46 Contrast Media: Gadolinium Chelates with Extracellular Distribution

The gadolinium (Gd) chelates are the dominant class of contrast media for MRI. They are clear, colorless fluids, formulated without bacteriostatic additives for intravenous administration. The standard dose (excluding use in MR angiography) is 0.1 mmol/kg, which corresponds to 15 mL for a 75-kg patient (with all agents except one formulated at a concentration of 0.5 molar). The distribution of the agents is to the extracellular space.

Lesion enhancement occurs by one of two mechanisms: disruption of the blood–brain barrier (for intraaxial brain lesions) and lesion vascularity. The gadolinium ion is strongly paramagnetic, leading to a reduction in both T1 and T2, which is visualized on T1-weighted images as an increase in signal intensity. In **Fig. 46.1**, thin section T1-weighted images are illustrated at the level of the internal auditory canal, revealing a soft tissue mass (a vestibular schwannoma) on the right pre-contrast (**Fig. 46.1a**), which demonstrates prominent enhancement post-contrast (white arrow, **Fig. 46.1b**). Enhancement of normal vascular structures includes the nasal turbinates (black arrow, **Fig. 46.1b**) and choroid plexus, easily recognized markers of post-contrast scans. Clinically, contrast enhancement is used both for improved lesion detection and characterization. Contrast injection is routinely performed in the question of neoplastic disease, infection, inflammation, and vascular abnormalities, with broad overall indications. In recent years, the field of contrast-enhanced MR angiography has developed as an additional major application of the gadolinium chelates.

The word "chelate" comes from the Greek root *chelos*, meaning claw. The safety basis of the gadolinium chelates rests with the ability of the chelate to hold extremely tightly the

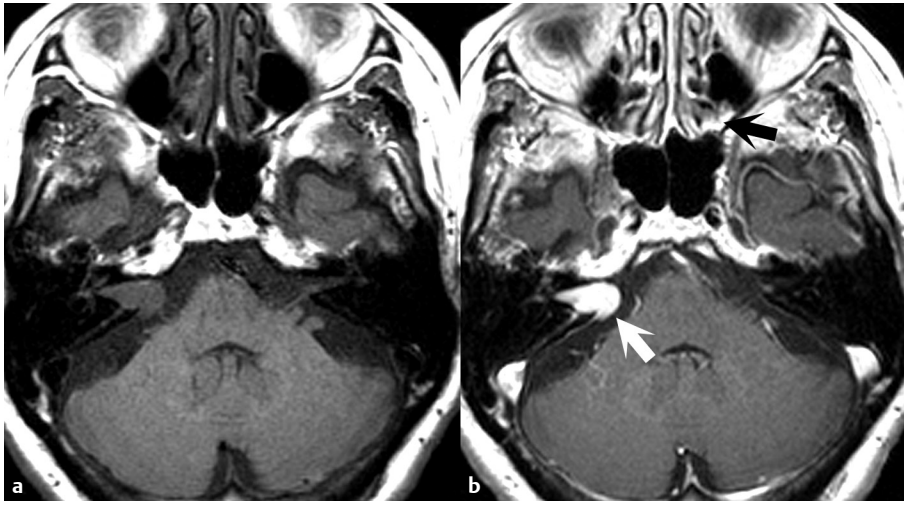

Fig. 46.1

gadolinium ion and assure near 100% excretion. Gadolinium is a heavy metal, a member of the transition elements (atomic number 64), and as such is extremely toxic in elemental form (Gd^{3+}). The gadolinium chelates are 100% renally excreted, with the exception of two agents with combined renal and hepatobiliary excretion (MultiHance and Eovist).

The gadolinium chelates currently available for clinical use can be differentiated on the basis of charge (ionic or nonionic), structure (linear or cyclic), and stability (**Figs. 46.2 and 46.3**). Given that the gadolinium ion carries a +3 charge, if the ligand, for example, is HP-DO3A (that for ProHance, with a charge of −3), the metal chelate itself will carry a net charge of zero, and thus be nonionic. In the U.S. market, considering only the gadolinium chelates with 100% renal excretion, there are four nonionic agents (Gadavist, ProHance, Omniscan, and Optimark) and two ionic agents (Magnevist and Dotarem). The structure of the chelate can be linear or macrocyclic (ring-like), with the cyclic chelates demonstrating higher in vivo stability and thus an improved safety margin. Gadavist (nonionic), ProHance (nonionic), and Dotarem (ionic) are the macrocyclic chelate agents available both in the United States and internationally.

