Eur. Radiol. 9, 998–1004 (1999) © Springer-Verlag 1999

European Radiology

Original article

Field strength and dose dependence of contrast enhancement by gadolinium-based MR contrast agents

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Received: 20 March 1998; Revision received: 25 June 1998; Accepted: 22 July 1998

Abstract. The relaxivities r_1 and r_2 of magnetic resonance contrast agents and the T_1 relaxation time values of tissues are strongly field dependent. We present quantitative data and simulations of different gadolinium-based extracellular fluid contrast agents and the modulation of their contrast enhancement by the magnetic field to be able to answer the following questions: How are the dose and field dependences of their contrast enhancement? Is there an interrelationship between dose and field dependence? Should one increase or decrease doses at specific fields? Nuclear magnetic relaxation dispersion data were acquired for the following contrast agents: gadopentetate dimeglumine, gadoterate meglumine, gadodiamide injection, and gadoteridol injection, as well as for several normal and pathological human tissue samples. The magnetic field range stretched from 0.0002 to 4.7 T, including the entire clinical imaging range. The data acquired were then fitted with the appropriate theoretical models. The combination of the diamagnetic relaxation rates ($R_1 = 1/T_1$ and $R_2 = 1/T_2$) of tissues with the respective paramagnetic contributions of the contrast agents allowed the prediction of image contrast at any magnetic field. The results revealed a nearly identical field and dose-dependent increase of contrast enhancement induced by these contrast agents within a certain dose range. The target tissue concentration (TTC) was an important though nonlinear factor for enhancement. The currently recommended dose of 0.1 mmol/kg body weight seems to be a compromise close to the lower limits of diagnostically sufficient contrast enhancement for clinical imaging at all field strengths. At low field contrast enhancement might be insufficient. Adjustment of dose or concentration, or a new class of contrast agents with optimized relaxivity, would be a valuable contribution to a better diagnostic yield of contrast enhancement at all fields.

Key words: MR imaging – Contrast agents – MR field strength

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Introduction

In an article published in 1988 [1] the influence and interrelationship of the magnetic field strength and the relaxation times of tissues, relaxivity of contrast agents, and image contrast was described. During the past years, there has been some dispute about both field and dose dependence of contrast enhancement of gadolinium-based extracellular fluid (ECF) contrast agents. In some papers the authors have referred to or extrapolated the data presented previously. This paper presents some additional data and results on field and dose/concentration dependence of contrast enhancement with the aim to shed more light in answering the following questions:

1. Is there a diagnostically best and safest dose, e.g., 0.05, 0.1, 0.2, or even 1.0 mmol/kg body weight?
2. Is there really less enhancement at certain fields?
3. Is there an interdependence and can dose be optimized for a particular field?

Dose

In 1987, Niendorf and coauthors published a dose-finding study for gadopentetate dimeglumine and concluded that 0.1 mmol/kg body weight should be the recommended dose for central nervous system pathology [2]. This study was performed at low field (0.35 T). At medium and high fields, Haustein and coauthors concluded that doses of less than 0.1 mmol/kg body weight may be inadequate in providing sufficient contrast between

brain lesions and surrounding tissue [3, 4]. They also stated that the optimal dose of a gadolinium-based ECF agent may vary with clinical indication.

Runge et al. [5] and Haustein et al. [6] showed higher contrast-to-noise ratios at a dose of 0.3 mmol/kg body weight in patients with different enhancing brain lesions. Runge et al. demonstrated better enhancement with high-dose application in primary brain tumors [7], experimental bacterial meningitis [8], and animal studies of acute cerebral infarction [9]. Mathews et al. showed the same enhancement pattern in patients [10].

Yuh et al. summarized their experience by proposing the following indications for double or triple dose applications of ECR contrast agents: small lesions, lesions with limited blood–brain barrier breakdown, studies of regional cerebral blood volume, and differentiation of scar from disc in the postoperative spine [11]. Mathews et al., in a review paper [12], added to this list primary brain tumors and detection of early brain infection.

