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Administration of Gadopentetate Dimeglumine in MR Imaging of Intracranial Tumors: Dosage and Field Strength

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Purpose: To investigate the efficacy of 0.025, 0.05 and 0.1 mmol/kg gadopentetate dimeglumine in MR imaging of patients with intracranial tumors at mid and high field strength. **Methods:** In 88 patients, an open-label phase III multicenter dose-finding study was performed at 0.5, 1.0, and 1.5 T MR units. Before and after (5, 15, 25 minutes) intravenous administration of gadopentetate dimeglumine, imaging was performed with T1-weighted spin-echo sequences. **Results:** With 0.1 mmol/kg yielding the highest values, tumor enhancement and numerical tumor/brain contrast showed dose-dependent 5-minute postcontrast values ($P < 0.05$). Compared to 5-minute postcontrast values, there was no significant change at 15 and 25 minutes. Although the lowest values of enhancement were found at 0.5 T, differences in enhancement among the field strengths were not statistically significant. The numerical data were confirmed by visual assessment of tumor/brain contrast. Eighty to 90% of cases had diagnostically valuable enhancement at 0.1 mmol/kg, 50% at 0.05 mmol/kg, and 10% at 0.025 mmol/kg ($P < 0.05$). There were no adverse events. **Conclusion:** Our results confirm that 0.1 mmol/kg gadopentetate dimeglumine is more effective at enhancing intracranial tumors than lower doses at mid and high field MR units.

Index terms: Contrast media, paramagnetic; Magnetic resonance, contrast enhancement; Brain neoplasms, magnetic resonance

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Gadopentetate dimeglumine (Gd-DTPA) has been shown to be an effective and safe contrast agent for MR imaging of the central nervous system (CNS) (1–6). The current dose recommendation of 0.1 mmol Gd-DTPA/kg body weight for CNS studies emerged from a dose-finding study performed by Niendorf et al at a field strength of 0.35 T. However, as part of the phase-II clinical trial of Gd-DTPA, only 11 patients with intracranial tumors could be enrolled in the study (7).

Tumors such as meningiomas and neuromas show marked contrast enhancement after intravenous administration of 0.1 mmol Gd-DTPA/kg (8, 9), indicating that a smaller dose may be feasible. An obvious advantage of lower dosages of Gd-DTPA would be the cost reduction and a further improvement in the safety index of Gd-DTPA. However, both factors have to be balanced against the potential risk of missing lesions, especially those with relatively faint contrast enhancement. Niendorf et al (7) reported an anecdotal case in which detection of poorly enhancing lesions even required a dosage of 0.2 mmol/kg Gd-DTPA. It was the aim of the present brain tumor study to evaluate whether the dose of 0.1 mmol/kg Gd-DTPA is required to consistently obtain diagnostically adequate lesion contrast at mid and high field MR units.

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Materials and Methods

This was a randomized, open-label multicenter dose-finding study. Enrollment in the study was limited to patients with presumed intracranial tumors showing contrast enhancement on computed tomography (CT) performed within 7 days of the magnetic resonance (MR) examination. In addition, only nonpregnant patients aged between 18 and 75 years who had not received iodinated contrast agents within 24 hours were investigated.

Ninety patients were enrolled in the study at three medical centers in Germany from August 1988 until February 1989. After exclusion of two patients (one patient with lack of CT contrast enhancement who had been entered into the study by error; one patient with nonneoplastic disease), 88 patients (mean age 48 ± 15 years) provided valid data for statistical analysis of efficacy. Histologic proof of the diagnosis was available in 72 patients, and the diagnosis was based on typical findings on plain and contrast-enhanced CT in 16 patients (Table 1).

