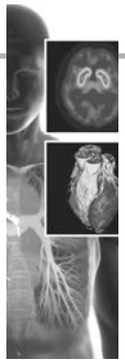

Safety and clinical usefulness of gadoteric acid including post-marketing surveillance

MRI is an essential diagnostic tool in making definite diagnoses and determining therapeutic strategies. Extracellular gadolinium (Gd)-based contrast agents (GBCAs) have been widely used within clinical settings. GBCAs are chelated to improve the safety due to the potent toxicity of the Gd ion itself. Nephrogenic systemic fibrosis (NSF) has been reported in association with the use of GBCAs in patients with serious renal dysfunction. Gd-DOTA, a solution of the Gd complex containing a macrocyclic structure (gadoterate), is characterized by excellent chelate stability and low risk for NSF. Gd-DOTA has been shown to have an good tolerance overall and an excellent efficacy in clinical practice. This contrast agent is an option for risk reduction when contrast-enhanced MRI is indicated in patients with renal dysfunction.

KEYWORDS: contrast enhancement ■ gadolinium ■ gadoteric acid ■ Gd-DOTA ■ meglumine gadoterate ■ MRI ■ nephrogenic systemic fibrosis

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MRI, introduced in the clinical setting in the early 1980s, has become an essential diagnostic tool because it provides excellent soft tissue contrast and multiplanar observation. There are 6279 running MRI devices in Japan as of April 2011, and the number of MRI examinations performed in 2008 is estimated to be approximately 10,000,000, showing that MRI plays an important role in making definite diagnoses and determining therapeutic strategies [1,2].

For MRI, extracellular gadolinium (Gd)-based contrast agents (GBCAs) such as gadoteric acid (Gd-DOTA, Magnescope®, Guerbet Japan KK, Tokyo, Japan; Dotarem®, Guerbet, Roissy CdG, France) have been used in the clinical setting since the 1980s.

For the last 20 years, multiple articles have described the clinical benefits of extracellular GBCAs [3–7].

GBCAs are chelated to improve safety because of the potent toxicity of the Gd ion itself. These contrast agents, after intravenous administration, are nonspecifically distributed from blood to tissue extracellular fluid, and are excreted via the kidney within approximately 24 h after administration without being metabolized. Recent reports describe the onset of nephrogenic systemic fibrosis (NSF) in association with the use of extracellular GBCAs in patients with serious renal dysfunction. NSF manifests with symptoms such as skin swelling, sclerosis and pain with the onset of several days to months, sometimes several years, after the administration of Gd. In advanced cases, limb joint contracture significantly limits the activity of daily living. NSF can also cause fibrosis of internal organs which may lead to death [8,101]. NSF presumably results from the *in vivo* release of the Gd ion from extracellular GBCAs, and skin and tissue deposition of the free ion [9,10].

Gd-DOTA is a GBCA that has been marketed worldwide since its first approval in France in 1989. In Japan, Gd-DOTA was approved in 2000. As of 2011, this contrast agent has been registered in 75 countries and marketed in 68 countries [Guerbet, Data on File]. Gd-DOTA, a solution of the Gd complex containing a macrocyclicstructure (gadoterate), is characterized by excellent chelate stability and has a low risk of causing the onset of NSF [11].

Chemistry & physical properties of Gd-DOTA

In the development of Gd contrast agents for MRI, it is most critical to improve the stability of the chelate to prevent the release of toxic free Gd^{3+} ion. Gd-DOTA, with the macrocyclicstructure, has a potent binding affinity for the Gd^{3+} ion. Its ligand is 1, 4, 7, 10-tetraazacyclododecane-1, 4, 7, 10-tetraacetic acid (DOTA; Figure 1). The molecular formula is $C_{16}H_{25}GdN_4O_8$, and its molecular weight is 753.86 g/mol. Metal complexes are generally dissociated to metals and chelating agents upon the effect of pH. It has been confirmed that Gd-DOTA is a stable complex within the pH ranges of 4.7 to 9.7 (*in vitro*), requiring no stabilizer or capture agent (i.e., free ligand added to the pharmaceutical solution) to inhibit the release of the Gd^{3+} ion during the shelf life [102]. The osmotic

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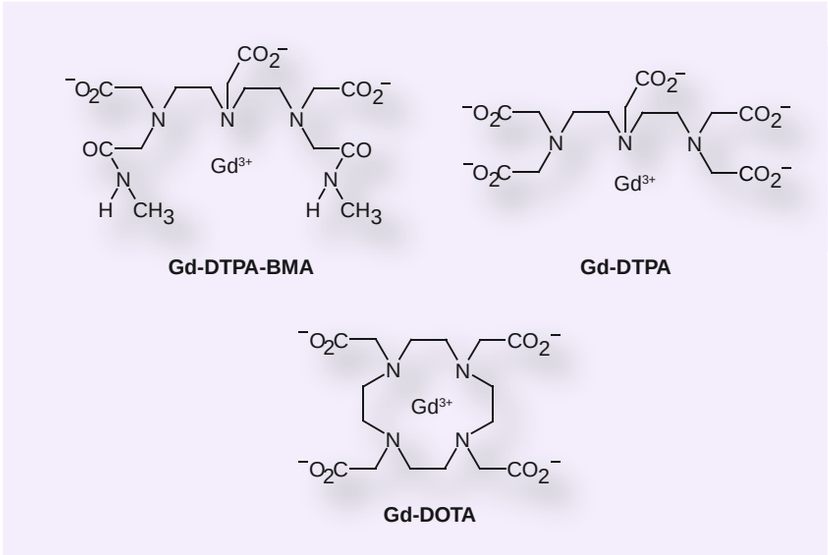

