Gadobenate

Gd-BOPTA

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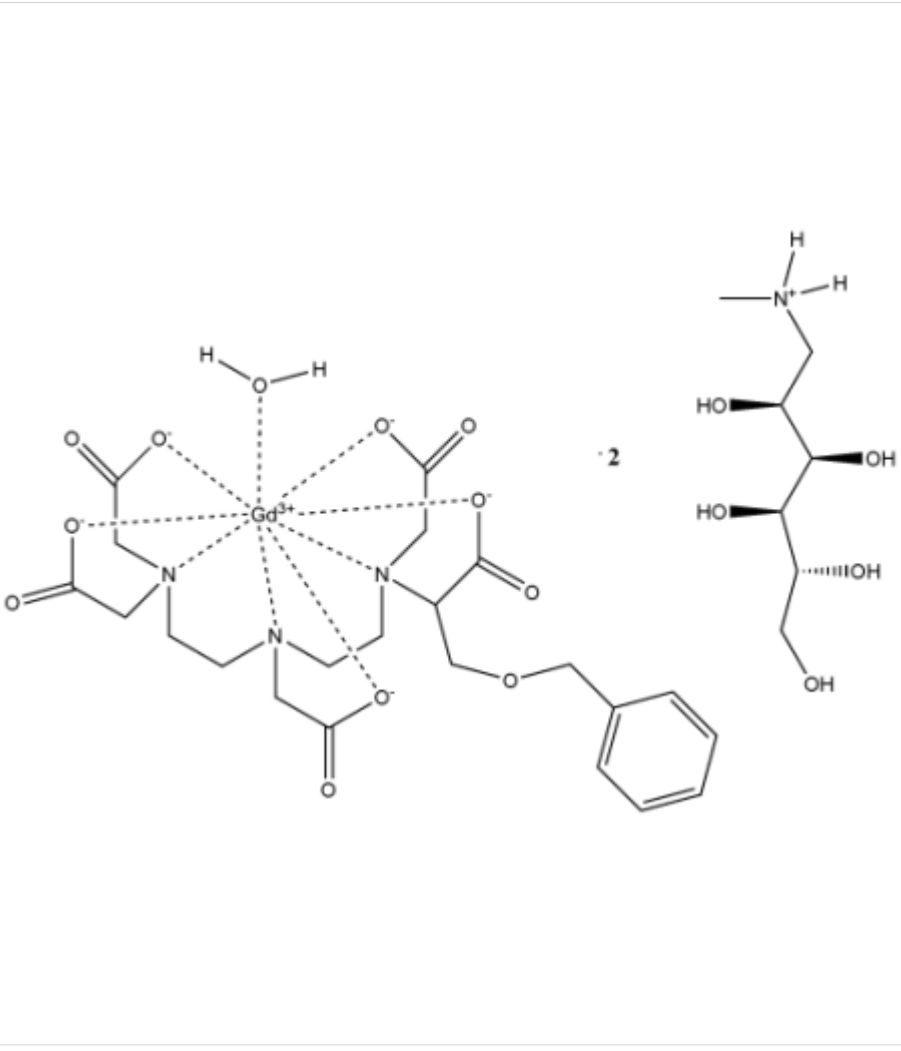
Chemical name:	Gadobenate
Abbreviated name:	Gd-BOPTA
Synonym:	MultiHance®, B-19036, Gd-BOPTA/Dimeg, gadobenate dimeglumine, (4*RS*)-[4-carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oato(5-)]gadolinate (2-) dihydrogen with 1-deoxy-1-(methylamino)-D-glucitol (1:2)
Agent Category:	Compound
Target:	Non-targeted, CNS
Target Category:	Blood-brain barrier breakdown
Method of detection:	Magnetic resonance imaging (MRI)
Source of signal/ contrast:	Gadolinium (Gd)
Activation:	No



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Studies:	• *In vitro* • Rodents • Other non-primate mammals • Non-human primates • Humans	Structure of Gadobenate.

Background

[PubMed]

Gadobenate (Gd-BOPTA) is a paramagnetic contrast agent for magnetic resonance imaging (MRI) that was approved by the United States Food and Drug Administration (US FDA) in 2004 for imaging the central nervous system to visualize lesions with abnormal blood-brain barrier (BBB) or abnormal vascularity of the brain, spine, and associated tissues (1-3).