Mayr et al. [13] came to the conclusion that high-dose administration of contrast agents is more cost-effective than standard dose.

On the other hand, it is also known that very high doses of contrast lead to contrast reduction or even elimination because T2 effects may take over [14]. Doses higher than the recommended dose also give rise to questions of possible toxicity or tolerance problems.

Field strength and dose

Although the original recommendation concerning dose referred to data acquired at low field [2], most of the data related to dose published afterwards are based on mostly anecdotal experience acquired on high-field equipment.

The possible diagnostic importance of the relationship between dose and field strength was described in 1988 [1]. In recent years there has been an increase in the use of low-field equipment, and numerous publications deal with the relationship between magnetic field strength and contrast enhancement created by ECF agents. The authors rely either on empirical data based on imaging results at different fields or on secondary sources for the discussion of this topic. Most of them include data acquired at high field as well as either mid- or low-field machines [15–20] and describe an increase in contrast enhancement at a given dose between medium and high field. Different recommendations are made by the authors concerning the dose of contrast agent. There are suggestions to decrease the CA dose at high field [16] or to increase the dose of contrast agent at low field in order to guarantee optimum contrast enhancement [21, 22].

In this article we present quantitative data and contrast simulations of different contrast agents and discuss the dependence of contrast enhancement on field strength and dose. Important for their characterization and their behavior related to field strength and dose are their nuclear magnetic relaxation dispersion (NMRD) profiles and the field-dependent relaxation behavior of those tissues with which they come in contact. We have discussed the fundamentals of these implications in previous publications [1, 23].

Materials and methods

Samples

Human brain samples from several different patients were examined, among them normal gray matter, white matter and glioblastoma. The relaxation rate values of the samples chosen for the simulations represented mean values. The glioblastoma sample was tumorous tissue without necrosis or edema.

The ECF contrast agents tested were gadopentetate dimeglumine (Gd-DTPA; Magnevist and Magnograf), gadoterate meglumine (Gd-DOTA; Dotarem), gadoteridol injection (Gd-HP-DO3A; ProHance), and gadodiamide injection (Gd-DTPA-BMA; Omniscan).

These four contrast agents do not interact with albumin; therefore, the relaxivities expected in protein-containing media will be the same [24]. There is no empirical evidence that the clinical efficacy of the four different compounds included in this study is influenced by their net charge, structure, osmolality, or viscosity. Their standardized relaxivities ($s^{-1} \times mmol^{-1} \times L$; at 20 MHz, 37 ± 2 °C, 1 mM) [25] are as follows: gadopentetate dimeglumine 3.8 ± 0.1, gadoterate meglumine 3.5 ± 0.1, gadodiamide injection 3.8 ± 0.1, and gadoteridol injection 3.7 ± 0.1 [26].

Experimental determination of relaxation rates and relaxivities

Proton NMRD profiles representing the relaxation rate R_1 or, in the case of the contrast agents, the relaxivity r_1, vs the magnetic field strength, were acquired with an NMR field cycling relaxometer (FCS, Honesdale, Pa.). Measurements were obtained between 10 kHz (0.0002 T) and 50 MHz (1.2 T), and additional measurements were made on an MSL200/15 system (Bruker, Rheinstetten, Germany) at 200 MHz (4.7 T). All data were acquired at 37 °C. T_2 values of the tissue samples were determined by standard Carr-Purcell-Meiboom-Gill procedures in a Minispec system at 20 MHz (Bruker, Rheinstetten, Germany). For proton density determination, the samples were weighed before the NMR measurements; afterwards, they were dried at 70 °C for at least 7 days and weighed again to estimate their water content. Details of all measurement procedures have been published elsewhere [1, 27, 28].