Patients were given detailed information on the purpose of the study, and written informed consent to perform MR imaging with Gd-DTPA was obtained. At each center, patients were randomized to one of three dosages of Gd-DTPA (Schering AG, Berlin, Germany): 0.025, 0.05, or 0.1 mmol/kg body weight. MR imaging was performed using standard head coils on three MR systems operating at 0.5, 1.0, and 1.5 T. Intermediate and T2-weighted spin-echo (SE) images (SE 1,600/30,70/1 (TR/TE/excitations) at 0.5 T; SE 3,000/25,90/1 at 1.0 T; SE 2,600/30,100/1 at 1.5 T) were obtained prior to Gd-DTPA injection to determine representative slices showing the tumor to its largest extent. T1-weighted acquisitions (SE 400/30/2 at 0.5 T; SE 400/35/2 at 1.0 T; SE 350/20/2 at 1.5 T) were performed in the representative slice before and 5, 15, and 25 minutes after administration of Gd-DTPA. Images were obtained in the axial plane in 83 patients and in the sagittal plane in five patients. Each trial center was provided with a cylindrical plastic tube (2.5-cm diameter, 8-cm length) containing an aqueous solution of 4 mmol/L of Gd-DTPA that was attached to the patients' head or the inside of the head coil and imaged simultaneously as an external standard.

Quantitative Assessment

Measurements of the signal intensity in pre- and postcontrast T1-weighted images were performed in normal brain, edema, tumor, and in the external standard using an operator-defined region-of-interest (ROI) technique. Measurements of a given structure in a given patient were always made with the same sized circular ROI, including an area of at least several pixels. The signal intensity of normal brain tissue was measured in the white matter of the contralateral hemisphere relative to the lesion. The signal intensity of perifocal edema was determined in an area that was hyperintense in T2-weighted scans but which did not display contrast enhancement in postcontrast T1-weighted images. The signal intensity of tumor tissue was measured in enhancing areas. In cases of inhomogeneous contrast enhancement of tumor tissue, the area of maximum enhancement was selected for measurement.

To compensate for potential instrument-dependent changes over time in a given patient, pre- and postcontrast signal intensity values for normal brain, tumor, and edema were related to the intensity of the external standard. The normalized signal intensity (SI) of each of the three tissues at a given time point was calculated as follows:

$$SI_{tissue}\ (\text{arbitrary units (a.u.)}) = (S_{pre}/S_t) \times S_{tissue\ t}$$

with S_{pre} = signal intensity of the external standard on the precontrast scan, S_t = signal intensity of the external standard at time t, and $S_{tissue\ t}$ = measured signal intensity of the tissue (brain, edema, tumor) at time t. Tumor enhancement on postcontrast images was calculated as follows:

TABLE 1: Field strength, dose level of Gd-DTPA, and diagnoses in 88 patients

Field Strength (T)	Dose (mmol/kg)	Glioma		Extraaxial[a]		Other[b]		Number of Patients
		+	nd	+	nd	+	nd	
0.5	0.025	5	1	2		1 b	1 a	10
	0.05	6		1	2	1 g		10
	0.1	3		5	1		1 a	10
1.0	0.025	4		4		2 a, e		10
	0.05	1		6	2	1 f		10
	0.1	1		9				10
1.5	0.025	4		4			1 a	9
	0.05	3	1	1	1	2 c, e	2 a, a	10
	0.1	3	1	2	1	1 g	1 d	9
Total		30	3	34	7	8	6	88

Note:—+ = diagnoses confirmed by histology; nd = no histology.

[a] Meningioma, acoustic neuroma, pituitary adenoma, clivus chordoma, craniopharyngioma.

[b] a = metastasis, b = cavernoma, c = angioblastoma, d = angiofibroma, e = sarcoma, f = lymphoma, g = germinoma.

$$\text{enhancement (\%)} = (SI_{\text{tumor post}} - SI_{\text{tumor pre}})/SI_{\text{tumor pre}} \times 100$$

Numerical tumor/brain contrast was calculated and expressed as magnitude values according to the following equation:

$$\text{tumor/brain contrast (\%)} = (SI_{\text{tumor}} - SI_{\text{brain}})/SI_{\text{brain}} \times 100$$

Visual Assessment

Tumor/brain contrast was independently assessed by two investigators (M.L., H.P.N.) who had not previously seen the cases and had no data on case history and contrast dosage. From the appearance of images, the readers could identify the field strength, but not what dosage was used. The precontrast and 5-minute postcontrast pairs of T1-weighted images were displayed side by side. Time for reviewing was unlimited. Pre- and postinjection tumor/brain contrast were rated using a four grade scale: no (0), poor (+), moderate (++), and excellent (+++) contrast. No contrast was defined as isointensity of tumor versus normal brain. Poor contrast was equivalent to slight hypo- or hyperintensity of tumor relative to normal brain. Contrast was rated moderate when tumor tissue was clearly hypo- or hyperintense versus normal brain. Excellent contrast applied to markedly hypo- or hyperintense tumors. No or poor contrast was further defined as diagnostically inadequate, whereas moderate or strong contrast was defined as diagnostically adequate. In case of disagreement between the two readers, the patient was assigned to the lower or to the intermediate grading.