Conventional, water-soluble, paramagnetic contrast agents are generally metal chelates with unpaired electrons, and they work by shortening both T_1 and T_2 relaxation times of surrounding water protons to produce the contrast-enhancing effect (1, 2). At normal clinical doses, 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 BBB. They can be used to enhance signals of 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 perfused and nonperfused areas in other organs (1, 2, 4).

Gadolinium ion (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, 5-7). Gadopentetate dimeglumine (Gd-

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DTPA) was the first intravenous MRI contrast agent used clinically, and a number of similar gadolinium 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-BOPTA has a linear framework and is ionic. The BOPTA ligand was originally developed as a potential hepatobiliary agent for MRI (8). It is a modification of the DTPA molecule based on the belief that the addition of a benzoylmethyl group to the backbone of DTPA would increase the liver uptake of Gd-BOPTA. The hepatobiliary excretion of Gd-BOPTA appears to be species dependent, and only 2-5% of the dose is excreted via the biliary system in humans. Because of weak/transient interactions between Gd-BOPTA and macromolecules that reduce the tumbling rate of the Gd-BOPTA molecules, Gd-BOPTA demonstrates increased r_1 and r_2 relaxivities (efficiencies in shorteningT_1 and T_2 relaxation times) in solutions containing serum proteins (9-11).

The commercial formulation of Gd-BOPTA is a meglumine salt (Gd-BOPTA/Dimeg) and is available as a 0.5 M injection with a recommended dose of 0.1 mmol/kg (0.2 ml/kg) either as a rapid intravenous infusion or bolus injection for CNS MRI imaging (3, 12). It has an osmolality of 1970 osmol/kg and viscosity of 5.3 mPas at 37°C.

Both renal and extra-renal toxicities have been reported following the clinical use of gadolinium in patients with underlying kidney disease (13-15). 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]

Felder et al. (16) first synthesized the BOPTA ligand in 1987. Uggeri et al. (17) reported that the synthesis of BOPTA consisted of two major steps. Diethylenetriamine was first selectively monoalkylated on a primary amino group with 2-chloro-3-(phenylmethoxy)propanoic acid in water at 50°C for 40 h. The intermediate product was isolated as *N*-[2-[(2-aminoethyl)amino]ethyl]-*O*-(phenylmethyl)-DL-serine tris-(hydrochloride) with the yield of 58%. This intermediate compound was then fully carboxymethylated with bromoacetic acid in water at pH 10 and room temperature for 15 h, and the yield of BOPTA was 21%. Gd-BOPTA dimeglumine salt was prepared by mixing BOPTA with *N*-methylglucamine and Gd_2O_3 at 80°C for 1.5 h.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In *in vitro* studies, Gd-BOPTA/Dimeg at a concentration of 30 mM caused a slight reduction of the contractile force in a rat papillary muscle preparation, and a mild decrease of both amplitude and contraction rate in isolated guinea pig atria (18).

The water proton relaxation of Gd-BOPTA in a protein-free aqueous solution was measured at 20 MHz, 39°C and pH 7.4, and its longitudinal (r_1) and transverse (r_2) relaxivities values in $mM^{-1}s^{-1}$were reported to be 4.39 ± 0.01 and 5.56 ± 0.02, respectively (11, 17). The conditional stability constant (log $K^{\star}_{ML}$) of Gd-BOPTA determined by competition complexation experiments was 18.4 at pH 7.4 and 20°C. The r_1 relaxivity of Gd-BOPTA in heparinzed human plasma was reported to be 9.7 $mM^{-1}s^{-1}$. Cavagna et al. (19) reported that no binding of Gd-DOPTA/Dimeg to serum proteins could be detected using equilibrium dialysis (detection sensitivity at equilibrium constants = or < 5 mM) against rat, rabbit, or human plasma. With the use of different bovine serum albumin (BSA) concentrations, an *in vitro* nuclear magnetic relaxation dispersion (NMRD) profile of Gd-BOPTA/Dimeg was constructed to show that protein concentrations had a strong influence on Gd-BOPTA/Dimeg relaxivity (20).

Caravan et al. (21) in a 2003 study found that the ion-nuclear distance of Gd to a coordinated water proton, $r_{Gd\text{-}H}$, was 3.1 ± 0.1 Å for Gd-BOPTA and four other Gd complexes. Partition coefficients of Gd-BOPTA/Dimeg in the systems of n-butanol or n-octanol with 0.01 M phosphate buffer pH 7.3 were found to be 0.0067 and 0.0016, respectively (22).

