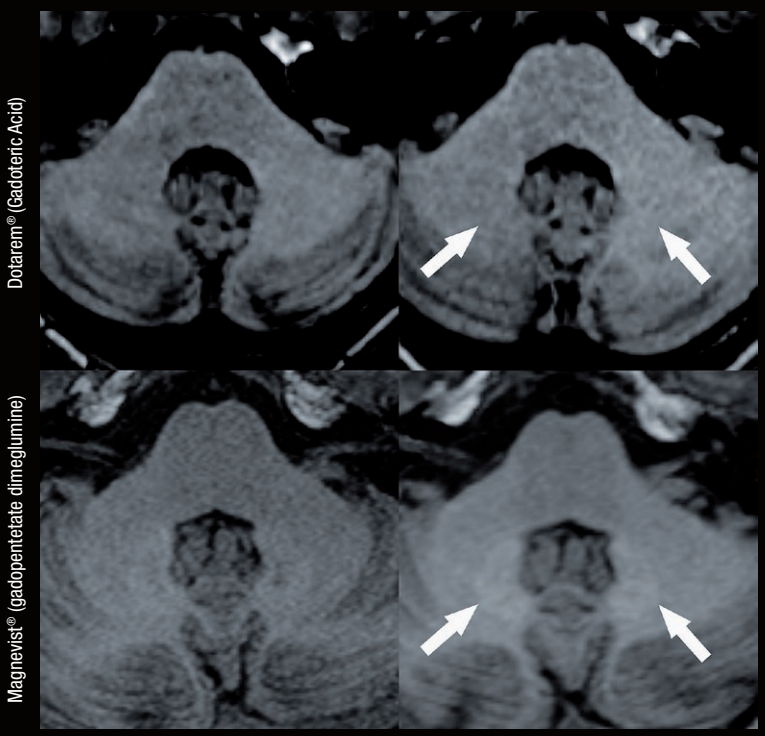
Gadolinium retention in the brain

Not all Gadolinium-based Contrast Agents (GBCAs) induce visible brain T1w hyperintensities related to dechelated Gd[1]



Guerbet

Dotarem® is a trade mark of Guerbet
Magnevist® is a trade mark of Bayer

T1w hyperintensities in the Dentate Nucleus (DN) on unenhanced MR images have been reported:

- After repeated injections of **linear GBCAs (L-GBCAs)** [1,2,3]
- Caused by **retention of gadolinium in the brain tissue** [3]
- In patients with **normal renal function** [1,2,3]

Some patients, such as those with brain tumors, multiple sclerosis or breast cancer, may require serial GBCA-enhanced MRI examinations. Gadolinium may accumulate in the brain following repeated injections of L-GBCAs. The clinical consequences of this retention are unknown today.

This brochure gives an overview and latest updates about hyperintensities and gadolinium retention as of January 2018.

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Key abbreviations

SI: Signal Intensity
GBCA: Gadolinium based Contrast Agent
L-GBCA: Linear GBCA
M-GBCA: Macrocyclic GBCA

DN: Dentate Nucleus
GP: Globus Pallidus
MCP: Medium Cerebellar Peduncle
DCN: Deep Cerebellar Nuclei

1. HYPERINTENSITIES

a) Not all GBCAs induce visible brain T1w hyperintensities - clinical evidence

Molecule stability		Macrocyclic GBCAs		
		Ionic >	Non ionic	>
		Dotarem® (Gadoteric Acid)	Prohance® (gadoteridol)	Gadovist® (gadobutrol)
Hyperintensities studies	Adults	• Radbruch (I) 2015[1] • Radbruch (III) 2016[4] • Eisele 2016[5] • Radbruch (IV) 2017[6] • Bae 2017[7] • Lee 2017[8] • Splendiani 2018[9] • Eisele 2018[10] • Saake 2019[11] • Hannoun 2019[12] • Kavak 2019[13] • Spendiani 2019[14] • Bennani-Baiti 2019[15]	• Kanda (II) 2015[21]	• Stojanov 2016[24] • Radbruch (II) 2015[25] • Radbruch (III) 2016[4] • Cao (I) 2016[26] • Radbruch (IV) 2017[6] • Bae 2017[7] • Schlemm 2017[27] • Langner 2017[28] • Müller 2017[29] • Bjørnerud 2017[30] • Yoo 2018[31] • Behzadi 2018[32] • Moser 2018[33] • Jaulent 2018[34] • Kang 2018[35] • Moreno 2018[36] • Splendiani 2018[9] • Kelemen 2018[37]
	Children	• Rossi Espagnet 2017[16] • Radbruch (V) 2017[17] • Ryu 2018[18] • Pozeg 2019[19] • Topcuoglu 2019[20]	• Young 2018[22, 23]	• Young 2018[22] • Renz 2018[38] • Bhargava 2018[39]

No hyperintensities found Non-conclusive or questionable study design* Hyperintensities found

The clinical studies listed in the table below evaluate the correlation between cumulative doses of various GBCAs and presence of hyperintensities in the brain on unenhanced T1-weighted images. The table includes retrospective studies with patients who received: 1/ repeated injections of a single GBCA during the study period, 2/ repeated injections of a single class of GBCA (macrocyclic or linear) during the study period, or 3/ subsequent injections of different GBCAs for which the period of injection of each GBCA is identified and studied.