Figure 1. Structures of the ligands and the type of gadolinium chelete complex formed.
Gd-DOTA: Gadoteric acid; Gd-DTPA: Gadopentetate dimeglumine; Gd-DTPA-BMA: Gadodiamide.

pressure is 1350 mOsm/kg H_2O, and the viscosity is 2.0 mPa·s at 37°C. Thermodynamic and conditional stability is an index of Gd^{3+} ion and ligand dissociation, while the kinetic stability indicates the dissociation rate of the Gd^{3+} ion and the ligand. Gd-DOTA has the highest thermodynamic stability (log10 K_{THERM} = 25.8), conditional stability (log10 K_{cond} = 18.8) and kinetic stability of all available Gd–chelate complexes (Table 1) [9,11,12–16].

Relaxivity is the physical basis of contrast enhancement. In plasma at 37°C, T_1 relaxation is 3.6 (3.4–3.8) mM^{-1} s^{-1}, and T_2 relaxation is 4.3(3.4–5.2) mM^{-1} s^{-1} at 1.5 T. At 3 T, T_1 relaxation is 3.5 (3.3–3.7) mM^{-1} s^{-1}, and T_2 relaxation is 4.9(4.0–5.8) mM^{-1} s^{-1} [17].

Pharmacokinetics & pharmacodynamics of Gd-DOTA

Gd-DOTA is nonspecifically distributed from blood to tissue extracellular fluid rapidly after administration. After the intravenous administration of Gd-DOTA, plasma Gd concentration showed a biphasic biexponential decay (Figure 2) [18–20]. In a Japanese Phase I study in adult male volunteers, calculating plasma pharmacokinetic parameters at the standard dose of 0.1 mmol/kg, the half-life was 5.9 ± 3.2 min in the distribution phase (α phase) and 1.21 ± 0.16 h in the elimination phase (β phase) (Table 2). The area under the blood concentration time curve (AUC) was 994.8 ± 105.7 nmol•h/ml. The cumulative urinary excretion of Gd-DOTA was 89% or higher 6 h after administration and 95% or higher 24 h after dosing. HPLC-based analysis of urinary metabolites detected only unchanged Gd-DOTA. These results indicated that Gd-DOTA, after intravenous administration, underwent no metabolism and was excreted unchanged in urine.

The median lethal dose (LD50) in mice of Gd-DOTA is 10.6 mmol/kg and is nearly twice that of Gd-DTPA [18].

Clinical efficacy & safety of Gd-DOTA

■ Phase II study

A Japanese Phase II study of a GCP clinical trial in adult inpatients in whom lesions were confirmed in the brain and spinal cord, heart and thoracic region, abdominal region and limbs and MRI was required for diagnosis [21]. The dose of Gd-DOTA was set within the range where the safety of this drug was confirmed in healthy adults in the Phase I study. Taking into account the clinical dose in France, three doses of 0.05, 0.10 and 0.2 mmol/kg were established so that Gd-DOTA would be adequately safe and provide sufficient contrast enhancement.

T_1- and T_2-weighted MRI images were performed before contrast and T_1-weighted MRI images were taken on the same sections and with the same imaging technique after administration of Gd-DOTA.

A total of 158 patients received Gd-DOTA and all were eligible for the the analysis set. They were randomized to one of the three dose groups. There were 52 patients in the 0.05 mmol/kg group, 52 patients in the 0.1 mmol/kg group and 54 patients in the 0.2 mmol/kg group. No significant difference was found in the distribution of sex, age, complications, medical history or use of prior medication among the three dose groups. Major diseases were glioma (23.6%) and meningioma (21.8%) in the brain and spinal cord, myocardial infarction (34.1%) and lung tumor (46.3%) in the heart and thoracic region, and hepatocellular carcinoma (12.9%), renal cell carcinoma (16.1%) and uterine cervical cancer (11.3%) in the abdominal pelvic region. Most lesions were neoplastic except for cardiac lesions.

■ Efficacy

In the analysis set, T_1-weighted images were taken in 155 patients and dynamic imaging were performed in 70 patients. Gd-DOTA was effective in patients in whom contrast enhancement of T_1-weighted images was good or excellent. The efficacy rate was 84.4% in the 0.05 mmol/kg group, 95.8% in the 0.1 mmol/kg

Table 1. General characteristics of currently marketed gadolinium chelates used for MRI.

