



## Pharmaceutical and safety aspects of gadolinium-based contrast agents

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**A contrast agent can substantially improve the diagnostic quality of magnetic resonance imaging. Gadolinium-based contrast agents are a very similar class of pharmaceuticals. But they differ in two important aspects, the complex stability and the ability to enhance the MRI signal intensity.**

**M**agnetic resonance imaging (MRI) provides excellent soft tissue images. For several diagnoses, however, a contrast agent (CA) can substantially improve the diagnostic quality. For example, the use of Gadovist as a contrast agent increased the metastatic brain lesions detected in 53% of patients compared to unenhanced MRI procedures, leading to a change in therapy for 20% of patients [1]. Therefore, contrast agents are used in 30–40% of MRI examinations. Unlike iodinated CAs used for X-ray imaging, MRI contrast agents can provide negative and

positive contrast. The principal of MRI contrast agents works by changing the magnetic moment. Therefore, only paramagnetic elements or molecules can be used as contrast agents. Gadolinium-, manganese- and iron-containing agents are used for contrast-enhanced clinical MRI imaging. Iron causes a negative contrast and is therefore called a negative contrast agent. Gadolinium and manganese usually causes a signal increase and are therefore called positive CAs.

### Structural and functional aspects

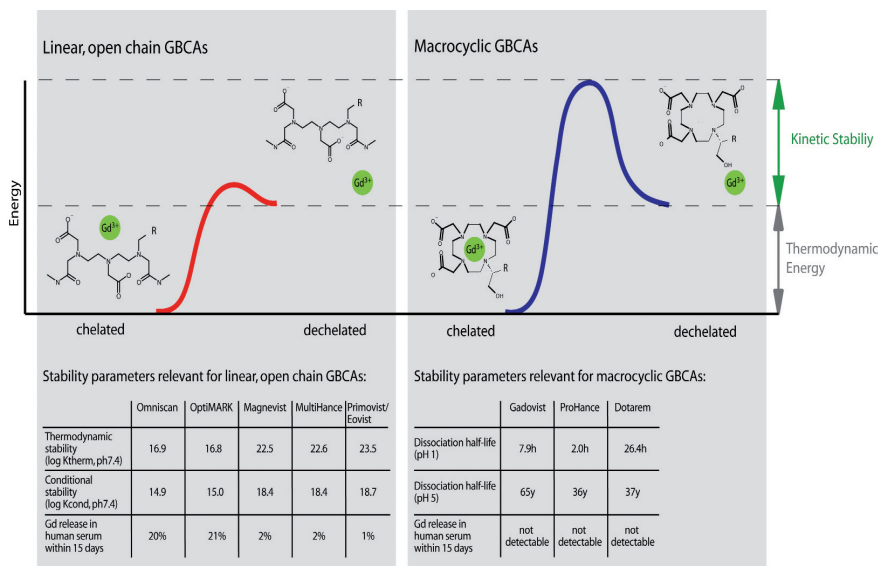
Since IV application of manganese- and

iron-based CA do not play a clinically relevant role, this article will focus on the pharmaceutical and safety aspects of gadolinium-based contrast agents (GBCAs). Several agents have been approved since the first GBCA, Magnevist, was approved in 1988. All GBCAs contain a central  $Gd^{3+}$  ion complexed by a ligand. They are prepared by chelating  $Gd_2O_3$  with their respective ligands. Based on the molecular structure of those ligands, GBCAs can be divided into two classes: the linear open chain class and the macrocyclic class. In all complexes, the central  $Gd^{3+}$  ion is coordinated by the ligand at eight of the

