, globus pallidus-to-thalamus signal intensity ratio; DN/Po, dentate nucleus-to-pons signal intensity ratio.

The CE-MRC protocol consisted of axial T2- (TR/TE, 3000/33 milliseconds; section thickness gap, 5 mm to 0.5 mm; field of view, 20 mm; matrix size, 288 x 192) and T1-weighted images (TR/TE, 550/12 milliseconds; section thickness gap, 5 mm to 0.5 mm; field of view, 20 mm; matrix size, 288 x 160) in

all three orthogonal planes, before and after intrathecal administration of 0.5 to 1 mL of gadopentetate (Magnevist; Bayer, Germany). The newly performed brain MRI scans were completed using the same 3T system and the same protocol, except that there were no contrast material administrations.

The authors evaluated hyperintensities in the deep nuclei of the brain in six patients with normal renal function after intrathecal administration of a linear ionic GBCA. The delay between CE-MRC and the control MRI ranged between two and 12 years, and all patients were doing well on their control visit.

For visual analysis, T1 signal hyperintensity of the GP, putamen, pons, and DN were scored on a 4-point scale. For quantitative analysis, using the unenhanced T1-weighted images oval regions of interests were placed within the DN, central pons, GP, and thalamus on different image slice positions.

On visual analysis, five patients had T1 signal hyperintensity of the DN and GP, whereas the DN/pons signal intensity and the GP/thalamus signal intensity were found to be increased in all six.

Intrathecal administration is an established method in patients with suspected intracranial hypotension, CSF leakage, and those evaluated with arachnoid cysts. There have also been recent reports concerning the use of intrathecal GBCA in the potential assessment of the glymphatic function of the brain. It has been demonstrated in rats that administration of gadopentetate (Magnevist) into the cisterna magna resulted in distribution throughout the entire brain, giving proof of function of the glymphatic pathway. Similar observation in a human has also been recently published as a case report.

A second important difference of this article from previous reports is in the total number of injections and amount of GBCA administered. All patients included in this study received only a single dose of gadopentetate (Magnevist) intrathecally. Although the total amount is very small (0.5–1 mL), it is directly introduced to the subarachnoid space, is not diluted in the blood, does not have to cross the blood-brain barrier, and therefore may explain the rationale for similar imaging results as in patients who received repeated intravenous injections of the same GBCA in larger amounts.

In addition, the observation that the affected brain areas are the same regardless the way of injection of GBCA may also point to the importance of the glymphatic pathway in understanding gadolinium retention in the CNS.

The authors note that the small sample size and lack of autopsy results are important limiting factors for this report. Although the intrathecal route is an accepted way of administration for GBCA, it is certainly much less frequent compared with intravenous injection. It is also very likely for a patient having a CE-MRC, to have prior or future MRI studies conducted with intravenous injection of gadolinium. Therefore, when the aim is to observe the effect of intrathecally injected GBCA alone, the patient population from a single site is even less. Another possible limitation is that this study includes only patients with normal renal function who only underwent CE-MRC with a linear GBCA.

The authors conclude that brain MRI abnormalities do occur after intrathecal administration of GBCA as well, and the glymphatic pathway can help in understanding this deposition.

Comments

This study appears to support the hypothesis that GBCAs reach the brain via the CSF.

3.1.4.11 Flood *et al.* [32]

The aim of this study was to determine whether repeated exposure of the paediatric brain to a linear GBCA is associated with an increase in signal intensity relative to that in GBCA-naive control subjects at unenhanced T1-weighted MRI.

The authors evaluated 46 paediatric patients who had undergone at least three GBCA-enhanced MR examinations (30 patients for two-group analysis and 16 for pre- and post-GBCA exposure comparisons) and 57 age-matched GBCA-naive control subjects (Table 17).

The SI in the globus pallidus, thalamus, dentate nucleus, and pons was measured at unenhanced T1-weighted MR imaging. Globus pallidus–thalamus and dentate nucleus–pons SI ratios were calculated and compared between groups and relative to total cumulative gadolinium dose, age, sex, and number of and mean time between GBCA-enhanced examinations. Analysis included the Wilcoxon signed rank test, Wilcoxon rank sum test, and Spearman correlation coefficient.

Table 17: Summary of group characteristics

Characteristic	Two-Group Comparison		
	GBCA-exposed Patients (n = 30)	GBCA-naive Control Subjects (n = 57)	Pre- and Post-GBCA Comparison (n = 16)
Age			
Mean (y)	10.1 ± 4.8	9.1 ± 5.5	8.3 ± 4.1
Range	69 d to 18 y	60 d to 19 y	310 d to 18 y
Sex			
M	20	31	13
F	10	26	3
Mean no. of contrast-enhanced MR examinations	5.9 ± 2.7	0	5.8 ± 2.1
Mean interval between contrast-enhanced examinations (d)	122 ± 86
Mean accumulated gadolinium dose (g)	16.2 ± 10.1
Initial MR findings necessitating follow-up			
Extracranial neoplasm	14	0	5
Pituitary abnormality	6	0	4
Transient parenchymal enhancement	3	0	2
Orbit/optic nerve abnormality	3	0	0
Mild volume loss	1	0	0
Perimesencephalic lipoma	1	0	0
Cavernous sinus cyst	1	0	0
Clival mass	1	0	0
Sinus disease	0	0	3
Choroid plexus abnormality	0	0	1
Unilateral temporalis muscle abnormality	0	0	1
No. of subjects with unenhanced T1-weighted images			
MPRAGE sequence	30	57	7
Spin-echo sequence	0	0	9
Matched pre- and postcontrast MR sequences	16

Note.—Except where indicated, data are numbers of subjects.

Patients who underwent multiple GBCA-enhanced examinations had increased signal intensity ratios within the DN (Figure 39).

Mean signal intensity ratio ± standard error of the mean for two-group comparison:

- 1.007 ± 0.0058 for GBCA-naive group and
- 1.046 ± 0.0060 for GBCA-exposed group [P < .001].

Mean signal intensity ratio for pre- and post-GBCA comparison:

- 0.995 ± 0.0062 for pre-GBCA group and
- 1.035 ± 0.0063 for post-GBCA group [P, .001]

There was no enhanced ratio in the GP.

Mean signal intensity ratio for two-group comparison:

- 1.131 ± 0.0070 for GBCA naive group and
- 1.014 ± 0.0091 for GBCA-exposed group [P = .21].

Mean signal intensity ratio for pre- and post-GBCA comparison:

- 1.068 ± 0.0094 for pre-GBCA group and
- 1.093 ± 0.0134 for post-GBCA group [$P = .12$].

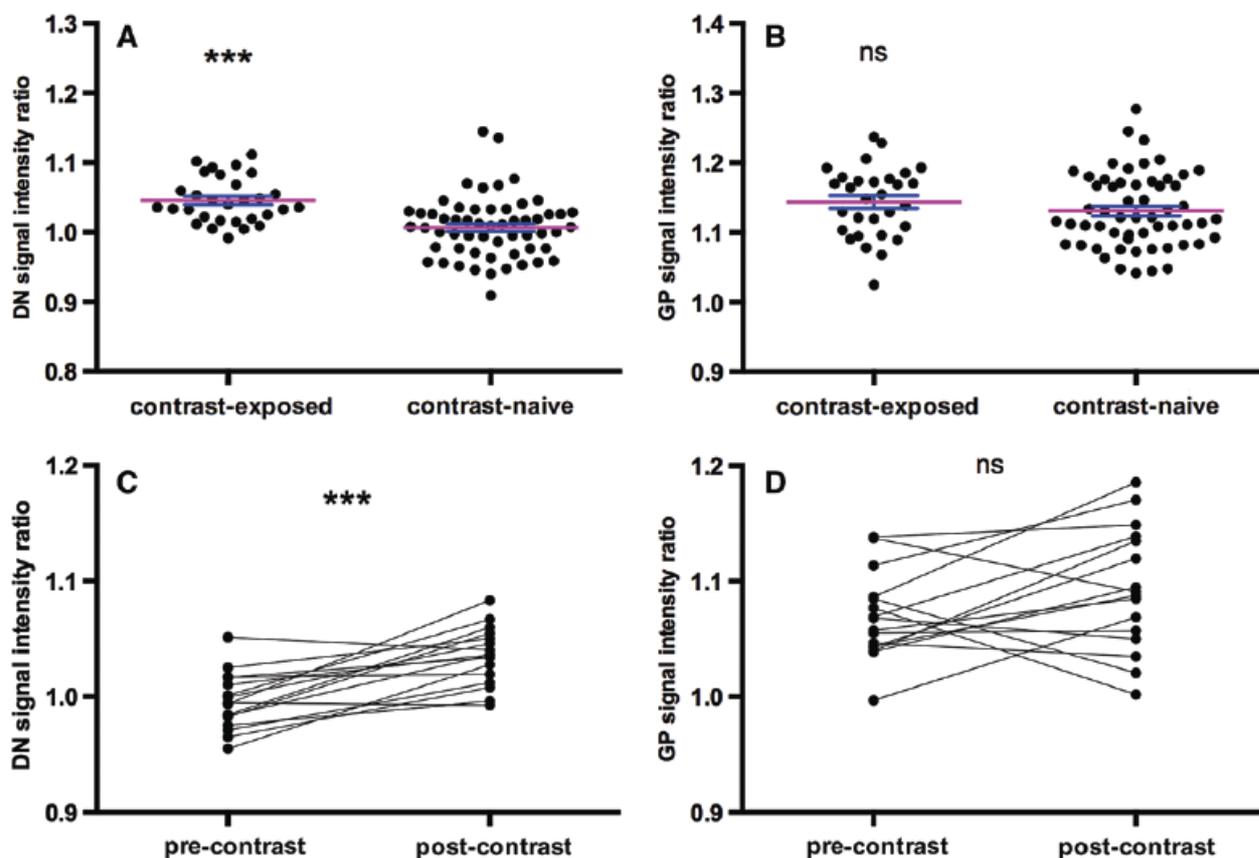


Figure 38: Column scatter graphs show intraparenchymal signal intensity increases with repeated exposure to linear GBCA. ns = not significant, *** = statistically significant. A, B, Two-group comparison of intraparenchymal SI ratios, comparing GBCA-exposed patients with age-matched GBCA-naive control subjects, demonstrates increased signal intensity after repeated contrast material exposures within, A, DN but not, B, GP. Magenta line in A & B indicates mean; blue lines indicate \pm standard errors of mean. C, D, Comparison of intraparenchymal SI ratios before and after GBCA exposure demonstrates increased SI after repeated contrast material exposures within, C, DN but not, D, GP.

