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AJNR Am J Neuroradiol 1987, 8 (5) 803-815
http://www.ajnr.org/content/8/5/803

Dose Administration of Gadolinium-DTPA in MR Imaging of Intracranial Tumors

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Eleven patients with intracranial tumors were investigated with MR imaging at different dose levels of gadolinium-DTPA to determine a safe and effective dose for imaging intracranial tumors. The patients were divided into two groups. Baseline spin-echo images were obtained with a repetition time of 800 msec and an echo time of 35 msec, and a total of 0.1 mmol of gadolinium-DTPA/kg (six patients) or 0.2 mmol gadolinium-DTPA/kg (five patients) was injected according to a fractionated incremental dose regime (0.025, 0.025, and 0.05 mmol/kg and 0.05, 0.05, and 0.1 mmol/kg, respectively). Postcontrast MR was performed after each injection. In group 1 the best visualization was achieved after the third injection in four cases. In one glioblastoma and in a pituitary adenoma tumor margins were well defined at lower dose levels. In group 2, with five patients, the total dose of 0.2 mmol of gadolinium-DTPA/kg (0.05, 0.05, and 0.1) significantly improved tumor visualization after the third injection in only one patient with multiple metastases. No short-term side effects were encountered. In a range of parameters measured in both serum and whole blood, slight transient elevation of serum iron levels was the only appreciable change.

As a result of our investigation we conclude that 0.1 mmol of gadolinium-DTPA/kg is a safe and suitable dose for brain-tumor imaging. In selected cases 0.2 mmol/kg may increase the diagnostic yield.

The results of preclinical studies and of the first use of gadolinium-DTPA in humans (20 healthy male volunteers) suggest that 0.1 mmol of gadolinium-DTPA/kg is a well-tolerated and effective dose for MR imaging [1–4]. In its first clinical use in patients, a favorable result was obtained with this dose in the contrast enhancement of brain tumors [4–12]. However, there is no clinical proof as to whether doses other than 0.1 mmol/kg may be even more suitable with respect to tolerance and efficacy. With regard to safety, the lowest effective dose must be established. On the other hand, detection and characterization of a lesion may be further improved with higher doses. The purpose of the present study of 11 patients was to determine the optimum dose of gadolinium-DTPA for visualization of brain tumors on contrast-enhanced MR.

Subjects and Methods

We studied six women and five men 41–74 years old who had intracranial tumors. Histologic confirmation was available in six cases. In the other cases the diagnoses were based on the clinical findings and on the results of plain and contrast-enhanced CT (Table 1). A contrast-enhanced CT scan (300 mg I/kg) of the lesion was a precondition for enrollment in the study. CT examinations were performed within 1 week before the MR investigations.

As gadolinium (Gd)-DTPA is an investigational drug, a strict protocol was established for the examination. Each patient was given detailed information, both oral and written, on the purpose of the study. Written informed consent was obtained in all cases.

MR was performed with a Siemens Magnetom operating at 0.35 T. The signal was received by a head coil (internal diameter, 25 cm) with a 1- × 1-mm nominal spatial resolution in the imaging plane. The slice thickness was 10 mm. For adequate comparison with CT, transverse

Dedicated to Professor W. Frommhold on the occasion of his 65th birthday.

Received May 30, 1986; accepted after revision March 9, 1987.

Presented in part at the annual meeting of the American Society of Neuroradiology, San Diego, January 1986.

This work was supported by grant 01 VF 142, Bundesministerium für Forschung und Technologie, Bonn.

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***AJNR* 8:803–815, September/October 1987**
0195–6108/87/0805–0803

TABLE 1: Summary of Patients with Intracranial Tumors and Tumor Changes by Dose of Gd-DTPA