NMRD data processing and calculation of plain contrast

The NMRD data acquired were postprocessed and fitted with the appropriate models. Particularly the inner-sphere contribution to the relaxivity was fitted accord-

ing to the Solomon-Bloembergen theory assuming one coordinated water molecule in fast exchange with the bulk. The outersphere mechanism was calculated through the model developed by Freed [30] and others [28, 29]. For details of the theoretical background see other papers [31, 32]. For the four gadolinium chelates studied, both contributions are equally important. According to these theories, the T_2 relaxivity profiles of these fast tumbling molecules are almost identical to the T_1 relaxivity profiles.

For the calculations of relaxation times after contrast enhancement the following assumptions were made:

1. Proton density of the target region is not influenced by the injection of a contrast agent.
2. T_2 relaxation times of non-enhanced tissues remain the same in the medical imaging range [33, 34]. T_2 values of enhanced tissues change in a way similar to T_1 values, depending on the concentration of the contrast agent in the target region.

Typically, meningiomas, neuromas, large metastases and glioblastomas (high-grade astrocytomas) reveal the most intense contrast enhancement; therefore, glioblastoma was selected as the pathological tissue for the simulations.

Calculation of enhancement by the different contrast agents

The relaxivities (r_1) of the four different contrast agents were added to the relaxation rates (R_1) of glioblastoma at the respective field strength.

The results represent the relaxation rates of enhanced tissue at different field strengths and a contrast agent concentration of 1 mM. These values can be adjusted to the desired TTC by multiplying by the desired concentration.

$$R_{1TT} = R_1 + r_1 \times TTC, \quad (1\,a)$$
$$R_{2TT} = R_2 + r_2 \times TTC, \quad (1\,b)$$

where R_{1TT} and R_{2TT} are the respective relaxation rates in the target tissue. From these data the reciprocal values (T_1 and T_2 values) were calculated. With these and the proton-density values, signal intensities for given repetition (TR) and echo times (TE) were calculated using the standard steady-state equation for spin-echo (SE) pulse sequences:

$$SI = \varrho \times [1\text{-}e^{(TE\text{-}TR)/T1)}] \times e^{-TE/T2}, \quad (2)$$

where SI is the signal intensity, ϱ is proton density, TE is echo time, and TR is repetition time. $T_1$and T_2 are the respective relaxation times. For our simulations, two different SE pulse-sequence parameters (TR/TE = 250/12 ms and TR/TE = 500/12 ms) were chosen to be close to commonly used clinical protocols. They were kept the same all over the field range, although in the clinical setting often longer repetition times are chosen to allow the acquisition of several parallel slices through the object at a time. This procedure, however, sacrifices T_1-weighting. For the calculation of contrast behavior, the following equation was applied:

$$C = (SI_P\text{-}SI_S)/(SI_P + SI_S), \quad (3)$$

where C is contrast in percent (relative contrast), SI_P is the signal intensity of the pathological tissue, and SI_S is the signal intensity of the surrounding tissue for the given SE sequence [14].

Target tissue concentration

The data shown are for a lesion at the time of peak enhancement. Depending on the pathology, this happens during either the diffusion or the early washout phase, usually 1.5–6.0 min after injection.

In the best case, the manufacturer-recommended single-dose concentration of the contrast agent (i.e., 0.1 mmol/kg body weight) leads to a TCC of ≥ 0.5 mM. This assumption was made based on the fact that the ECF space comprises, depending on the reference literature used, 18–25 % of the body weight [35–37]. In a recently published paper on the topic, the ECF space is quoted with only 15 % of the body weight [18].

As the basis for our calculations, we chose 20 %. In a person with a body weight of 75 kg, the ECF space is 15 L. If 15 mL of the clinical formulation of an ECF contrast agent are injected into this person (= 7.5 mmol), the concentration of the compound in the ECF space at equilibrium under the condition of even distribution will be 7.5 mmol/15 L = 0.5 mmol/L; the concentration will be slightly higher if the ECF space is smaller, slightly lower if the ECF space is larger. In many pathological lesions the TTC will be lower. The result correlates well with the measurements of Weinmann et al. [38].