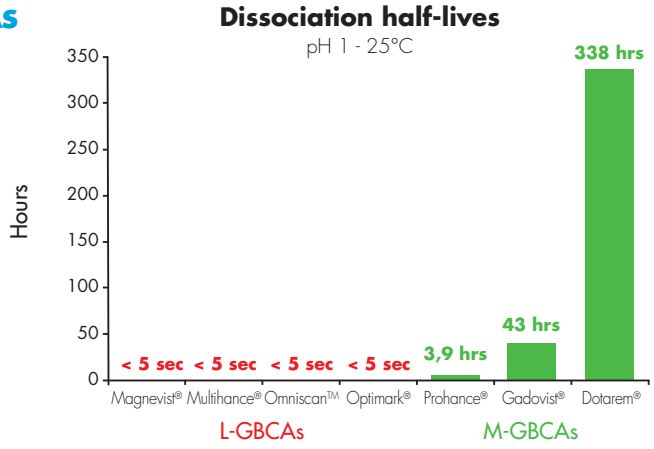
Linear GBCAs			
Ionic			> Non ionic
Primovist® (gadoxetic acid disodium)	**Magnevist®** (gadopentetate dimeglumine)	**Multihance®** (gadobenate dimeglumine)	**Omniscan™** (gadodiamide)
• Kahn 2017[40] • Ichikawa 2017[41] • Conte 2017[42] • Holesta 2018[43] • Kim 2018[44]	• Kanda (I) 2014[45] • Radbruch (I) 2015[1] • Kanda (II) 2015[21] • Radbruch (II) 2015[25] • Cao (I) 2016[26] • Tanaka 2016[46] • Bae 2017[7] • Schlemm 2017[27] • Kuno 2017[47] • Behzadi 2018[32] • Tamrazi 2018[48]	• Weberling 2015[2] • Ramalho (I) 2015[52] • Ramalho (II) 2016[53] • Bolles 2018[54]	• Kanda (I) 2014[45] • Errante 2014[57] • McDonald 2015[3] • Ramalho (I) 2015[52] • Quattrocchi 2015[58] • Ramalho (II) 2016[53] • Tanaka 2016[46] • Bae 2017[7] • Ichikawa 2017[41] • Marie 2018[59] • Quattrocchi 2018[60] • Koiso 2019[61] • Zivadinov 2019[62]
	• Hu 2016[49] • Flood 2017[50] • Renz 2018[38] • Flood 2019[51]	• Schneider 2017[55] • Kinner 2018[56]	• Young 2018[22, 23]

* Stojanov 2016[24]: no visible hyperintensities and absence of control group. The results were questioned by Cao et al. 2016[26], Radbruch et al. 2015[25] and Runge 2015[63].
Ramalho I[52] & II[53], 2015 & 2016: studies design questioned on the number of injections and area of normalization.
Ichikawa[41] & Conte[42] 2017: studies design questioned on the volume administered to patients, lower than Kahn 2017[40].
Rossi Espagnet 2017[16]: no visible hyperintensities. The results were questioned by two letters to the editor (Lancelot 2017[64] and Radbruch 2017[65]).
Splendiani 2018[9] : the differences were not statistically significant across the entire patient population.
Bjørnerud 2017[30]: results questioned on the high windowing, the enhancement observed (located also outside the DN), the similarity pre/post in enhancement, the decrease of noise in the full image, the timing between injections too short to allow full wash-out of the Gd complex.
Schneider 2017[55]: study design questioned on the dose (half dose was injected instead of full dose).

b) Why these differences: various molecular structures, various stabilities[66]

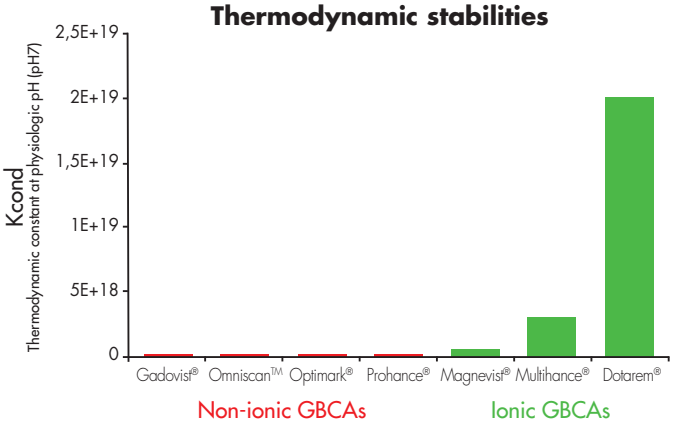
Kinetic stability: M-GBCAs > L-GBCAs

- The kinetic stability represents the speed of free gadolinium release from the original GBCAs complex.
- The lower the kinetic stability, the shorter the dissociation half-life, thus the faster the release of free gadolinium.
- It is typically measured in vitro under very acidic conditions (pH 1).[67]
- At a pH>5, M-GBCAs demonstrate a dissociation half-life of 36-65 years in comparison to 5-7 days for L-GBCAs.[67]



Thermodynamic stability: ionic GBCAs > non ionic GBCAs

- The thermodynamic stability is another parameter measuring the propensity to release gadolinium.
- The higher the thermodynamic stability, the lower the quantity of free gadolinium released.



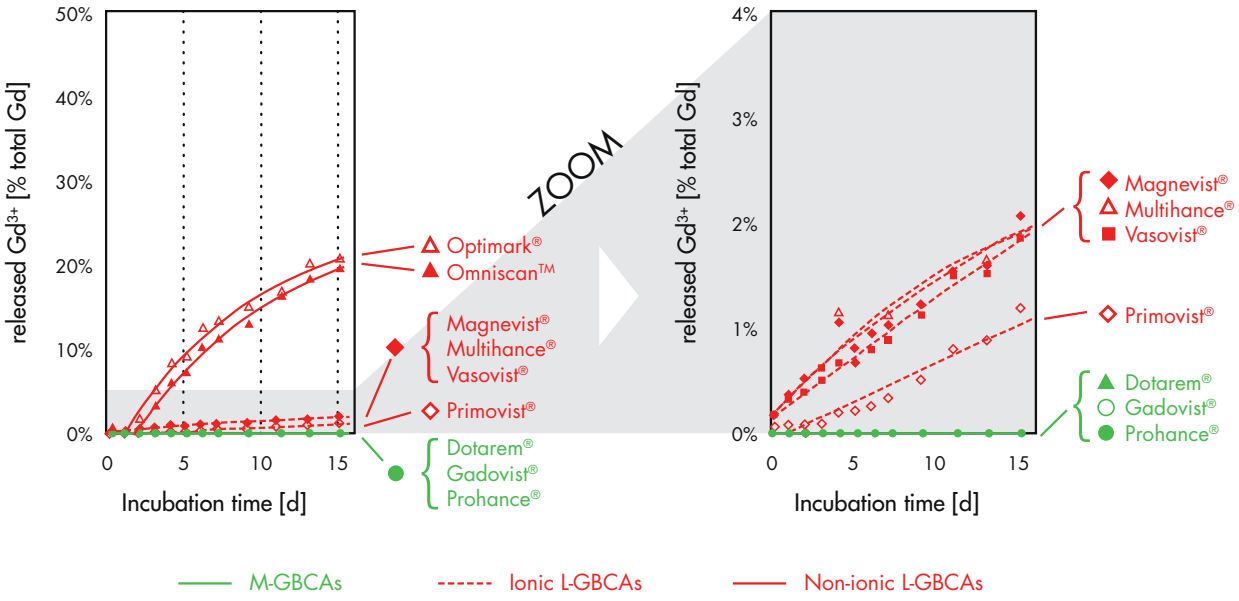
Stability of GBCAs in human serum[67]