Group: Case No.	Age	Gender	Diagnosis	Histology	% Change[a]/Tumor Demarcation by Dose (in mmol/kg)				
					Preenhancement	0.025	0.05	0.1	0.2
1, Maximum dose of 0.1 mmol/kg:									
1	56	F	Glioblastoma (grade IV)	Confirmatory	0/Poor	13/None	8/Poor	9/Good	. . .
2	52	M	Glioblastoma	Not done	0/Poor	16/Poor	12/Fair	2/Good	. . .
3	41	M	Glioblastoma (grade IV)	Confirmatory	0/None	20/None	1/Poor	22/Good	. . .
4	51	F	Glioblastoma	Not done	0/Fair	22/Poor	16/Good	3/Good	. . .
5	74	M	Metastasis (bronchial carcinoma)	Confirmatory	0/None	10/None	16/Fair	6/Good	. . .
6	47	M	Pituitary adenoma	Confirmatory	0/Fair	12/Good	9/Good	16/Good	. . .
2, Maximum dose of 0.2 mmol/kg:									
7	43	M	Glioblastoma	Not done	0/None	. . .	25/Poor	6/Good	11/Good
8	45	F	Multiple metastases (unknown primary)	Not done	0/None	. . .	16/None	4/Fair	12/Good[b]
9	67	F	Acoustic neuroma	Confirmatory	0/Fair	. . .	73/Good	6/Good	6/Good
10	60	F	Meningioma	Confirmatory	0/Poor	. . .	7/Fair	5/Good	6/Good
11	73	F	Lymphoma	Not done	0/Poor	. . .	14/Fair	7/Good	15/Good

[a] Percentage change is based on the difference in signal intensity between two consecutive scans.
[b] The increasing number of enhancing lesions was included in the assessment.

scanning planes were selected. The sagittal plane was used for the pituitary adenoma.

To define the representative slice position, a double-echo multiple-slice spin-echo (SE) sequence was used with a pulse-repetition time (TR) of 1600 msec and echo-delay times (TEs) of 35 and 70 msec (SE 1600/35, 70). In the representative slice, pre- and postcontrast scans (TR = 800 msec, TE = 35 msec) were obtained. Two averages were acquired on a 256 × 256 matrix. Scanning time for the SE 800/35 sequence was about 7 min.

At the time of investigation only one slice could be obtained by the multislice technique per 200 msec of TR. For efficient patient care a TR of 800 msec, which provides four slices at a time, was chosen rather than a TR of 400 msec (only two slices). A TE of 35 msec was the shortest TE available for multislice sequences. Selection of the SE 800/35 pulse sequence was supported by an estimation of signal intensity (SI) for Gd-DTPA in a dose range up to 1.0 mmol/L. Estimations were based on the relation of relaxivity and concentration of Gd-DTPA [2]. No major disadvantages were expected from the chosen TR of 800 msec as opposed to a shorter TR.

Gd-DTPA was IV injected according to a fractionated incremental dose regime (Fig. 1). In the first group (cases 1–6) Gd-DTPA was initially administered at a dose of 0.025 mmol/kg. Fifteen minutes after this first injection another 0.025 mmol/kg was injected, and 15 min later 0.05 mmol/kg more was injected. The recording of contrast-enhanced scans (SE 800/35) began 5 min after each injection; that is, at dose levels of 0.025, 0.05, and 0.1 mmol of Gd-DTPA/kg, respectively. The same protocol was used in the second group (cases 7–11). However, at each injection twice the amount of Gd-DTPA was given; that is, 0.05 mmol/kg for the first and second injections and 0.1 mmol/kg for the third injection. The imaged levels therefore were 0.05 mmol/kg on the first postcontrast scan, 0.1 mmol/kg on the second postcontrast scan, and 0.2 mmol/kg on the third postcontrast scan. In both groups total postcontrast investigation time starting with the first injection was 42 min per patient. In this article the postcontrast scans are referred to as the first, second, or third postcontrast scan.

All patients were observed during the MR investigation and questioned about side effects at the end of the examination and 24–48 hr later. Blood samples were taken immediately before the first injection of Gd-DTPA and 2 or 4 hr after it. Additional blood samples were taken at 24 and 48 hr after injection. Blood samples were analyzed for a variety of parameters including serum creatinine, blood urea, SGOT, SGPT, lactic dehydrogenase, blood screening and coagulation tests, and serum iron and bilirubin.

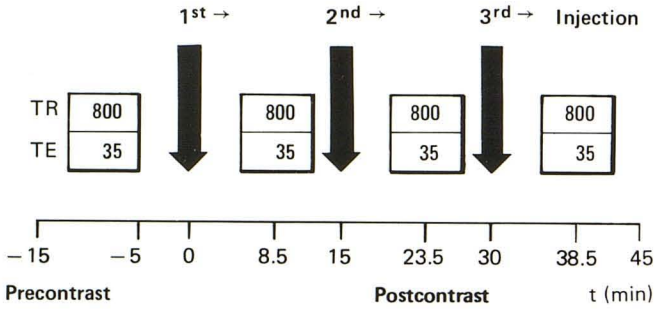

Fig. 1.—Imaging and dose protocol for both groups of patients. Each postcontrast SE 800/35 scan was started 5 min after respective injection. t = time.