	Gd-DTPA	Gd-EOB-DTPA	Gd-BOPTA	MS325	Gd-DTPA-BMA	Gd-DTPA-BMEA	Gd-HP-DO3A	Gd-BT-DO3A	Gd-DOTA
Generic name	Gadopentetate dimeglumine	Gadoxetic acid, disodium salt	Gadobenate dimeglumine	Gadofosveset, trisodium salt	Gadodiamide	Gadoversetamide	Gadoteridol	Gadobutrol	Gadoterate meglumine
Trade name	Magnevist®	Primovist®	Multihance®	Vasovist®	Omniscan®	OptiMARK™	ProHance®	Gadovist®	Dotarem®
Company	Bayer-Schering	Bayer-Schering	Bracco	EPIX	GE-Healthcare	Covidien	Bracco	Bayer-Schering	Guerbet
Chemical structure	Open chain	Open chain	Open chain	Open chain	Open chain	Open chain	Macrocyclic	Macrocyclic	Macrocyclic
Charge	Ionic	Ionic	Ionic	Ionic	Nonionic	Nonionic	Nonionic	Nonionic	Ionic
Concentration (M)	0.5	0.25	0.5	0.25	0.5	0.5	0.5	1	0.5
Osmolality at 37°C (mOsm/kg H_2O)	1960	688	1970	825	789	1110	630	1603	1350
Viscosity (mPa·s) at 37°C	2.9	1.19	5.3	2.06	1.4	2	1.3	4.96	2
Formulation	Free DTPA (1 mmol/l)	Ca-EOB-DTPA (trisodium salt; 1.5 mmol/l)	No formulation	Fosveset (0.325 mmol/l)	Ca-DTPA-BMA (caldiamide; Na^+ salt; 25 mmol/l)	Ca-DTPA-BMEA (Na^+ salt; 50 mmol/l)	$[Ca\text{-}HP\text{-}DO3A]_2$ (Ca^{2+} salt; 0.5 mmol/l)	Ca-BT-DO3A (Na^+ salt; 1.0 mmol/l)	No formulation
Hydrophilicity (log P butanol/water)	-3.16	-2.11	-2.33	-2.11	-2.13	N/A	-1.98	-2	-2.87
log K_{therm}	22.1	23.5	22.6	22.06	16.9	16.6	23.8	21.8	25.6
log K_{cond}	17.7	18.7	18.4	18.9	14.9	15	17.1	14.7	19.3
Kinetic stability	Low	Medium	Medium	Medium	Low	Low	High	High	High
Approving body	EMA, US FDA	EMA, FDA	EMA, FDA	EMA, FDA	EMA, FDA	EMA, FDA	EMA, FDA	EMA	EMA

BMA: Bismethylamide; BMEA: Bismethoxyethylamide; BOPTA: Benzyloxypropionictetraacetate; BT: Butrol; DO3A: Tetraazacyclododecane triacetic acid; DTPA: Diethylene triamine pentaacetic acid; EOB: Ethoxybenzyl diethylenetriamine pentaacetic acid; Gd: Gadolinium; HP: Hydroxypropyl; N/A: Not applicable.

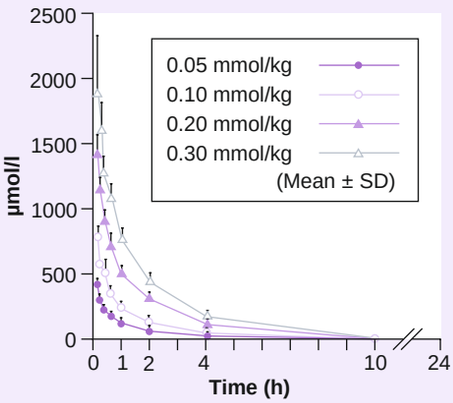

Figure 2. Graph showing time course of changes in plasma gadolinium concentration after intravenous administration of 0.05–0.3 mmol/kg of gadoteric acid in adult male volunteers.
SD: Standard deviation.
Reproduced with permission from [19].

group, and 98.0% in the 0.2 mmol/kg group, showing significant differences among the three dose groups. The χ^2 test showed that the efficacy rate was significantly higher in the 0.2 mmol/kg group compared with the 0.05 mmol/kg group ($p < 0.05$). The U-test demonstrated that the efficacy rate was significantly higher in the 0.1 and 0.2 mmol/kg groups compared with the 0.05 mmol/kg group ($p < 0.01$ and $p < 0.05$, respectively).

■ Safety

Adverse drug reactions occurred in 2 out of 158 (1.27%) patients; a distressed feeling of the chest and peculiar taste occurred in one patient. Both symptoms were mild and spontaneously resolved (within 1 min) without any treatment. There was no relationship between the dose of Gd-DOTA and onset of adverse reactions. Of 156 patients who were included in the analysis of the laboratory tests on blood (complete blood count, total bilirubin, ALT, AST, ALP, LDH, γ-GTP, urea nitrogen, creatinine, electrolytes and serum iron) and on urine (proteinuria, giucosuria and urobilinogenuria), four patients experienced significant changes in serum iron with a suspected relationship with Gd-DOTA; serum iron was reduced in three of the four patients. There was no correlation with the dose of Gd-DOTA in these three patients (Table 3). No statistically significant difference was observed in changes in any laboratory parameter except for LDH between before and after administration (Table 4).

■ Safety rating

The safety rating was evaluated by taking into account the type, severity and duration of adverse drug reaction, and laboratory data. The safety rate per group (i.e., percentage of patients in whom Gd-DOTA was 'safe') was 96.2% (50 out of 52 patients), 96.2% (50 out of 52 patients) and 98.2% (53 out of 54 patients), respectively, in the 0.05, 0.1 and 0.2 mmol/kg group, showing no significant difference among the three groups. The overall safety rate was 96.8% (153 out of 158 patients).

■ Clinical usefulness

The clinical usefulness was evaluated based on the global consideration of 'efficacy' and 'safety rating.' The usefulness rate, in other words, the percentage of patients in whom Gd-DOTA was 'effective' or 'very effective', was 84.4% (38 out of 45 patients), 95.8% (46 out of 48 patients), and 98.0% (49 out of 50 patients), respectively, in the 0.05, 0.1 and 0.2 mmol/kg group, showing significant differences among the three groups. The U-test identified significant differences between the 0.05 and 0.1 mmol/kg groups, and between the 0.05 and 0.2 mmol/kg groups ($p < 0.05$).