KEY POINTS

- Non-ionic L-GBCAs: free gadolinium (Gd^{3+}) released ~ 10 times higher than ionic linear GBCAs
- Ionic L-GBCAs: slower but continuous release of Gd^{3+}
- M-GBCAs: no release of Gd^{3+}

Comparison of the amounts of gadolinium released

From 1 mmol/L solutions
In native human serum from healthy volunteers
At 37°C during an incubation period of 15 days



This study suggests that the molecular structure of the GBCAs can impact their stability.

The graph colors shown on this page have been adapted for presentation purpose.

c) Selected pieces of evidence

Comparison between a M-GBCA (Dotarem®) and L-GBCAs (Magnevist® & Multihance®) - clinical study

Two clinical studies investigated the hyperintensities in the brains of patients with normal renal function.[1,2]

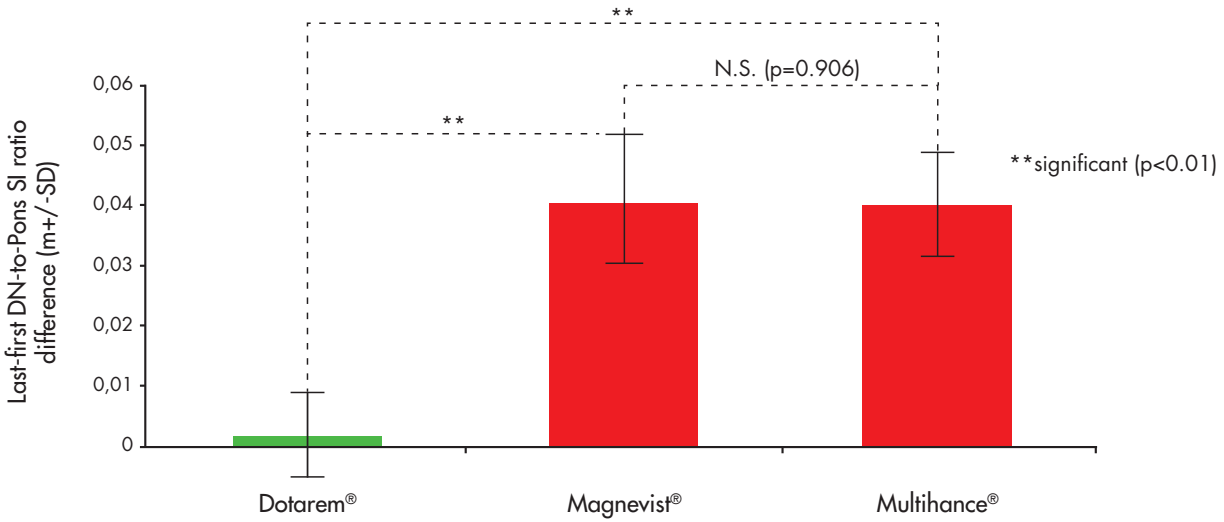
KEY POINTS

- Repeated administrations of Dotarem® did not induce hyperintensities in the Dentate Nucleus (DN) and Globus Pallidus (GP)
- Same level of hyperintensities in the DN following repeated administrations of the L-GBCAs Multihance® and Magnevist®

	Radbruch[1] study	Weberling[2] study
Materials & methods	• Retrospective comparison of Dotarem® and Magnevist®. • 2 groups of 50 patients received at least 6 administrations of Dotarem® or Magnevist®. • Larger dose of Dotarem® per examination was used (mean dose: 27.07 mL) compared to Magnevist® (mean dose: 19.62 mL).	• Retrospective assessment of Multihance® and comparison with Dotarem® and Magnevist® with the results from the Radbruch[1] study. • 50 patients received an average of 7.7 CE-MRIs with Multihance®.
Conclusion	• *"This study indicates that an SI increase in the DN and GP on T1-weighted images is caused by serial application of the linear GBCA gadopentetate dimeglumine but not by the macrocyclic GBCA gadoterate meglumine."*	• *"The present study found an increase in SI in the DN after serial injections of gadobenate dimeglumine."* • *"Compared with previously published data, the difference in SI increase between gadopentetate dimeglumine and gadobenate dimeglumine was not significant for the DN-to-Pons ratio."*

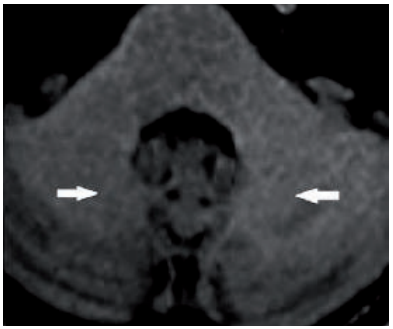
Graph of the mean DN-to-Pons SI ratio differences between the last and first MRIs[2]

Adapted from table 1, Weberling et al. 2015 [2]