Planchamp et al. (23) used a hollow-fiber bioreactor to study the transport of Gd-BOPTA/Dimeg into rat hepatocytes. They reported that the results supported a transporter-mediated mechanism, and the Michaelis-Menton constant (K_m) was estimated to be 270 μM. In another isolated rat liver study, the uptake of Gd-BOPTA into hepatocytes and its subsequent biliary excretion appeared to be highly temperature dependent (24).

Animal Studies

Rodents

[PubMed]

In rats, Gd-BOPTA/Dimeg rapidly distributed in the extravascular and extracellular compartments, and it showed a marked affinity for biliary excretion (19, 25). The biodistribution study showed that Gd-BOPTA/Dimeg was found mainly in the liver and kidney. Vittadini et al. (26) conducted pharmacokinetic studies of Gd-BOPTA/Dimeg (0.05 mmol/kg) in rats and found that the blood kinetics (distribution $t_{½}$, elimination $t_{½}$ and apparent volume of distribution V_d) and excretion kinetics of 6 h (total clearance, urinary excretion and biliary excretion) were 3.8 ± 0.5 min, 15.05 ± 0.54 min, 165.1 ml/kg and 13.9 ml/min/kg, 54.8 ± 8.8% injected dose (ID), 38.6 ± 7.3% ID, respectively. Cavagna et al. (19) reported that the bile and urine eliminations of Gd-BOPTA in rats at 8 h were 52% ID and 46% ID, respectively. There was no or weak binding of Gd-BOPTA/Dimeg to plasma proteins and no apparent biotransformation of the compound.

The acute i.v. LD_{50} of Gd-BOPTA/Dimeg in rats was 6.6 (5.8-7.5, $n = 5$) mmol/kg at 6 ml/min and 9.2 (8.1-10.4) mmol/kg at 0.2 ml/min (27). No observed effect levels (NOEL) were observed in rats with repeated doses up to 0.3 mmol/kg/day. Only a mild and transient reduction in heart rate was observed at the dose of 1 mmol/kg (18). Luzzani et al (28). studied the brain penetration and neurological effects of Gd-BOPTA in rats with various i.v. and intracisternal injection doses of ^{153}Gd-BOPTA. At 0.01 mmol/kg of intracisternal injection of ^{153}Gd-BOPTA/Dimeg, the motor coordination was slightly impaired. No neurological effect was observed with i.v. doses of ^{153}Gd-BOPTA up to 2 mmol/kg. Noce et al. (29)did not find any effect of Gd-BOPTA on cerebral glucose metabolism after an intracerebral dose of 120 nmol/rat. In the same study, no genotoxic potential was observed in mutagenicity tests, and the reproductive performance and development of offspring were not affected at doses up to 20 times the human dose.

The acute i.v. LD_{50} of Gd-BOPTA/Dimeg in mice was 5.7 (5.3-6.2, $n = 5$) mmol/kg at 6 ml/min and 7.9 (7.5-8.3) mmol/kg at 0.2 ml/min (27). The intracerebral LD_{50} was 1.02 mmol/kg (26). In another preclinical study in rats, Gd-BOPTA/Dimeg at the i.v. dose of 1 mmol/kg caused a decrease of blood pressure of about 15%, a decrease of heart rate of about 7%, but no significant ECG alterations (22).

With the use of MRI imaging (2 Tesla, T_1-weighted), *in vivo* relaxivity (r_1) values of Gd-BOPTA/Dimeg (200 μmol/kg) in the blood, normal and infracted myocardium of rats were determined to be 6.19, 4.05, and 10.03 $mM^{-1}s^{-1}$, respectively (20). In comparison, the corresponding values for Gd-DTPA were reported to be 3.41, 3.52, and 5.32 $mM^{-1}s^{-1}$.

Pastor et al. (30) studied the hepatic kinetics of Gd-BOPTA/Dimeg with the use of MRI (1.5 Tesla, T_1-weighted) in a perfused rat liver model. They found that the hepatic activity uptake $t_{½}$ was 4.8 ± 0.3 min, and the washout $t_{½}$ was 17.5 ± 2.8 min.

Other Non-Primate Mammals

[PubMed]

Lorusso and colleagues showed that Gd-BOPTA/Dimeg distributes into plasma, extracellular fluid, and intrahepatocytic space in both rabbits and dogs (25). Gd-BOPTA was not metabolized and was cleared from plasma by renal and biliary excretion.