Statistical Analysis

The primary variables to assess the diagnostic value of different doses of Gd-DTPA in the population under study were percentage of tumor enhancement, numerical tumor/brain contrast, and visual tumor/brain contrast, each 5 minutes after administration of Gd-DTPA. The null hypothesis was that there is no difference between dose levels of Gd-DTPA with respect to the primary variables. The alternative hypothesis was that the primary variables are dose-dependent. The study was designed for 10 patients per dose group and field strength, in order to achieve an 80% chance of detecting a difference of 1.33 standard deviations at a significance level of 5%.

The numerical values of tumor enhancement and tumor/brain contrast were evaluated by analysis of variance (ANOVA) (10). The hypotheses tested were: 1) there is no treatment-by-center interaction, and 2) the dose groups are not different with respect to the corresponding variables. There were not enough cases in the two subgroups, intraaxial and extraaxial tumors, to perform statistical tests comparing the different dosages and field strengths. The SI changes in normal brain during postcontrast imaging were evaluated by a Student's *t*-test at each time point, dose level, and field strength, with no adjustments made for multiple comparisons. The data of the visual evaluation of tumor/brain contrast were evaluated with Fisher's Exact Test applied for each field strength. To measure the interobserver variability, the kappa coefficient for multiple raters was used (11). The kappa coefficient measures the observed amount of agreement corrected for the amount of agreement expected by chance alone. To interpret the strength of agreement when kappa is positive, Landis and Koch (12) have suggested the following guidelines: <0 poor, 0–0.20 slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial and 0.81–1.00 denoting almost perfect agreement.

The SI values were expressed as mean ± standard deviation for each dose level at each of the three centers and represented as graphs for normal brain, edema, and tumor as a function of time. The means (± standard deviation) of numerical tumor/brain contrast and the data of the visual evaluation of tumor/brain contrast were tabulated by field strength, dose level, and time.

Safety Assessment

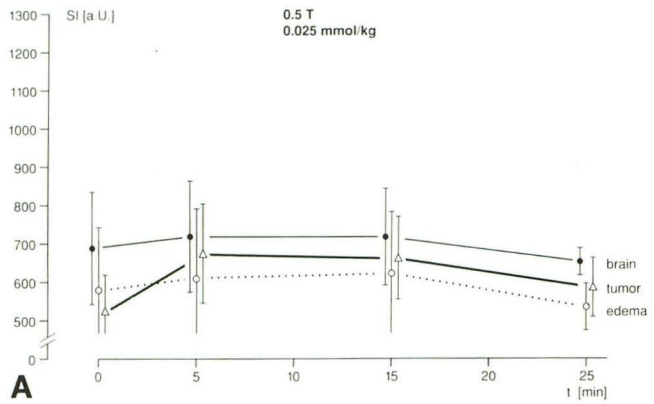
At the end of the MR examination, all patients were asked in a nonsuggestive manner about the presence of adverse events. In particular, they were not questioned using a specific list of possible reactions.

