Gadolinium-1,4,7,10-tetraazacyclododecane-*N,N′,N′,N‴*-tetraacetic-monoamide-24-cascade-polymer

24GdDOTACP

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Chemical name:	Gadolinium-1,4,7,10-tetraazacyclododecane-*N,N',N",N"'*-tetraacetic-monoamide-24-cascade-polymer	
Abbreviated name:	24GdDOTACP	
Synonym:	Gadomer-17®, SHL 643A	
Agent category:	Small molecule	
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 • Non-human primates • Humans	No structure is available in PubChem.

Background

[PubMed]

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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 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).

24-Gadolinium-1,4,7,10-tetraazcyclododecane-*N,N',N",N"'*-tetraacetic monoamide $(GdDOTA)_{24}$-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 gadolinium-1,4,7,10-tetraazcyclododecane-N,N',N",N"'-tetraacetic monoamide (Gd-DOTA) moieties are covalently bound at the molecular surface (12, 13). Each Gd-DOTA 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 DOTA 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. DOTA is a macrocyclic and can form a stable complex with Gd(III). Gd-DOTA has an *in vitro* stability five orders of magnitude greater than that of Gd-DTPA (14). This greater stability allows for reduction of the *in vivo* toxicity caused by the dissociation of free Gd(III) in the metabolic process (14). Attaching Gd-DOTA 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 (17). 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 (17, 18). $(GdDOTA)_{24}$-cascade-polymer is a blood pool agent of intermediate size that can

effectively delineate small vessels, detect capillary permeability, improve myocardial ischemia detections, estimate blood flow and blow volume, and characterize tumors.

Synthesis

[PubMed]

Nicolle et al. described a detailed synthesis of the dendritic backbone of free 24mer amine (13). 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 procurer 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 (13). Coupling of a three-fold molar excess p-nitrophenyl ester of DOTA with the free 24mer amine generated dendritic DOTA ligand, followed by complexation with Gd_2O_3 to form $(GdDOTA)_{24}$-cascade-polymer (13). This compound has 24 GdDOTAs and the molecular mass is 17.753 kDa. Because the compound has a globular shape, the apparent molecular weight is 30–35 kDa (12). $(GdDOTA)_{24}$-cascade-polymer is commercially available (Schering AG, Berlin, Germany) and is currently undergoing phase II clinical trials (19, 20).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The relaxivities of $(GdDOTA)_{24}$-cascade-polymer in water or blood plasma were measured at several magnetic field strengths and temperatures (11, 12). The T_1 relaxivity in water was 17.3 ± 0.1 mmol $Gd^{-1} \cdot s^{-1}$ at 0.47 T (20 MHz) at 39°C and 12.6 ± 0.1 mmol $Gd^{-1} \cdot s^{-1}$ at 2 T (85 Hz) at 22°C. In blood plasma, the T_1 relaxivity increased slightly to 18.3 ± 0.4 mmol $Gd^{-1} \cdot s^{-1}$ and 13.5 ± 0.1 mmol $Gd^{-1} \cdot s^{-1}$, respectively. In comparison, the T_1 relaxivity of GdDOTA in water was 3.84 mmol $Gd^{-1} \cdot s^{-1}$ at 0.47 T. The T_2 relaxivity was higher than the T_1 relaxivity. In water, the T_2 relaxivity was 22.4 ± 0.1 mmol $Gd^{-1} \cdot s^{-1}$ at 0.47 T and 20.0 ± 0.1 mmol $Gd^{-1} \cdot s^{-1}$ at 2 T, and increased to 29.3 ± 2.3 mmol $Gd^{-1} \cdot s^{-1}$ and 21.4 ± 0.3 mmol $Gd^{-1} \cdot s^{-1}$ in plasma, respectively. The osmolality and viscosity at 0.5 mol/L at 37°C were measured to be 0.38 (osmol/kg) and 7 mPa/s, respectively (11).

The relaxation properties of water were examined with ^1H nuclear magnetic resonance (NMR) dispersion spectroscopy (NMRD) at different magnetic field strengths and with ^{17}O NMR spectroscopy at different temperatures (13). The electron spin relaxation rates of Gd(III) were examined with electron paramagnetic resonance (EPR) spectrometers at three operating frequencies (9.4, 150, and 225 GHz) (13). Three types of kinetic parameters that determine the relaxation rate constant were calculated from these measurements. The water exchange kinetic rate constant (k_{ex}) was calculated to be 1.0 x

10^6 s^{-1} at 25°C. This value is very similar to those found for gadolinium DOTA-monoamide derivatives. The local and the global rotation correlation times (τ_s and τ_g) for the bound Gd-DOTA moieties were found to be 760 ± 120 ps and 3,050 ± 250 ps, respectively. The electron relaxation time τ_v was found to be 46 ± 3 ps at 25°C (13).

Animal Studies

Rodents

[PubMed]

The pharmacokinetic study in rats was conducted at a dose of 0.1 mmol Gd/kg (12). The concentration in blood plasma was measured by gamma (γ) counting of the radioactive ^{153}Gd-labeled $(GdDOTA)_{24}$-cascade-polymer after a bolus injection. The elimination from the blood was biphasic in the rats with a total plasma clearance of 8.1 ml/min per kg. The half-life was 2 min for the initial arterial phase with a blood volume (Vc) of 0.04 L/kg and 37 min for the steady-state phase with a total blood volume (Vss) of 0.13 L/kg.