The contrast medium used was an aqueous, stable solution of the di-N-methylglucamine salt of the DTPA complex of gadolinium (Schering AG, Berlin) in a concentration of 0.5 mol/L. Gd-DTPA was IV injected into the antecubital vein via a plastic indwelling cannula at an injection rate of about 10 ml/min. To ensure complete administration of Gd-DTPA the catheter was flushed with 5 ml saline immediately after each injection.

The effect of the contrast agent was assessed visually by three independent observers and evaluated quantitatively. Visual assessment of enhanced scans was based on (1) the evaluation of the degree of SI changes (no change, slight increase, moderate increase, or strong increase) and (2) the effect of SI changes on demarcation of enhancing tumor tissue from adjacent tissues (demarcation impossible, poor demarcation, fair demarcation, or good demarcation).

For quantitative evaluation, data processing was used as described elsewhere [13]. The SIs of tumor tissue, of presumably necrotic portions of the tumor, or perifocal edema, and of normal brain tissue were measured by the region-of-interest (ROI) technique on pre- and postcontrast SE 800/35 images. The SI measurements of tumor tissue were done in the enhancing portion of the lesion. When the tumor tissue was not directly visible on precontrast scans, the ROI was determined from the postcontrast scans by using anatomic structures and/or matrix coordinates as a guide. The SI of "necrotic" tissue in MR was measured in those portions of the tumor that showed no or only minimum enhancement on CT and exhibited inhomogeneously high SI on precontrast T2-weighted images as well as only minimal increases of SI after injection of Gd-DTPA. SI measurements of edema were done in those areas that were identified as high-SI regions on the SE 1600/70 scans and that displayed no visually appreciable SI increase on postcontrast scans (SE 800/35). The SI of normal brain tissue was measured in the white matter of both hemispheres.

In each patient SI values were obtained in the SE 800/35 sequence at various dose levels. For all four measurements receiver and transmitter attenuation values were adjusted automatically. To account for slightly different settings of these values an intraindividual correction factor was obtained. Therefore, with each brain scan an external standard solution (1.5 mmol of Gd-DTPA/L) was imaged simultaneously in a cylindrical plastic tube (2.5-cm diameter, 8-cm length). This tube was attached to the inside of the head coil. Correction factors for the SI values of tumor, "necrotic" tissue, edema, and normal brain in each scan were obtained as follows. The respective SI value of the external standard at each scanning time was divided by the arithmetic mean of the four SI values measured on the external standard for all four SE 800/35 scans of each patient. SIs for tumor, "necrotic" tissue, edema, and normal brain were measured on each corresponding scan and were then multiplied by the respective correction factor. The result was the corrected SI value, which was used for quantitative evaluation.

Results

Group 1 (0.1 mmol Gd-DTPA/kg)

Visual assessment.—Of six tumors, a doughnut-shaped glioblastoma (case 4) and a pituitary adenoma (case 6) were differentiated from adjacent tissue on precontrast SE 800/35 scans (Fig. 2A). In the other cases an abnormality was definite, but the exact tumor outline could not be established (Fig. 3A).

At a dose level of 0.025 mmol of Gd-DTPA/kg slight (cases 1 and 5), moderate (cases 2 and 3), and strong (cases 4 and 6) SI increases were observed in two cases each (Figs. 2B and 3B). The strong SI increase provided improved demarcation of the pituitary adenoma (case 6). In one glioblastoma (Fig. 2B) the strong enhancement of the primarily hypointense lesion resulted in roughly the same degree of contrast between tumor and edema. Tumor was poorly differentiated from edema, although there had been fair tumor demarcation before administration of contrast material.