Our considerations are meant for static imaging. They are not directly applicable for monitoring dynamic behavior after bolus injection where gadolinium concentrations change rapidly and local vascular concentration might be one order of magnitude higher than TTC [39].

Results

Contrast agents and tissue relaxation data

At the clinical imaging field range (0.2–2.0 T), the standardized relaxivities r_1 profiles of all four ECF contrast agents are nearly identical. These NMRD profiles reveal a pronounced decrease in relaxivities from low imaging fields to approximately 0.4 T; from there on the decrease is slower and nearly proportional to field strength (Fig. 1).

The relaxation rates R_1 of frontal gray and white matter as well as of tumor tissue of a glioblastoma are presented in Fig. 2. They also show a pronounced decrease at low field, becoming less marked in the mid-

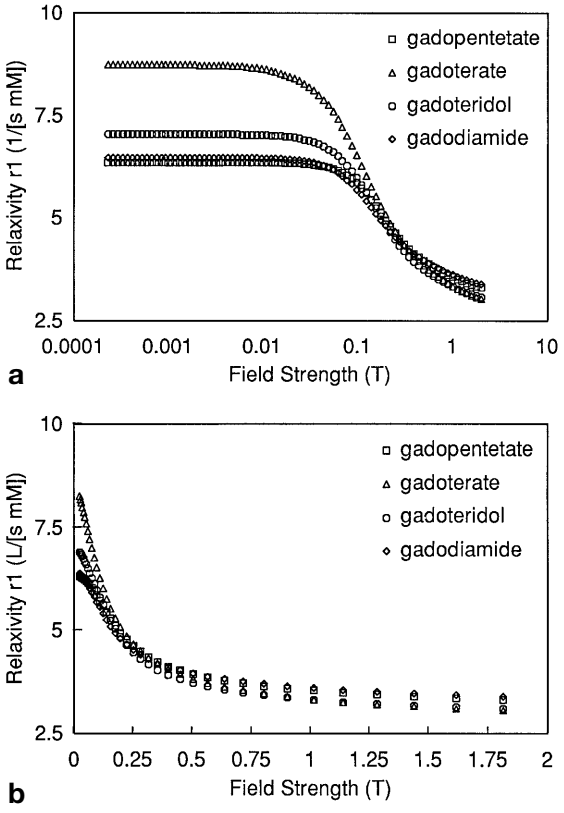

Fig. 1 a, b. Nuclear magnetic relaxation dispersion profiles of four different extracellular fluid contrastagents. **a** Entire measured range, logarithmic scale. **b** Imaging field range, regular scale

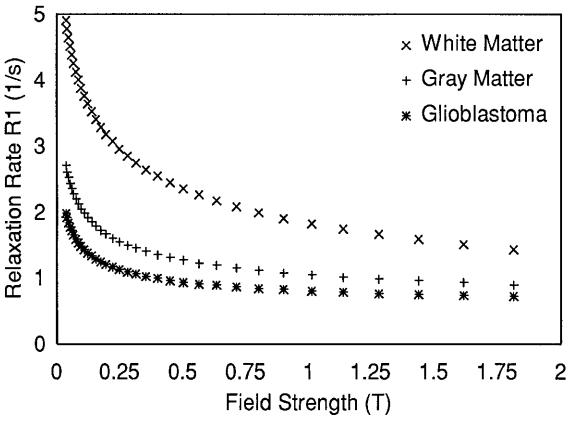

Fig. 2. Nuclear magnetic relaxation dispersion profiles of frontal gray matter, white matter, and tumor tissue of a glioblastoma