Morisetti et al. (27) found no adverse effects of Gd-BOPTA/Dimeg treatment on rabbit dams or on fetuses at a dose of 0.3 mmol/kg per day. Cavagna et al. (19) used MRI (2 Telsa, T_1-weighted) to perform the *in vivo* determination of the relaxation rate of Gd-BOPTA/Dimeg (0.1 mmol/kg) in rabbit blood. The longitudinal relaxation rate was 1.93 ± 0.06 s^{-1} at 5 min after injection.

No significant cardiovascular and respiratory effects of Gd-BOPTA/Dimeg at i.v. dose of 1 mmol/kg (10 ml/min) in Large White pigs (18). In a myocardial ischemia Yucatan micropig model, i.v. doses of Gd-BOPTA/Dimeg up to 3 mmol/kg did cause dose-dependent cardiovascular changes.

Port and colleagues (31) used a rabbit experimental model to determine that the dynamic relaxivity ($r_{1dynamic}$) of Gd-BOPTA in plasma was 5.2 $mM^{-1}s^{-1}$ (60 MHz) at the bolus phase (0-15 sec postinjection) when 93% of Gd-BOPTA was present in the free form. The $r_{1dynamic}$ was 6.7 $mM^{-1}s^{-1}$ at the postbolus phase (1-5 min postinjection) when 82% of Gd-BOPTA remained in the free form.

Non-Human Primates

[PubMed]

The NOEL dose of Gd-BOPTA/Dimeg was found to be 0.25 mmol/kg/day (i.v.) in Cynomolgus monkeys (27) In the doses ranging from 0.25 to 3 mmol/kg, the maximal plasma concentration and the area under the plasma concentration-time curve were linearly related to the dose (25). Runge (32) studied MRI (1.5 Tesla, T_1-weighted) of Gd-BOPTA/Dimeg at the dose of 0.1 mmol/kg in rhesus monkeys (n = 4). The enhancements (percent increase in signal intensity before injection) of the muscle, kidneys, and spleen were maximum at 2 min (40 ± 17%), 5 min (164 ± 25%), and 5 min (92 ± 25%) after injection, respectively. Two peaks of liver enhancement were observed with 114 ± 45% occurred immediately and then with 136 ± 23% occurred at 30 min after injection.

Human Studies

[PubMed]

The Phase I study by Spinazzi et al. (33) and the Phase II clinical trial by Rosati et al (34). reported the safety and pharmacokinetics data of Gd-BOPTA/dimeg. The pharmacokinetics profile was studied in 28 healthy volunteers. Gd-BOPTA/Dimeg was given in seven different i.v. doses ranging from 0.05 mmol/kg to 0.4 mmol/kg. In the dose range from 0.005 mmol/kg to 0.2 mmol/kg, the pharmacokinetics value ranges (n = 4) of the distribution $t_{½}$, elimination $t_{½}$, V_d, and the total clearance (CL) were 0.084-0.36 h, 1.17-1.68 h, 0.074-0.142 liter/kg, 0.170-0.248 liter/kg, and 0.098-0.133 liter/h/kg, respectively. In the dose range from 0.2 mmol/kg to 0.4 mmol/kg, the value ranges (n = 4) of the distribution $t_{½}$, elimination $t_{½}$, V_d, and CL were 0.48-0.605 h, 1.95-2.02 h, 0.147-0.158 liter/kg, 0.261-0.282 liter/kg, and 0.093-0.098 l/h/kg, respectively. In 72 h, 89-95.2% of the injected dose was eliminated unchanged by the kidneys and about 0.6-3.5% was excreted in the bile. With the use of equilibrium dialysis, the complex did not appear to bind measurably to plasma proteins. Safety studies in 39 volunteers indicated an18% of adverse events as compared with 14% in the placebo group (n = 14). The most frequent adverse events were altered sensation at the injection site, nausea, and sweating. In 127 patients with intracranial lesions, Gd-BOPTA/Dimeg (0.1-0.2 mmol/kg) provided better diagnostic information in 95% of the cases than those of MRI without contrast.

Phase III double-blind, multicenters (28 centers), randomized, parallel group comparative studies with 410 CNS patients had shown that Gd-BOPTA/Dimeg at doses of 0.05-0.15 mmol/kg and 0.1-0.2 mmol/kg had comparable safety and efficacy profiles as Gd-DTPA-

BMA at doses of 0.1 mmol/kg and 0.3 mmol/kg for imaging of CNS lesions (35, 36). Other studies had investigated the potential usefulness of Gd-BOPTA/Dimeg for liver imaging [PubMed] and magnetic resonance angiography [PubMed].

Supplemental Information

[Disclaimers]

Gadobenate package insert

Gadobenate multipack package insert

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