52 Contrast Media: Gadolinium Chelates with Extracellular Distribution

The only agents approved today for use in MRI as contrast media are the gadolinium (Gd) chelates. As administered, these are clear, colorless fluids, formulated without bacteriostatic additives, with the typical route of injection being intravenous. The standard dose (excluding some specialty applications) is 0.1 mmol/kg, which corresponds to 15 mL for a 75-kg patient, for the agents formulated at 0.5 molar concentration. The distribution in the body 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. 52.1**, 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. 52.1a**), which demonstrates prominent enhancement post-contrast (**Fig. 52.1b**, *white arrow*). Enhancement of normal highly vascular structures includes the nasal turbinates (**Fig. 52.1b**, *black arrow*) 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 prior decades, the field of contrast-enhanced MR angiography 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 gadolinium ion and assure near 100% excretion. Gadolinium is a heavy

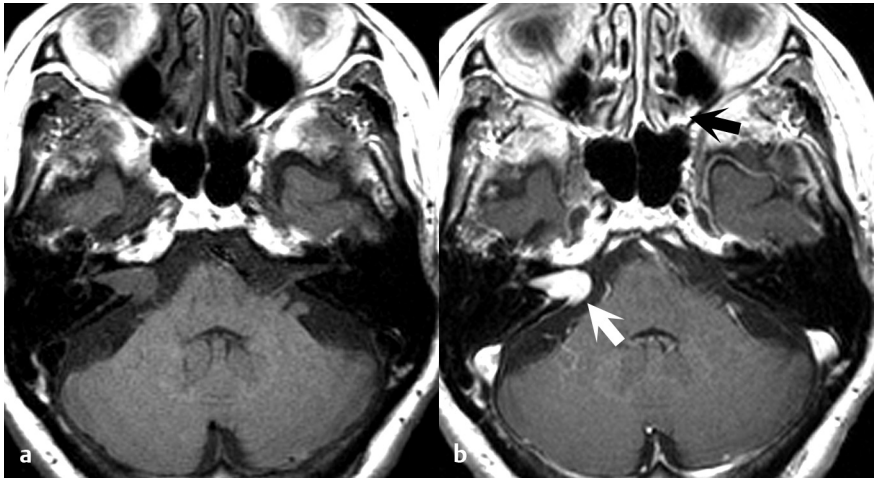

Fig. 52.1 Vestibular schwannoma, prior to and following Gd chelate injection.

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/Primovist).

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 (**Fig. 52.2**; **Table 52.1**). 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. Considering the gadolinium chelates with 100% renal excretion - and specifically only those still approved world-wide, there are two nonionic agents (Gadavist and ProHance) and one ionic agent (Dotarem). The structure of the chelate can be linear or macrocyclic (ring-like), with the cyclic chelates demonstrating higher in vivo stability and thus improved safety. 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 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 followed Omniscan injection, although a substantial number of cases were also documented following injection of Optimark and 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.

A further reassessment of safety is ongoing due to the recognition of accentuated accumulation of Gd in the brain (and body) in patients with normal renal function following injection of the linear Gd chelates. This was first described in 2014, being recognized initially on imaging in the dentate nucleus. Of the agents involved, Magnevist has been replaced with Gadovist by Bayer, and Optimark (formerly manufactured by Covidien) with Dotarem by Guerbet. In July 2017, the European Medicines Agency (EMA) recommended suspension of the marketing authorizations for four linear chelates – Omniscan, Optimark, MultiHance and Magnevist, with the exception of the liver indication for MultiHance and the intra-articular indication for Magnevist - with these changes generally being implemented world-wide.

Contrary to an often-used marketing/sales approach, the extracellular, renally excreted 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.

Table 52.1 The Characteristics of the Clinically Approved (and those withdrawn) Gadolinium-Based Contrast Agents