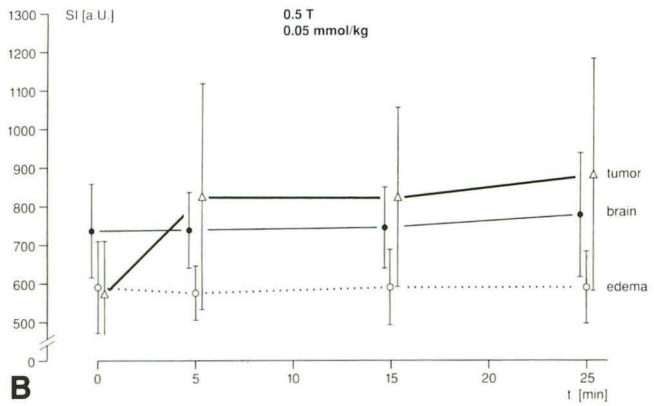
Results

Quantitative Evaluation

Figures 1 to 3 show the results of the SI measurements in normal brain, edema, and tumor tissue before and after administration of Gd-DTPA at the three field strengths and dose levels. Mean values of the SI in normal brain slightly increased at 5 minutes postcontrast relative to unenhanced images, with minimal changes thereafter up to 25 minutes. These increases of SI were statistically significant, regardless of field strength and administered dose of Gd-DTPA ($P < 0.05$). Perifocal edema was present in only 51 of the 88 patients, thus precluding a statistical evaluation as for normal brain.

Precontrast mean values in tumor tissue were always lower compared to normal brain. Statistical analysis showed that there were no pretreatment differences of tumor SI between the dose groups. Five minutes after administration of Gd-DTPA, dose-dependent increases of SI occurred in tumor tissue. Accordingly, the percentage of contrast enhancement was higher ($P < 0.05$) for 0.1 mmol/kg Gd-DTPA compared to the lower dosages (Fig. 4). Although the lowest values of enhancement were found at 0.5 T, differences in enhancement among the field strengths were not statistically significant.





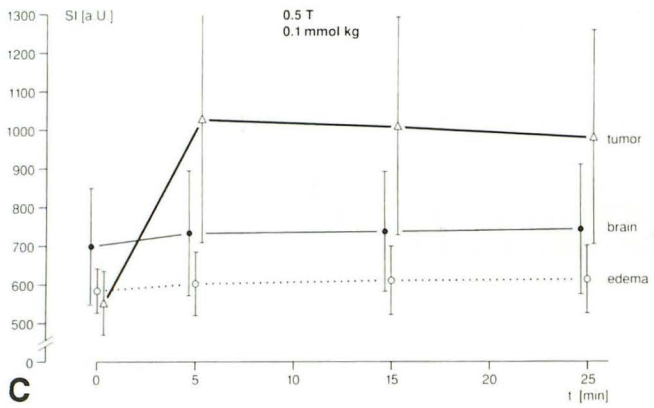
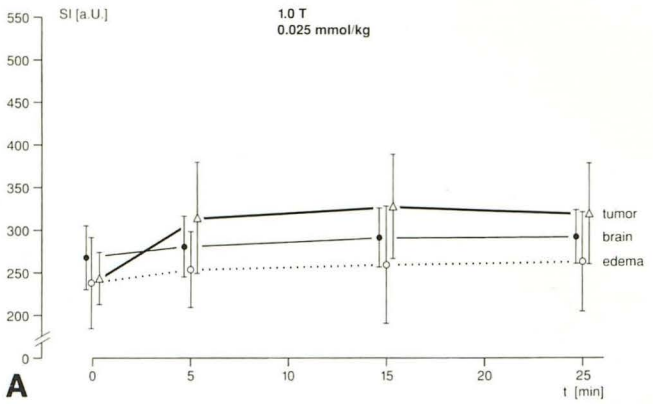
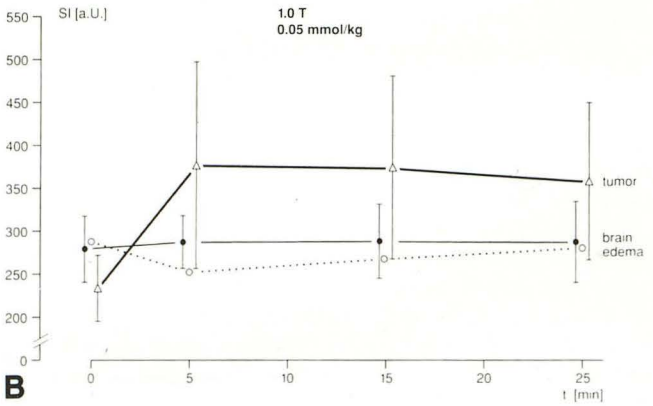


Fig. 1. Mean values (± standard deviation) of normalized tissue signal intensity obtained at 0.5 T before (0 min) and 5, 15, 25 min after administration of Gd-DTPA (0.025 mmol/kg (*A*), 0.05 mmol/kg (*B*) and 0.1 mmol/kg (*C*). Means of normal brain and tumor are offset in time.





