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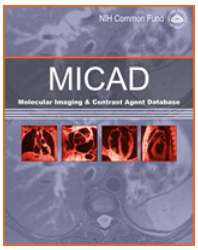

Gadobutrol

Gd-DO3A-butrol

Kenneth T. Cheng, PhD[1]

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Chemical name:	Gadobutrol
Abbreviated name:	Gd-DO3A-butrol
Synonym:	[1,4,7-Tris(carboxymethyl)-10-(1-(hydroxymethyl)-2,3-dihydroxypropyl)-1,4,7,10-tetraazacyclododecanato] gadolinium(III); Gadovist®; 10-[(1*SR*,2*RS*)-2,3-dihydroxy-1-hydroxymethylpropyl]-1,4,7,10-tetraazacyclodecane-1,4,7-triacetic acid, gadolinium; Gd-BT-DO3A; Gd^{3+}-10-(2,3-dihydroxy-1-hydroxymethylpropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid; Gadolinium, (10-(2,3-Dihydroxy-1-(hydroxymethyl)propyl)-1,4,7,10-tetraazacyclodecane-1,4,7-triacetato(3-)-N1,N4,N7,N10,O1,O4,O7)-
Agent Category:	Compound
Target:	Nontargeted, blood pool, extracellular fluid space
Target Category:	Nonspecific filling of extracellular fluid space
Method of detection:	Magnetic resonance imaging (MRI)
Source of signal:	Gadolinium (Gd)
Activation:	No

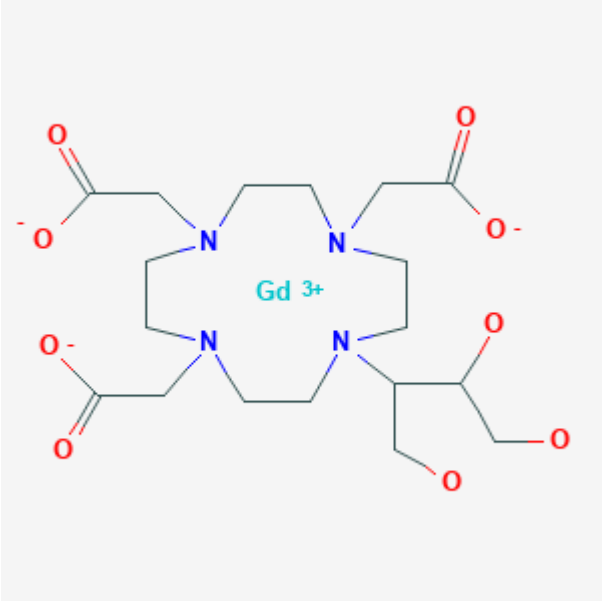

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Table continued from previous page.

Studies:	• *In vitro* • Rodents • Other non-primate mammals • Humans	Click on the above structure for additional information in PubChem.

Background

[PubMed]

Gadobutrol (Gd-DO3A-butrol) is a nonionic, paramagnetic contrast agent developed for tissue contrast enhancement in magnetic resonance imaging (MRI) (1-3).

Water-soluble paramagnetic contrast agents are generally metal chelates with unpaired electrons, and they work by shortening both the T_1 and T_2 relaxation times of surrounding water protons to produce the signal-enhancing effect (1, 2, 4). At normal clinical doses of 0.1-0.2 mmol/kg, the T_1 effect tends to dominate. Current agents are water-soluble compounds that distribute in the extracellular fluid and do not cross the intact blood-brain barrier (BBB). They are often used to enhance signals of central nervous system (CNS) tissues that lack a BBB (e.g., pituitary gland), extraaxial tumors (e.g., meningiomas), and areas of BBB breakdown (e.g., tumor margins). In these cases, small or multiple CNS lesions are more clearly delineated with contrast enhancement. In addition, contrast enhancement can highlight vasculature, delineate the extent of disease, and confirm the impression of normal or nonmalignant tissues. These contrast agents can also be used in a similar nonspecific manner to enhance contrast between pathologies and surrounding normal areas in other organs (1, 2, 5).