At a dose level of 0.05 mmol of Gd-DTPA/kg the pituitary adenoma (case 6) displayed a slight increase in SI when compared with the preceding dose level. In four cases (cases 1–3 and 5) SI increases were scored as moderate (Fig. 3C). One glioblastoma (case 4) showed a strong SI increase (Fig. 2C). Except for this case and for the pituitary adenoma, tumor margins still were poorly defined relative to surrounding tissue at a dose level of 0.05 mmol Gd-DTPA/kg. In one glioblastoma (case 1) a second area anterior to the first showed slight enhancement (Fig. 3C).

At a dose level of 0.1 mmol of Gd-DTPA/kg slight increases in SI occurred in two cases (cases 4 and 6) when compared with the dose level of 0.05 mmol/kg (Fig. 2D). A moderate SI increase was observed in a cerebral metastasis. In the other cases (cases 1–3) SI increases were scored as strong. The moderate and strong SI increases, respectively, resulted in well-defined tumor margins (cases 1–3 and 5) at the dose level of 0.1 mmol Gd-DTPA/kg (Fig. 3D). In case 1 the second enhancing region was verified and clearly identified as a lesion (Fig. 3D). The slight SI increases in cases 4 and 6 did not improve tumor demarcation further (Fig. 2D).

Quantitative evaluation.—In all six cases the SI curves showed a marked increase in SI values of tumor tissue on all postcontrast measurements as compared with precontrast scans (Figs. 2E, 3E, and 4). A continuous increase of SI in tumor tissue was recorded with each injection, even though the percentage increase from one dose level to the next was small in some cases (Table 1). In three (cases 1, 2, and 4) of four glioblastomas the highest increase in SI was measured after the first injection. This increase in SI grew smaller with each of the subsequent injections in cases 2 and 4. In case 1 the incremental increases were almost equal after the second (8%) and third (9%) injections. In case 3 the SI increases were almost equal after the first (20%) and third (22%) injections, with only a very slight increase after the second injection (1%). In the cerebral metastasis (case 5) and pituitary adenoma (case 6) the greatest SI increases between two scans were recorded after the second and third injections, respectively.

In five cases (cases 1–5) "necrotic" tumor tissue was detected. Three SI measurements (case 3, pre- and first postcontrast scan; case 4, third postcontrast scan) could not be obtained because of positional changes exceeding the extent of "necrosis." In all cases the SI of "necrotic" tissue on postcontrast scans was higher than the SI on the precontrast scan. However, with the exception of the first dose level of 0.025 mmol/kg, the magnitude of SI increases was markedly less than that of enhancing tumor tissue. Thus the difference between the SI of enhancing tumor tissue and of tumor "necrosis" grew remarkably larger after the second injection, with further improvement after the third injection (Fig. 4).

In five cases perifocal edema was detected (cases 1–5). As opposed to SI curves of tumor tissue, the SI of edema showed only insignificant changes after the injection of Gd-DTPA (Fig. 4). A slight increase in SI was always measured after the first injection and also after the second injection; however, after the third injection, SI values showed a slight decrease as compared with the second injection in all but one case (case 3).

In all cases and at all dose levels the postcontrast SI values of normal brain tissue were minimally higher as compared with those on precontrast scans. There were only insignificant differences between the different dosages (Fig. 4).