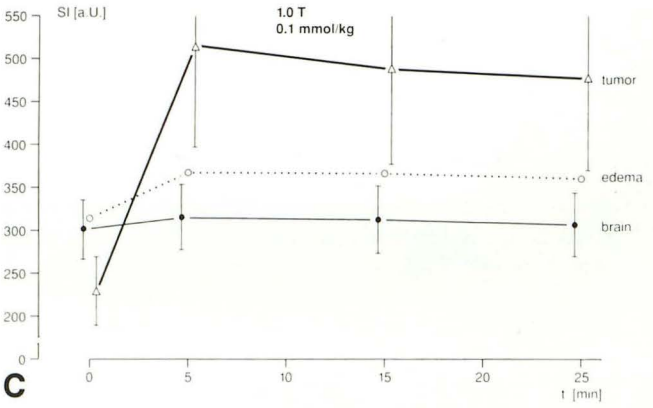


Fig. 2. Mean values (± standard deviation) of normalized tissue signal intensity obtained at 1.0 T before (0 min) and 5, 15, 25 min after administration of Gd-DTPA (0.025 mmol/kg (*A*), 0.05 mmol/kg (*B*) and 0.1 mmol/kg (*C*). Means of normal brain and tumor are offset in time.

Table 2 summarizes mean values of numerical tumor/brain contrast. Mean values ranged from 12% to 23% on unenhanced images. Five minutes after administration of Gd-DTPA, mean values of tumor/brain contrast increased with dose at each field strength ($P < 0.05$). Peak mean postinjection tumor/brain contrast occurred at 5 minutes without major changes of mean values thereafter. Tumor/brain contrast at either 5, 15, or 25 minutes after Gd-DTPA administration was numerically higher to that on plain images in 11 of 29 patients examined with 0.025 mmol/kg, in 21 of 30 patients studied with 0.05 mmol/kg, and in 26 of 29 patients who received 0.1 mmol/kg Gd-DTPA. In the latter group, the histologic diagnoses of the three tumors with inferior post-