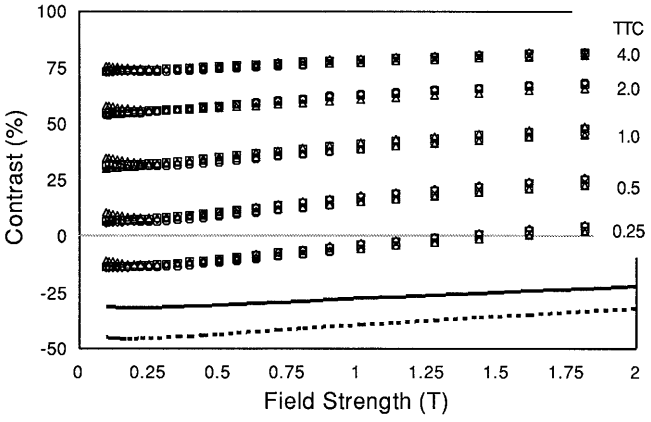

Fig. 3. Pure T_1 contrast between white matter and different non-enhanced and enhanced brain tissues vs field strength. *Dotted line* contrast between white matter and glioblastoma; *solid line* contrast between white matter and gray matter. Contrast between white matter and glioblastoma, enhanced by gadopentetate dimeglumine *(squares)*, gadoterate meglumine *(triangles)*, gadodiamide injection *(diamonds)*, and gadoteridol injection *(circles)*. The target tissue concentration (TTC) is given in millimoles per liter

and high-field range. The following ϱ/T2 values (percent/millisecond) were measured: white matter 72/89, gray matter 82/105, and glioblastoma 78/133.

Image contrast

The ECF agents included in this study are commonly used as T_1 (i.e., positive) agents. Therefore, we present pure T_1 contrast in Fig. 3. Although such calculated T_1 images are rarely acquired in routine diagnostic imaging, they do demonstrate the main effect of the application of ECF agents without the interference of other factors.

In plain, i.e., non-enhanced, imaging the pathology would appear dark on pure T_1 images. By shortening its T_1 relaxation time with the help of a contrast agent, the lesion brightens. This means that, at low contrast agent concentrations, lesion contrast is easily lost or even completely extinguished. Only at higher TTCs does the lesion reveal positive contrast relative to its surroundings.

In clinical routine, SE sequences are most commonly used for plain and enhanced studies of the central nervous system. Figures 4 and 5 present the results of the two T_1-weighted SE sequences (TR/TE: 250/12 ms and TR/TE: 500/12 ms). They depict the contrast between white matter and gray matter as well as between white matter and glioblastoma without contrast enhancement (light-gray and medium-gray lines in the negative range). This inherent contrast is negative at any field. Best plain contrast is seen at low or medium field as described previously [1].

When contrast agents are applied, enhancement of the glioblastoma can be observed; contrast moves in the positive direction. It is apparent that the enhancement is both field- and dose dependent. Half the recommended dose (TTC 0.25 mM) can reduce or erase contrast between white matter and glioblastoma completely. Visible contrast enhancement at all fields occurs with the recommended dose (TTC 0.5 mM). Double and quadruple doses (TTCs 1.0 and 2.0 mM, respectively) boost contrast enhancement. Increasing the TTC influences positive contrast enhancement more at high than at low field. Higher TTC begins to reverse enhancement (TTC 4.0 mM), i.e., the dose increase becomes counterproductive because T_2 influence takes over. This behavior is nearly identical in all four studied contrast agents. To better visualize the influence of too-

