

ON-LINE APPENDIX

Gadolinium

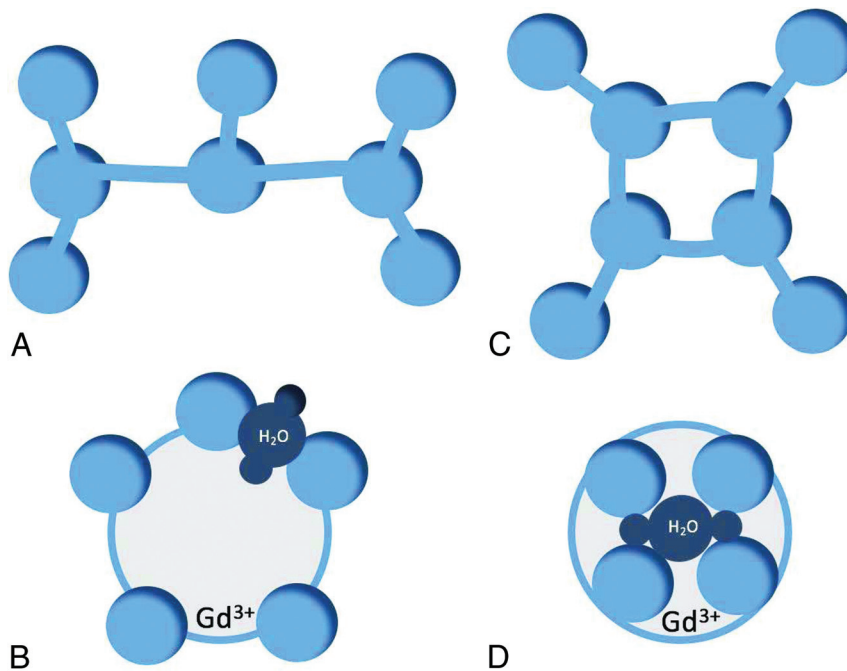
Gadolinium-based contrast agents are of 2 main classes: linear open-chain Gd^{3+} chelates and macrocyclic Gd^{3+} chelates (On-line Figure). In the macrocyclic structure, the Gd^{3+} ion is caged in the cavity of the ligand. Thus, the rate of dissociation of the Gd^{3+} ion from macrocyclic ligands is slower than that from linear ligands, resulting in greater molecular stability for macrocyclic ligands. Gd^{3+} stability is also determined by the rate of transmetallation. This process involves the exchange between Gd^{3+} and endogenous ions. Such endogenous ions present in the body that induce transmetallation include Na^+ , K^+ , Mg^{2+} , Ca^{2+} , Fe^{3+} , and Zn^{2+} . Free Fe^{3+} and Cu^{2+} , present in very small amounts in the blood, and Na^+ , K^+ , Mg^{2+} , and Cu^{2+} have a weak ability to chelate Gd^{3+} . Therefore, Zn^{2+} is assumed to play an important role in transmetallation with emphasis on linear agents compared with macrocyclic ligands (On-line Figure).^{1,2}

Gadolinium enhancement in the CNS occurs as a result of a combination of 2 primary processes: intravascular (vascular) enhancement and interstitial (extravascular) enhancement.³ CNS-approved Gd^{3+} chelates are relatively small and thus have exceedingly high tumbling rates that often exceed the resonant frequencies of water molecules at the clinically used MR imaging field strengths.⁴ The degree of enhancement is proportional to both the local concentration of contrast agent and the relaxivity of the water molecules surrounding the contrast agent.⁵ Relaxivity reflects the capability to shorten the water proton relaxation rates of T1 and T2/T2* and is an inherent property of the contrast molecule itself. The relaxivity of the contrast agent is also depen-

dent on the physiologic environment (ie, blood, interstitial fluids, intracellular space) as well as the capacity of the contrast media agent to interact with macromolecules in the blood (protein binding).⁶ Recent studies⁷ of Gd^{3+} relaxivity values in human blood have shown that r1 relaxivity values range between 3.9 and $4.6 \text{ L} \times \text{mmol}^{-1} \times \text{seconds}^{-1}$ at 1.5T compared with that of gadobenate at $6.2 \text{ L} \times \text{mmol}^{-1} \times \text{seconds}^{-1}$. The latter demonstrates a more significant relaxation time difference than the former. On-line Table represents the different types of Gd^{3+} and their chemical structure, half-life, excretion rate, and relaxivity (1.5T).

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ON-LINE FIGURE. Illustrations of the chemical structure of the linear (A and C) and macrocyclic (B and D) ligands and the linear and macrocyclic ligands surrounding Gd^{3+} with the attached water molecule (H_2O). Generally, linear ligands wrap around the Gd^{3+} ions (B), forming a more flexible chelate because the cages are not entirely closed, while macrocyclic ligands form a rigid cage with a preorganized cavity to fit the coordination sphere of the Gd^{3+} ion (D).

On-line Table: Types of linear and macrocyclic gadolinium-based contrast agents and their relaxivity, half-life, and clearance rates

Chemical Name	Solubility	r1 (L/mmol/s)	r2 (L/mmol/s)	Half-Life (Mean) (hr)	Clearance Rate (Mean) (hr) ^a
Linear					
Gd-DTPA	Ionic	4.1	4.6	1.4 ± 0.2 to 2.0 ± 0.7	72.9% ± 17.0% to 85.4 ± 9.7% (48)
Gadobenate dimeglumine (Gd-BOPTA)	Ionic	6.3	8.7	0.2 ± 0.13 to 1.6 ± 0.13	91% ± 13% (24)
Gd-DTPA bis-methylamide (Gd-DTPA-BMA)	Nonionic	4.3	5.2	0.2 ± 2.2 to 1.12 ± 0.16	95.4% ± 5.5% (24)
Gadoversetamide (Gd-DTPA-BMEA)	Nonionic	4.7	5.2	0.22 ± 0.12 to 1.73 ± 0.33	95.5 ± 17.4% (24)
Macrocyclic					
Gadoterate meglumine (Gd-DOTA)	Ionic	3.6	4.3	1.4 ± 0.2 to 2.0 ± 0.7	72.9% ± 17.0% to 85.4 ± 9.7% (48)
Gadoteridol (Gd-HP-DO3A)	Nonionic	4.1	5.0	0.20 ± 0.04 to 1.57 ± 0.08	94.4% ± 4.8% (24)
Gadobutrol (Gd-BT-DO3A)	Nonionic	5.2	6.1	1.33–2.13	90% (12)

Note:—r indicates relaxivity.^a The number in parentheses represents hours.