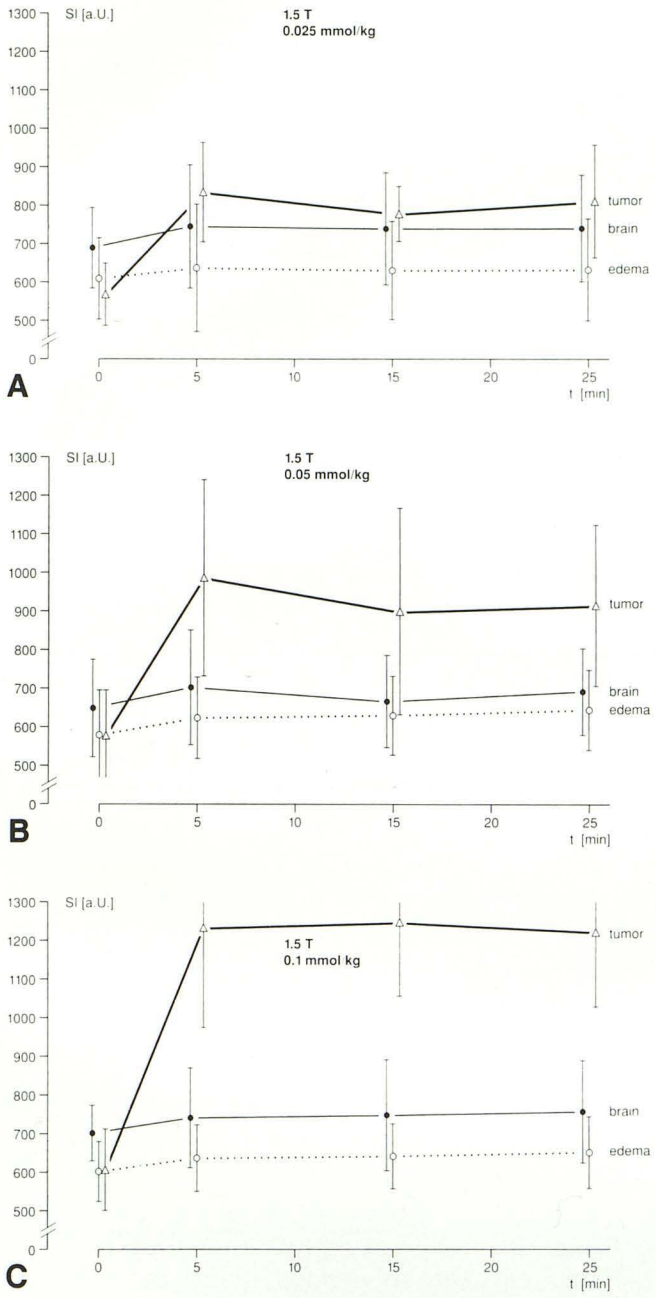


Fig. 3. Mean values (± standard deviation) of normalized tissue signal intensity obtained at 1.5 T before (0 min) and 5, 15, 25 min after administration of Gd-DTPA (0.025 mmol/kg (*A*), 0.05 mmol/kg (*B*) and 0.1 mmol/kg (*C*). Means of normal brain and tumor are offset in time.

contrast values were meningioma of the olfactory nerve sheath, grade III astrocytoma, and grade III oligodendroglioma.

Individual time courses of contrast were reviewed for substantial, delayed enhancement, defined as increase in numerical tumor/brain contrast of at least 50% at 15 or 25 minutes after contrast infusion compared to both 5-minute and

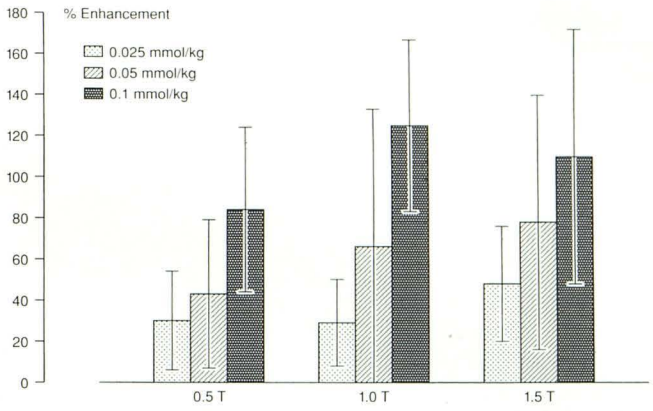


Fig. 4. Mean values (± standard deviation) of lesion enhancement (%) as a function of Gd-DTPA dose and field strength. The percentage of enhancement was calculated as described, with use of data from the 5-minute postcontrast image.

plain scans. This applied to two out of the 29 cases studied with 0.025 mmol/kg (one acoustic neuroma, one glioblastoma), and to four of the 30 patients who received a dose of 0.05 mmol/kg Gd-DTPA (two glioblastomas, one convexity meningioma, one craniopharyngioma). At the dose level of 0.1 mmol/kg Gd-DTPA, two gliomas, one clivus chordoma, one pinealoma, and one pituitary adenoma showed substantial, delayed enhancement.

Visual Evaluation

Table 3 summarizes the results of the visual evaluation of tumor/brain contrast on plain and 5-minute postcontrast images. In all cases, tumor/brain contrast was diagnostically inadequate on plain T1-weighted images. Tumor/brain contrast was rated moderate or strong, ie, diagnostically adequate, on postcontrast images in three of 29 cases examined with 0.025 mmol/kg, in 15 of 30 patients studied with 0.05 mmol/kg, and in 25 of 29 patients who received 0.1 mmol/kg Gd-DTPA. Postcontrast ratings were dose-dependent ($P < 0.05$), with 0.1 mmol/kg Gd-DTPA yielding the highest rating at each field strength. A review of the 11 cases with substantial, delayed enhancement revealed no differences in the visual assessment of contrast 15 and 25 minutes after dosing compared to 5 minutes postcontrast. The comparison of the ratings of tumor/brain contrast performed independently by the two readers revealed a kappa value for interobserver variability of −0.02 (poor agreement) for precontrast images and 0.66 (substantial agreement) for postcontrast images.