There was a significant correlation between dentate nucleus SI and total cumulative gadolinium dose ($r = 0.4$; 95% confidence interval [CI]: 0.03, 0.67; $P = .03$), but not between dentate nucleus SI and patient age ($r = 0.23$; 95% CI: 0.15, 0.56; $P = .22$), sex (mean SI ratio: 1.046 ± 0.0072 for boys and 1.045 ± 0.0110 for girls; $P = .88$), number of contrast-enhanced examinations ($r = 0.13$; 95% CI: 0.25, 0.48; $P = .49$), or time between contrast-enhanced examinations ($r = 0.06$; 95% CI: 0.42, 0.32; $P = .75$).

Increased DN–pons signal intensity ratios on unenhanced T1-weighted MR images in paediatric patients with repeated exposure to a linear GBCA are consistent with the adult data and are likely related to intracranial gadolinium deposition. However, the lack of a corresponding statistically significant increase in GP– thalamus signal intensity ratios is contrary to the findings in adult studies. One possible explanation for this discrepancy is that paediatric patients needed more GBCA exposure to demonstrate the signal intensity ratios found in adults.

The authors concluded that signal intensity in the paediatric brain increases on unenhanced T1-weighted MR images with repeated exposure to a linear GBCA.

3.1.4.12 Ichikawa *et al.* [33]

The authors performed a retrospective study to evaluate whether an association exists between T1-signal increase in the DN on unenhanced MRI and previous administration of gadoxetic acid (Primovist) and gadodiamide (Omniscan).

A total of 132 patients (mean age, 68.8 ± 11.6 years) who underwent imaging between December 2000 and April 2016 were divided into four groups: patients with five or more administrations of gadoxetic acid, only one administration of gadoxetic acid, no gadolinium-based contrast agent (GBCA) administration or chronic liver disease, and or more administrations of gadodiamide (Figure 40).

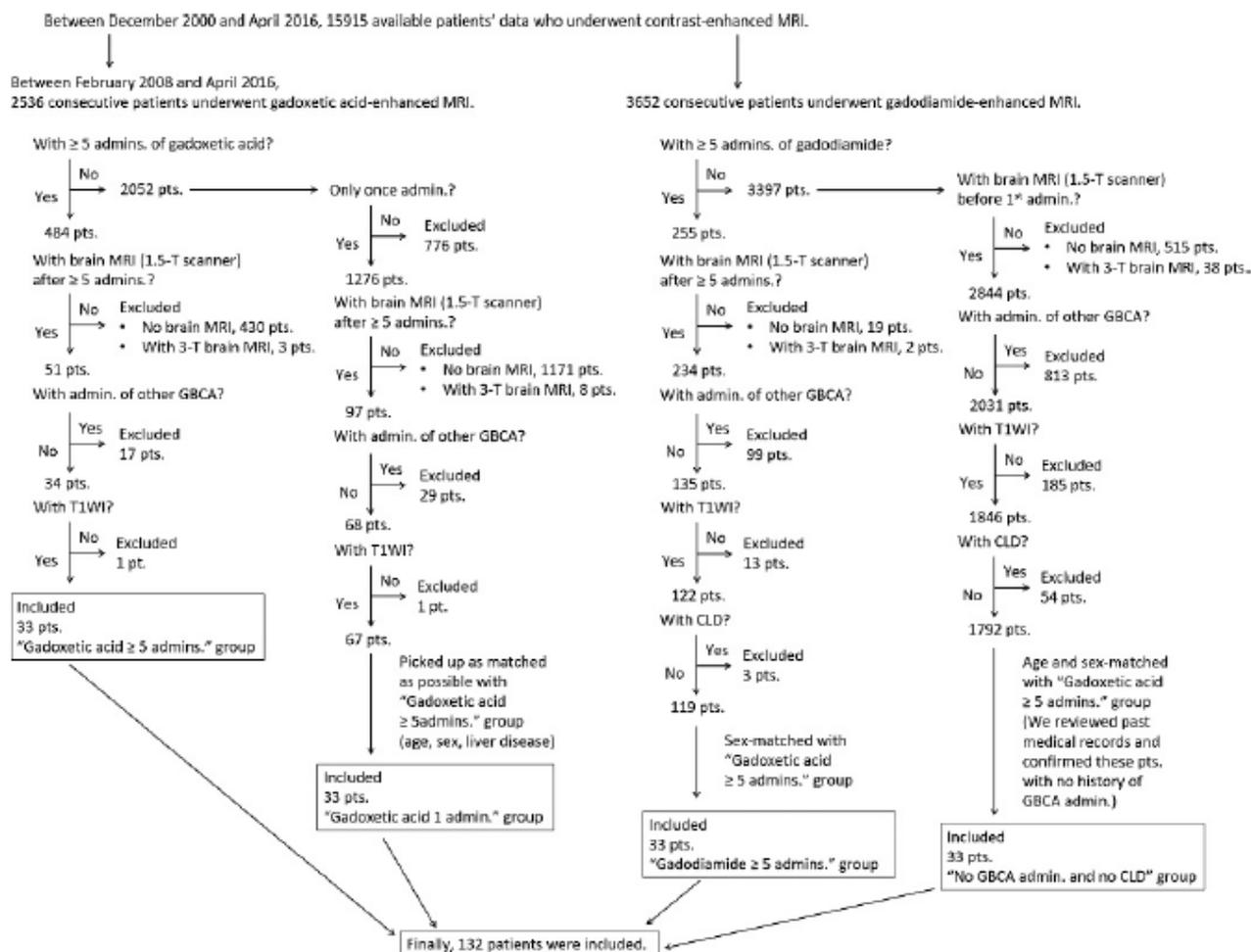


Figure 39: Inclusion criteria for participant enrolment

The clinical indications for the gadodiamide-enhanced MRI were follow-up study for meningioma (n = 11), astrocytic tumors (n = 7), oligodendroglial tumours (n = 3), metastatic tumours (n = 3), acoustic neurinoma (n = 2), malignant lymphoma (n = 1), pituitary adenoma (n = 1), hemangioblastoma (n = 1), germinoma (n = 1), multiple sclerosis (n = 1), carotid-cavernous fistula (n = 1), and mycotic sinusitis (n = 1).

Unenhanced T1-weighted images were quantitatively analyzed by two radiologists. Intergroup comparison of DN-to-pons signal intensity ratios was performed by the Dunn test, with the no GBCA administration and no chronic liver disease group as control. Interobserver agreement was assessed by intraclass correlation coefficients.

The DN-to-pons ratio of the “gadodiamide ≥ 5 administrations” group was significantly higher (P < 0.0001) and those of the “gadoxetic acid ≥ 5 administrations” and “gadoxetic acid one

administration” groups did not differ significantly ($P = 0.3912$ and 1.0000 , respectively) compared with the DN-to-pons ratio of the “no GBCA administration and no chronic liver disease” group (Figure 41). The interobserver intraclass correlation coefficient for measurement of DN-to-pons ratio was excellent (0.835 ; 95% confidence interval, 0.767 – 0.883).

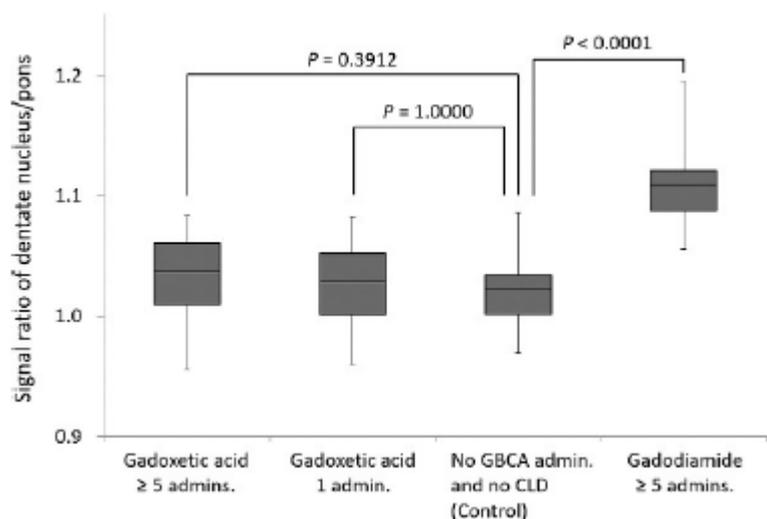


Figure 40: Signal ratios of DN to pons in the four groups

The present study has several limitations. First, the authors used a section thickness of 5 mm for acquisition of unenhanced T1-weighted images using the spin-echo sequence. Because the DN is not a large structure, on unenhanced T1-weighted images acquired before or after nine administrations of gadoxetic acid the results might have been influenced by the partial volume effect.