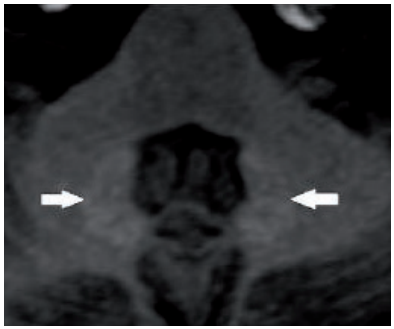


Unenhanced T1w MRI scans

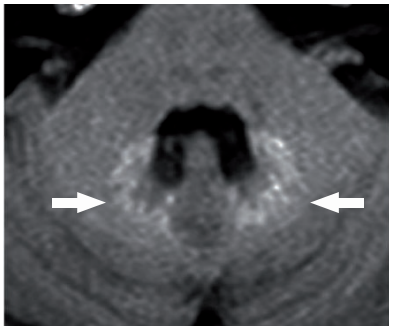
6 administrations of Dotarem®[1]



6 administrations of Magnevist®[1]



15 administrations of Multihance®[2]



Comparison between a M-GBCA (Dotarem®) with L-GBCAs Preclinical study[68]

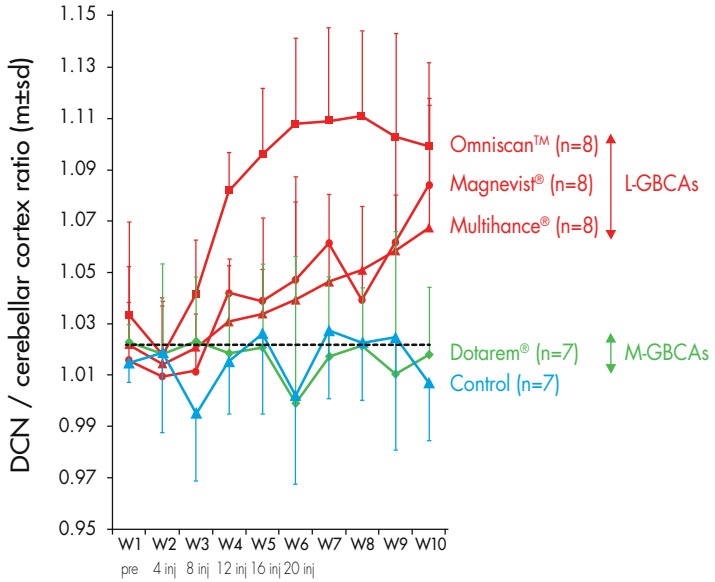
Findings of clinical studies were confirmed by several studies conducted on rats, including Robert et al. 2016.[68]

KEY POINTS

- L-GBCAs: presence of T1 hyperintensities in the Deep Cerebellar Nuclei (DCN)
- Dotarem® or saline: no change over 10 weeks

Materials & methods	• The healthy rats received 20 intravenous injections of 0.6 mmol Gd/kg of one exclusive GBCA. • 4 injections per week performed, for 5 weeks. • T1-weighted MRI performed before injection and once a week during the 5 weeks of injections and for another 4 additional weeks after contrast period. • Blinded image analysis of MRI scans, including signal intensity measurements in the DCN.

Signal intensity after repeated injections of each GBCA



Another study[69] conducted on rats evaluated the T1w hyperintensities in the brain, up to 24 days, after repeated administration of L-GBCAs (Omniscan™, Magnevist®, Multihance®) and M-GBCAs (Dotarem®, Gadovist®). This study found:

- **Hyperintensities in the DCN after repeated administration of L-GBCAs,**
- **No hyperintensities in the DCN for the M-GBCAs.**

d) Controversies in clinical studies

Various studies about hyperintensities have been released, using different protocols. Protocols chosen could impact the sensitivity of a study and its results.

Number of injections & volume injected

- At least 6 injections are needed to have a clear hyperintensity effect.[57, 58, 70]
- If the volume and/or the number of injections are too low, hyperintensities in the brain may not be seen with some L-GBCAs.[41, 42, 52, 53]
- For instance, in the Ramalho studies,[52, 53] the number of Multihance® injections was below 6, and the two studies concluded repeated injections of Multihance® do not trigger hyperintensities.
- However, other studies[2,54] concluded repeated injections of the same product lead to presence of hyperintensities in the brain. In these studies, the patients received more than 6 injections of Multihance®.

Area of normalization

- If the area of normalization is not appropriately chosen, it may also influence the results of a study.
- McDonald et al.[3] demonstrated the Pons is the area where there is the least gadolinium deposition.
- Data from the Cao study[26] showed that the Pons is more sensitive than the Cerebellar Peduncle (CP).

Age effect in children

- A study demonstrated that brain T1 is significantly related to age. Indeed, in children, the brain T1 Signal Intensity (SI) varies with the age.[71]

- In hyperintensities studies conducted in children, this variation may influence the results. Comparison to a control group or use of specific statistics is required.

- For instance, in the Rossi Espagnet study,[16] the SI increase calculated after repeated injections of Dotarem® may be related to brain maturation. Indeed, no visible hyperintensities are seen on the MR scans published in the study. Moreover, two other studies using specific statistics or a control group demonstrated the absence of hyperintensities in the pediatric brain after repeated injections of Dotarem®.[17]

- Pozeg[19] et al. demonstrated that repeated exposure to gadoterate meglumine was not associated with brain hyperintensity in the pediatric patients, **whereas age importantly contributed to the signal intensity changes in several deep brain nuclei.**

- Flood[51] et al. exhibited that increased age correlates with increased signal intensity in all brain locations, except the frontal gray matter, irrespective of sex. The biologic mechanisms may be related to chronologic changes in myelin density, synaptic density, and water content. Establishing age-dependent signal intensity parameters in the structurally normal pediatric brain enhance gadolinium-deposition research by providing an improved understanding of the confounding effect of age.