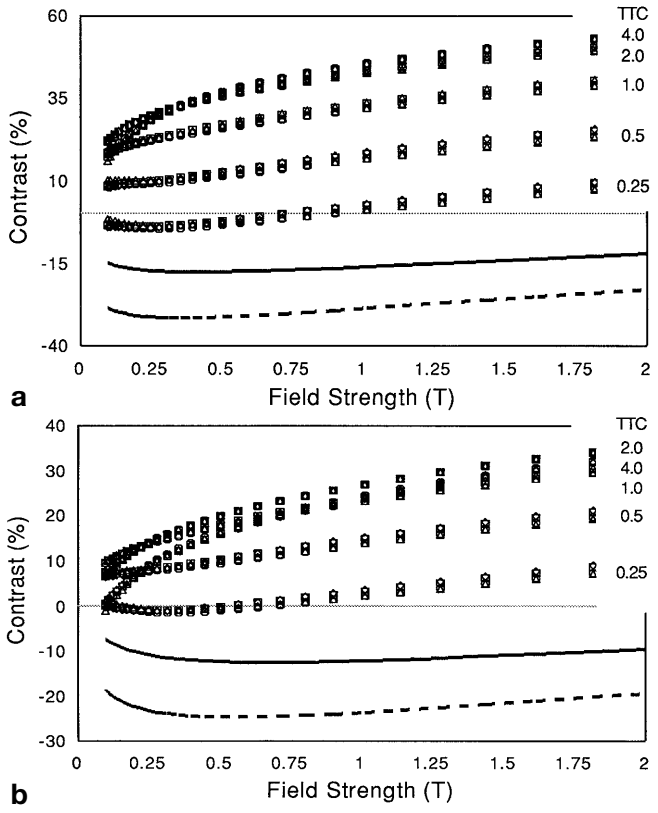

Fig. 4 a, b. Contrast on two T_1-weighted spin-echo pulse sequence (**a** TR/TE: 250/12 ms; **b** TR/TE: 500/12 ms) between white matter and different non-enhanced and enhanced brain tissues vs field strength. *Dotted line* contrast between white matter and glioblastoma; *black line* contrast between white matter and gray matter. Contrast between white matter and glioblastoma, enhanced by gadopentetate dimeglumine *(squares)*, gadoterate meglumine *(triangles)*, gadodiamide injection *(diamonds)*, and gadoteridol injection *(circles)*. The TTC is given in millimoles per liter. The differences in contrast enhancement between the four compounds are negligible. Note different scale between **a** and **b**