This Phase II study examined the efficacy and safety of Gd-DOTA in MRI of cerebral and spinal cord diseases, cardiac and thoracic diseases, and abdominal and limb diseases, and the clinical optimum dose of this drug. Study results confirmed potent contrast enhancement by Gd-DOTA, and the clinical efficacy and safety of this drug. It was concluded that 0.1 mmol/kg was at least the clinical optimum dose of this drug for all these indications.

Table 2. Pharmacokinetic parameters after intravenous administration of gadoteric acid.

Dose (mmol/kg)	$t_{1/2}$ α (min)	$t_{1/2}$ β (h)	Volume of distribution (ml/kg)	Clearance (ml/min/kg)
0.05	5.0 ± 1.2	1.20 ± 0.19	164.5 ± 22.8	1.6 ± 0.3
0.1	5.9 ± 3.2	1.21 ± 0.16	176.5 ± 31.8	1.7 ± 0.2
0.2	7.1 ± 3.3	1.43 ± 0.20	193.5 ± 28.0	1.6 ± 0.1
0.3	15.4 ± 14.3	1.46 ± 0.28	216.4 ± 64.5	1.7 ± 0.3

$t_{1/2}$: Half-life.
Data taken from [19].

Table 3. Changes in serum iron after administration of gadoteric acid.

Injected dose(mmol/kg)	Before administration (μg/dl)	After administration (μg/dl)
0.05	178	43†
0.1	132	192†
0.1	101	12‡
0.1	69	30§

†1 day after injection.
‡2 days after injection.
§3 days after injection.
Data taken from [21].

■ Phase III study

Results of the Phase II study confirmed contrast enhancement effect by Gd-DOTA and its safety and clinical usefulness. The clinical optimum dose of this drug was established as 0.1 mmol/kg [22–32].

In a Japanese Phase III study participating 15 institutions, the efficacy and safety of Gd-DOTA were evaluated in comparison with the control agent, gadopentetate dimeglumine (Gd-DTPA, Magnevist®, Bayer Yakuhin, Osaka, Japan; Magnevist®, Bayer HealthCare Pharmaceuticals Inc., NJ, USA), which had been widely used and was considered to be a reference product at the start of this clinical study.

This was a GCP clinical trial in adult inpatients and outpatients with confirmed or suspected lesions in the brain and spinal cord, heart and thoracic region, and abdominal region and limbs, and MRI was required for diagnosis. Outpatients were eligible if they could be followed. This was a comparative study between Gd-DOTA and Gd-DTPA (both drugs administered at 0.1 mmol/kg). Patients who underwent kidney imaging were given these at 0.05 mmol/kg. The actual dose was calculated based on body weight on the day of administration. MRI protocol was the same as in the Phase II study. Specifically, MRI was performed with the same technique as used in the daily practice at each study center. It was mandatory to take T_1-weighted and T_2-weighted images (or comparative images) before administration and T_1-weighted images (or comparative images) after dosing. Patients underwent dynamic imaging to the furthest extent possible. T_1-weighted images were taken on the same sections and with the same imaging technique before and after administration. T_2-weighted images were obtained on the same sections as T_1-weighted images. Cardiac MRI was conducted, in principle, by the spin echo (SE) method. The TR was the RR interval on the ECG, and only T_1-weighted images were required.

Exposed films were blinded by study centers and patient numbers. The controller randomized the order of reading by the studied regions. The efficacy of the study drugs was evaluated by consensus at the image reading committee. The laboratory tests on blood (complete blood count, total bilirubin, ALT, AST, ALP, LDH, γ-GTP, urea nitrogen, creatinine, electrolytes, serum iron and ferritin) and on urine (proteinuria, giucosuria and urobilinogenuria) were performed within 1 week before administration and on the next day to 3 days after dosing.

In patients with clinically significant changes, the relationship with the study drug was assessed, and the patients were followed for the course of the relevant laboratory parameter.

A total of 304 patients received the study drugs and were all eligible for the analysis set.

■ Efficacy

The efficacy rate, the primary efficacy end point in this study, was 92.5% (135 out of 146 patients) in the Gd-DOTA group and 95.2% (140 out of 147 patients) in the Gd-DTPA group, showing no significant difference between the two groups (χ^2 test; p = 0.323). The difference in efficacy rate

Table 4. Changes in lactate dehydrogenase after administration of gadoteric acid.

Injected dose (mmol/kg)	n	Before administration (μg/dl) (mean ± SD)	After administration (μg/dl) (mean ± SD)	Statistical analysis (paired t-test)
0.05	51	316.5 ± 155.7	321.7 ± 184.0	p = 0.614 (NS)
0.1	50	347.1 ± 205.6	321.0 ± 172.9	p = 0.013*
0.2	54	369.1 ± 301.3	333.1 ± 245.1	p = 0.039*

**p < 0.05.*
NS: Not significant; SD: Standard deviation.
Data taken from [21].

between the two groups was -2.8% with a 90% CI of -7.4–1.8%, confirming the equivalence of the two agents.

■ Safety

There were a total of 21 onsets of clinically significant changes in laboratory values in 16 patients in the Gd-DOTA group (147 patients were included in the analysis of laboratory data), and the relationship with the investigational drug was 'probable' or 'related', including increased GOT in three patients, increased serum iron in six patients, and decreased serum iron in three patients. In the Gd-DTPA group (148 patients were included in the analysis of laboratory data), there were a total of 20 onsets of clinically significant changes in laboratory values in 19 patients, and the relationship with the control drug was 'probable' or 'related,' including increased serum iron in 12 patients, decreased serum iron in four, and increased ferritin in two. There were significant differences in changes before and after administration in γ-GTP, BUN and serum iron in the Gd-DTPA group (paired t-test). For serum iron, a significant difference was identified between the two groups (t-test; p = 0.010) (Table 5).