Second, most patients in the “gadodiamide ≥ 5 administrations” group had not undergone brain MRI previously. Therefore, instead of comparing DN-to-pons signal intensity ratios between brain MRI scans acquired before and after five or more administrations of gadodiamide, as would have been ideal, the authors performed comparisons among the “gadodiamide ≥ 5 administrations,” “gadoxetic acid one administration,” and “no GBCA administration and no chronic liver disease” groups, with the “no GBCA administration and no chronic liver disease” group as control.

In addition, there were differences in patient data in terms of age, eGFR, time between first gadolinium administration and last MR scan, and underlying liver diseases between these groups. Moreover, the authors were unable to include patients with chronic liver disease but without a history of GBCA administration in the present sample because of the difficulty in identifying such patients.

The authors concluded that hyperintensity in the DN on unenhanced T1-weighted images is associated with previous administration of gadodiamide but not gadoxetic acid. Although the number of administrations for the two GBCA groups was identical, the administered dose of gadoxetic acid was only a quarter the amount of gadolinium as those with gadodiamide. This difference might influence the results of this study.

3.1.4.13 Zhang *et al.* [34]

The aim of this study was to explore the extent of signal hyperintensity in the brain on unenhanced T1-weighted MRI with increasing GBCA doses in patients who received 35 or more linear GBCA administrations.

Among an estimated 179,121 contrast material–enhanced MR imaging studies performed over the 15-year study period, computerized searching identified 33 (0.02%) patients with 35 or more GBCA-enhanced MR examinations. However, in seven (21%) of the 33 patients, some GBCA administrations were macrocyclic GBCA; therefore, these patients were excluded. In 13 (39%) of the 33 patients, no

baseline MR images obtained before GBCA administration were available; therefore, these patients also were excluded (Table 18).

Table 18: Demographic data

Parameter	Finding
Current age (y)*	51 ± 13 (21–68)
Male-to-female ratio	8:5
Total no. of linear GBCA injections*	43 ± 5 (39–59)
Time between initial and final GBCA injection (y)*	8.2 ± 1.6 (6.5–12.1)
Time between final injection and final measurement (y)*	60 ± 26 (23–100)
Primary MR imaging indication	
High-grade glioma	
Glioblastoma multiforme	3
Anaplastic oligodendroglioma	3
Low-grade glioma	
Astrocytoma	1
Oligodendroglioma	1
Nonglioma brain primary	
Lymphoma	2
Cerebellar medulloblastoma	1
Meningioma	1
Germinoma	1
History of neurosurgery	11
History of any chemotherapy	
Molecularly targeted therapy	2
Ankylating agents	6
Both ankylating agents and molecularly targeted therapy	1
Other chemotherapy	3
Radiation	
Whole brain	0
Tumor selective	10
Abnormal liver function	0
Abnormal renal function	0

Note.—Unless otherwise indicated, data are numbers of findings.
* Data are mean ± standard deviation. Data in parentheses are the range.

Unenhanced T1-weighted images of the brain in patients after six, 12, and 24 GBCA administrations and after the final GBCA administration were independently reviewed by three radiologists to identify sites where T1 signal intensity was increasing. Areas identified by all three observers as increasing in T1 signal intensity when compared with baseline images were further analyzed with a quantitative region of interest analysis measuring the rate of signal increase per injection and the total change after 24 linear GBCA administrations relative to reference tissues that did not show T1 shortening.

Qualitative analysis of 13 patients with 39–59 linear GBCA administrations showed visually detectable T1 shortening in the:

- dentate nucleus (n = 13)
- globus pallidus (n = 13)
- substantia nigra (n = 13)
- posterior thalamus (n = 12)
- red nucleus (n = 10)
- colliculi (n = 10)
- superior cerebellar peduncle (n = 7)
- caudate nucleus (n = 4)
- whole thalamus (n = 3)
- putamen (n = 2) (Table 19).

Quantitative analysis enabled confirmation of signal intensity increases on unenhanced T1-weighted images relative to reference tissues in the DN (0.53% signal intensity increase per injection, $P < .001$), GP (0.23% increase, $P = .009$), posterior thalamus (0.26% increase, $P < .001$), substantia nigra (0.25% increase, $P = .01$), red nucleus (0.25% increase, $P = .01$), cerebellar peduncle (0.19% increase, $P = .001$), and colliculi (0.21% increase, $P = .02$).

Prior reports of signal intensity increases on unenhanced T1-weighted images in the DN and GP do not mention the substantia nigra, red nucleus, posterior thalamus, cerebellar peduncle, or colliculi. This likely reflects the smaller mean number of GBCA administrations in those studies. The detection of gadolinium in so many locations challenges our understanding of GBCA biodistribution (Figure 42).

Table 19: Brain structures appearing hyperintense relative to adjacent tissue on unenhanced T1-weighted images at baseline and after 6, 12, 24 and all GBCA injections

Brain Structure	Baseline (%)	After Six GBCA Injections (%)	After 12 GBCA Injections (%)	After 24 GBCA Injections (%)	After Final GBCA Injection (%)*
Dentate nucleus	0 (0, 2)	69 (44, 94)	100 (98, 100)	100 (98, 100)	100 (98, 100)
Substantia nigra	23 (0.12, 46)	77 (54, 100)	100 (98, 100)	100 (98, 100)	100 (98, 100)
Globus pallidus	31 (6, 56)	62 (36, 88)	92 (77, 100)	100 (98, 100)	100 (98, 100)
Posterior thalamus	0 (0, 2)	0 (0, 2)	54 (27, 81)	85 (66, 100)	92 (77, 100)
Red nucleus	0 (0, 2)	8 (0, 23)	23 (0.12, 46)	62 (36, 88)	77 (54, 99)
Colliculi	0 (0, 2)	0 (0, 2)	31 (6, 56)	62 (36, 88)	77 (54, 99)
Superior cerebellar peduncle	0 (0, 2)	0 (0, 2)	23 (0.12, 46)	38 (12, 64)	54 (27, 81)
Head of caudate	0 (0, 2)	0 (0, 2)	8 (0, 23)	15 (0, 34)	31 (6, 56)
Body of caudate	0 (0, 2)	0 (0, 2)	8 (0, 23)	23 (0.12, 46)	31 (6, 56)
Whole thalamus	0 (0, 2)	0 (0, 2)	0 (0, 2)	8 (0, 23)	23 (0.12, 46)
Putamen	0 (0, 2)	0 (0, 2)	8 (0, 23)	15 (0, 34)	15 (0, 34)

Note.—Data are the percentage of 13 patients in whom the structure is hyperintense on unenhanced T1-weighted MR images. Data in parentheses are 95% confidence intervals.

* Total number of GBCA injections in each patient ranged from 39 to 59 (mean, 43 injections).

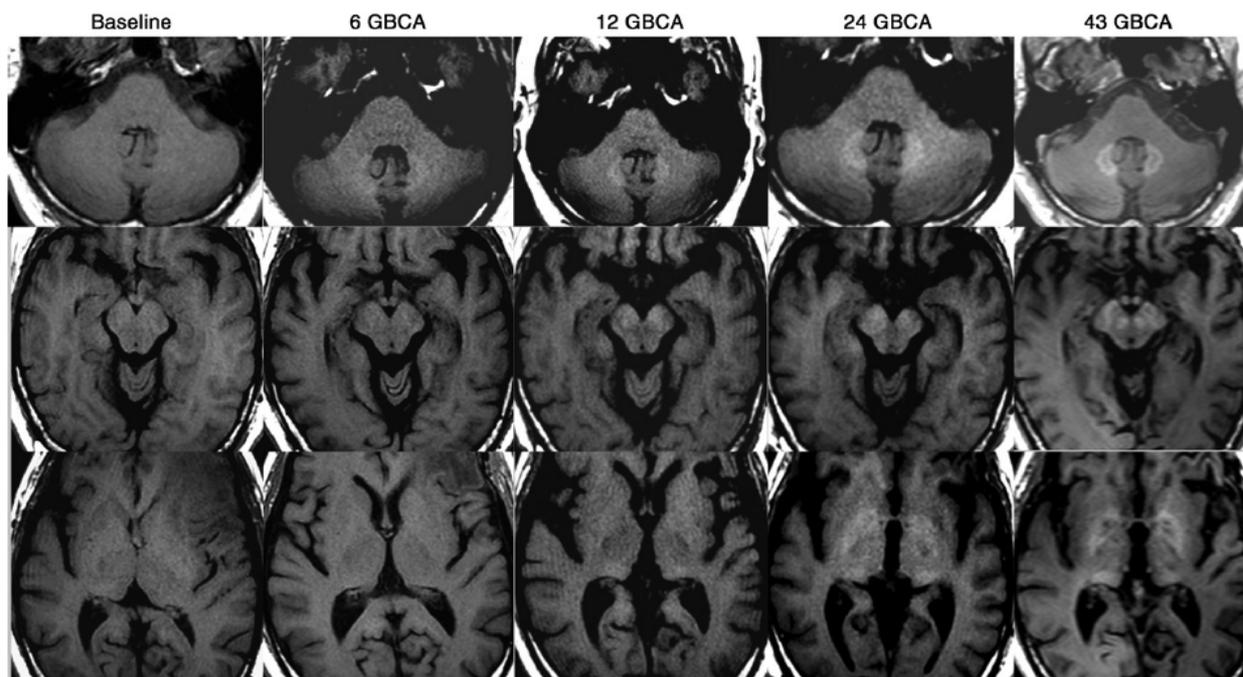


Figure 41: MR images in a 52-year-old man with left frontal glioblastoma. Dentate nucleus (top), cerebral peduncle, substantia nigra, and red nucleus (middle), and globus pallidus and posterior thalamus (bottom) eventually all have increased unenhanced T1 signal intensity after 43 linear GBCA administrations

In this cohort, all patients had brain tumours. This was a confounding variable, but there was no significant difference between signal intensity changes ipsilateral to the tumours versus those contralateral to the tumours. This suggests that the blood-brain barrier breakdown associated with brain tumours does not confer any greater GBCA accumulation in nearby tissues.