	Magnevist	Dotarem	ProHance	Omniscan	Gadovist/ Gadavist	OptiMARK	MultiHance	Primovist/ Eovist	Vasovist/Ablavar
acronym	Gd-DTPA	Gd-DOTA	Gd-HP-DO3A	Gd-DTPA-BMA	Gd-DO3A-Butrol	Gd-DTPA-BMEA	Gd-BOPTA	Gd-EOB-DTPA	MS-325
generic name	Gadopentetate dimeglumine	Gadoterate meglumine	Gadoteridol	Gadodiamide	Gadobutrol	Gadoversetamide	Gadobenate dimeglumine	Gadoxetic acid disodium	Gadofosveset trisodium
manufacturer	Bayer	Guerbet	Bracco	GE Healthcare	Bayer	Covidien	Bracco	Bayer	
first approval*	1988	1989 in Europe	1992 in USA	1993 in USA	1998 in Europe	1999 in USA	1997 in Europe	2004 in Europe	2005 in Europe
doses (mmol/kg)**	0.1	0.1–0.3	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 date varies from country to country
** approval for the highest dose indicated is dependent on country
*** values in L $mmol^{-1}sec^{-1}$ (plasma, 37°C)
K_{therm} = thermodynamic stability constant
K_{cond} = conditional stability constant
$t_{½}$ = dissociation half-time at pH 1.0 and 25°C

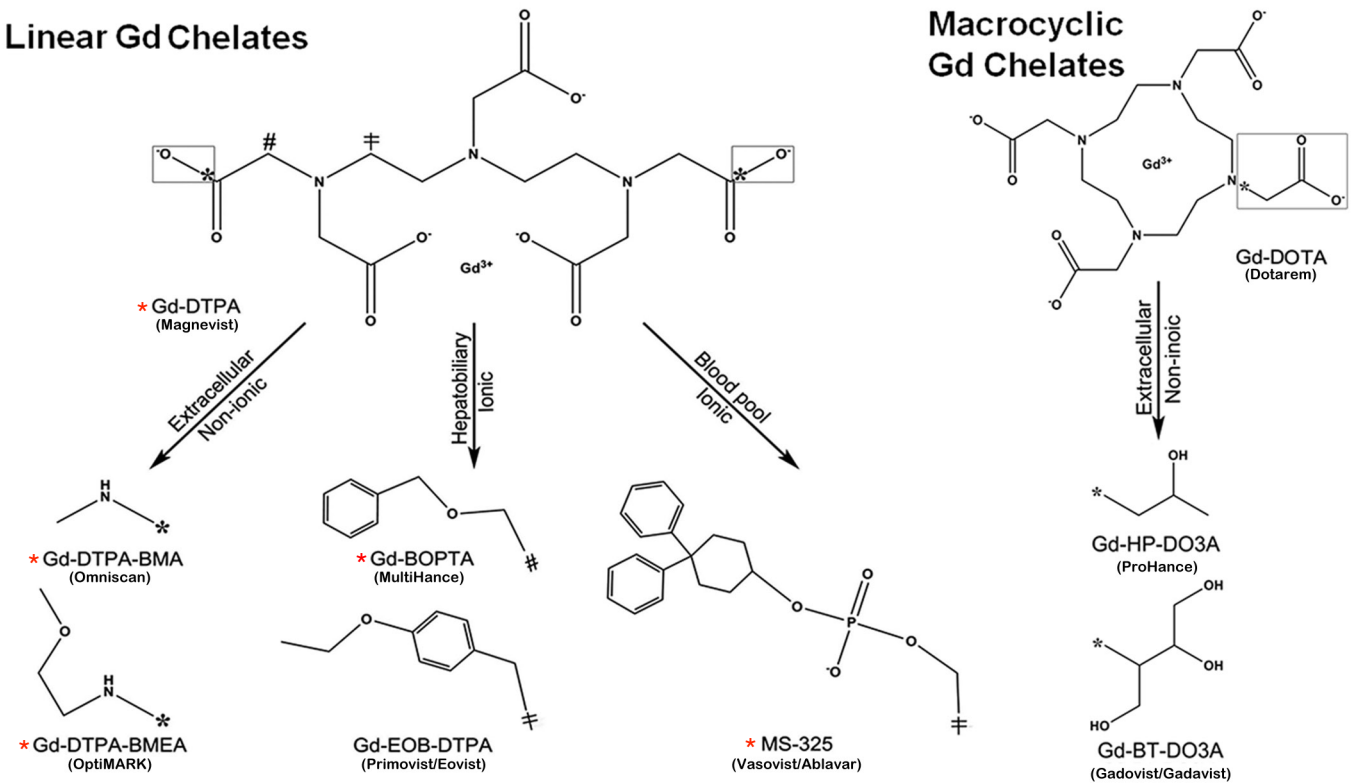

Fig. 52.2 Structural formulas for the Gd chelates developed commercially, including those now withdrawn or otherwise restricted in use*.