The biodistribution in rats was investigated at 24 h, 7 days, and 14 days after an intravenous injection of the ^{153}Gd-labeled $(GdDOTA)_{24}$-cascade-polymer at a dose of 0.1 mmol Gd/kg (12). About 80% of the injected dose (ID) was excreted in the first hour in urine as $(GdDOTA)_{24}$-cascade-polymer, and 91% ID in the first day. Fecal elimination was <1%. At 14 days after injection, only 0.12% ID was detected in the kidney, 0.04% in the liver, 0.04% in the gastrointestinal tract, and 0.50% in the carcass. The acute systemic tolerance LD_{50} after a single intravenous injection was found to be ≥20 mmol/kg in rats (21) and ≥30 mmol Gd/kg in mice (12).

The extravasation properties associated with leaky vasculatures were measured in hamsters bearing amelanotic melanomas (22). Fluorescein isothiocyanate (FITC)-labeled $(GdDOTA)_{24}$-cascade-polymer was administrated intravenously at a dose of 0.2 mmol/kg. An *in vivo* fluorescence microscopy was used to examine the tumors in the dorsal skin fold chamber. $(GdDOTA)_{24}$-cascade-polymer was found to leak into the interstitial space in the area of neovascularized tumors immediately after injection and into the tumor-free tissues in the area with neoplastic tumor 5 min later. Dynamic MRI permitted the calculation of the rate for the agents leaking into the interstitial space after a bolus injection. This rate as a measure of vascular permeability was used to differentiate various tumors in rodent models (23-26). The applications included lymph node tumor metastasis (23), gliomas (24), malignant breast tumors (25), infiltrating ductal carcinomas (26), R3230 AC adenocarinomas (21), human skin HaCaT-ras-A-5RT3 carcinomas, and prostate R3327-AT1 carcinomas (27). $(GdDOTA)_{24}$-cascade-polymer was also used in a study of myocardial diseases for delineation of very small microvascular obstructions in ischemically injured myocardium of rats (28).

Other Non-Primate Mammals

[PubMed]

A pharmacokinetic study was also carried out in rabbits at a dose of 0.05 mmol Gd/kg and in dogs at a dose of 0.1 mmol Gd/kg (12). The concentration in blood plasma was measured by gamma (γ) counting of the radioactive ^{153}Gd-labeled $(GdDOTA)_{24}$-cascade-polymer after a bolus injection. Elimination from blood was biphasic, and the total plasma clearance was 4.4 ml/min per kg in the rabbits and 3.5 ml/min per kg in the dogs. The half-life in the rabbits was 4 min for the arterial phase with Vc of 0.041 L/kg and 28 min for the steady-state phase with Vss of 0.10 L/kg. The half-life in the dogs was 11 min for the arterial phase with Vc of 0.071 L/kg and 110 min for the steady-state phase with Vss of 0.19 L/kg.

Dong et al. measured the enhancement effects in abdominal and thoracic MR angiography in dogs at five doses (0.01, 0.025, 0.05, 0.1, and 0.2 mmol Gd/kg) (11). The signal-to-noise ratio increased at doses >0.01 mmol/kg and was found in aorta, inferior vena cava, portal vein, renal arteries and veins, celiac trunk, superior mesenteric artery, and pulmonary arteries and veins. The signal-to-noise was three-fold greater in the aorta in the arterial phase and four-fold greater in the aorta and the inferior vena cava in the steady-state phase in comparison with that of small Gd-chelates. Clarke et al. studied the steady-state phase angiography properties of $(GdDOTA)_{24}$-cascade-polymer in the aorta of health rabbits at four doses (0.015, 0.025, 0.05, and 0.1 mmol Gd/kg) (29). The enhancement was also tested in the pulmonary MR angiography in pigs (30, 31) and in the coronary angiography in pigs (32) and cats (33).

Misselwitz et al. studied the interstitial MR lymphography in dogs at three doses (0.001, 0.0025, and 0.01 mmol/kg) on a 1.5-T MR imager (34). With a dose >0.0025 mmol/kg, the enhancement of 120–168% occurred 15 min after injection. Depending on the dosage, the maximum signal increase ranging from 450–960% was observed at 60–90 minutes after injection. Torchia et al. performed the detection of the sentinel lymph nodes in pigs by dynamic MR lymphangiography on a 0.2-T MR imager (35). $(GdDOTA)_{24}$-cascade-polymer was also used to evaluated the effects of various treatments of VX2 carcinomas in rabbits models, such as radio frequency ablations (36) and x-ray irradiations (37).

Non-Human Primates

[PubMed]

A pharmacokinetic study was also performed in cynomolgus monkeys at a dose of 0.1 mmol Gd/kg (12). The concentration in blood plasma was measured by gamma (γ) counting of the radioactive ^{153}Gd-labeled $(GdDOTA)_{24}$-cascade-polymer after a bolus injection. The elimination from the blood was biphasic in the monkeys with a total plasma clearance of 4.3 ml/min per kg. The half-life was 9 min for the initial arterial phase with Vc of 0.06 L/kg and 168 min for the steady-state phase with Vss of 0.21 L/kg.

Human Studies

[PubMed]

Herborn et al. conducted MR angiography of coronary arteries in 12 healthy male volunteers (age range, 26–36 years; average age, 32.3 years) (19). Fast T_1-weighted, three-dimensional, gradient-echo images were acquired with a 1.5-T MR imager at a dose of 0.1 mmol Gd/kg. The study was further extended to the patients with angiographically proven coronary artery disease (20). Twelve patients (seven men, five women; age range, 47–78 years; average age, 61.3 years) with luminal narrowing >50% were examined with the same imaging protocols. No significant changes in pulse rate, arterial blood pressure, oxygen saturation, hematology, and urinalysis were found for both groups after the injection. Satisfactory tolerance was reported for all participants without acute or later-phase adverse effects. The blood to myocardium contrast-to-noise ratio increased significantly in the 30 minutes after injection and led to a considerable improvement in the imaging qualities.

NIH Support

HL38698, CA82923,

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