**Table 1: Physical aspects of GBCAs marketed in Europe**

Structural class	Non-ionic linear		Ionic linear			Macrocyclic		
	Trade name	Omniscan	OptiMARK	Magnevist	MultiHance	Primovist/Eovist	Gadovist	ProHance
Generic names	Gadodiamide	Gadoversetamide	Gadopentetate dimeglumine	Gadobenate dimeglumine	Gadoxetate	Gadobutrol	Gadoteridol	Gadoterate dimeglumine
	GD-DTPA-BMA	Gd-DTPA-BMEA	Gd-DTPA	Gd-BOTA	Gd-EOB-DTPA	Gd-BT-DO3A	Gd-HP-DO3A	Gd-DOTA
Concentration [mol/L]	0.5	0.5	0.5	0.5	0.25	1.0	0.5	0.5
Excess ligand	5.0%	10.0%	0.1%	0%	0.5%	0.1%	0.1%	0%
$R_1$ Relaxivity at 3T in plasma at 37°C [Lmmol <sup>-1</sup> s <sup>-1</sup> ]	4.0	4.5	3.7	5.5	6.2	5.0	3.7	3.5
Viscosity [mPa*s]	1.4	2.0	2.9	5.3	1.19	3.7	1.3	2.0
Osmolality [mOsm/kg H <sub>2</sub> O]	790	1,100	1,960	1,970	668	1,910	630	1,350
Excretion	renal	renal	renal	renal, 4-5% hepatobiliary	50% renal; 50% hepatobiliary	renal	renal	renal
Manufacturer	GE	Covidien	Bayer Schering Pharma	Bracco	Bayer Schering Pharma	Bayer Schering Pharma	Bracco	Guerbet

**Figure 1: Stability aspects of GBCAs**



The upper panel depicts the energy level for linear open chain (left) and macrocyclic (right) GBCAs. Please notice the additional activation energy needed for chelating and dechelating of macrocyclic agents, due to steric hindrance. Therefore the complex stability of macrocyclic GBCAs is best described by the kinetic dissociation half-life. The complex stability of linear open chain GBCAs is best described by the thermodynamic stability or conditional stability constant (lower panel). These theoretical considerations are also reflected for example by the difference in  $Gd^{3+}$  release under physiological conditions [7].

CAs, since GBCAs are used at significantly lower doses and volumes (5–20 mL) compared to iodinated CAs (100–300 mL). For example, the osmotic load per kg body weight is significantly lower after the administration of GBCAs compared to low osmolar iodine CAs.

## Pharmacokinetics

All GBCAs have a low molecular mass of about 500 Da, are extremely hydrophilic complexes and are excreted unmetabolised in the urine. They have similar pharmacokinetic properties with similar plasma half-lives, and, due to their small size, extracellular GBCAs are excreted almost exclusively by passive glomerular filtration through the kidneys with neither secretion nor reabsorption. However, protein binding GBCAs are also excreted to varying degrees by the hepatobiliary route (MultiHance 3–4% and Primovist/Eovist 50%). The specific uptake of Primovist/Eovist by hepatic anion transporters greatly facilitates the detection of liver lesions [4].

nine coordination sites of the  $Gd^{3+}$  ion. One coordination site of the  $Gd^{3+}$  ion interacts with a proton of a water molecule, which is essential for its signal enhancement mechanism. GBCAs are mainly used for influencing the so-called T1 shortening. This effect depends on the relaxivity and the concentration.  $R_1$  relaxivity best describes the efficacy to increase the signal enhancement for the most important T1 imaging sequences by the GBCAs. The GBCAs exhibit similar paramagnetic effects, with Gadovist ( $5.0 \text{ Lmmol}^{-1}\text{s}^{-1}$  at 3 T in serum) showing the highest  $R_1$  relaxivity and Dotarem the lowest  $R_1$  relaxivity ( $3.5 \text{ Lmmol}^{-1}\text{s}^{-1}$  at 3T in serum) for the non-protein binding GBCAs (see Table 1). Gadovist has, due to the higher concentration, also the highest T1 shortening per volume [2]. The relaxivity of the GBCAs is also dependent on the magnetic field strength, temperature, protein binding and surrounding [2].

The majority of GBCAs are formulated at a concentration of 0.5 M. One exception is Gadovist, a macrocyclic agent formulated at a concentration of 1.0 M. Therefore, Gadovist possesses double the relaxivity per volume compared to all the other agents. This higher volume relaxivity is helpful for fast magnetic resonance angiography or dynamic and functional studies, such as brain or tumour perfusion [3]. GBCAs are typically approved for IV administration at a concentration of 0.1–0.3 mmol/kg body weight, depending on the product and the label in the respective country. For example, Gadovist is approved in Europe for CNS examinations in a dose up to 0.3 mmol/kg body weight. All GBCAs are formulated as hypertonic solutions with an osmolality between 630–1970 mOsm/kg and viscosities between 1.3–5.3 mPa\*s (see Table 1). In general, the physicochemical properties of GBCAs are of less importance for their safety compared to the iodinated

In patients with normal renal function, the plasma half-life of GBCAs is about 70–100 min, with about 98% excreted within 24 hours post injection. In a patient with chronic kidney disease, however, the circulation time of these agents is prolonged, with plasma half-lives of up to 30 hours in severe renal impairment [5]. Therefore, exposure of a patient to GBCAs depends not only on the administered dose but also on the renal status of the patient.