The authors state that the study did have some limitations. There were only 13 patients who had undergone more than 35 linear GBCA administrations, and data were available for quantitative analysis in only 11 patients. For linear regression analysis, not all time points were precisely at six, 12, and 24 GBCA injections; this also was due to the need to ensure consistent field strength and pulse sequence type. All patients had a similar history of brain tumour, and none of these patients had analytic proof of gadolinium accumulation in the brain tissues. Accordingly, the authors do not know definitively that these changes are directly related to the linear GBCA administrations; false-positive findings are possible. The possibility that these results derive from some aspect of the patient's tumour or treatment is also a consideration.

The authors conclude that increased signal intensity on unenhanced T1-weighted images was seen in the posterior thalamus, substantia nigra, red nucleus, cerebellar peduncle, colliculi, DN, and GP.

3.1.4.14 Semelka *et al.* [35]

Participants were recruited from two online gadolinium toxicity support groups. The survey was anonymous and individuals were instructed to respond to the survey only if they had evidence of normal renal function, evidence of gadolinium in their system beyond 30 days of MRI, and no pre-existent clinical symptoms and/or signs of this type.

Inclusion criteria were as follows: (a) subjects with normal renal function who experienced severe and persistent symptoms with onset from 1 to 365 days following GBCA administration; and (b) who had laboratory evidence of presence of gadolinium in their body beyond 30 days following the inciting MRI examination.

Finally, direct medical examination was performed by a physician with expertise in NSF, on three random participants, one in the early stage and two in the late stage, to verify physical exam findings.

42 subjects responded to the survey (age: 28–69, mean 49.1 ± 22.4 years). The most common findings were: central pain ($n = 15$), peripheral pain ($n = 26$), headache ($n = 28$), and bone pain ($n = 26$). Only subjects with distal leg and arm distribution described skin thickening ($n = 22$). Clouded mentation and headache were the symptoms described as persistent beyond three months in 29 subjects.

Residual disease was present in all patients. Twenty-eight patients described symptoms following administration of one brand of GBCA, 21 after a single GBCA administration and seven after multiple GBCA administrations, including: gadopentetate, $n = 9$; gadodiamide, $n = 4$; gadoversetamide, $n = 4$; gadobenate, $n = 4$; gadobutrol, $n = 1$; gadoteridol, $n = 2$; and unknown, $n = 4$ (Figure 43).

The authors state that many of the respondents' reported signs and symptoms are consistent among subjects, and include various findings similar, but less severe than found in NSF. Based on these results, the authors' propose a name for this presumed disease process in subjects with normal renal function and gadolinium toxicity, gadolinium deposition disease (GDD).

At least 60% of the subjects showed a glove-and-sock distribution of disease associated with intense sharp "pins and needles" or burning pain, and skin changes, resembling NSF. Other examples of similar but less severe changes compared to NSF include: tissue in NSF is often described as woody and joint contractions severe, whereas subjects in our survey have reported as spongy or rubbery, and joint flexures minimal.

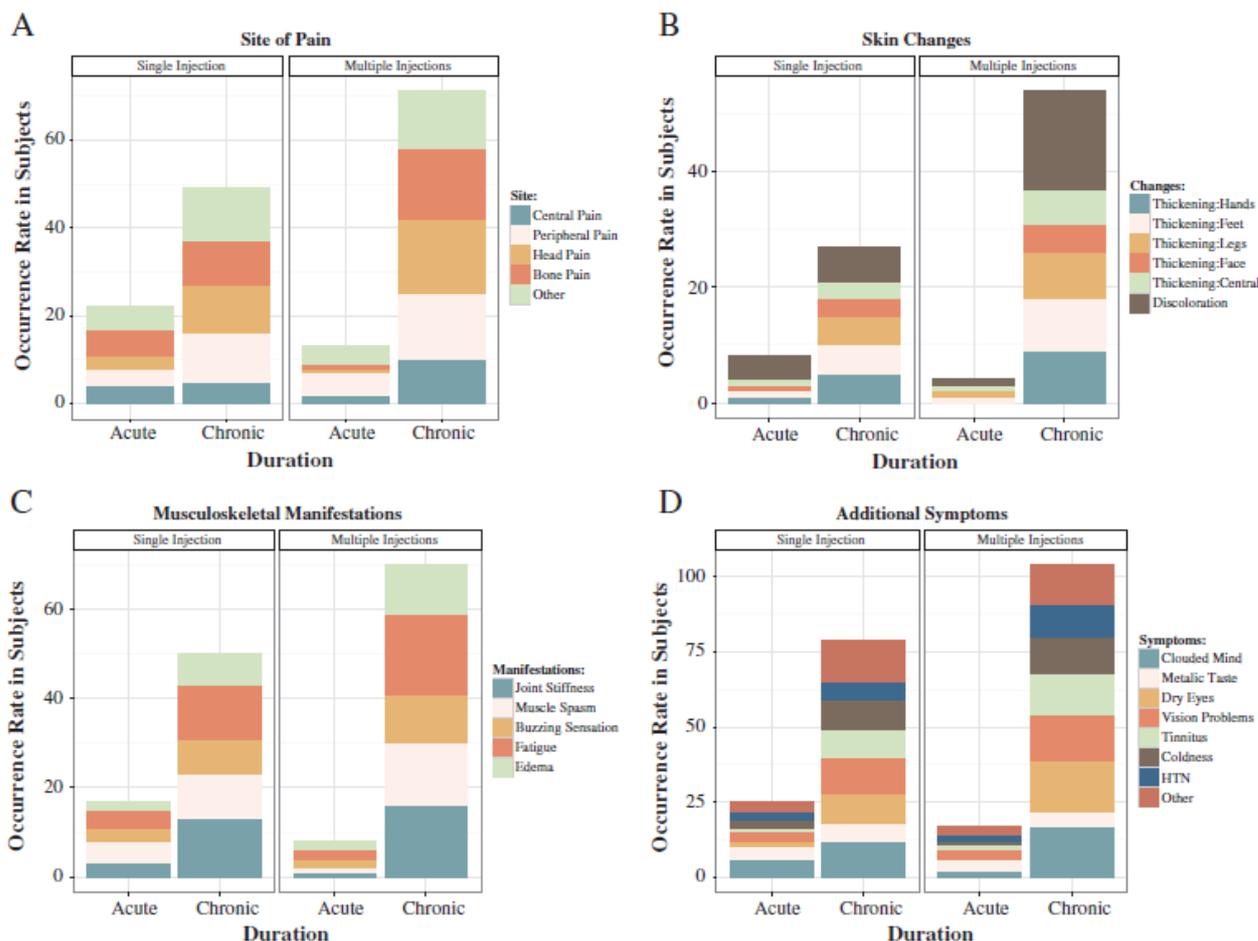


Figure 42: Graphic representation of the symptoms occurrence rate in early (b3 months) and chronic phase (N3 months): pain location (A), skin changes (B), musculoskeletal manifestations (C) and additional symptoms (D).

In reviewing the agents, the suspected causative GBCAs whose unconfounded use resulted in reported symptoms, were also those more related to NSF. However, some individuals also reportedly developed this disease following MultiHance, a linear agent with intermediate stability, but also after macrocyclic agents, which are the most stable. In this survey, the only agent that was not associated with presumed toxicity was Dotarem. It should however be acknowledged that Dotarem is the most recently FDA-approved GBCA and has probably the lowest number of doses administered in the USA, where this data is acquired from.

The authors note that there are various limitations of this study. Major problems include that it is a survey and relies on knowledge and integrity of the respondents. A control group of subjects who received multiple administrations of GBCAs, but who do not have symptoms would be helpful. As an anonymous survey with predefined questions, the authors neither asked nor had access to the clinical indications for the MR examinations.

The authors conclude that gadolinium toxicity appears to arise following GBCA administration, which appears to contain clinical features seen in NSF, but also features not observed in that condition.

Comments

These cases are potentially confounded by the patients underlying condition (which required imaging) and could also represent conversion disorders and other anxiety-related conditions.

3.1.4.15 Comments on the clinical information

A number of clinical studies have been published which show an increase in signal intensity in the brain on non-enhanced MRI. These are generally single institution cases series. The indication for MRI with contrast varies between and within these series. It is not yet clear if the indication confounds the outcomes, although the animal studies suggest that it doesn't. The numbers of patients included in the studies are generally small due to difficulties in ensuring that only one agent has been administered. Most authors still consider that there is a risk the patient may have been administered a mix of agents as this does not seem to be well documented in the patient notes or there is the possibility they obtained a scan elsewhere. In addition, all the case series were retrospective with little control on the timing of scans or the parameters used in the scans.

Increased signal intensity is seen on MRI without contrast mainly in two brain areas, the DN and GP. The majority of studies show an increase in signal intensity after administration of linear agents. Only one study (mentioned in the systematic review) claimed a signal intensity with a macrocyclic agent; this study has been discredited as the supporting published MRI image does not show any signal intensity increase.