Gd-DOTA was effective and safe in the data analysis by imaged regions at each study center in this Phase III study (Table 6). Oudkerk also reported from their double-blind, randomized clinical trial comparing Gd-DTPA and Gd-DOTA that Gd-DOTA is as safe a contrast agent as Gd-DTPA and has similar diagnostic efficacy [33].

Large-scale post-marketing surveillance of Gd-DOTA

Gd-DOTA has been marketed as a contrast agent for intravenous use for more than 20 years. There were multiple post-marketing surveillance studies including many patients for the investigation of the clinical usefulness and adverse drug reactions of Gd-DOTA.

In a German multicenter study by Maurer *et al.*, adverse events and image quality were evaluated in a total of 84,621 patients with or without risk factors (45.4% males and 54.6% females, mean age of 52.0 ± 16.9 years) [34]. One or more risk factors were found in 22.9% of the patients, for example, allergic disposition, onset of allergic reaction in the previous imaging procedure and renal impairment. Diagnosis was possible in 99.7% of the patients. Image quality was good or excellent in 97.1% of patients. Adverse events, for example, nausea and vomiting, and urticaria, occurred in 0.34% of the patients. Most of these events were mild. Significant adverse events occurred in eight of the 84,621 patients. The incidence of these events was significantly higher in patients with a history of allergy (0.62%; p < 0.001) and patients with a history of allergic reaction to contrast agents (1.23%; p < 0.001). The authors reported that there was no increase in the onset of adverse events in patients with renal disorders.

Ishiguchi *et al.* reported the results of a Japanese large-scale study in 3444 patients (1300 inpatients and 2144 outpatients) [35]. Gd-DOTA was 'effective' or 'very effective' in almost all patients (99.53%). There were 40 onsets of adverse events in 32 patients (incidence of all adverse events: 0.93%). Most events were gastrointestinal disorders (0.49%) and mild, with no onset of any serious event. Moderate adverse events occurred in four patients, nausea and hepatic impairment in two patients each. The authors concluded that the low incidence of adverse reactions (<1%) and the absence of serious adverse reactions reported during the survey period were consistent with a good tolerance for Gd-DOTA. The use of Gd-DOTA as an MRI-enhancing contrast medium in the clinical practice setting thus appears to be safe and effective. A representative clinical case is shown in Figure 3.

Emond *et al.* reported the results of the post-marketing study involving neonates and infants.

Table 5. Changes in laboratory values after administration of gadoteric acid and gadopentetate dimeglumine.

Laboratory test	Contrast agent	n	Before administration (mean ± SD)	After administration (mean ± SD)	Statistical analysis (paired t-test)	Change in values (mean ± SD)	Statistical analysis (t-test)
γGTP	Gd-DOTA	145	62.8 ± 119.7	61.7 ± 127.4	p = 0.710 (NS)	-1.1 ± 34.3	p = 0.729 (NS)
(U/l)	Gd-DTPA	141	56.5 ± 94.9	54.4 ± 87.7	p = 0.039*	-2.1 ± 12.1	
BUN	Gd-DOTA	146	15.1 ± 4.5	15.5 ± 8.6	p = 0.483 (NS)	0.4 ± 6.8	p = 0.092 (NS)
(mg/dl)	Gd-DTPA	144	15.7 ± 4.9	15.0 ± 4.9	p = 0.005**	-0.6 ± 2.6	
Iron	Gd-DOTA	126	88.3 ± 48.2	89.4 ± 52.5	p = 0.679 (NS)	1.2 ± 31.3	p = 0.010*
(μg/dl)	Gd-DTPA	131	81.8 ± 46.3	95.8 ± 56.6	p = 0.001**	14.0 ± 46.8	

**p < 0.05; **p < 0.01.*
BUN: Blood urea nitrogen; Gd-DOTA: Gadoteric acid; Gd-DTPA: Gadopentetate dimeglumine; NS: Not significant; SD: Standard deviation.
Data taken from [22].

Table 6. Summary of results of Phase III studies in Japan evaluating gadoteric acid-enhanced MRI.

Region/disease	n	MRI (Tesla)	Efficacy (%)	Safety (%)	Ref.
Overall	146	N/A	92.5	97.4	[22]
Liver, uterus	20	N/A	100	100	[23]
Brain, spinal cord	20	N/A	100	100	[24]
CNS	20	1.0	95	100	[25]
Acute myocardial infarction	20	1.0	90	100	[26]
Hepatic tumor	4	1.5	100	100	[27]
Hepatic mass	20	1.5	95	100	[28]
Liver, pelvis	16	N/A	100	100	[29]
Kidney, pancreas	15	1.5 or 1.0	100	100	[30]
Pelvis	7	0.3 or 1.5	71	100	[31]
Pelvic organ	10	N/A	78	90	[32]

N/A: Not applicable.