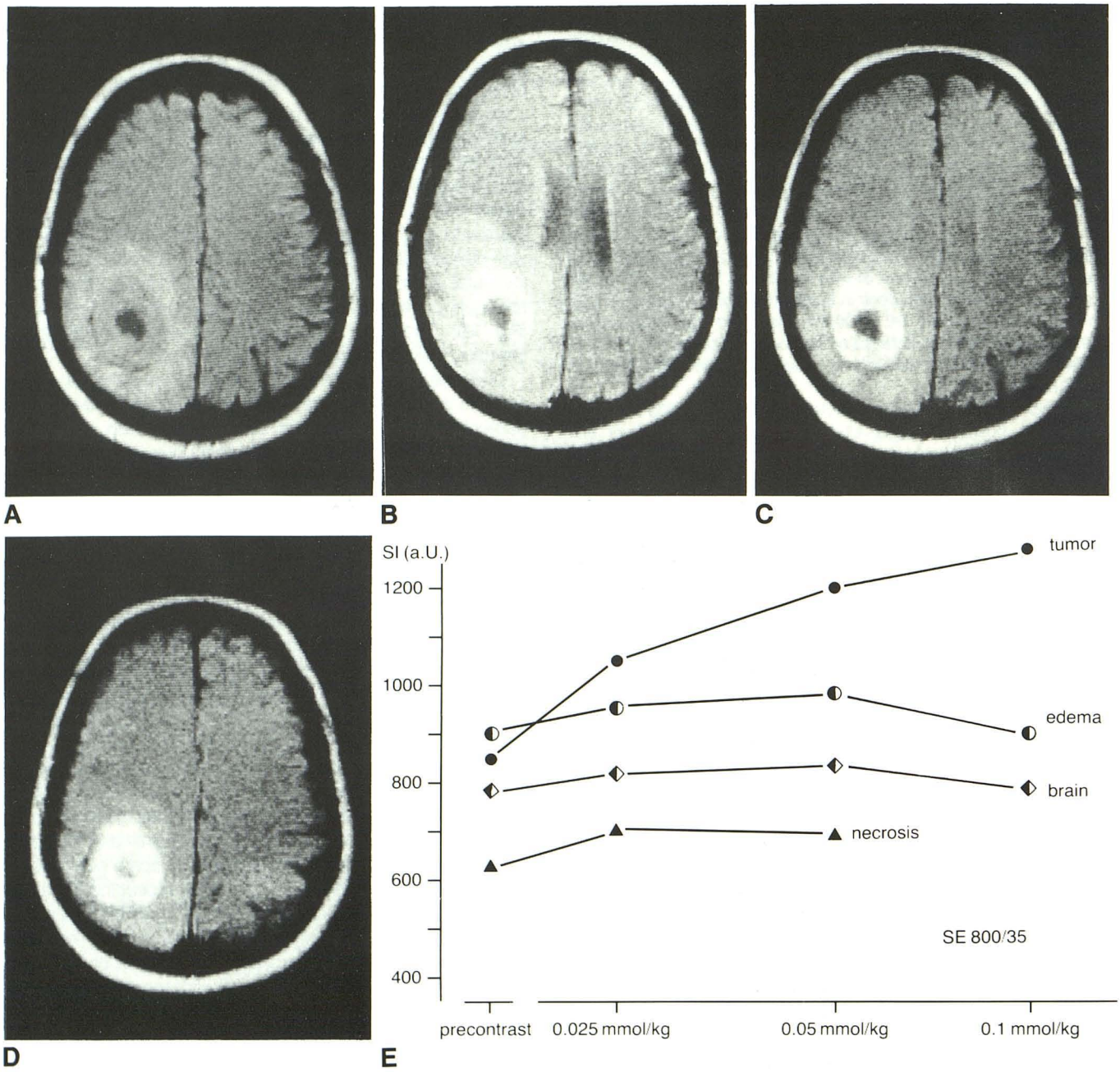

Fig. 2.—Case 4: 51-year-old woman with presumed right parietooccipital glioblastoma. SE 800/35 images.

***A*, Before enhancement. Area of very low signal intensity in right occipital region is well differentiated from doughnut-shaped ring of intermediate signal intensity. This ring in turn is surrounded by roughly differentiable area of higher signal intensity, confirmed as perifocal edema on unenhanced T2-weighted image.**

***B*, 0.025 mmol of Gd-DTP/kg. Strong increase in signal intensity but no improvement of contrast vs perifocal edema. Slightly different slice position resulted from patient movement.**

***C*, 0.05 mmol of Gd-DTPA/kg. Strong increase in signal intensity relative to previous dose level results in well-defined tumor margins with good differentiation of tumor tissue from central "necrosis" and from perifocal edema.**

***D*, 0.1 mmol of Gd-DTPA/kg. Further increase in signal intensity of tumor tissue but no further increase of diagnostically useful information or contrast enhancement. Slightly different slice position may at least partly account for now poorly defined margin between tumor and "necrosis."**

***E*, Signal-intensity (SI) values of tumor tissue, "necrotic" tissue, edema, and normal brain. Due to positional changes signal-intensity measurement of "necrotic" tissue could not be performed at dose level of 0.1 mmol Gd-DTPA/kg. Signal-intensity values are in arbitrary units (a.U.).**