2. GADOLINIUM RETENTION

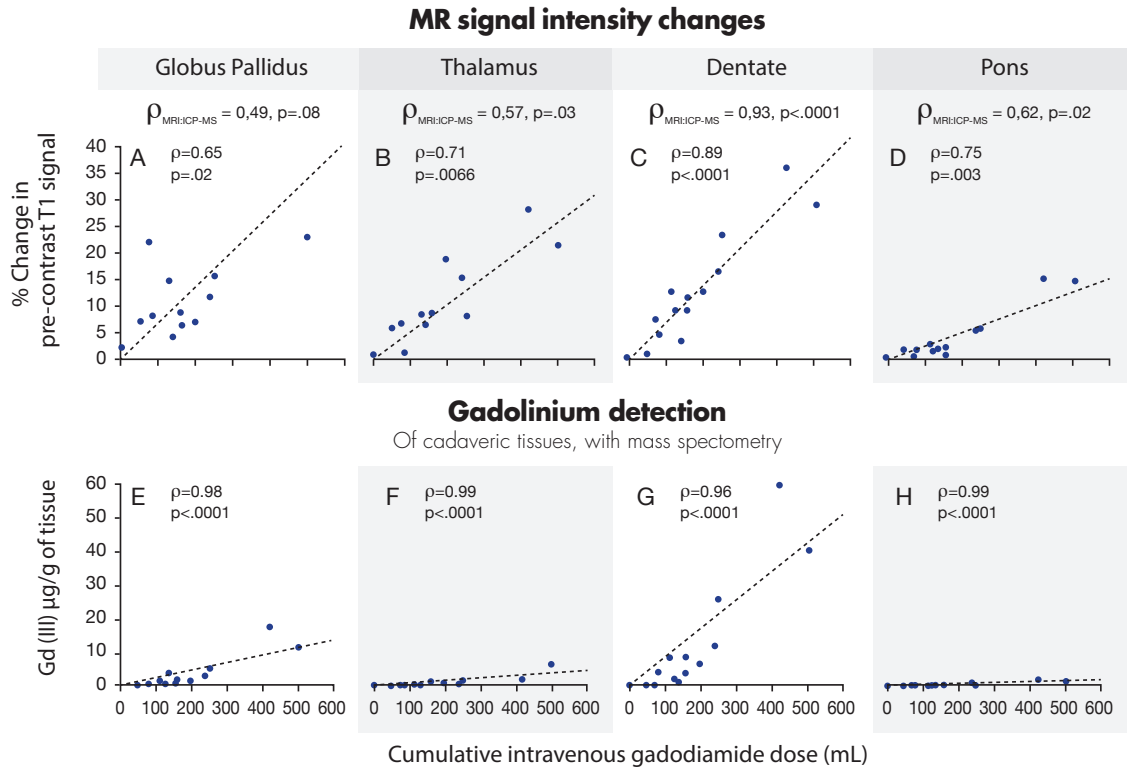
a) Hyperintensities are caused by gadolinium retention

Post-mortem study

The study McDonald et al. [3] detected retention of gadolinium in patients presenting hyperintensities in the brain.

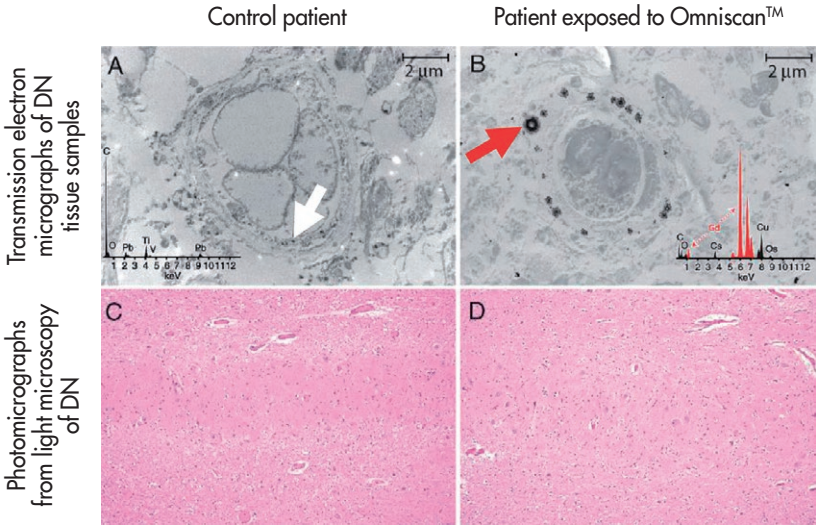
KEY POINTS

- **Neuronal tissue deposition of gadolinium** appears to be cumulative over a patient's lifetime:
  - After injections of a **single non-ionic L-GBCA, Omniscan™**
  - In patients with **normal renal function**



Materials & methods	• Comparative study between post-mortem neuronal tissue samples from 13 patients who underwent at least 4 GBCA-enhanced brain MRIs with those from 10 patients who did not receive any GBCA (control group). • Analysis performed with inductively coupled plasma mass spectrometry (ICP-MS), transmission electron microscopy, and light microscopy.
Conclusion	• Patients exposed to multiple doses of L-GBCA: measurable quantities of gadolinium deposited in their brain tissues ranging from 0.1 to 58.8 µg gadolinium per gram of tissue. • Control group: no detectable levels of gadolinium. • *"Our findings suggest that intravenous administration of GBCA is associated with dose-dependent deposition in neuronal tissues that is unrelated to renal function, age, or interval between exposure and death."*

Tissue localization and cellular response to gadolinium retention



A, B: X-ray spectra are also shown for selected electron-dense foci (arrow); gadolinium peaks in spectra are indicated by red overlay.
C = carbon, Cs = cesium, Cu = copper, Gd = gadolinium, O = oxgen, Os = osmium, Pb = lead, Ti = titanium, V = vanadium.