## Complex stability

When assessing the complex stability of different GBCAs, they are classically compared on the basis of the thermodynamic stability constant (log  $K_{therm}$ ), valid at pH 14, or the conditional stability constant (log  $K_{cond}$ ), calculated for pH 7.4 on the basis of log  $K_{therm}$ . This consideration, however, neglects kinetic stability differences. This parameter is especially relevant when considering the complex stability of macrocyclic

GBCAs (Gadovist, ProHance and Dotarem). Due to their rigid ring structure and steric hindrance, these GBCAs are generally considered to be kinetically inert (see Figure 1). Therefore, the thermodynamic stability constant and the conditional stability constant are of lesser relevance for the macrocyclic GBCAs [6].

Although all of these agents have a very high level of complex stability, there are differences in complex stability within the linear, open chain group (see Figure 1). For example, the two non-ionic compounds (Omniscan and OptiMARK) are considerably less stable than the ionic linear agents (Magnevist, MultiHance and Primovist/Eovist) [6]. The different complex stability of linear, open chain group is most adequately described by the thermodynamic stability or conditional stability constant. In chemical terms, those differences in complex stability are easy to understand given that the lower negative charge (3-) of the non-ionic linear agents results in a weaker electrostatic interaction with the positive  $Gd^{3+}$  ion (3+) than the ligands of the ionic linear agents (5-). The non-ionic, linear compounds are formulated with a considerable amount of Gd free, calcium-bound ligand in order to reduce the occurrence of free  $Gd^{3+}$  ions *in vivo*.

These theoretical considerations led to the grouping of GBCAs into three classes with regard to the complex stability (macrocyclic, ionic linear and non-ionic linear GBCAs), which is supported by experiments *in vitro* and *in vivo*. For example, in human serum, 10-fold higher  $Gd^{3+}$  is released from the non-ionic linear GBCAs than from the ionic linear GBCAs *in vitro*, whereas no  $Gd^{3+}$  release could be observed from any of the macrocyclic GBCAs [7]. Various studies in rodents have shown that the highest Gd values were measured after administration of the least stable agents, while the lowest Gd levels are observed after administration of the

most stable agents [6, 8]. Preclinical data is also in agreement with studies in humans, where significantly lower Gd concentrations were observed in hip bone biopsies after administration with a macrocyclic GBCA compared to administration with a non-ionic linear GBCA [9]. The data strongly suggests that exposure to Gd not only depends on the administered dose but also on the complex stability of the chosen agent.

## Tolerance to GBCAs

Generally, GBCAs are very well tolerated and have established an excellent safety profile. For example, in six prospectively planned surveillance studies conducted with Gadovist, including 14,422 patients, the overall incidence of one adverse drug reaction (ADR) was about 0.55% [10]. There have been no major differences in the incidence rate of ADRs between GBCAs reported. Furthermore, the lower volume and lower dose administered are most likely the reason that GBCAs have a lower incidence of renal complications compared to iodinated CAs.

Recently, IV administration of GBCAs has been linked to nephrogenic systemic fibrosis (NSF), which has been diagnosed in patients with severe renal impairment (glomerular filtration rate  $<30$  mL/min/1.73 m<sup>2</sup>) and in patients with acute renal insufficiency of any severity due to hepato-renal syndrome or in the perioperative liver transplantation period\*. Most of the reported cases have been in patients receiving haemodialysis or peritoneal dialysis [11]. NSF is a severe systemic disease typically characterised by fibrosis of the skin and connective tissues with an increase in CD34 positive fibroblast-like cells and a considerable increase in collagen bundles on the cellular level [11].