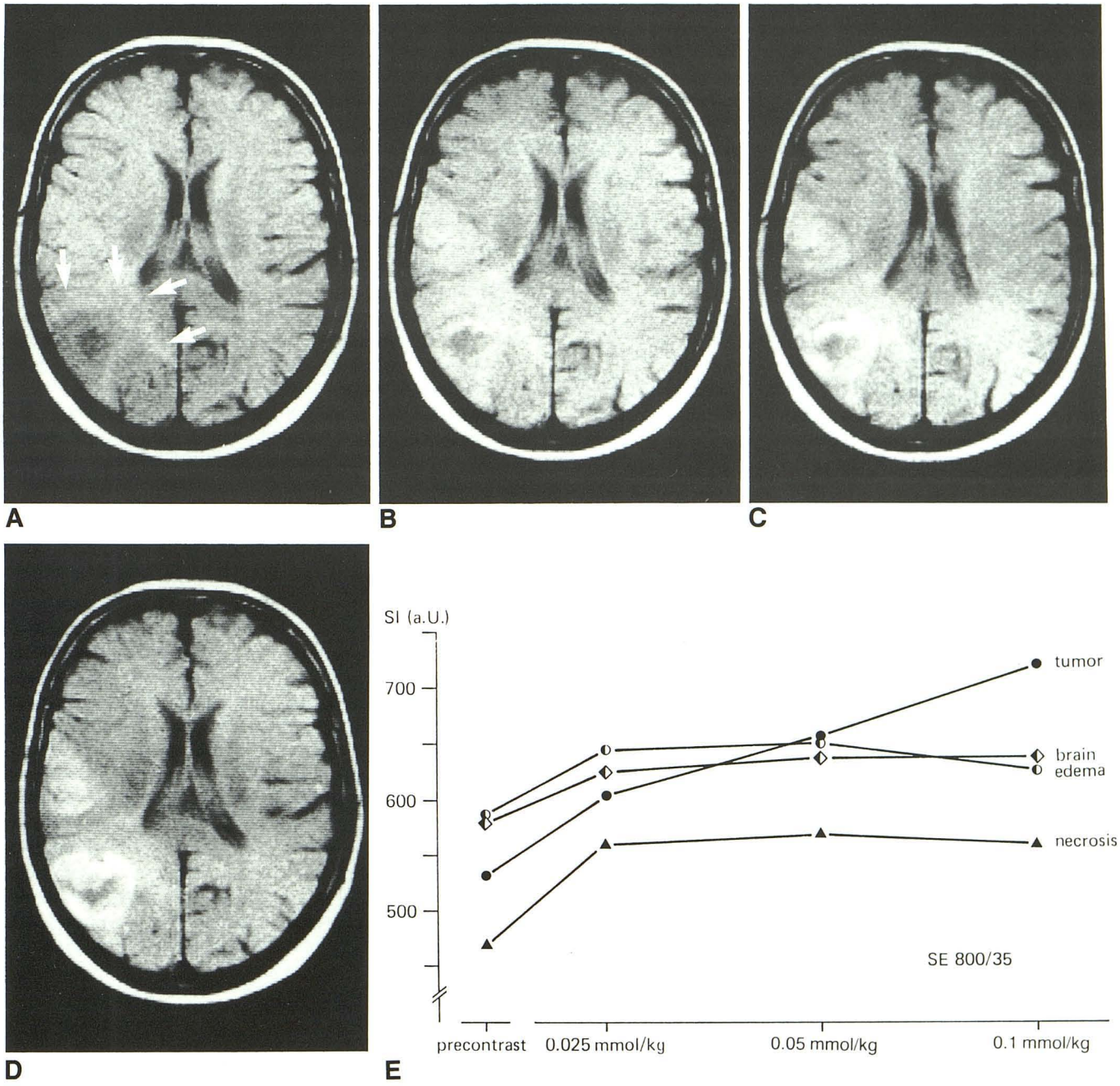

Fig. 3.—Case 1: 56-year-old woman with right parietooccipital glioblastoma. SE 800/35 images.