Gadolinium(III) (Gd^{3+}), a lanthanide metal ion with seven unpaired electrons, has been shown to be very effective at enhancing proton relaxation because of its high magnetic moment and very labile water coordination (2, 6-9). Gadopentetate dimeglumine (Gd-DTPA) was the first intravenous MRI contrast agent used clinically, and a number of similar Gd chelates have been developed in an effort to further improve clinical efficacy, patient safety and patient tolerance. The major chemical differences among these Gd chelates or Gd-based contrast agents (GBCAs) are the presence or absence of overall charge, ionic or nonionic, and their ligand frameworks (linear or macrocyclic). Gd-DO3A-butrol has a macrocyclic framework and is neutral (10, 11). The DO3A-butrol ligand was developed based on the belief that high overall hydrophilicity of an agent is generally associated with very low protein binding and good biological tolerance (12). It is a modification of the Gd-DO3A compound in which a trihydroxybutyl group is attached to the macrocyclic ligand to ensure high hydrophilicity. The ligand contains two chiral carbons at C-13 and C-14, therefore, the product is a racemic mixture of (13R, 14S)– and (13S, 14R)–. The Gd(III) in Gd-DO3A-butrol has a coordination number of 9. Gd-DO3A-butrol is a water-soluble, highly hydrophilic compound with a partition coefficient between n-butanol and buffer at pH 7.6 of ~ 0.006 (13).

Gd-DO3A-butrol is not commercially available in the United States, but it is commercially available in Canada at a concentration of 1.0 mmol/ml (604.72 mg/ml) for contrast enhancement during cranial and spinal imaging with MRI and MR angiography. At this concentration, it has an osmolarity of 1117 mOsm/kg at 37 °C, viscosity of 4.96 mPa at 37 °C, and log P(n-octanol/water) of –5.4 at 25 °C.

Both renal and extra-renal toxicities have been reported following the clinical use of gadolinium in patients with underlying kidney disease (14-16). In 2007, the US FDA requested manufacturers of all GBCAs to add new warnings about exposure to GBCAs increases the risk for nephrogenic systemic fibrosis (NSF) in patients with advanced kidney disease.

Synthesis

[PubMed]

Vogler et al. (17) discussed the general method for preparing the macrocyclic core based on the Richman-Atkins method. In this method, 5-amino-2,2-dimethyl-6-hydroxy-1,3-dioxepan was treated with tosyl aziridine to give 1,7-ditoxyl-4-(6-hydroxy-2,2-dimethyl-1,3-dioxepan-5-yl)-1,4,7-triazaheptane. This compound was deprotonated with sodium ethoxide and reacted with the tritosylate of diethanolamine to give a macrocyclic intermediate. It was then treated with lithium in liquid ammonia to remove the tosyl groups to give a mono-substituted tetramine, which was then alkylated with chloroacetic acid at pH 9-10. DO3A-butrol was produced by a final treatment with diluted hydrochloric acid. The ligand was reacted with gadolinium oxide in water at 90 ºC to produce Gd-DO3A-butrol.