Most of the cases reported in the literature to date have been associated with the administration of one specific agent, the non-ionic linear Omniscan,

but there have been reports involving other agents [12, 13]. Based on the currently prevailing theory that Gd dissociated from the underlying chelate may play a role in the development of NSF, as well as on the results of animal and *in vitro* studies, it is believed that, complex stability is an important consideration in attempting to understand the pathogenesis of NSF.

## Conclusion

While GBCAs, as a group, share several common characteristics, they differ in complex stability and in their ability to enhance the MRI signal intensity. Macrocyclic GBCAs (Gadovist, Prohance and Dotarem) have the lowest likelihood to release Gd under clinical conditions, while the non-ionic linear GBCAs (Omniscan and OptiMARK) have highest likelihood. Minor differences exist in regards to signal enhancement, with Gadovist demonstrating the highest level and Dotarem the lowest level of signal enhancement for the non-protein binding GBCAs.

\*Bayer has recently received a few reports of possible NSF in patients who were reported to have mild to moderate renal impairment. As these reports contained limited information, Bayer is attempting to obtain the information necessary to allow the reports to be properly evaluated [14].

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## References

1. Lemke AJ, Sander B, Balzer T, et al. [Safety and use of gadobutrol in patients with brain tumors (phase III trial)]. *Rofo*. 1997;167(6): 591-8.
2. Rohrer M, Bauer H, Mintorovitch J, et al. Comparison of magnetic properties of MRI contrast media solutions at different magnetic field strengths. *Invest Radiol*. 2005; 40(11):715-24.

3. Tombach B, Benner T, Reimer P, et al. Do highly concentrated gadolinium chelates improve MR brain perfusion imaging? Intraindividually controlled randomized crossover concentration comparison study of 0.5 versus 1.0 mol/L gadobutrol. *Radiology*. 2003;226(3):880-8.
4. Zech CJ, Herrmann KA, Reiser MF, Schoenberg SO. MR imaging in patients with suspected liver metastases: value of liver-specific contrast agent Gd-EOB-DTPA. *Magn Reson Med Sci*. 2007;6(1): 43-52.
5. Schuhmann-Giampieri G, Krestin G. Pharmacokinetics of Gd-DTPA in patients with chronic renal failure. *Invest Radiol*. 1991;26(11):975-9.
6. Schmitt-Willich H. Stability of linear and macrocyclic gadolinium based contrast agents. *Br J Radiol*. 2007;80(955):581-2.
7. Frenzel T, Lengsfeld P, Schirmer H, et al. Stability of gadolinium-based magnetic resonance imaging contrast agents in human serum at 37 degrees C. *Invest Radiol*. 2008;43(12):817-28.
8. Pietsch H, Lengsfeld P, Jost G, et al. Long-term retention of gadolinium in the skin of rodents following the administration of gadolinium-based contrast agents. *Eur Radiol*. 2009;19(6):1417-24.
9. White GW, Gibby WA, Tweedle MF. Comparison of Gd(DTPA-BMA) (Omniscan) versus Gd(HP-DO3A) (ProHance) relative to gadolinium retention in human bone tissue by inductively coupled plasma mass spectroscopy. *Invest Radiol*. 2006;41(3): 272-8.
10. Palkowitsch P, Voth M. Summary of the safety data for Gadobutrol and Gadofosveset. *Eur Radiol Suppl*. 2009;18:(Suppl 5):E47-E54.
11. Cowper SE, Boyer PJ. Nephrogenic systemic fibrosis: an update. *Curr Rheumatol Rep*. 2006;8(2):151-7.
12. Wertman R, Altun E, Martin DR, et al. Risk of nephrogenic systemic fibrosis: evaluation of gadolinium chelate contrast agents at four American universities. *Radiology*. 2008; 248(3):799-806.
13. Prince MR, Zhang H, Morris M, et al. Incidence of nephrogenic systemic fibrosis at two large medical centers. *Radiology*. 2008; 248(3):807-16.
14. Sieber MA, Pietsch H, Walter J, et al. A pre-clinical study to investigate the development of nephrogenic systemic fibrosis: a possible role for gadolinium-based contrast media. *Invest Radiol*. 2008;43(1):65-75.