Hyperintensities are caused by Gd retention

b) Gd levels remaining in the body are higher after administration of linear GBCAs compared to macrocyclic GBCAs

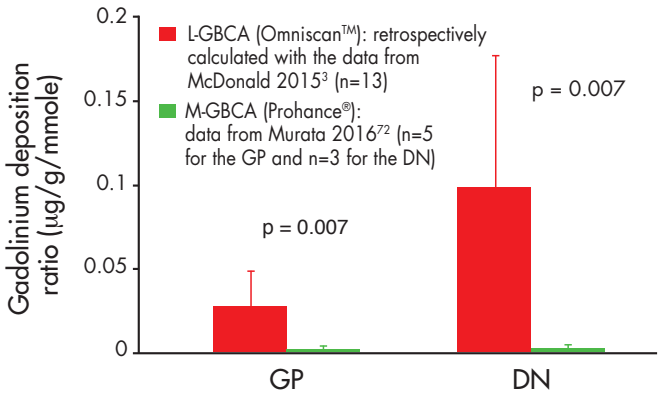
KEY POINT

- In both clinical and preclinical studies, levels of gadolinium retained after administration of M-GBCAs are significantly lower than after L-GBCAs

Clinical study results - example[72]

Median ratio of amount of gadolinium retained in the brain

Per gram of tissue per millimole of administered dose



- The study suggests the macrocylic GBCA Prohance® is retained "*at a ratio greater than 20 times lower compared with the Group 1 agent*" Omniscan™.

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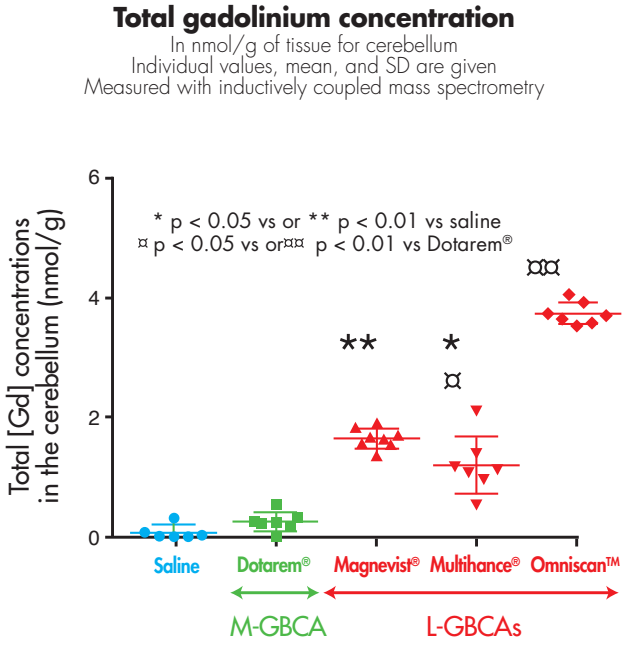
Preclinical study - example[68]



- *"Repeated administrations of the linear GBCAs gadodiamide, gadobenate dimeglumine, and gadopentetate dimeglumine to healthy rats were associated with progressive and significant T1 signal hyperintensity in the DCN, along with Gd deposition in the cerebellum. This is in contrast with the macrocyclic GBCA gadoterate meglumine for which no effect was observed."*

Gd levels remaining are higher after L-GBCAs

c) Presence of Gd associated to macromolecules after injection of linear GBCAs

Gadolinium retention studies retrospectively conducted in humans present several limitations. Further research is needed to fully understand the wash-out kinetics of GBCAs and if gadolinium remains chelated over time. Preclinical studies help providing some answers to limitations met in clinical studies.

Form & kinetics of gadolinium in preclinical data after 24 days [73]

A bioanalytical study in rat brain tissue was initiated to investigate whether the residual Gd is present as intact GBCA or in other chemical forms after 24 days.

KEY POINTS

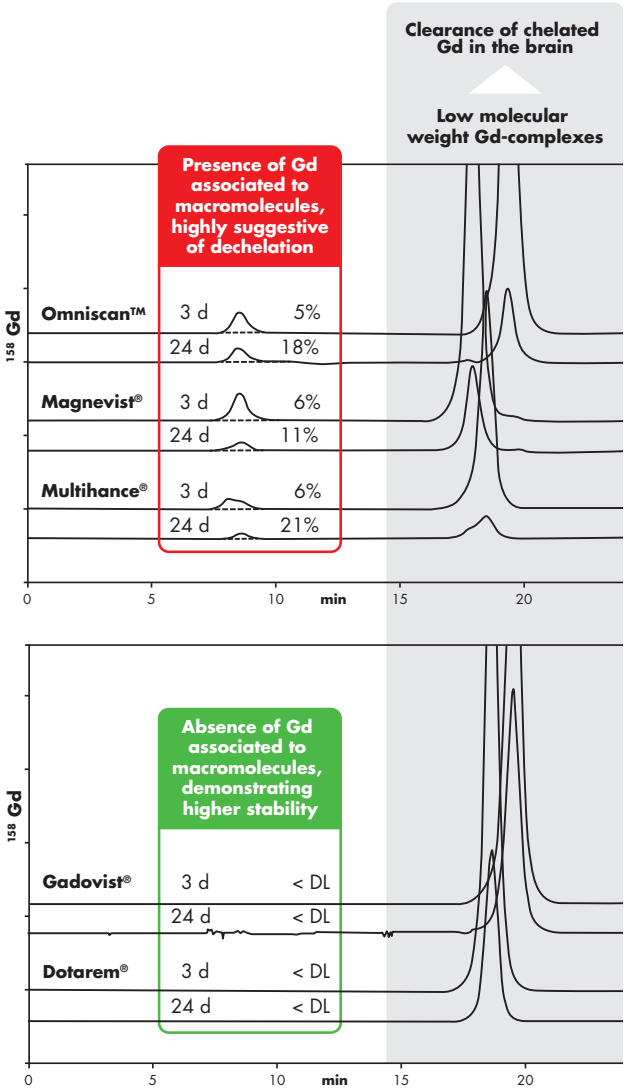
- Presence of **intact complex of gadolinium** (GBCA) for **all contrast agents**
- **Only for L-GBCAs:** presence of **Gd associated to macromolecules, highly suggestive of dechelation**
- **Only for M-GBCAs: absence of Gd associated to macromolecules,** demonstrating **higher stability**

Materials & methods	• 6 groups of 10 rats – 10 IV injections of GBCA at 2.5 mmol/kg/day over 2 weeks • Sacrifice on day 3 and day 24 after the last injection • Collection and homogeneization of cerebrum, cerebellum and pons • Quantification and characterization of Gd in the soluble tissue fraction

Chromatograms of the soluble fractions of cerebellum homogenates from rats after 3 days and 24 days

L-GBCAs

M-GBCAs



d = days

Presence of Gd associated to macromolecules after L-GBCAs

Form & kinetics of gadolinium in preclinical data after 1 year [74]

A study was initiated to compare the long-term brain elimination kinetics and gadolinium species in healthy rats after repeated injections of L-GBCA Omniscan™ or M-GBCA Dotarem®.