Platzek et al. (12) described three approaches to synthesizing the DO3A-butrol ligand. One approach was preferred because it involved fewer steps and allowed scaled up production for clinical applications. In this approach, 1-(1-(hydroxymethyl)-2,3-dihydroxypropyl)-1,4,7,10-tetraazacyclododecane tetrahydrochloride was first prepared. The compound was then reacted with chloroacetic acid at 70 ºC and pH 9-10 for 18 h. The yield was 65%. Gd-DO3A-butrol was then prepared by adding Gd_2O_3 to the ligand in water and stirring at 90 ºC for 6 h. Cation- and anion exchange resins were then added at room temperature, and the mixture was stirred for 30 min. The resins were recollected by filtration, and charcoal was added to the filtrate and refluxed for 1 h. The solution was filtered and evaporated to dryness. The residue was redissolved in water and ethanol, and then was refluxed for 2 h. Gd-DO3A-butrol was collected by filtration and drying under vacuum (12 h at 60 ºC). The yield was 87%. Mass spectroscopy (FAB) gave the following results: *m/e* 606 $[(M + H)^+]$; *m/e* 1211 $[(2M + H)^+]$. The infrared spectrum (KBr) had peakls at 3560, 3280, 2980, 2975, 2940, 2920, 2880, 2870, 1650, 1600, and 1380 cm^{-1}. The structure was determined by X-ray crystallography.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Pintaske et al. (18) determined the *in vitro* relaxivity of Gd-DO3A-butrol and other compounds (Gd-DTPA and Gd-BOPTA) in human plasma obtained from healthy volunteers. Measurements of Gd-DO3A-butrol in concentrations of 0.01 mM up to 64 mM at 37 ºC were made with 0.2–, 1.5–, and 3.0– Tesla (T) clinical scanners. The longitudinal relaxation rates (r_1; liter x $mmol^{-1}$ x s^{-1}) of Gd-DO3A-butrol were 5.5 ± 0.3, 4.7 ± 0.2, and 3.6 ± 0.2, at 0.2, 1.5, and 3T, respectively. The transverse relaxation rates (r_2; liter x $mmol^{-1}$ x s^{-1}) of were 10.1 ± 0.3, 6.8 ± 0.2, and 6.3 ± 0.3, at 0.2, 1.5, and 3 T, respectively. In comparison, these values were lower for Gd-DTPA but higher for Gd-BOPTA.

Vogler et al. (17) measured the *in vitro* physico-chemical properties of Gd-DO3A-butrol. The osmolality was found to be 0.57 osmol/kg for the 0.5 M concentration and 1.39 osmol/kg for the1 M concentration. The distribution coefficient (butanol/water) was 0.006, and the viscosity was 1.43 cP for the 0.5 M concentration and 3.7 cP for the 1 M concentration. The T_1-relaxivity (liter x $mmol^{-1}$ x s^{-1}) in plasma was determined to be 5.6 at 0.45 T and 6.1 at 2 T. There was negligible protein binding of about 2.7% in plasma. With use of rat mast cells, the I_{50} (the concentration at which histamine was released) was found to be greater than 250 mM. The I_{50} value for lysozyme inhibition (the concentration at which 50% of the enzyme was inhibited) was greater than 300 mM.

Animal Studies

Rodents

[PubMed]

Vogler et al. (17) studied the long-term elimination and biodistribution of 0.25 mmol/kg Gd-DO3A-butrol in rats. More than 90% of the i.p. injected dose (ID) was excreted by the kidneys in 2 h and 100% in 7 days. The total amount remaining in the body decreased from 0.71% ID on day 1 to 0.15% ID on day 7 after injection. Inductively-coupled plasma atomic emission spectrometry (detection limit was 0.01 ppm or 65 nM) showed that only the kidneys, bones, and blood contained an amount of the agent above the detection limit after 7 days. The % ID of these organs were 0.06 ± 0.01, 0.01 ± 0.00, and 0.01 ± 0.00, respectively. The acute toxicity (lethal dose (LD_{50})) in mice was 23 mmol/kg. In a neural tolerance study, the median LD_{50} (lethal dose; n = 10) and effective dose (ED_{50}) of Gd-DO3A-butrol in rats after intracisternal injection were 86 µmol/kg and 18 µmol/kg, respectively. In comparison, the LD_{50} and ED_{50} for Gd-DTPA were 740 µmol/kg and 73 µmol/kg, respectively. The study suggested that macrocyclic compounds had lower cerebral tolerance and that linear compounds had higher cerebral tolerance. Imaging studies in rat models with cerebral infarct, brain tumors, and intramuscular tumors showed contrast enhancements (0.3 mmol/kg Gd-DO3A-butrol) in all three pathologic areas. A dose-dependent increase in the signal intensity of the intramuscular tumors was observed.