The identification of nephrogenic systemic fibrosis (NSF) in 1997 and the subsequent, although delayed, recognition of its cause has led to a reassessment of gadolinium chelate use in MRI. NSF is an uncommon but serious acquired systemic disorder affecting patients with severe renal insufficiency, now known to be due to gadolinium chelate administration. Limb contractures and pain are prominent features, with the disease fatal in a small percent of cases. Development of the disease is due to gadolinium chelate dissociation, with deposition of the free metal, and is thus related to chelate stability, dose, and cumulative (lifetime) dose. The vast majority of documented cases have followed Omniscan injection, although a substantial number of cases have also been documented following injection of Optimark or Magnevist. Early in 2007, the use of Omniscan (and subsequently Optimark and Magnevist) was banned in patients with an estimated GFR less than 30 mL/min/1.73 m^2 by European authorities, with the FDA adopting a similar policy after some delay. Cautious use of the macrocyclic agents, with high thermodynamic and kinetic stability, is felt acceptable even in CKD4 (CKD, chronic kidney disease) and CKD5 ($<$ 30 and $<$ 15 mL/min/1.73 m^2 glomerular filtration rate [GFR]) patients. In terms of incidence of the disease, this has been reported to be as high as 18% in CKD5 (dialysis) patients when given Omniscan.

Contrary to an often-used marketing/sales approach, the gadolinium chelates cannot be differentiated on the basis of common major reactions. All share the same safety profile in this regard, with nausea reported in 1.5% and urticaria in 0.5% of all injections. Health care personnel should be aware of the potential (although rare) for severe anaphylactoid reactions, with treatment identical to that for an iodinated contrast reaction. Patients with asthma, prominent allergies, or known drug sensitivities (including allergy to iodinated contrast media) are at increased risk for a severe anaphylactoid reaction.

The Characteristics of the Clinically Approved Gd-Based Contrast Agents

Acronym	Gd-DTPA	Gd-DOTA	Gd-HP-DO3A	Gd-DTPA-BMA	Gd-DO3A-Butrol	Gd-DTPA-BMEA	Gd-BOPTA	Gd-EOB-DTPA	MS-325
Trade Name	Magnevist	Dotarem	ProHance	Omniscan	Gadovist/ Gadavist	OptiMARK	MultiHance	Primovist/ Eovist	Vasovist/Ablavar
Generic Name	Gadopentetate Dimeglumine	Gadoterate Meglumine	Gadoteridol	Gadodiamide	Gadobutrol	Gadover-setamide	Gadobenate Dimeglumine	Gadoxetic acid Disodium	Gadofosveset Trisodium
Company	Bayer	Guerbet	Bracco	GE–Healthcare	Bayer	Covidien	Bracco	Bayer	Lantheus
First approval*	1986, EU	1989, EU	1992, USA	1993, USA	1998, EU	1999, USA	1997, EU	2004, EU	2005, EU
Doses (mmol/kg)‡	0.1	0.1–0.2	0.1–0.3	0.1	0.1	0.1	0.05–0.1	0.025	0.03
Concentration (M)	0.5	0.5	0.5	0.5	1.0	0.5	0.5	0.25	0.25
Excess chelate (mg/ml)	0.4	0	0.2	12	0.5	28.4	0	1.0	
Structure	Linear	Macrocyclic	Macrocyclic	Linear	Macrocyclic	Linear	Linear	Linear	Linear
Ionicity	Ionic	Ionic	Nonionic	Nonionic	Nonionic	Nonionic	Ionic	Ionic	Ionic
Osmolality (mOsm/kg H_2O, 37°C)	1960	1350	630	789	1603	1110	1970	688	825
Viscosity (mPa · s, 37°C)	2.9	2.0	1.3	1.4	5.0	2.0	5.3	1.2	2.1
Log K_{therm}§	22.1	25.6	23.8	16.9	21.8	16.6	22.6	23.5	22.1
Log K_{cond}¶	17.7	19.3	17.1	14.9	14.7	15.0	18.4	18.7	18.9
$T_{½}$‖	<5 s	338 h	3.9 h	<5 s	43 h	<5 s	<5 s	<5 s	<5 s
Relaxivity (r1/r2, 1.5 T)**	3.9–4.1/ 4.6–5.3	3.6/4.3	4.1/5.0	4.3/5.2	4.7–5.2/ 6.1–7.5	4.7/5.2	6.3–7.9/ 8.7–18.9	6.9/8.7	19.0/34.0
Relaxivity (r1/r2, 3 T)**	3.7–3.9/5.2	3.5/4.9	3.7/5.7	4.0/5.6	4.5–5.0/ 6.3–7.1	4.5/5.9	5.5–5.9/ 11.0–17.5	6.2/11.0	9.9/60.0
Clearance	Renal	Renal	Renal	Renal	Renal	Renal	96% renal 4% hepatic	50% renal 50% hepatic	79%–94% (mean, 84%) renal ~5% hepatic

* Specific approval varies from country to country.
‡ Approval for the highest dose indicated is dependent on country.
§ K_{therm} = Thermodynamic stability constant.
¶ K_{cond} = Conditional stability constant.
‖ $T_{½}$ = Dissociation half-time at pH 1.0 and 25°C.
** Values in L $mmol^{-1}$ s^{-1} (plasma, 37°C).
EU indicates Europe; USA, United States of America.