That the signal intensity seen on MRI was due to gadolinium has been confirmed in autopsy studies. Two autopsy studies found gadolinium in brain after administration of linear GBCAs, one preliminary study found gadolinium in the brain after administration of macrocyclic agents. This finding seems at odds with the other evidence. The form of the gadolinium was not determined and in some cases may have been due to soluble gadolinium still chelated. This was a preliminary study which did not determine the form of Gd or the location within the brain.

Although a signal intensity increase in the brain is seen after administration of linear GBCAs it is still not clear if there is a difference between these agents. In addition it appears that at least five intravenous administrations of linear GBCA are needed before a signal intensity is seen on MRI. However, when the GBCA is given intrathecally only one administration was needed to result in a signal intensity increase.

The effect appears to be similar in children, although signal intensity was only seen in DN not GP.

For patients given more than 35 administrations of linear GBCA, the amount of deposition increases with signal intensity increase on MRI seen in more brain regions. The location of the gadolinium deposits appears to be in the capillary endothelium and neural interstitium. Other heavy metals were detected in similar deposits in the brain in the same studies. These studies were not specifically designed to investigate whether the deposited gadolinium can be removed from the brain. The fact that signal intensity increase is seen years after administration suggests that the gadolinium is not removed.

In general, authors of these studies state that no adverse effects have been noted from gadolinium deposition. However, a patient action group has been formed in the US by patients who believe they have been harmed by GBCAs. The symptoms they report seem to be general symptoms that could be attributed to many different syndromes or conditions. At least one patient has reported symptoms in association with macrocyclic GBCA administration for which there is little to no evidence of brain deposition. Also patients report symptoms after only one administration whereas brain deposits were generally only visible after five or more administrations. Most patients undergoing MRI have significant health conditions which may be confounding factors.

In conclusion, a signal intensity increase on unenhanced MRI has been seen in the brain of patients administered linear GBCAs generally more than five times. That this signal intensity increase was due to gadolinium has been confirmed in autopsy studies. To date no histopathological changes have been noted and the evidence of a clinical effect is extremely weak.