One hundred and four neonates and infants, ranging in age from 3 days to 18 months, were enrolled and received one injection of Gd-DOTA (volume: 0.6–4 ml). No adverse event was reported after the Gd-DOTA injection. Image quality was rated as 'excellent/good' for Gd-DOTA enhanced MRI in 102 (98.0%) children. They concluded that their results suggested that immediate adverse effects were negligible following intravenous administration of Gd-DOTA in neonates and

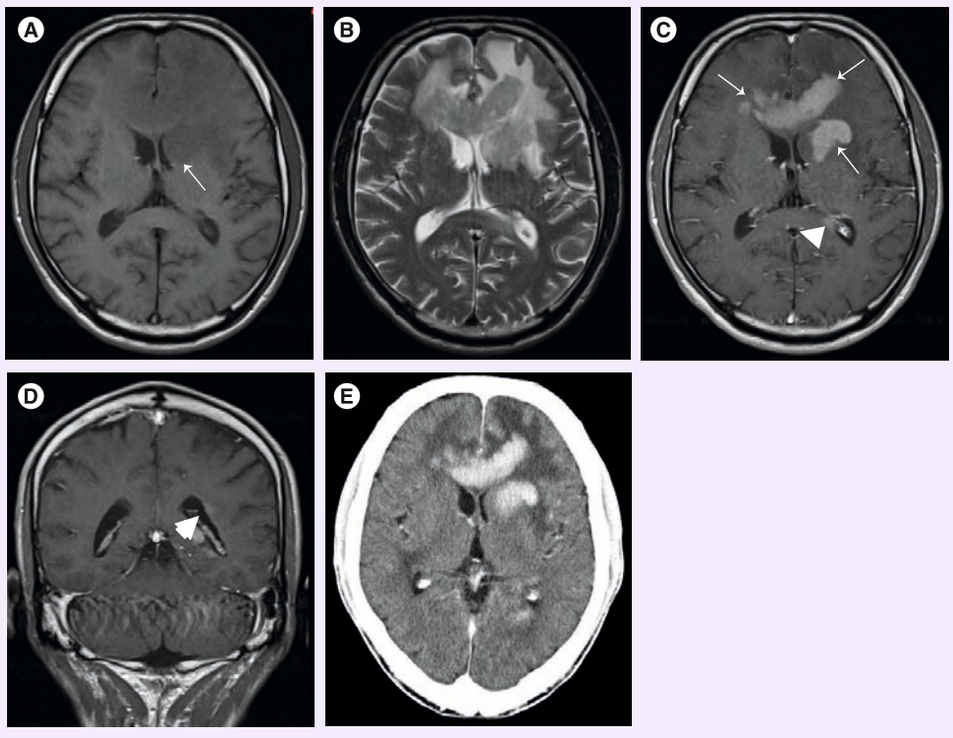

Figure 3. MR and CT images of a patient with brain tumor. (A) Precontrast T_1-weighted image shows a low signal intensity area in bilateral frontal white matter. Deformity of the frontal horn of the left lateral ventricle is seen (arrow). **(B)** T_2-weighted image shows a high signal intensity area in bilateral frontal white matter. **(C)** T_1-weighted image after intravenous administration of gadoteric acid demonstrates enhancing masses in the left frontal white matter extending to the right frontal lobe across the genu of the corpus callosum (arrows). An enhancing lesion at the posterior horn of the left lateral ventricle is also demonstrated (arrowhead). **(D)** Contrast-enhanced coronal T_1-weighted image clearly demonstrates the mass adjacent to posterior horn of the left lateral ventricle (arrowhead). **(E)** Contrast-enhanced CT image shows an enhancing lesion in the frontal area. However, the lesion adjacent to the left lateral ventricle, shown in the MR images, is barely seen.

infants who were undergoing MRI on clinical indication [36].

Gd contrast agents & NSF

Many articles and warnings have recently been published concerning the association between Gd contrast agents and NSF in MRI.

In 2000, Cowper *et al.* reported scleromyxoedema-like cutaneous diseases in renal dialysis patients and mentioned the first case of NSF occurred in 1997 [37].

Based on a report of 25 patients experiencing NSF from the Danish Health Authority, the US FDA issued the first public health advisory in June 2006 for healthcare professionals and general public on the risk of NSF after administration of Gd contrast agents [103].

All 25 patients had serious renal dysfunction, and many of these patients underwent periodic dialysis. NSF occurred within 3 months (2 weeks to 3 months) after the dosing of Gd contrast agents, indicating for the first time the association between NSF and Gd contrast agents. This report attracted a high level of interest, leading to publications of similar announcements and reports [8,38–41,101,104].

Definition of NSF

NSF is a rare disease characterized by hyperplasia of cutaneous connective tissues. Initial symptoms are pain, pruritus, swelling and erythema, with these symptoms usually occuring in lower limbs. Thickened skin and subcutaneous tissues occurring in limbs, sometimes in the trunk, resembling a 'woody' texture and brawny plaques. Lesions are usually bilaterally symmetrical in limbs and the trunk, with fibrosis of internal organs, for example, muscle, diaphragm, heart, liver and lungs. Symptoms usually progress in several days to weeks, leading to contractures, such as disturbed joint mobility, and cachexia and occasional death. Experts in NSF diagnosis developed a clinicopathological diagnostic system for NSF, as described by Girardin *et al.* A consensus scoring system incorporating a clinical and histopathological atlas was devised to guide and standardize the evaluation and diagnosis of NSF [42].

Relationship between NSF & Gd contrast agents

The accurate mechanism of NSF onset is not yet fully understood. The following evidences have indicated the association between NSF and Gd.

There are two categories of Gd contrast agents (macrocyclic and linear ligand). Thermodynamic stability depends on the chemical structure of the Gd chelate (Table 1). In patients with renal impairment, Gd contrast agents remain in the body for long periods of time. In several studies, Gd was detected by a biopsy of skin samples from patients with impaired renal function who experienced NSF after the administration of Gd contrast agents [43,44]. It is considered from this report that the Gd ions are associated with endogenous calcium and phosphate ions, and that free Gd ions in the body deposit in the skin and tissues, leading to fibrosis [45].