Several rat studies (19-23) showed that Gd-DO3A-butrol was effective in providing contrast enhancement for MRI in glioma, brain ischemia, hepatocellular carcinoma, and the lymphatic system.

Other Non-Primate Mammals

[PubMed]

Vogler et al. (17) performed Gd-DO3A-butrol pharmacokinetics studies in beagle dogs. The elimination t½ and the plasma clearance were 45 ± 3.6 min and 3.75 ± 0.30 ml/min/kg, respectively. The total volume of distribution at steady state (Vss) was 0.23 ± 0.02 liter/kg. High-performance liquid chromatography analysis of the plasma and urine samples showed that Gd-DO3A-butrol was not metabolized.

The abdominal MRI enhancement properties of Gd-DO3A-butrol were investigated in pigs (24). Images of 40 and 80 µmol/kg doses were conducted on a 1.5 T imager. Gd-DO3A-butrol gave signal intensity curves similar to those produced by extracellular agents. Significant enhancement was found in all tissues except the trunk muscles. Kalinoski et al. (25) used 1 M Gd-DO3A-butrol in a dose of 2 mmol/kg to demonstrate the feasibility of producing X-ray contrast enhancement with computed tomography (CT) in pigs

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

Staks et al. (26) investigated the pharmacokinetics, dose proportionality, and tolerability of Gd-DO3A-butrol in healthy volunteers. Two double-blind, randomized, placebo-controlled phase I studies were conducted for testing a low concentration (0.5 M; doses = 0.04, 0.1, 0.2, 0.3, and 0.4 mmol/kg; n = 55) and a high concentration (1 M; doses = 0.3, 0.4, and 0.5 mmol/kg; n = 36). From the data for 24 volunteers, pharmacokinetic parameters were calculated from an open two-compartment model. The values for plasma elimination half-life ($t_{½p,\beta;h}$), V_{ss} (liter/kg), renal clearance (ml/min/kg), and 72-h total renal excretion (Urine, 72 h (% ID)) for a 0.1 mmol/kg dose were 1.78 ± 0.43, 0.21 ± 0.02, 1.56 ± 0.18, and 98 ± 3.33, respectively. For a 0.4 mmol/kg dose, these values were 1.33 ± 0.21, 0.15 ± 0.02, 1.45 ± 0.22, and 96.6 ± 5.61, respectively. Plasma Gd-DO3A-butrol decreased bioexponentially, and the volume of distribution was within the extracellular fluid space. Elimination occurred primarily through the renal route. Biotransformation analysis of the urine and plasma samples revealed no

metabolites from Gd-DO3A-butrol. No significant changes were observed in serum chemistry/hematology, or urine chemistry/urinalysis. No clear dose-dependent adverse events were found between the low-dose and high-dose studies. The most common adverse events were smell sensation (12.5%) and taste sensation (15%).

Tombach and Heindel (27) and Huppertz and Rohrer (28) summarized clinical studies for the clinical applications of 1 M Gd-DO3A-butrol. In 29 phase I to phsae III studies (2523 subjects and 2662 doses), Gd-DO3A-butrol was distributed in the extracellular fluid with a plasma terminal t½ of 1.7-2 h. Approximately 98% of the dose was excreted unchanged in the urine within 12 h. The studies indicated that 1 M Gd-DO3A-butrol had an excellent safety profile with doses ranging from 0.04 to 1.5 mmol/kg. Overall, 8.5% of the patients reported related and unrelated adverse events. For contrast enhancement, analysis of efficacy data showed results comparable to results to other commercially available 0.5 M Gd- chelates in studies of the CNS (677 patients), and angiography (676 patients).

In a study of the pharmacokinetics of 1 M Gd-DO3A-butrol in 21 patients with chronic renal failure, Tombach et al. (29) reported that the extracellular distribution of Gd-DO3A-butrol remained unchanged but the mean elimination $t_{½}$ increased compared with that of healthy volunteers. Other human studies have shown the potential clinical usefulness of 1 M Gd-DO3A-butrol in various CNS and vascular diseases [PubMed].

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