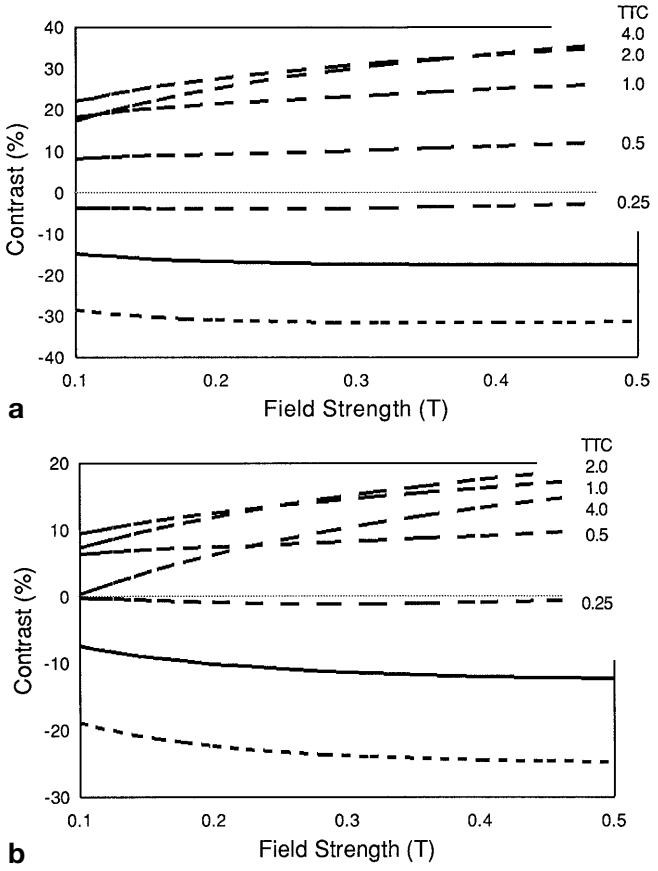

Fig. 5 a, b. Same as Fig. 4, gadopentetate dimeglumine only, low- to mid-field range. Contrast in a T_1-weighted spin-echo pulse sequence (**a** TR/TE: 250/12 ms; **b** TR/TE: 500/12 ms) between white matter and different non-enhanced and enhanced brain tissue vs field strength. *Dotted line* non-enhanced contrast between white matter and glioblastoma; black line: non-enhanced contrast between white matter and gray matter. *Dotted lines marked with TTC* contrast between white matter and enhanced glioblastoma at increasing TTC (in millimoles per liter). There are significant differences in contrast enhancement between 0.25-, 0.5-, and 1. 0-mM TTC. **a** Doubling TTC from 1.0 to 2.0 mM still increases contrast with the heavily T_1-weighted sequence, and doubling from 2.0 to 4.0 mM does not change enhancement at high field and decreases contrast at low field. **b** Increasing the dose beyond double dose (= 1.0 mM TTC) is counterproductive because it decreases contrast enhancement

low and too-high concentrations, Fig. 5 shows the behavior of gadopentetate dimeglumine at low field.

Discussion

The average field strength of MR imaging equipment and the clinical use of contrast agents varies significantly depending on the region of the world [40]. In the past years, there has been a significant change of trend towards the utilization of low-field equipment, particularly in the United States. In this context it has often been overlooked or ignored that field strength can influence contrast enhancement induced by MR contrast agents.

At present, four gadolinium-based ECF contrast agents are available for clinical application: gadopentetate dimeglumine, gadoterate meglumine, gadodiamide injection, and gadoteridol injection. Enhancement after the injection of these contrast agents in the central nervous system is modulated by six major factors: (a) the histology and physiology of the target tissue, particularly its microvasculature or protection by the blood–brain barrier; (b) the overall distribution volume; (c) the original concentration and dose of the contrast agent; (d) the intrinsic relaxation times of the target tissue; (e) the *in situ* relaxivity of the contrast agent; and (f) the hardware and software features of the MR imaging equipment used, particularly the pulse-sequence parameters chosen.

Some recent publications deal with the relationship between magnetic field strength and contrast enhancement created by these contrast agents. The authors use either empirical, mostly anecdotal, data based on imaging results at different fields or secondary sources for the discussion of this relationship [15–22].

Our results have shown that, comparing the contrast enhancement vs field strength at a given dose, there is a marked modulation of contrast with field. In the worst

case, this modulation may lead to an extinction of contrast occurring with the manufacturer-recommended dose at low field. This observation holds in a similar way for dose at a given field strength. Too low a dose may lead to a loss of contrast, whereas the currently recommended dose of 0.1 mmol/kg body weight should create some contrast enhancement in most cases. Extremely high doses offset the enhancement due to the growing influence of T_2 effects. This effect is visible at low and even medium field; it becomes less pronounced at high fields.

We found no straightforward easily predictable correlation between contrast enhancement, dose, and field strength, although, within certain limits, there is a trend toward increasing enhancement with field strength and dose.

Comparison of enhancement in images acquired at different field strength with the same contrast agent dose is difficult. Special care must be taken when monitoring therapy or in follow-up of patients.

Because enhancement patterns in body tissues may differ, our results can be extrapolated to other regions of the body only if proper care is applied. A projection from ECF contrast agents to other gadolinium-containing contrast agents e. g., targeted agents, is not possible due to the different character of uptake and/or binding of such contrast agents. Given that the enhancement mechanisms of MR contrast agents differ completely from those of X-ray contrast media, a direct adaptation of, for example, double-dose contrast-enhanced CT to MR imaging is not feasible.

Uptake of a contrast agent in a lesion is influenced by numerous histological and histopathological factors, of which tissue vascularity seems most important. Various other factors act upon tissue relaxation rates, among them water compartmentalization, diffusion through susceptibility gradients, possible binding of contrast agents to proteins, or release of components of the contrast agent. However, in our calculations and simulations we have assumed that the lesion of interest has the highest possible uptake at the time of signal intensity calculation and image acquisition at the given application dose. In reality, this might not be the case, and lower concentrations of the contrast agent might influence signal intensity. Small or poorly enhancing lesions may not reach this optimal target tissue concentration with the currently recommended clinical dose of 0.1 mmol/kg body weight. This means that this dose lies close to the lower end of the diagnostic range.

