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MR contrast agents, the old and the new

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Abstract

Magnetic resonance (MR) contrast agents are increasingly being used to help detect and characterize various neoplastic, inflammatory and functional abnormalities. The extracellular, non-specific contrast agents gadolinium chelates are by far the most widely used. Over the past few years a number of MR organ specific contrast agents have been introduced. MRI contrast agents are generally safe and well tolerated. The present review summarizes the properties, main characteristics and imaging applications of commercially available compounds as well as safety of these agents in normal and high-risk patients.

Keywords: Contrast media; Magnetic resonance (MR); Gadolinium chelates; Iron oxide; Manganese; Safety

1. Introduction

Today, magnetic resonance (MR) contrast media are administered in 40–50% of all MR examinations [1]. They are diagnostic pharmaceutical compounds containing paramagnetic or superparamagnetic metal ions that affect the MR-signal properties of surrounding tissues. They are administered to enhance tissue contrast, to characterize lesions and to evaluate perfusion and flow-related abnormalities [2,3]. They include non-specific extracellular contrast agents and organ-specific contrast agents, mostly liver specific contrast agents [4–6]. Gadolinium chelates are the most widely used extracellular, non-specific contrast agents. Organ specific contrast agents include superparamagnetic iron oxides particles, manganese-based preparations and gadolinium-based agents with a high hepatobiliary excretion. Iron oxide particles are mainly T_2-agents whereas gadolinium and manganese agents are mainly T_1-agents. Their use in many clinical indications is justified because, in conjunction with improved imaging techniques, these safe and image-enhancing contrast agents add morphologic and functional information compared to unenhanced MR images. Although theoretical safety concerns exist, MR contrast agents have been shown in clinical use to be safe and well tolerated. However, the rate of adverse events seems higher with liver specific contrast agents than with extracellular gadolinium chelates [5,7]. This article describes the commercially available compounds, as well as their mechanisms of action, biodistributions, toxicities and tolerance profiles in normal and high-risk patient populations.

2. Non-specific extracellular gadolinium chelates

Currently, seven Gd chelates are approved for clinical use in the international market (Table 1): Magnevist® (gadopentetate dimeglumine; Schering AG, Berlin, Germany), Dotarem® (gadoterate meglumine; Guerbet, Aulnay-sous-bois, France), Omniscan® (gadodiamide; Nycomed, Oslo, Norway), and ProHance® (gadoteridol; Bracco SpA, Milan, Italy). In addition, Gadovist® (gadobutrol; Schering AG) has received approval in Germany and Switzerland, and MultiHance® (gadobenate dimeglumine; Bracco SpA) is an extracellular contrast agent but also a liver specific product. OptiMARK® (gadoversetamide; Mallinkrodt, St. Louis, USA) is available only in the USA. Gadolinium (Gd), a paramagnetic metal in the lanthanide series is their active constituent. These paramagnetic agents can be classified into four main categories according to their biochemical structure, e.g., macrocyclic versus linear, and to their charge, ionic versus non-ionic (Fig. 1).

For clinical use, the recommended dose is 0.1 mmol/kg; however, gadodiamide and gadopentetate are approved for MR angiography at doses up to three times the standard, and gadoterate at a dose of twice the standard (Table 1). In addition, the doses

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Table 1
Approval status of gadolinium (Gd) chelates in clinical use