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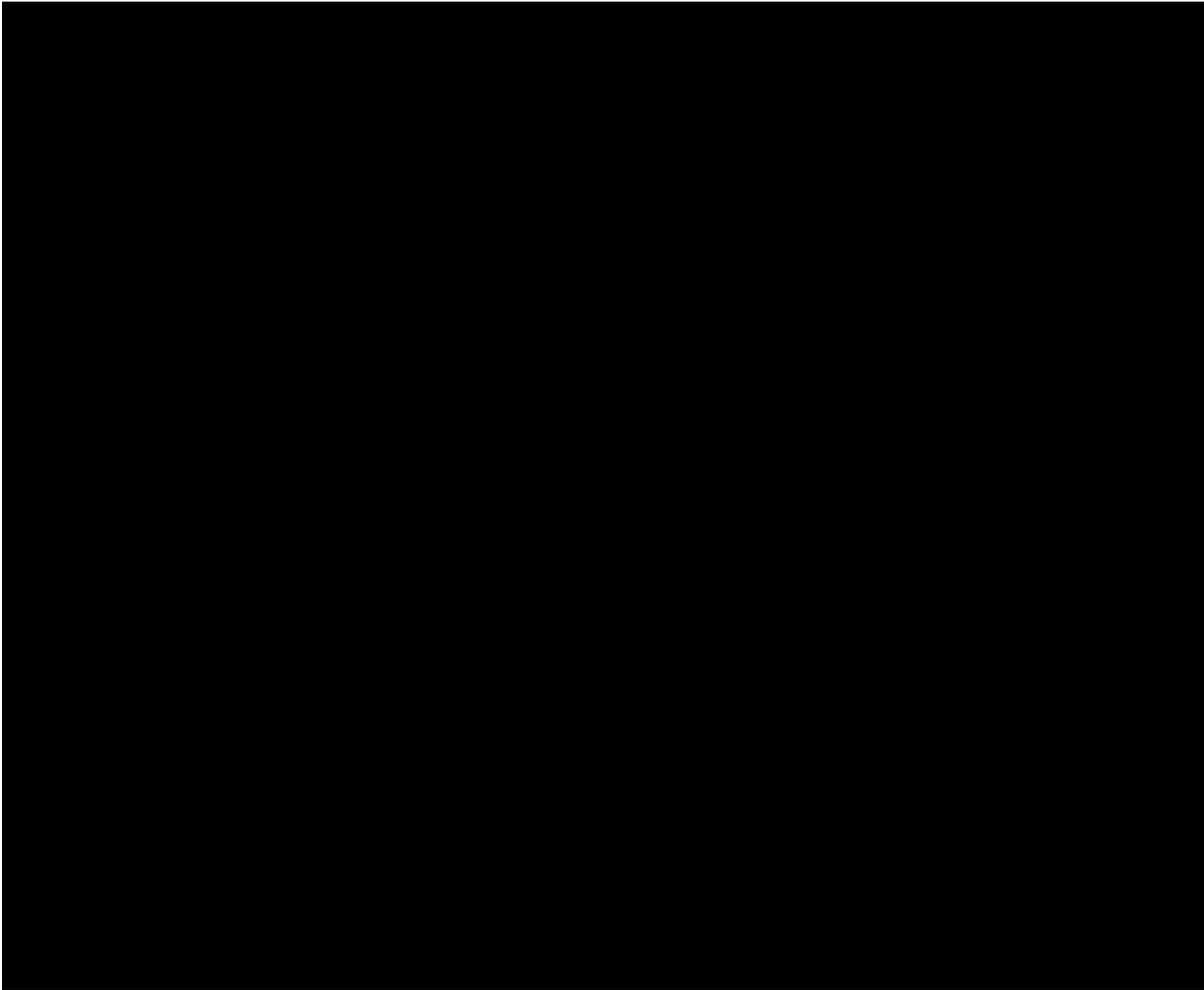
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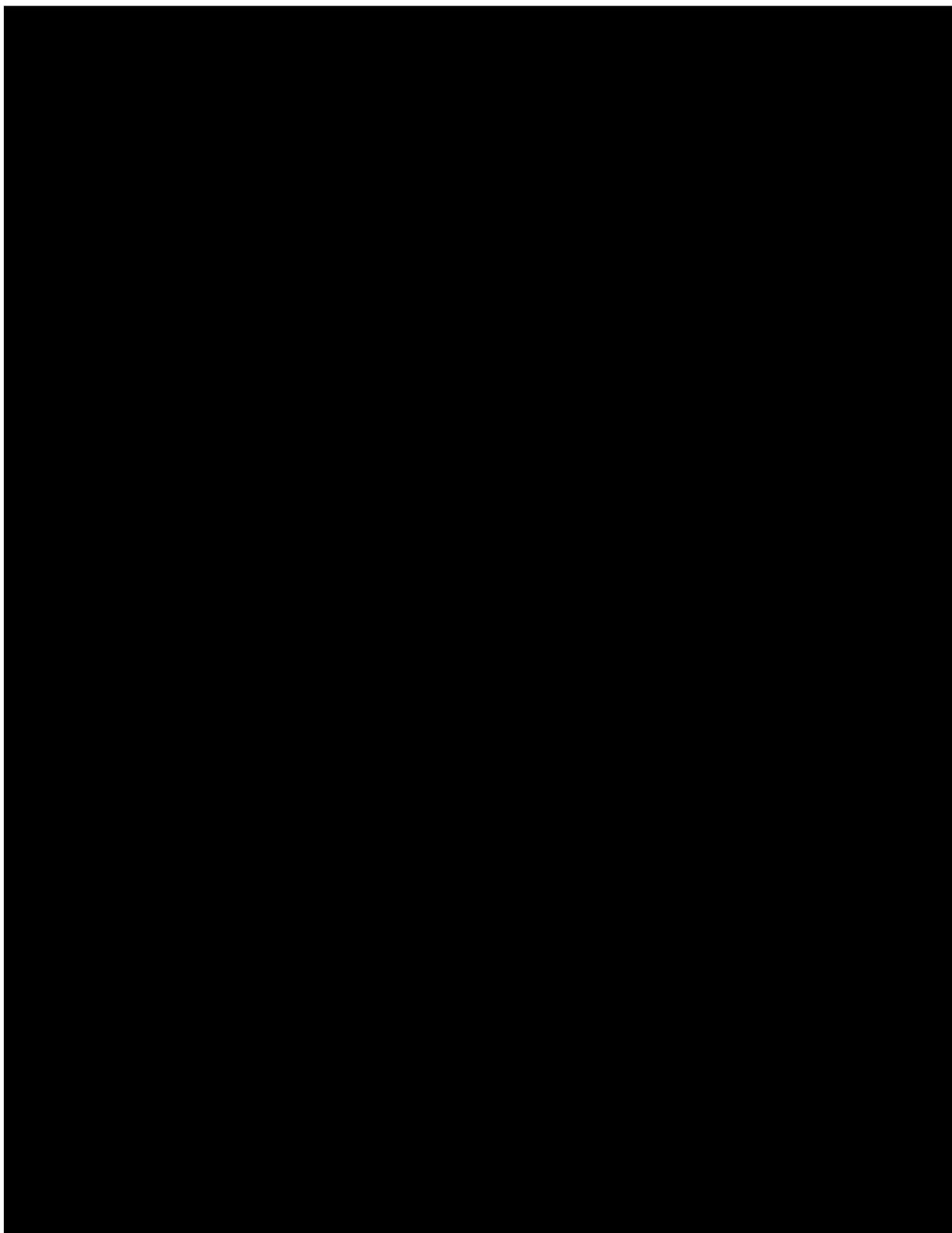
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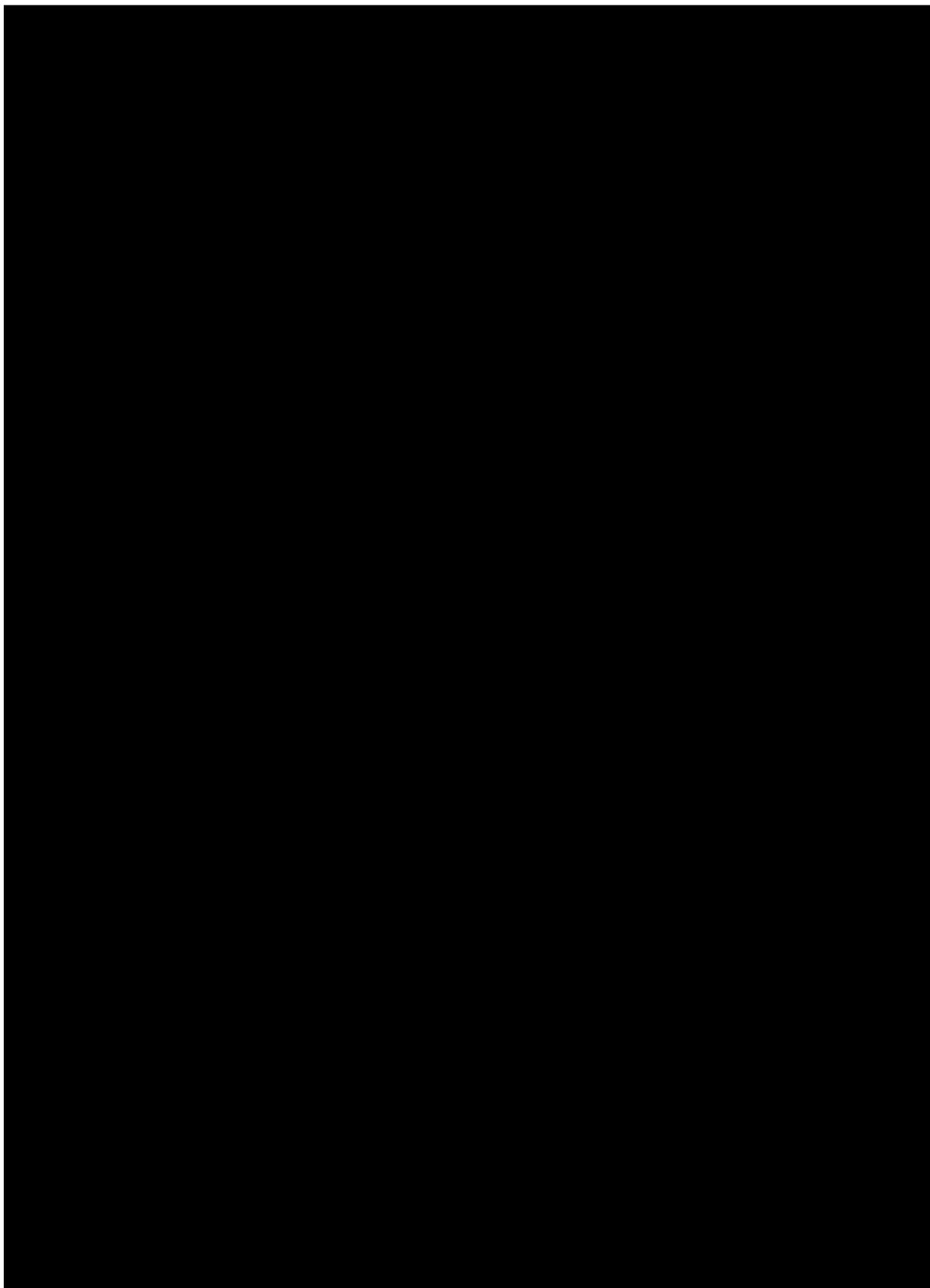
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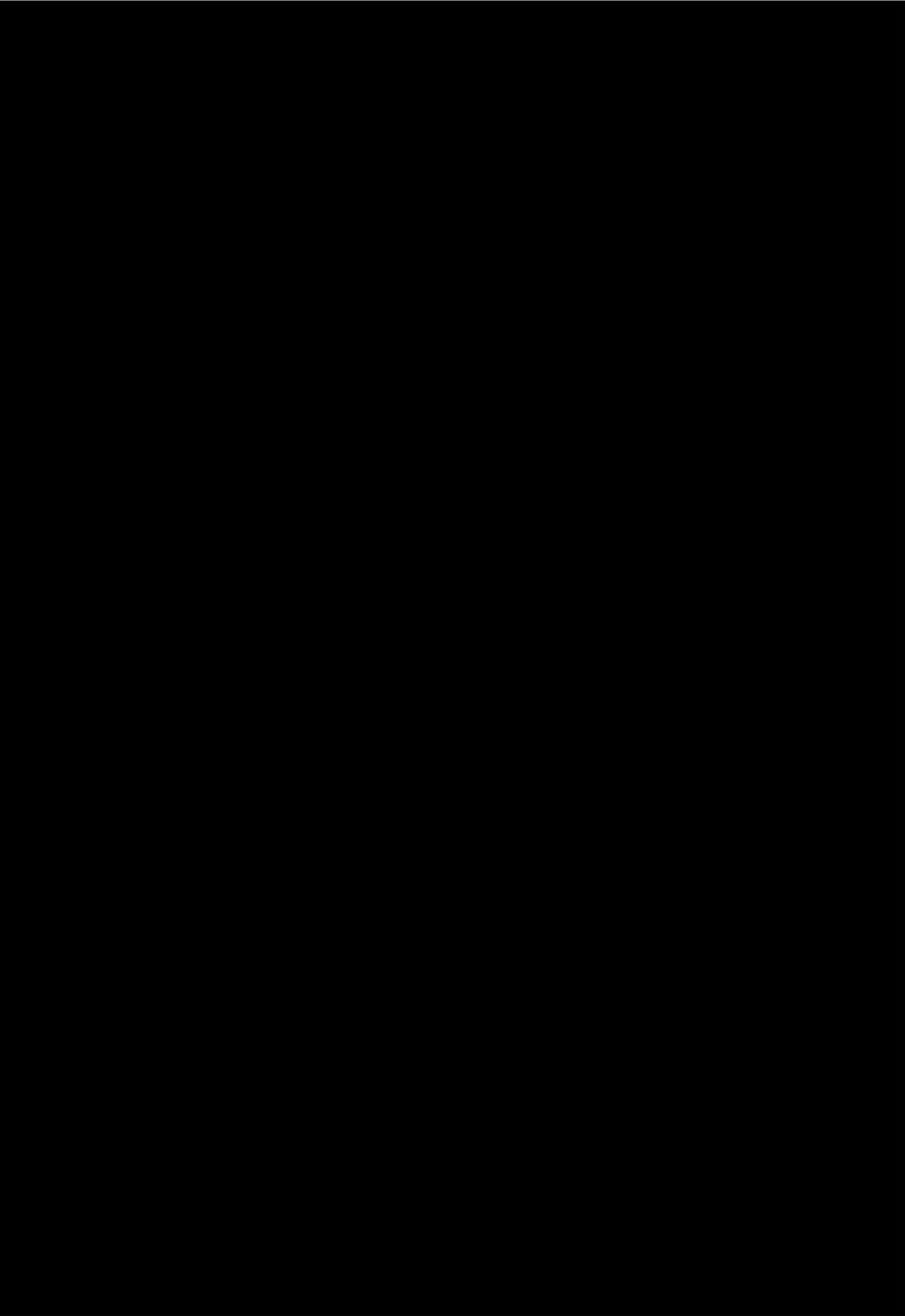