Fig. 46.2

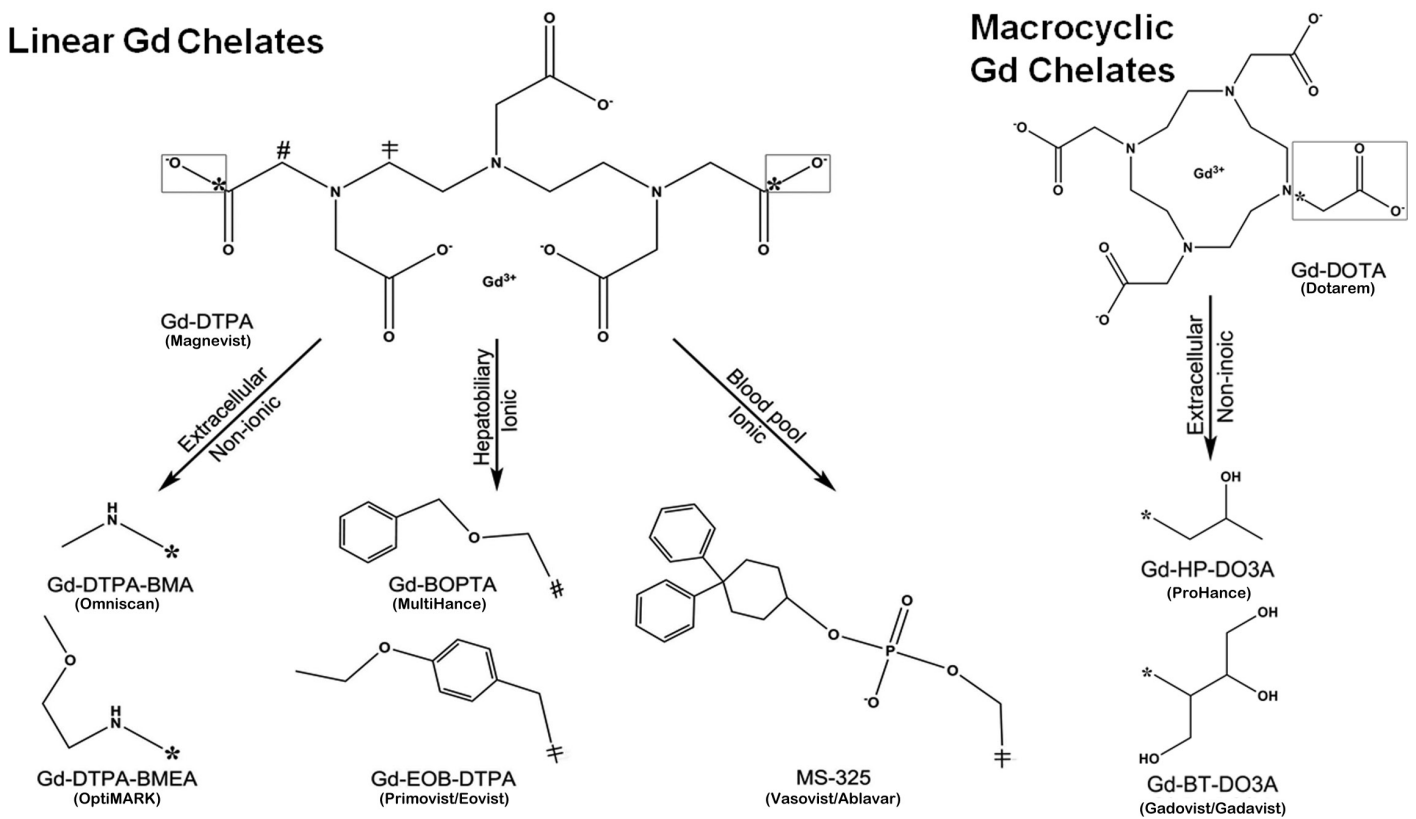
Linear Gd Chelates
Gd-DTPA
(Magnevist)
Extracellular
Non-ionic
Hepatobiliary
Ionic
Blood pool
Ionic
Gd-DTPA-BMA
(Omniscan)
Gd-BOPTA
(MultiHance)
Gd-DTPA-BMEA
(OptiMARK)
Gd-EOB-DTPA
(Primovist/Eovist)
MS-325
(Vasovist/Ablavar)
Macrocyclic
Gd Chelates
Gd-DOTA
(Dotarem)
Extracellular
Non-inoic
Gd-HP-DO3A
(ProHance)
Gd-BT-DO3A
(Gadovist/Gadavist)

Fig. 46.3