In addition to the hypothesis that free Gd ion resulting from transmetallation with endogenous metal(s) might deposit in the dermis or other organs, the attraction of circulating $CD34^+$ fibrocytes to these sites to initiate the process of fibrosis, might be another factor involved in the mechanism of NSF [9].

In addition to Gd, possible risk factors include renal disorders, inflammatory states including surgical procedures, use of erythropoietin, hypercalcemia and hyperphosphatemia. The use of contrast-enhanced MR angiography has been rapidly increasing over the years, and Gd contrast agents have been administered up to 40–60 ml, which is higher than the usual dose range. This is probably one factor leading to increased onsets of NSF [46,47].

The incidence of NSF differs among several Gd contrast agents that are currently in the market [48]. There are particularly more reports of NSF in patients treated with gadodiamide (Gd-DTPA-BMA, Onmiscan®, GE Healthcare, Lawrence, MA, USA; Omniscan, Daiichi-Snkyo Co. Ltd., Tokyo, Japan) whose thermodynamic and kinetic stabilities are low.

■ Regulatory positions

Based on the above since 2006, the regulatory authorities including the FDA, Medicines and Healthcare Products Regulatory Agency (MHRA), and European Medicines Agency (EMA) issued safety information, and warnings, guidelines, and manuals [103–107]. The European Society of Urogenital Radiology (ESUR) Guidelines on 2007 describes that the high-risk population includes patients with stage 4 and stage 5 (GFR < 30 ml/min) chronic kidney disease (CKD), patients on dialysis and patients with decreased renal function who have received or are waiting for liver transplantation. Based on no previous reports of NSF among patients with GFR of 60 ml/min or higher, this guideline also refers to the at-risk population including patients with stage 3 (GFR = 30–59 ml/min) CKD, and children not older than 1 year because of immature

Table 7. Classification of gadolinium-based contrast agents with risk of nephrogenic systemic fibrosis.

Risk of NSF	ACR (USA)	EMA (Europe)
High risk	Gadodiamide (Omniscan®)	Gadodiamide (Omniscan®)
	Gadopentetate dimeglumine (Magnevist®)	Gadopentetate dimeglumine (Magnevist®)
	Gadoversetamide (OptiMark™)	Gadoversetamide (OptiMARK™)
Medium risk	–	Gadoxetic acid (Primovist®)
		Gadofosveset (Vasovist®)
		Gadobenate dimeglumine (Multihance®)
Low risk	Gadoteric acid (Dotarem®)†	Gadoteric acid (Dotarem®)
	Gadoteridol (ProHance®)	Gadoteridol (ProHance®)
	Gadobenate dimeglumine (Multihance®)	Gadobutrol (Gadovist®)
	Gadobutrol (Gadovist®)†	

†*Not approved by the US FDA.*
ACR: American College of Radiology; NSF: Nephrogenic systemic fibrosis.
Data taken from [104,106].

renal function. This guideline recommends that pregnant women should be regarded in a similar way to children younger than 1 year old.

The above guidelines describe that, upon the use of Gd contrast agents, the risk of NSF and the risk of not conducting Gd-based contrast imaging should be constantly compared, and that the benefits and risks of Gd-based contrast imaging should be considered with particular caution in patients with decreased renal function, patients who have undergone liver transplantation and newborns.

Recently, Wang *et al.* reported that among 52,954 contrast-enhanced MR examinations in conformity with their institutional restrictive GBCA guidelines, 6454 (12%) procedures were performed in patients with an estimated glomerular filtration rate of 30–59 ml/min/1.73 m^2 and 36 patients with an estimated glomerular filtration rate lower than 30 ml/min/1.73 m^2 underwent contrast-enhanced MRI for emergent indications. None of these patients experienced NSF [49].

The risks of NSF by various Gd contrast agents have been evaluated (Table 7). The Agency's

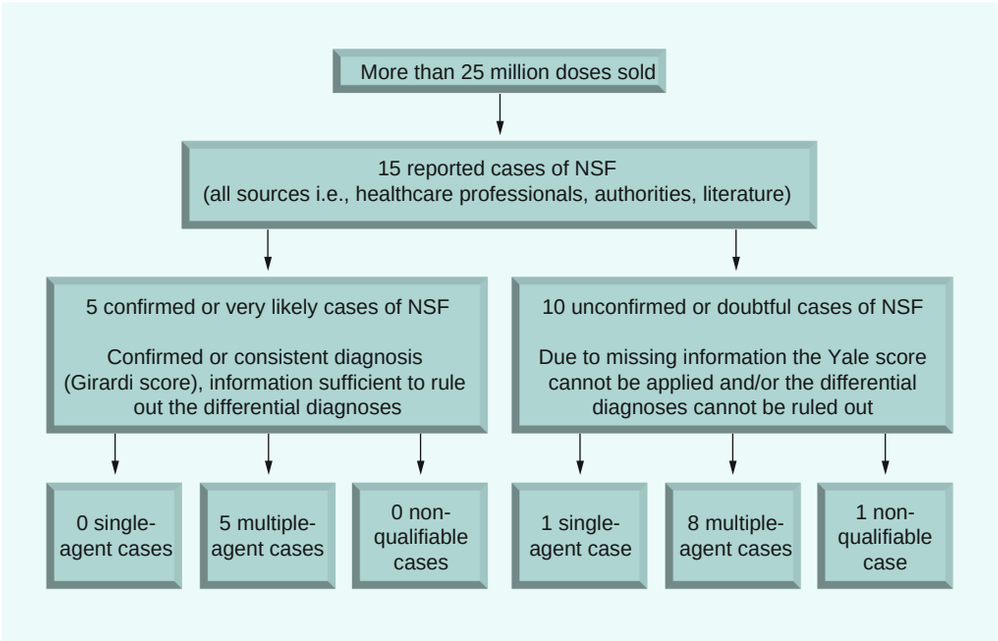

Figure 4. Nephrogenic systemic fibrosis cases reported for patients having received gadoteric acid.
NSF: Nephrogenic systemic fibrosis.
Reproduced with permission from [108].

