Gadolinium-diethylenetriamine pentaacetic acid-24-cascade-polymer

24GdDTPACP

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Created: October 2, 2007; Updated: December 4, 2007.

Chemical name:	Gadolinium-diethylenetriamine pentaacetic acid-24-cascade-polymer	
Abbreviated name:	24GdDTPACP	
Synonym:	GdDTPA-cascade-24-polymer, Gd-DTPA-24-cascade-polymer, 24-gadolinium-DTPA-cascade-polymer, Gd-DTPA-24-cascade-polymer, Gd-DTPA-cascade-polymer	
Agent category:	Macromolecule	
Target:	Other	
Target category:	Other – blood pool agent	
Method of detection:	Magnetic Resonance Imaging (MRI)	
Source of signal/contrast:	Gadolinium	
Activation:	No	
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals	No structure is available in PubChem.

Background

[PubMed]

Magnetic resonance imaging (MRI) delineates soft tissues by sampling the signal of tissue water protons to detect abnormalities in anatomy, pathology, and functionality in the human body. The imaging contrast, defined as the relative brightness of various parts of the body, is primarily determined by the tissue structures and the spin relaxation times of

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NLM Citation: Zhang H. Gadolinium-diethylenetriamine pentaacetic acid-24-cascade-polymer. 2007 Oct 2 [Updated 2007 Dec 4]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

the water protons (the longitudinal relaxation time (T_1) and the transverse relaxation time (T_2)). Many physiological processes, including blood flow, diffusion, perfusion, and chemical exchange, also affect the imaging contrast. To improve the imaging contrast, a variety of experimental parameters can be optimized. Imaging contrast can be improved locally by using contrast agents specifically targeted to tissues and organs (1, 2). Blood pool agents are paramagnetic contrast agents designed to remain in the blood for a prolonged time compared to the conventional contrast agents like gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA). Blood pool agents are normally macromolecules attached gadolinium chelates or iron oxide nanoparticles (1). Their large size prevents them from diffusing through the endothelium of normal tissue and entering into interstitial space in detectable amounts before being completely excreted from body. In addition to the applications in magnetic resonance angiography (3-5), blood pool agents are used to target necrotic myocardium (6, 7), to access myocardial viability (8), and to detect various tumors (9, 10).

$(GdDTPA)_{24}$-cascade-polymer is a synthetic polymeric gadolinium complex designed as a blood pool contrast agent for MRI (11, 12). The main molecular frame is a dendritic structure (dendrimer) built from a tri-mesoyl[benzene-1,3,5-tricarbonyl] core surrounded by two generations of 6 and 12 L-lysine residues. 24 Gd-DTPA moieties are covalently bound at the molecular surface (13). Each Gd-DTPA moiety contains lanthanide Gd(III) of high electron spin (7/2) and long electron relaxation time (14). Gd(III) forms a very stable complex with DTPA and leaves one structural water in rapid exchange with the bulk water of tissues. As a result, the T_1 relaxation time of tissue water protons reduces significantly. Attaching Gd-DTPA to a macromolecule generates a field-dependent paramagnetic enhancement effect (PRE) (15, 16). The efficacy increases substantially as a result of the increase of the effective rotation correlation time τ_R. The synthesis of dendrimer starts with formation of a core. Monomers are assembled radially according to certain dendritic rules and cascade to higher generations like a starburst. Dendrimers built in this way have a globular shape, which provides an open surface for attaching various species such as imaging agents and therapeutic drugs (13). As a carrier for MRI contrast agents, dendrimers possess a mono-dispersed, well-defined, and stable molecular structure with rigid branch segments, allowing the synthesis of paramagnetic particles with well-defined size and efficacy (13, 17).

Synthesis

[PubMed]

Nicolle et al. described a detailed synthesis of the dendritic backbone of free 24mer amine (18). First the monomer *N,N'*-(iminodi-2,1-ethandiyl)-bis[N2,N6-bis[(benzyloxy)carbonyl]-L-lysinamide) was prepared in a single step from commercially available starting materials. Three equivalents of the monomer were then reacted with the central core benzene-1,3,5-tricarbonyl trichloride to produce the benzyloxycarbonyl-protected 12mer amines with 80% yield. This precursor was converted to the free 12mer amine and subsequently treated with N_a,N_t-dibenzyloxy-carbonyl-L-lysine-p-nitrophenyl

