

53 New High-relaxivity Gd Chelates

In the regulatory context of nephrogenic systemic fibrosis (NSF) and Gd retention in brain and other organs, the lowest gadolinium based contrast agent (GBCA) dose should be used that provides sufficient enhancement for diagnosis in routine practice. Thus, the development of next-generation high-relaxivity GBCAs meets a very real medical need. By revisiting the GBCA dose-response relationship, such agents would allow reduction of the injected Gd dose with the same efficacy as the former agents and/or improve lesion detection and characterization by use of standard dose, 0.1 mmol/kg.

In the past, a few high-relaxivity GBCAs made their way to market. This includes the blood pool agent gadofosveset trisodium (Ablavar, Lantheus Medical Imaging) which non-covalently binds to human serum. It was indicated for MRA but production was discontinued in 2017 due to poor sales. Another high-relaxivity GBCA, gadobenic acid, has transient non-covalent weak binding to serum albumin and is partially eliminated in the bile. However, the increase in relaxivity is marginal, with this agent as well largely withdrawn from clinical use (being a linear agent and substantially less stable *in vivo* compared to the macrocyclic agents).

Several academic groups and companies are currently investigating next generation, high-relaxivity agents. Among these, gadopixelenol (Guerbet, France) is the leading compound and has now entered phase III clinical trials.

Gadopixelenol is a Gd-complex based on a pyclen macrocyclic structure (**Fig. 53.1**), offering excellent stability (thermodynamic and kinetic), and high r_1 relaxivity (around two-fold that of currently available GBCAs). The conditional thermodynamic constant $\log K_{\text{cond}}$ (at pH 7.4) is 15.5 and there is high kinetic inertness under acidic conditions, with a dissociation half-life of 20 ± 3 days compared with 4 ± 0.5 days for gadoterate meglumine, 18 hours for gadobutrol, and less than 5 seconds for gadodiamide and gadopentetate dimeglumine. Due to improved water access to the Gd^{3+} ion, gadopixelenol exhibits a very high relaxivity,

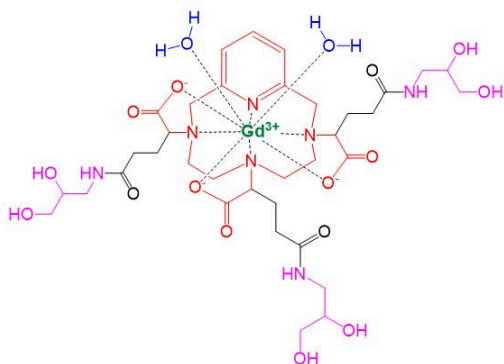


Fig. 53.1 Structural formula for the Gd chelate gadopixelenol.

independent from protein binding, with an r_1 value of $12.2 \text{ mM}^{-1}\text{s}^{-1}$ in water at 37°C and 1.41 T. Moreover, when measured in human serum at 37°C , the r_1 value remained relatively stable with increasing clinical magnetic field ($r_1 = 12.8 \text{ mM}^{-1}\text{s}^{-1}$ at 1.41 T and $11.6 \text{ mM}^{-1}\text{s}^{-1}$ at 3 T).

In studies performed on rats with hepatic colorectal metastases, gadopixelenol at 0.1 mmol/kg led to significantly better lesion enhancement compared with gadobutrol or gadoterate meglumine, both used at 0.1 mmol/kg. Moreover, in a randomized and blinded study using a rat brain tumor model, gadopixelenol resulted in statistically significant two-fold higher change in CNR at 0.1 mmol/kg, with CNR similar at 0.05 mmol/kg as compared to gadoterate meglumine, gadobutrol and gadobenate dimeglumine, all three at 0.1 mmol/kg.

A phase IIb study was performed in 272 patients with known or highly suspected lesions with disrupted blood-brain barrier and randomized to 1 of 4 doses of gadopixelenol (0.025, 0.05, 0.1, 0.2 mmol/kg) and to 1 series of 2 MR scans: gadopixelenol then gadobenate dimeglumine at 0.1 mmol/kg or vice versa (Invest Radiol 2020;55: 129–137). Gadopixelenol showed a linear relationship between the dose and CNR increase. Gadopixelenol at 0.1 and 0.2 mmol/kg showed a statistically significant superiority (CNR of more than 30%) over gadobenate dimeglumine, while the CNR was of similar magnitude between gadopixelenol at 0.05 mmol/kg and gadobenate dimeglumine at 0.1 mmol/kg. Similar results were obtained for lesion-to-brain ratio and contrast enhancement percentage. Mean scores for lesion visualization variables, particularly lesion contrast enhancement, tended to be higher with gadopixelenol at 0.1 and 0.2 mmol/kg compared with gadobenate dimeglumine. All three blinded readers in this study expressed an overall diagnostic preference for images with gadopixelenol at 0.1 mmol/kg (45.3%, 50.9%, or 86.8% of images) or expressed no preference (49.1%, 49.1%, or 9.4%, respectively). A similar safety profile (specifically regarding acute reactions) was observed between gadopixelenol and gadobenate dimeglumine. Thus, gadopixelenol with its very high relaxivity (and thus contrast effect) will likely provide two benefits clinically: 1) by using half of the standard dose to get the same efficacy in most conditions of MR imaging, and 2) by using the standard dose to obtain higher efficacy, which can be useful in clinical conditions such as imaging of late enhancement in cardiac MR examinations or for better detection of brain metastases in cancer staging or in brain radiosurgery (Fig. 53.2).

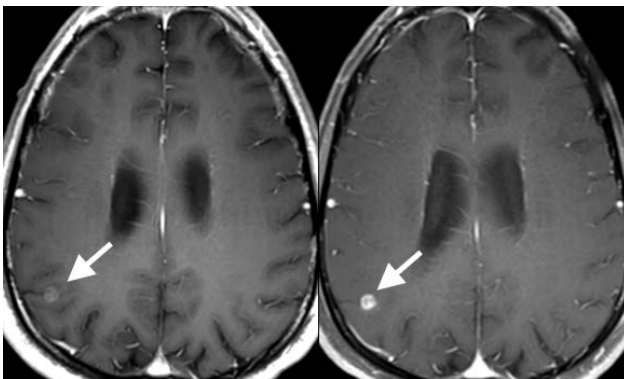


Fig. 53.2 Brain metastasis from lung cancer, images obtained after a dose of 0.1 mmol/kg, gadobenate dimeglumine vs gadopixelenol (adapted from Invest Radiol 2020;55: 129–137).