Numerous additional uncertainties contribute to the enhancement in the target tissue, among them the distribution space. The ECF space decreases with age. According to the literature, in a subject of 75 kg body weight, the ECF space can be as low as 11.25 L and as high as 18.75 L. This means that the TTC could be between 0.42 and 0.66 mmol/L. With TTCs at the lower end, there might not be enough enhancement in persons with a large ECF space.

The optimal contrast-to-noise ratio depends also on the pulse sequence used. In our simulations we used heavily T_1-weighted SE sequences. Contrast-enhanced gradient-echo sequences can show a lower contrast-to-noise ratio [41].

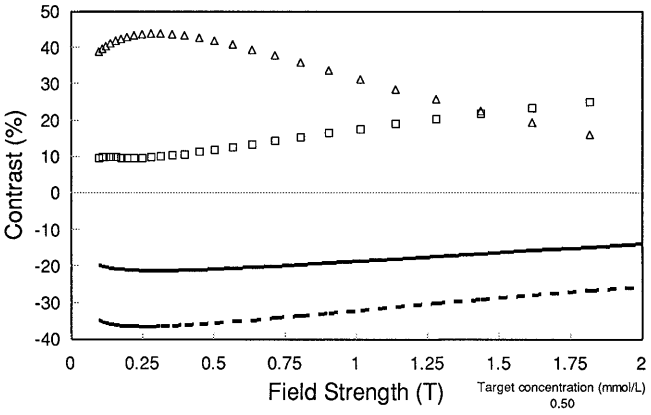

Fig. 6. Contrast on a T_1-weighted spin-echo pulse sequence (TR = 125 ms, TE = 6 ms) between white matter and different non-enhanced and enhanced brain tissue vs field strength. *Dotted line* contrast between white matter and glioblastoma; *solid line* contrast between white matter and gray matter. Contrast between white matter and glioblastoma, enhanced by gadoteridol injection *(squares)* and by a USPIO-type contrast agent *(triangles)*. Target tissue concentration of contrast agents 0.5 mmol/L. Note that in this case pulse sequences are stronger T_1-weighted than those in the previous figures; imaging protocols must be adjusted to this kind of contrast agent

For contrast-enhanced examinations often the same or similar pulse-sequence parameters are used independent of the field strength. To gain optimum enhancement both TR and TE must be properly adjusted. This, however, can collide with the desire to acquire as many parallel slices as possible during a single imaging study and represents a particular and additional dilemma at low field. Yet, the cheapest and easiest approach to achieve optimum enhancement after injection of ECF contrast agents is the adjustment of pulse-sequence parameters according to field strength.

Individual dose adjustment according to field strength and clinical question seems to be an inefficient and questionable procedure. The safest and most practical way to guarantee enhancement in CNS indications would be doubling the dose or the concentration of ECF agents at all fields. Cutting the dose of ECF contrast agents, as is done in some instances to save money, is dangerous and might lead to the complete extinction of contrast in the area of interest. Increasing the dose to more than five times the currently recommended dose may have similar results, particularly at low field.

In the long run, a new class of contrast agents with optimized relaxivity adjusted to the field-dependent relaxation behavior of tissues would be a valuable replacement for the existing ECF agents. They would guarantee enhancement and, thus, better diagnostic yield at any field strength. Figure 6 shows the contrast enhancement vs field strength of an exemplary ultrasmall superparamagnetic iron oxides (USPIO)-type contrast agent. With this kind of contrast agent, enhancement at medium and high field would be similar to the present ECF

agents. At low field contrast enhancement would be far better. Contrast agents with such behavior would be advantageous as general-purpose unspecific agents at all fields.

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