ester to produce the protected 24mer amine with >80% yield. The protected 24mer was further converted to the free 24mer amine (18). Coupling of a three-fold molar excess DTPA-ethyl ester with the free 24mer amine generated dendritic DTPA ligand, followed by complexation with Gd_2O_3 to form $(GdDTPA)_{24}$-cascade-polymer.This compound has 24 GdDTPAs and the molecular mass is 17 kDa. Because the compound has a globular shape, the apparent molecular weight is 30–35 kDa (11, 12). $(GdDTPA)_{24}$-cascade-polymer is commercially available (Schering AG, Berlin, Germany).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The *in vitro* T_1 relaxivity of $(GdDTPA)_{24}$-cascade-polymer was determined to be 11.9 mmol $Gd^{-1} \bullet s^{-1}$ at 0.47 T (20 MHz) at 40°C (12) and slightly decreased to 10 mmol $Gd^{-1} \bullet s^{-1}$ at 2 T (85 MHz) at 37°C (19). This relaxivity is two-fold higher than that of the single GdDTPA, which is 4.9 mmol $Gd^{-1} \bullet s^{-1}$ at 2 T (85 MHz) at 37°C (19).

Animal Studies

Rodents

[PubMed]

The half-life time in rat plasma was measured to be 0.5 hr. Within 7 days, 99% of the agent was eliminated in the urine. The 50% lethal dose (LD_{50}) was >30 mmol Gd/kg in the rat (12).

Schwickert et al. measured the MR angiographic properties of $(GdDTPA)_{24}$-cascade-polymer (19). The peritumoral vessels were examined in rats bearing subcutaneous R32030 mammary adenocarcinomas on a 2-T MRI imager. At a dose of 0.05 mmol Gd/kg, $(GdDTPA)_{24}$-cascade-polymer was used to effectively define the peritumoral vessels and the tumor rims. Su and colleagues performed a pharmacokinetic study of $(GdDTPA)_{24}$-cascade-polymer in three animal tumor models in rats and mice (20). Dynamic contrast-enhanced MR imaging was used to examine the enhanced kinetics on a 1.5-T MRI imager. A dose of 0.07 mmol Gd/kg was administrated intravenously to rats bearing Walker 256 or R2320AC tumors and nude mice bearing human MCF7 carcinomas. The kinetic profiles suggested that $(GdDTPA)_{24}$-cascade-polymer was predominately confined to the intravascular space. This low, whole-body distribution volume allowed for evaluation of the vascular volume, but its intermediate molecular size permitted a slow diffusion into the interstitial space through the vascular leakage and the rate of the leaking was used as the measure of vasculature permeability in tumors or other diseases. Roberts et al. used $(GdDTPA)_{24}$-cascade-polymer to assess the acute or reperfused myocardial ischemia in rats because this type of contrast agent was more easily accumulated in the normal myocardium than in the ischemic region (20, 21). Dynamic, cardiac-gated, T_1-weighted images were acquired on a 2-T MRI imager. The signal enhancement for the acute myocardial ischemia was found to be primarily located in

normal myocardium but was negligible in ischemic myocardial muscle. The capillary permeability in the reperfused myocardial ischemia was found to have a five-fold increase compared to that of the normal myocardium. The temporal window available for imaging was ~18 min in rodents.

Other Non-Primate Mammals

[PubMed]

Adam et al. conducted signal enhancement measurement in the liver, renal cortex, pancreas, and trunk muscle of pigs at 1.5 T (11, 12). Five minutes after an i.v. injection of a dose of 0.05 mmol Gd/kg, 81% of the agent remained in the circulating blood. Signals in all organs peaked within 1 to 2 min and the enhancement lasted >30 min. The muscle was the only exception to have a slight signal enhancement compared to other organs such as liver, renal cortex, and pancreas. In a study of canine breast tumors in dogs at 1.5 T, a dose of 0.025 mmol Gd/kg was administrated to dogs that were diagnosed to have spontaneously occurring breast tumors 1.5–4.2 cm in diameter (22). The results showed that $(GdDTPA)_{24}$-cascade-polymer allowed differentiation between benign and malignant breast lesions. Tacke et al. evaluated hypovascularized liver tumors (2–3 cm in diameter) in rabbits with a dose of 0.02 mmol Gd/kg (23). Single-slice, fast, low-angle shot (FLASH) gradient-echo images were collected on a 1.5-T MRI imager. Although the agents preceded a prolonged and incomplete distribution into the interstitial space of the tumor, the tumor remained hypointense, which yielded a marked contrast of tumor and liver tissue. The agents were eliminated from the body by glomerular filtration as the $(GdDTPA)_{24}$-cascade-polymer.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

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