Gd chelate; trade name	Body region(s) approved	Approval	Approved doses (mmol/kg) for body imaging	Approved doses (mmol/kg) for CNS[a] imaging	Approved doses (mmol/kg) for MR angiography	Approved doses (mmol/kg) for children
Gadopentetate dimeglumine; Magnevist®	CNS[a], whole body	USA, EU, Jpn	0.1	0.1–0.2	0.1–0.3[b]	0.1
Gadodiamide; Omniscan®	CNS[a], whole body	USA, EU, Jpn	0.1–0.3	0.1–0.3	0.1–0.3	From 6 months: 0.1
Gadoterate meglumine; Dotarem®	CNS[a], whole body	EU	0.1	0.1–0.3	0.2	0.1
Gadoteridol; ProHance®	CNS[a], whole body	USA, EU, Jpn	0.1–0.3	0.1–0.3	Not approved	From 2 years and above: 0.1; 6 months–2 years: caution; <6 months: contraindicated
Gadobutrol; Gadovist®	CNS[a], MRA	EU, Canada	Not approved	0.1–0.3	0.1–0.15 Imaging of 1 field of view 0.2–0.3 Imaging of > 1 field of view	Not approved <18 years
Gadobenate dimeglumine; MultiHance®	CNS[a], liver	USA, EU	Liver: 0.05	0.1	Not approved	Not approved <18 years
Gadoversetamide; OptiMARK®	CNS[a], liver	USA	0.1	0.1	Not approved	Not approved <18 years
Gd-EOB-DTPA; Primovist® (Europe), Eovist® (USA)	Liver	USA, EU	25 μmol/kg or 0.1 ml/kg	Not approved	Not approved	Not approved <18 years

[a] CNS: central nervous system.
[b] Gadopentetate dimeglumine (Magnevist®) is approved for whole body imaging and for doses of 0.1–0.3 mmol/kg but does not have a trial-based approval for MR angiography.

approved for CNS imaging range from 0.1 to 0.3 mmol/kg except for gadobenate. In most indications, rapid T_1-weighted imaging is required to maximize enhancement between the normal tissues and focal lesions.

2.1. Mechanisms of action

Gd is a powerful paramagnetic ion with seven unpaired electrons. It disturbs the relaxation of nearby water protons, causing decreases of both T_1 and T_2 relaxation times, the effects on T_1 relaxation times being stronger with the concentrations used in clinical practice [2]. Shortening of T_1 relaxation time in tissues, as observed after administration of the standard 0.1 mmol/kg dose, produces an increase of signal intensity (positive enhancement). The following parameters affect the image contrast: field strength, pulse sequence, imaging parameters, distribution of the Gd chelate and its local concentration. The expected post contrast decrease of T_1 relaxation time is more pronounced on spin-echo sequences with short repetition (TR) and echo (TE) times, and gradient-echo images with short repetition times and a high flip angle. In gradient-echo imaging, the T_1 sensitivity can be optimized by using short TR ($TR < T_1$) and short TE values (to minimize the loss of signal due to T_2 effects). In clinical practice, T_1 relaxivity profiles are almost identical for the currently available Gd contrast agents, except for gadobenate dimeglumine which possesses elevated T_1 relaxivity due to a unique capacity for weak, transient interaction with serum albumin [8]. At high concentrations, e.g. as observed in the normal urinary tract, T_2 effects predominate and produce a decrease of signal intensity on T_1- and T_2-weighted MR images.

Free Gd is toxic in vivo; the binding to a chelate complex makes the ion chemically inert. After chelation, the rate of renal excretion of the Gd complex is increased approximately 550-fold compared with pre chelation values [9]. Despite differences among the chelating molecules, e.g. ionic charge and linearity, currently used non-specific gadolinium chelates appear to have remarkably similar diagnostic efficacies and safety profiles [10–13].

2.2. Biodistribution

Gd complexes are hydrophilic, are excreted unmetabolized in urine and are considered extracellular-fluid markers. Their molecular masses (around 500 Da) are low, explaining that they are rapidly cleared from the intravascular space through the capillaries into the interstitial space, and therefore their biodistribution is non-specific. They do not cross an intact blood-brain barrier. Due to their rapid equilibration in the interstitial space of both normal tissues and tumors, the use of dynamic MR imaging after bolus injection makes the best use of the narrow imaging window with a transiently increased tumor-to-normal tissue contrast. Gd chelates are excreted unchanged by passive glomerular filtration with >95% excreted by 1 day [13]; <0.1% of the injected dose is eliminated via feces. The biologic elimination half-life is approximately 1.5 h [14] with renal clearance for healthy persons of 1.1–1.8 ml min^{-1} kg^{-1}. There is no detectable biotransformation, decomposition, or serum pro-