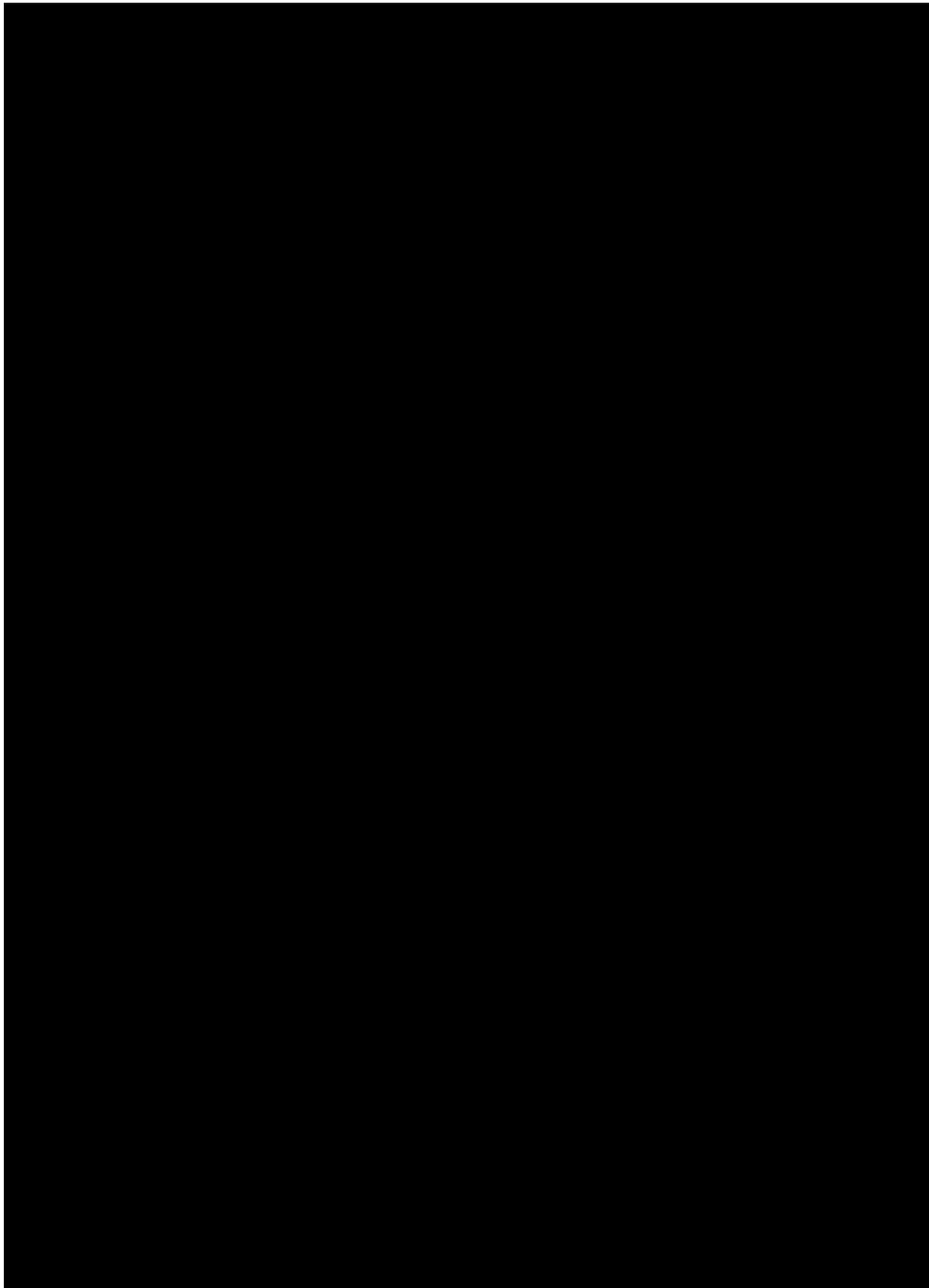
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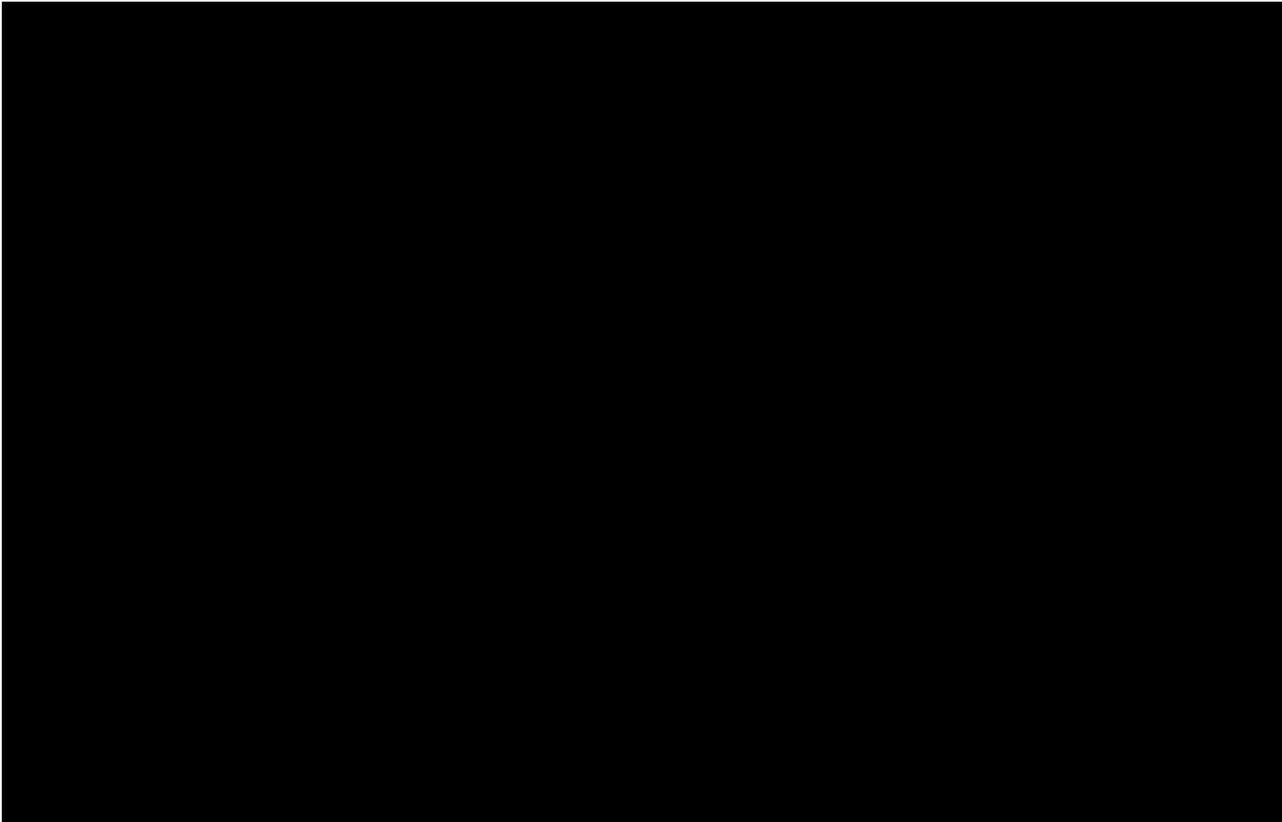
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3.3 CARM data

CARM have received 344 reports where the suspected medicine(s) was a GBCA (Annex 7). The majority of these cases describe allergic and physiologic reactions. The most commonly reported GBCA was gadobenic acid followed by gadoteric acid, but this probably reflects the usage of the different GBCAs. There were 38 cases describing reactions in the nervous system SOC. However, these are mostly reported with other terms indicative of an allergic or physiologic reaction.

4.0 DISCUSSION AND CONCLUSIONS

GBCAs are used to enhance MR images. These medicines are often essential for obtaining good images for diagnosis of various conditions and monitoring them. Up to this point GBCAs were considered to be safer than iodine based contrast agents. The major previous safety concern was NSF, but this has been successfully managed, with no new cases reported recently. The efficacy and need for these agents has been confirmed.

The current safety concern is whether gadolinium deposits in the brain of people who have had GBCAs administered. Gadolinium may also deposit in the bones and skin.

That gadolinium may be deposited in the brain was first hypothesised based on unusual signal intensities seen in parts of the brain in patients having non-contrast MRI. This hypothesis was considered confirmed after autopsy studies measured gadolinium in decedent's brains at concentrations proportional to the cumulative dose of GBCA.

The current evidence from human and preclinical studies suggests that the following scenario occurs following GBCA administration.

All GBCAs spread through the blood into the CSF after administration. The GBCA crosses the CSF-brain barrier at the choroid plexus. After moving through the brain interstitium the GBCA is gradually cleared from the brain and the rest of the body. This clearance may take up to two months (Guerbet preliminary data from ER-16-00005). The stability of the gadolinium chelate thus becomes important. The less stable the chelate the greater the potential (over the weeks it takes to fully clear the GBCA) for dechelation and deposition of gadolinium to occur. The deposited gadolinium in the brain is then observed on MRI. Macrocyclic chelates are more stable than linear ionic chelates which in turn are more stable than linear non-ionic chelates. In general, the stability of the agents determined in the *in vitro* study matches the data on MRI signal intensity increase in clinical and pre-clinical studies.

It is important to remember that MRI does not identify all the gadolinium in the brain. The autopsy studies found gadolinium in areas of the brain not associated with a signal intensity increase on MRI. MRI does not detect gadolinium directly but the influence of gadolinium on protons (mainly from water), if there is little water surrounding the gadolinium it is not detected.

At this stage there is a lack of evidence to enable a full comparisons between all the GBCAs. However, the evidence points to little to no deposition with macrocyclic GBCAs and varying amounts of deposition with the different linear GBCAs.

The form of the gadolinium seen on MRI is still debated. For MRI studies performed within a few weeks after administration, the gadolinium may still be in the soluble chelated form. In patients with renal impairment and high phosphate levels, gadolinium phosphate may be deposited, otherwise it is thought that gadolinium binds to macromolecules. Once the gadolinium has been de-chelated and deposited the current evidence suggests that it is not removed over time. However, this can be difficult to check *in vivo* as a decrease in MRI signal intensity does not necessarily mean that gadolinium has been removed.

The location of the deposited gadolinium has also been investigated. In the human autopsy studies gadolinium was reported to be deposited in the capillary endothelium and neural interstitium. In rats deposits were found in capillary endothelium and intercellular connective tissue in the choroid plexus. Of note other metals were also found in these deposits in both humans and rats.

Histopathology of brain from humans and rats containing gadolinium deposits has not shown any abnormal findings to date.

No overt behavioural changes or neurological deficits have been noted in rats included in pre-clinical studies. Neither is there good information on resulting harm in humans. Although one group has

claimed that there is a gadolinium deposition disease. These cases are difficult to interpret, they could represent patients with anxiety disorders and are often confounded by the patient's underlying condition (ie, the reason they had a scan in the first place). In addition, some patient have symptoms after only one MRI or MRI with a macrocyclic GBCA for which no increase in signal intensity has been seen on MRI.

In summary, there is evidence that administration of GBCA (probably only the linear) results in deposition of gadolinium in the brain region. The evidence that the gadolinium deposits are within the brain is equivocal. No abnormal histopathological findings have been reported and there is no firm evidence of any clinical consequences.