Committee for Medicinal Products for Human Use (CHMP) of the EMA classifies Gd contrast agents into high-, medium- and low-risk agents based on the risk of NSF [104]. Agents in the high-risk group are contraindicated in patients with severe kidney problems, patients around the time of liver transplantation and newborn babies less than 4 weeks of age. In patients with moderate kidney disorders and infants up to 1 year of age, the dose of the high-risk agents should be limited to the minimum recommended dose. It is also required that all patients should undergo a renal function test before the use of these agents.

The agency advocates that the doses of medium- and low-risk agents should be limited to the minimum recommended dose in patients with severe kidney problems, patients around the time of liver transplantation, and neonates and infants up to 1 year of age, and there should be a period of at least 7 days between scans. The agency also recommends a renal function test before the use of medium- and low-risk agents in all patients.

The incidence of NSF differs among Gd contrast agents [50]. It is recommended for the reduction of NSF risk in at-risk patients that Gd contrast agents with a low risk of NSF should be used; in this context, the dose should not exceed 0.1 mmol/kg body weight. More than one dose should not be used during a scan and injections should not be repeated unless the interval between injections is at least 7 days.

■ Gd-DOTA & NSF

A report describes a very low incidence of NSF in patients given Gd-DOTA, which is classified in the low-risk group [108]. Among more than 25 million patients who received Gd-DOTA, 15 medically confirmed cases developed signs allowing the diagnosis of NSF. On the basis of the available information, the diagnosis of NSF is confirmed or consistent according to the Girardi score in only a third of the reported cases, and the causality of Gd-DOTA is doubtful in all cases (Figure 4). In all cases, the administration of Gd-DOTA preceded the first symptoms, except for one patient who developed NSF after injection of linear Gd chelates, the disease worsening after the patient had undergone several Gd-DOTA-enhanced MR angiography, in a context of degradation of the renal function due to graft rejection.

It is accepted that it is highly likely that Gd chelate stability is an important factor in the onset of NSF. Increased zinc excretion due to excess chelates is also regarded as an important factor in the onset of NSF. Gd chelate stability is lower for linear chelate agents, to which large amounts of excess chelates are added. By contrast, no excess chelate is added to Gd-DOTA, which has a macrocyclic molecular structure. Considering these findings, Gd-DOTA is associated with low risk of NSF.

Conclusion & future perspective

Gd-DOTA is characterized as a highly stable chelate with Gd ions. Gd-DOTA has been shown to have an overall good tolerance and an excellent efficacy in clinical practice. This contrast agent is an option for risk reduction when contrast-enhanced MRI is indicated in patients with renal dysfunction.

In the future, MRI units with higher magnetic fields (3 Tesla and more) will be popular and will make it possible to scan with higher spatial resolution in a shorter image acquisition time. CT is

Executive summary

Chemistry & physical properties

- Gadoteric acid (Gd-DOTA) is a solution to the gadolinium (Gd) complex containing a macrocyclic structure.
- Highest thermodynamic stability, conditional stability and kinetic stability among all available Gd-chelates marketed so far.
- No excess ligand is added to Gd-DOTA as it is not needed, because of its high stability. By contrast, large amounts of excess ligand are added to linear chelate agents.

Pharmacokinetics/pharmoacodynamics

- Extracellular Gd-based contrast agents are nonspecifically distributed after intravenous administration, from blood to tissue extracellular fluid, and are excreted via the kidney without metabolism.

Nephrogenic systemic fibrosis associated with Gd-based contrast agent administration

- Recent reports describe occurrence of nephrogenic systemic fibrosis (NSF) in association with the use of some Gd-based contrast agents in patients with serious renal dysfunction.
- The Gd ions may be replaced with endogenous metal ions, and free Gd ions may deposit in the skin and tissues, leading to fibrosis. It has been speculated that free Gd ions also bind to phosphoric acid to form Gd phosphate, which deposits in body tissues, stimulates macrophages, and causes cytokines secretion, resulting in skin fibrosis.
- Gd chelate stability may be an important factor in the onset of NSF.
- Considering these findings, Gd-DOTA is associated with a low risk of NSF.
- Gd-DOTA has been shown to have a good tolerance overall and excellent efficacy in clinical practice.

also a very useful diagnostic imaging modality, but the widespread use of CT will be associated with considerable radiation exposure to patients. MRI is a noninvasive imaging technique without ionizing radiation. Moreover, the Gd-based contrast agents did not seem to produce less allergic reaction than the iodine-based contrast agents used for CT. Some of the newer GBCAs, which demonstrate protein binding, are approved for use. They possess higher relaxivity, hepatobiliary excretion and prolonged residence in the bloodstream. The advantages of protein binding effects lead to either better lesion depiction and delineation and improved lesion enhancement in various applications, including in particular brain MR imaging, MR colonography and MR angiography [51–54]. Therefore, the use of MRI will be more popular as a less-invasive alternative to CT for many diseases.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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