KEY POINTS

- After repeated injections of the **L-GBCA Omniscan™, a large portion of Gd was trapped** with 75% retained in the cerebellum after 1 year, and with **binding of soluble Gd to macromolecules**
- After repeated injections of **M-GBCA Dotarem®, only traces of the intact chelated Gd** were observed, with **time-dependent clearance**

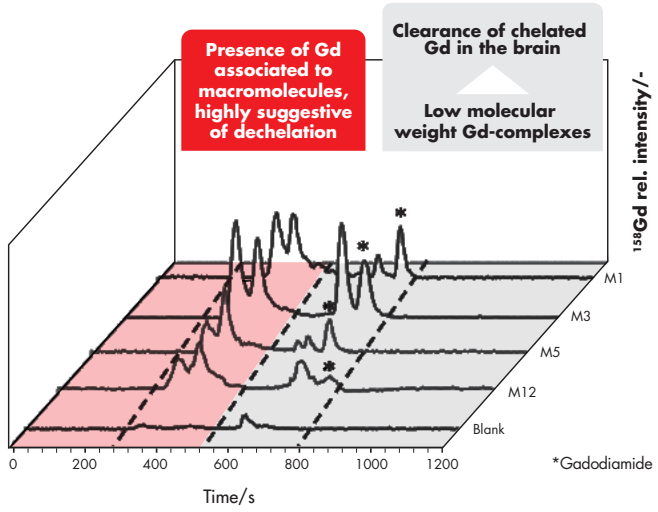
Materials & methods	• Animals received 5 doses of 2.4 mmol Gd/kg over 5 weeks • Rats were randomized to 7 groups with 0, 1, 2, 3, 4, 5, and 12 months (M0 to M12) of injection free period before sacrifice (n=10/product/time-point) • Brain sections were sampled to dose total gadolinium • Right half of the cerebellum at M1, M3, M5 and M12 was used for gadolinium speciation studies

M = month

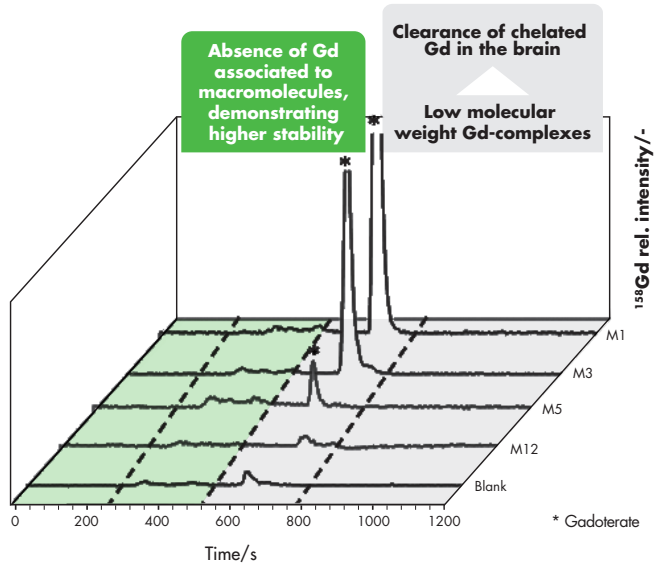
Chromatograms of the soluble fraction of cerebellum extracts after repeated injections of Dotarem® and Omniscan™ during 12 months of follow-up

(Examples of SEC-ICP-MS)

Omniscan™



Dotarem®



M = months

Presence of Gd associated to macromolecules after L-GBCAs

CONCLUSION

Chemical stability[66]

The chemical stability of GBCAs differs according to their structure. The dissociation half-lives demonstrate that M-GBCAs are more stable than L-GBCAs.

In vitro stability in physiological conditions[67]

Over a period of 15 days in human serum and at pH 7.4, Frenzel et al. 2008 showed L-GBCAs dissociate from their original compound whereas M-GBCAs do not (below LOQ).

No Brain Hyperintensities in normal renal function in adults and pediatric patients[69]

No visible brain hyperintensities related to dechelated Gd following repeated injections of M-GBCAs have been reported, contrary to L-GBCAs.

Rapid Gadolinium Washout and still chelation after 1 year[69, 73, 74]

As any drugs, there is a presence in the brain and cerebellum of all GBCAs after repeated intravenous administration. This presence is explained by a standard prolonged washout of the chelated form of the GBCAs. It has been demonstrated in a preclinical study[51] that Dotarem® has rapid and total washout in 5 months and remains chelated even after one year following the last injection. However, in the same study, following repeated injections of the L-GBCA Omniscan™, presence of Gd associated to macromolecules within the first month was demonstrated, highly suggestive of dechelation.

Clinical consequences unknown

Today, it remains unknown if gadolinium deposition could lead to potential long-term toxicity.