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- the available evidence shows that gadolinium is deposited in the brain after administration of all of the available GBCAs OR is there evidence to support a difference between the GBCAs
- there is evidence of harm resulting from deposition of gadolinium in the brain
- any regulatory action is required
- any communication or advice to healthcare professionals is required

6.0 ANNEXES

1. ANZ Radiologists Guide and newsletter
2. Presentation by Professor Radbruch
3. Case reports from Adis Insight
4. Information from GE Healthcare
5. Information from Bayer
6. Information from Obex/Guerbet
7. Overview of CARM cases

7.0 ABBREVIATIONS

CE	contrast enhanced
CKD	chronic kidney disease
CNS	central nervous system
CSF	cerebral spinal fluid
DCN	deep cerebellar nucleus
DN	dentate nucleus
DTPA	diethylenetriamine pentaacetic acid
EELS	electron energy loss spectroscopy
EMA	European medicines agency
FLAIR	fluid attenuated inversion recovery
FMRI	functional magnetic resonance imaging
GBCA	gadolinium based contrast agent
Gd	gadolinium
GdCA	gadolinium contrast agent
GDD	gadolinium deposition disease
GP	globus pallidus
ICP-MS	inductively coupled plasma mass spectroscopy
ISF	interstitial fluid
MALDI	matrix assisted laser desorption ionisation
MCP	middle cerebellar peduncle
MCT	monocarboxylic acid transfer
MRC	magnetic resonance cistenography
MRI	magnetic resonance imaging
MS	multiple sclerosis
NSF	nephrogenic systemic fibrosis
PC	phase contrast
Po	pons
PPM	parts per million
PRAC	pharmacovigilance risk assessment committee
RF	radio frequency
ROI	region of interest

SE	spin echo
SI	signal intensity
TEM	transmission electron microscopy
Th	thalamus

8.0 REFERENCES

1. Huckle, J.E., et al., *Gadolinium Deposition in Humans: When Did We Learn That Gadolinium Was Deposited In Vivo?* Invest Radiol, 2016. **51**(4): p. 236-40.
2. Kanal, E., *Gadolinium based contrast agents (GBCA): Safety overview after 3 decades of clinical experience.* Magn Reson Imaging, 2016. **34**(10): p. 1341-1345.
3. Ramalho, J., et al., *Technical aspects of MRI signal change quantification after gadolinium-based contrast agents' administration.* Magn Reson Imaging, 2016. **34**(10): p. 1355-1358.
4. Tweedle, M.F., *Gadolinium deposition: Is it chelated or dissociated gadolinium? How can we tell?* Magn Reson Imaging, 2016. **34**(10): p. 1377-1382.
5. Semelka, R.C., M. Ramalho, and M. Jay, *Summary of special issue on gadolinium bioeffects and toxicity with a look to the future.* Magn Reson Imaging, 2016. **34**(10): p. 1399-1401.
6. Murata, N., et al., *Gadolinium tissue deposition in brain and bone.* Magn Reson Imaging, 2016. **34**(10): p. 1359-1365.
7. Kanda, T., et al., *Gadolinium deposition in the brain.* Magn Reson Imaging, 2016. **34**(10): p. 1346-1350.
8. Prybylski, J.P., et al., *Gadolinium deposition in the brain: Lessons learned from other metals known to cross the blood-brain barrier.* Magn Reson Imaging, 2016. **34**(10): p. 1366-1372.
9. Swaminathan, S., *Gadolinium toxicity: Iron and ferroportin as central targets.* Magn Reson Imaging, 2016. **34**(10): p. 1373-1376.
10. Oner, A.Y., et al., *Intrathecal Contrast-Enhanced Magnetic Resonance Imaging-Related Brain Signal Changes: Residual Gadolinium Deposition?* Invest Radiol, 2016.
11. Ramalho, J., et al., *Gadolinium toxicity and treatment.* Magn Reson Imaging, 2016. **34**(10): p. 1394-1398.
12. Lancelot, E., *Revisiting the Pharmacokinetic Profiles of Gadolinium-Based Contrast Agents: Differences in Long-Term Biodistribution and Excretion.* Invest Radiol, 2016. **51**(11): p. 691-700.
13. Olchoway, C., et al., *The presence of the gadolinium-based contrast agent depositions in the brain and symptoms of gadolinium neurotoxicity - A systematic review.* PLoS One, 2017. **12**(2): p. e0171704.
14. Frenzel, T., et al., *Stability of gadolinium-based magnetic resonance imaging contrast agents in human serum at 37 degrees C.* Invest Radiol, 2008. **43**(12): p. 817-28.
15. Robert, P., et al., *T1-Weighted Hypersignal in the Deep Cerebellar Nuclei After Repeated Administrations of Gadolinium-Based Contrast Agents in Healthy Rats: Difference Between Linear and Macrocyclic Agents.* Invest Radiol, 2015. **50**(8): p. 473-80.
16. Robert, P., et al., *Linear Gadolinium-Based Contrast Agents Are Associated With Brain Gadolinium Retention in Healthy Rats.* Invest Radiol, 2016. **51**(2): p. 73-82.
17. Jost, G., et al., *Signal Increase on Unenhanced T1-Weighted Images in the Rat Brain After Repeated, Extended Doses of Gadolinium-Based Contrast Agents: Comparison of Linear and Macrocyclic Agents.* Invest Radiol, 2016. **51**(2): p. 83-9.
18. Jost, G., et al., *Penetration and distribution of gadolinium-based contrast agents into the cerebrospinal fluid in healthy rats: a potential pathway of entry into the brain tissue.* Eur Radiol, 2016.
19. Rasschaert, M., et al., *Moderate Renal Failure Accentuates T1 Signal Enhancement in the Deep Cerebellar Nuclei of Gadodiamide-Treated Rats.* Invest Radiol, 2016.
20. Lohrke, J., et al., *Histology and Gadolinium Distribution in the Rodent Brain After the Administration of Cumulative High Doses of Linear and Macrocyclic Gadolinium-Based Contrast Agents.* Invest Radiol, 2017.
21. Frenzel, T., et al., *Quantification and Assessment of the Chemical Form of Residual Gadolinium in the Brain After Repeated Administration of Gadolinium-Based Contrast Agents: Comparative Study in Rats.* Invest Radiol, 2017.

22. Smith, A.P., et al., *Clearance of Gadolinium from the Brain with No Pathologic Effect after Repeated Administration of Gadodiamide in Healthy Rats: An Analytical and Histologic Study*. *Radiology*, 2017. **282**(3): p. 743-751.
23. Kanda, T., et al., *High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material*. *Radiology*, 2014. **270**(3): p. 834-41.
24. Kanda, T., et al., *High Signal Intensity in Dentate Nucleus on Unenhanced T1-weighted MR Images: Association with Linear versus Macrocyclic Gadolinium Chelate Administration*. *Radiology*, 2015. **275**(3): p. 803-9.
25. Radbruch, A., et al., *Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent*. *Radiology*, 2015. **275**(3): p. 783-91.
26. McDonald, R.J., et al., *Intracranial Gadolinium Deposition after Contrast-enhanced MR Imaging*. *Radiology*, 2015. **275**(3): p. 772-82.
27. Kanda, T., et al., *Gadolinium-based Contrast Agent Accumulates in the Brain Even in Subjects without Severe Renal Dysfunction: Evaluation of Autopsy Brain Specimens with Inductively Coupled Plasma Mass Spectroscopy*. *Radiology*, 2015. **276**(1): p. 228-32.
28. Murata, N., et al., *Macrocyclic and Other Non-Group 1 Gadolinium Contrast Agents Deposit Low Levels of Gadolinium in Brain and Bone Tissue: Preliminary Results From 9 Patients With Normal Renal Function*. *Invest Radiol*, 2016. **51**(7): p. 447-53.
29. Quattrocchi, C.C., et al., *Gadodiamide and Dentate Nucleus T1 Hyperintensity in Patients With Meningioma Evaluated by Multiple Follow-Up Contrast-Enhanced Magnetic Resonance Examinations With No Systemic Interval Therapy*. *Invest Radiol*, 2015. **50**(7): p. 470-2.
30. Ramalho, J., et al., *High Signal Intensity in Globus Pallidus and Dentate Nucleus on Unenhanced T1-weighted MR Images: Evaluation of Two Linear Gadolinium-based Contrast Agents*. *Radiology*, 2015. **276**(3): p. 836-44.
31. Radbruch, A., et al., *No Signal Intensity Increase in the Dentate Nucleus on Unenhanced T1-weighted MR Images after More than 20 Serial Injections of Macrocyclic Gadolinium-based Contrast Agents*. *Radiology*, 2017. **282**(3): p. 699-707.
32. Flood, T.F., et al., *Pediatric Brain: Repeated Exposure to Linear Gadolinium-based Contrast Material Is Associated with Increased Signal Intensity at Unenhanced T1-weighted MR Imaging*. *Radiology*, 2017. **282**(1): p. 222-228.
33. Ichikawa, S., et al., *Contrast Agent-Induced High Signal Intensity in Dentate Nucleus on Unenhanced T1-Weighted Images: Comparison of Gadodiamide and Gadoteric Acid*. *Invest Radiol*, 2017.
34. Zhang, Y., et al., *Extent of Signal Hyperintensity on Unenhanced T1-weighted Brain MR Images after More than 35 Administrations of Linear Gadolinium-based Contrast Agents*. *Radiology*, 2017. **282**(2): p. 516-525.
35. Semelka, R.C., et al., *Gadolinium deposition disease: Initial description of a disease that has been around for a while*. *Magn Reson Imaging*, 2016. **34**(10): p. 1383-1390.