TABLE 2: Numerical tumor/brain contrast (%)

Field Strength (T)	Dose (mmol/kg)	Precontrast[a]	Postcontrast			Number of Patients
			5 min[b]	15 min	25 min	
0.5	0.025	23 ± 6	13 ± 11	12 ± 7	13 ± 7	10
	0.05	22 ± 6	23 ± 20	15 ± 14	18 ± 12	10
	0.1	19 ± 10	39 ± 26	36 ± 21	32 ± 20	10
1.0	0.025	12 ± 6	14 ± 12	13 ± 10	10 ± 8	10
	0.05	17 ± 5	35 ± 36	34 ± 34	34 ± 31	10
	0.1	23 ± 9	63 ± 33	55 ± 23	54 ± 23	10
1.5	0.025	17 ± 11	15 ± 11	14 ± 12	14 ± 11	9
	0.05	15 ± 7	48 ± 40	38 ± 33	37 ± 29	10
	0.1	14 ± 9	72 ± 53	73 ± 48	65 ± 34	9
Total						88

Note:—Data are mean ± standard deviation.

[a] Mean values were not dose-dependent ($P > 0.05$) (ANOVA).

[b] Mean values were dose-dependent ($P < 0.05$) (ANOVA).

TABLE 3: Visual assessment of tumor/brain contrast

Field Strength (T)	Dose (mmol/kg)	Precontrast[a]				5 Minutes Postcontrast[b]				Number of Patients
		0	+	++	+++	0	+	++	+++	
0.5	0.025	5	5	0	0	6	3	1	0	10
	0.05	2	8	0	0	3	2	2	3	10
	0.1	6	4	0	0	0	2	5	3	10
1.0	0.025	7	3	0	0	2	7	1	0	10
	0.05	8	2	0	0	1	4	4	1	10
	0.1	7	3	0	0	0	1	5	4	10
1.5	0.025	6	3	0	0	1	7	1	0	9
	0.05	4	6	0	0	0	5	4	1	10
	0.1	8	1	0	0	0	1	5	3	9
Total										88

Note:—No (0), poor (+), moderate (++), and excellent (+++) tumor/brain contrast.

[a] Ratings were not dose-dependent ($P > 0.05$) by Fisher's Exact Test.

[b] Ratings were dose-dependent at each field strength ($P < 0.05$) by Fisher's Exact Test.

Safety and Tolerance

There were no adverse events or reports of discomfort after Gd-DTPA injection.

Discussion

MR imaging of intracranial tumors is one of the established indications for the use of Gd-DTPA (1, 2). The data from the literature provide good evidence that 0.1 mmol/kg Gd-DTPA represents a well-tolerated dose for routine use in clinical practice (3–6). In the present study, none of the 90 patients reported adverse events, regardless whether 0.025, 0.05, or 0.1 mmol/kg of Gd-DTPA were injected. Taking into consideration the relatively low percentage of side effects collected from patient populations of up to 7,000 subjects (5), the subgroups of 30 patients per dose level were too small to assess differences in tolerance between the three dosages.

Contrast between tumor tissue and normal brain on Gd-DTPA-enhanced images depends on the degree of enhancement in both tissues. In our patients, the poor enhancement of normal brain versus the increasing degree of tumor enhancement resulted in a dose-dependent improvement of numerical lesion contrast. Differences among 0.025, 0.05, and 0.1 mmol/kg were statistically significant. To evaluate a radiologist's perception, contrast was also assessed visually. The two readers found diagnostically adequate tumor/brain contrast in 80% to 90% of the 29 cases

examined with 0.1 mmol/kg Gd-DTPA at all three field strengths. On the other hand, only 50% of tumors displayed diagnostically adequate lesion contrast on visual assessment when 0.05 mmol/kg were injected. The ratio of lesions showing diagnostically adequate contrast versus brain dropped down to 10% in the group of 29 patients who received the low dose of 0.025 mmol/kg Gd-DTPA. Thus, at mid and high field, only 0.1 mmol/kg consistently provided diagnostic results that justify the extra time and effort required to obtain contrast-enhanced images.