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Dotarem®: gadoteric acid
Gadovist®: gadobutrol
Prohance®: gadoteridol
Multihance®: gadobenate dimeglumine
Magnevist®: gadopentetate dimeglumine
Omniscan™: gadodiamide
Primovist®: gadoxetic acid disodium

DOTAREM 0.5 mmol/mL, solution for injection. **Composition:** For 100 mL of solution: active ingredient: Gadoteric Acid 27.932 g corresponding to: DOTA 20.246 g corresponding to gadolinium oxide 9.062 g. **Indications (*):** Medicinal product for diagnostic use only: Magnetic Resonance Imaging for cerebral and spinal disease, diseases of the vertebral column, and other whole-body pathologies (including angiography). Dotarem should be used only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI). **Posology and method of administration:** The recommended dose is 0.1 mmol/kg, i.e. 0.2 mL/kg in adults and children. The lowest dose that provides sufficient enhancement for diagnostic purposes should be used. The dose should be calculated based on the patient's body weight, and should not exceed the recommended dose per kilogram of body weight detailed in this section. In angiography, depending on the results of the examination being performed, a second injection may be administered during the same session if necessary. Angiography with Gadoteric acid is not recommended in children (0-18 years). In Encephalic and spinal MRI, in some exceptional cases, as in the confirmation of isolated metastasis or the detection of leptomeningeal tumours, a second injection of 0.2 mmol/kg may improve tumor characterisation and facilitate therapeutic decision making. For patients with impaired renal function and paediatric population (0-18 years) more than one dose should not be used during a scan, injections should not be repeated unless the interval between injections is at least 7 days. The product must be administered by strict intravenous injection. Depending on the amount of gadoteric acid to be given to the child, it is preferable to use gadoteric acid vials with a single use syringe of a volume adapted to this amount in order to have a better precision of the injected volume. In neonates and infants the required dose should be administered by hand. **Contraindications:** Hypersensitivity to gadoteric acid, to meglumine or to any medicinal products containing gadolinium. **Special warnings and precautions for use:** Dotarem must not be administered by subarachnoid (or epidural) injection. The usual precaution measures for MRI examination should be taken such as exclusion of patients with pacemakers, ferromagnetic vascular clips, infusion pumps, nerve stimulators, cochlear implants or suspected intracorporal metallic foreign bodies, particularly in the eye. **General particulars corresponding to all gadolinium contrast agents:** All gadolinium based contrast media can cause minor or major hypersensitivity reactions that can be life-threatening. These can occur immediately (within 60 minutes) or be delayed (within 7 days) and are often unpredictable. Because of the risk of major reactions, emergency resuscitation equipment should be available for immediate use. Hypersensitivity reactions can be aggravated in patients on betablockers and particularly in the presence of bronchial asthma. These patients may be refractory to standard treatment of hypersensitivity reactions with beta agonists. Impaired renal function: Prior to administration of gadoteric acid, it is recommended that all patients are screened for renal dysfunction by obtaining laboratory tests. There have been reports of Nephrogenic Systemic Fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with severe renal impairment (GFR < 30 ml/min/1.73 m^2). As there is a possibility that NSF may occur with Dotarem, it should

only be used in these patients after careful consideration. CNS disorders: As with other contrast agents containing gadolinium, special precautions should be taken in patients with a low seizure threshold. Precautionary measures, e.g. close monitoring, should be taken. All equipment and drugs necessary to counter any convulsions which may occur must be made ready for use beforehand. **Interactions with other medicinal products and other forms of interaction:** No interactions with other medicinal products have been observed. Formal drug interaction studies have not been carried out. **Fertility, pregnancy and lactation:** Gadoteric acid should not be used during pregnancy unless the clinical condition of the woman requires use of gadoteric acid. Continuing or discontinuing breast feeding for a period of 24 hours after administration of gadoteric acid, should be at the discretion of the doctor and lactating mother. **Effects on ability to drive and use machines:** No studies on the effects on the ability to drive and use machines have been performed. Ambulant patients while driving vehicles or operating machinery should take into account that nausea may incidentally occur. **Undesirable effects:** Uncommon (≥1/1000 to <1/100): hypersensitivity, headache, dysgeusia, dizziness, somnolence, paraesthesia (including burning sensation), hypotension, hypertension, nausea, abdominal pain, rash, feeling hot, feeling cold, asthenia, injection site reactions (extravasation, pain, discomfort, oedema, inflammation, coldness). Rare (≥1/10 000 to <1/1 000): anxiety, presyncope, eyelid edema, palpitations, sneezing, throat tightness, vomiting, diarrhea, salivary hypersecretion, Urticaria, pruritus, hyperhidrosis, chest pain, chills. Very rare (<1/10 000): anaphylactic reaction, anaphylactoid reaction, agitation, coma, convulsion, syncope, tremor, parosmia, conjunctivitis, ocular hyperaemia, vision blurred, lacrimation increased, tachycardia, cardiac arrest, arrhythmia, bradycardia, flushing, pallor, vasodilatation, hot flush, cough, dyspnoea, nasal congestion, respiratory arrest, bronchospasm, throat irritation, laryngospasm, pharyngeal oedema, dry throat, pulmonary oedema, erythema, angioedema, eczema, muscle cramps, muscular weakness, back pain, arthralgia, malaise, chest discomfort, pyrexia, face oedema, injection site necrosis (in case of extravasation), phlebitis superficial, decreased oxygen saturation, Not known : nephrogenic systemic fibrosis. **Overdose:** Gadoteric acid can be removed by haemodialysis. However there is no evidence that haemodialysis is suitable for prevention of nephrogenic systemic fibrosis. **Please note:** The peel-off tracking label on the vials or syringes should be stuck onto the patient record to enable accurate recording of the gadolinium contrast agent used. The dose used should also be recorded. If electronic patient records are used, the name of the product, the batch number and the dose should be entered into the patient record. **Pharmacological properties**: Pharmacotherapeutic group: paramagnetic contrast media for MRI, ATC code: V08CA02. **Presentation (*):** 5, 10, 15, 20, 60 & 100 mL in vial (glass) and 10, 15 & 20 mL in a prefilled syringe (glass). **Marketing authorization holder: (*) Information:** Guerbet - BP 57400 - F-95943 Roissy CdG cedex – FRANCE. Tel: 33 (0) 1 45 91 50 00. **Date of revision of this document**: February 2018

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