It is well known from both contrast-enhanced CT and MR imaging that brain tumors may show delayed uptake of contrast material (13, 14). Our study protocol, therefore, included postcontrast scans not only at 5 minutes, but also 15 and 25 minutes after injection of Gd-DTPA. Further increases of signal intensity in tumor tissue after the initial postcontrast scan occurred in a variety of tumors of which only 11 presented with substantial, delayed enhancement. However, in none of these patients, including six who received either 0.025 or 0.05 mmol/kg, did the review of the delayed images reveal diagnostically relevant improvement of contrast. Thus, delayed imaging did not compensate for lack of adequate contrast enhancement when low dosages, such as 0.025 and 0.05 mmol/kg Gd-DTPA, were administered.

In the present study, lesion contrast was calculated or visually assessed on the basis of comparison between signal intensity of tumor tissue and normal brain. However, contrast to adjacent structures is higher when hypointense perifocal edema is present. The inhomogeneous distribution of cases with edema among the groups of patients investigated at the three field strengths and with the three dosages precluded statistical work-up of tumor/edema contrast. An estimate of how tumor/edema contrast compares to tumor/brain contrast is obtained from the curves of mean values of signal intensity. It is obvious that lesion contrast versus hypointense edema is higher than versus normal brain, suggesting that lower dosages of Gd-DTPA may provide diagnostically adequate results. However, a dose recommendation not only has to apply to brain tumors with perifocal edema, but also to lesions adjacent to normal brain.

One of the aims of our study was to reevaluate the dose recommendation of 0.1 mmol/kg Gd-DTPA that was established at a field strength of 0.35 T (7) on MR units operating between 0.5 and 1.5 T. Two opposing field strength-dependent effects have to be considered when paramagnetic contrast agents are used: 1) T1 relaxation times increase with field strength, possibly increasing proton relaxation enhancement at a given concentration of Gd-DTPA (15); and 2) relaxivity of Gd-DTPA decreases with field strength, reducing the effect on proton relaxation (16). In our study, no statistically significant differences in enhancement among the field strengths were found. Various factors, including pulse sequence selection (17), may contribute to this finding.

Interestingly, high-dose rather than low-dose contrast-enhanced MR imaging is under discussion (18) as nonionic gadolinium chelates undergo clinical trials (19, 20). Tissue concentrations of gadolinium compounds in intracranial tumors are still compatible with the dominating effect of T1-shortening over T2-shortening when dosages up to 0.3 mmol/kg are intravenously injected (7, 19). Therefore, it is not surprising that tumor signal intensity increases with dosages from 0.025 to 0.1 mmol/kg, but also between 0.1 and 0.3 mmol/kg. Whether greater contrast enhancement beyond 0.1 mmol/kg will translate into improved sensitivity and diagnostically relevant improvement in lesion conspicuity remains to be shown in prospective studies comprising patient populations large enough to apply appropriate statistical methods.

Inhomogeneous distribution of various tumor types among field strengths and dose levels is another limitation of our study. However, a study protocol that prospectively defines the number of extra- and intraaxial tumors does not preclude that poorly as well as markedly enhancing lesions are included in both groups. In addition, a presumed extraaxial tumor, such as meningioma of the cerebellopontine angle, may turn out to be intraaxial, eg, metastasis. Another criticism of study might be the method of visual assessment of tumor/brain contrast. Pre- and postcontrast images of a given patient were read side by side. A more precise protocol would have been a separate review of pre- and postcontrast images in randomized order. Finally, a specific subgroup of disease, ie, intracranial tumors, was examined, introducing preselection bias. As a result, the general utility of 0.1 mmol/kg Gd-DTPA in routine CNS studies should not be extrapolated from our results.

In conclusion, our results confirm that the safe dose of 0.1 mmol/kg Gd-DTPA is more effective at enhancing intracranial tumors than lower doses

at mid and high field units. With this dosage, double dosing may only be necessary in selected cases (21). Further studies are needed to clarify whether a small dose reduction, eg, 0.08 mmol/kg Gd-DTPA, is affordable at high field strength.

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