***A*, Before enhancement. Lateral area of inhomogeneous signal intensity lower than that of normal brain tissue is seen in right occipital region. There is compression of posterior horn of lateral ventricle and effacement of sulci. Area of edema identified on T2-weighted unenhanced scan (*arrows*).**

***B*, 0.025 mmol of Gd-DTPA/kg. Suspected area has slight increase in signal intensity with poorly defined border of enhancing tissue caused by isointensity.**

***C*, 0.05 mmol of Gd-DTPA/kg. Enhancing portions of suspected area show moderate enhancement relative to normal brain tissue with poorly defined posterior and medial borders. In temporoparietal region an additional area now shows slight increase in signal intensity.**

***D*, 0.1 mmol of Gd-DTPA/kg. Occipital tumor is now well enhanced with good demarcation vs central "necrotic" area and vs surrounding brain tissue. Second area shows definite enhancement and is identified as additional lesion.**

***E*, Signal-intensity (SI) values of tumor tissue, "necrotic" tissue, edema, and normal brain. Signal-intensity values are in arbitrary units (a.U.).**

Group 2 (0.2 mmol Gd-DTPA/kg)

Visual assessment.—Results obtained with the fractional doses of 0.05 mmol/kg and 0.1 mmol/kg in group 2 were basically the same as the results in group 1 at the respective dose levels. Apart from a large acoustic neuroma, a dose of 0.1 mmol of Gd-DTPA/kg was indispensable for appropriate tumor visualization (Figs. 5–7).

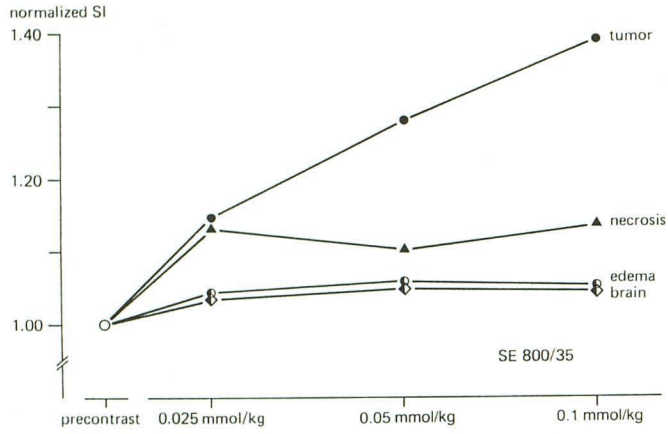

Fig. 4.—Dose-dependent signal-intensity (SI) changes on SE 800/35 images measured in tumor tissue, tumor "necrosis," perifocal edema, and normal brain in six patients (cases 1–6). Signal-intensity values are normalized to precontrast measurements.

At the dose level of 0.2 mmol Gd-DTPA/kg a further SI increase in a glioblastoma (case 7) was observed in a small area not suspected as tumor tissue at lower dose levels (Fig. 5D). In the case of multiple metastases (case 8) SI increases were seen in three lesions when compared with the dose level of 0.1 mmol Gd-DTPA/kg. Also two other lesions were displayed at 0.2 mmol/kg (Fig. 6D). In two cases (cases 10 and 11) slight increases in SI were observed, whereas in an acoustic neuroma (case 9) no further enhancement could be seen (Fig. 7D).

Quantitative evaluation.—The third injection, which doubled the image dose from 0.1 to 0.2 mmol Gd-DTPA/kg, produced a further increase in the SI of tumor tissue of 6–15% in all cases (Figs. 5E, 6E, 7E, and 8 and Table 1).

The only case in which a central necrosis was detected was case 7, a glioblastoma. After some decrease in SI was measured on the first (−8%) and second (−3%) postcontrast scans SI showed some increase (6%) on the third postcontrast scan.

In three cases perifocal edema was detected (cases 7–9). Case 7 showed a slight SI increase (5%) after the third injection, but the SI value remained below baseline. In cases 8 and 9 the recorded values were not significantly different from values obtained at the dose level of 0.1 mmol Gd-DTPA/kg.

When compared with the dose level of 0.1 mmol Gd-DTPA/kg, SI values of normal brain tissue remained almost constant except for a slight increase (4%) in case 7 (Figs. 5E and 8).

Tolerance.—In both groups the fractionated injections of Gd-DTPA were well tolerated by all patients. No side effects such as venous pain, nausea, or vomiting were recorded. The only appreciable changes measured were slight transient elevations of serum iron. In most cases serum iron levels were back to baseline 24 hr after injection. At 48 hr after injection baseline levels were reached in all cases.

Discussion

In 1984 the paramagnetic contrast agent Gd-DTPA became available for clinical research studies in MR [3, 4]. Reports of its use in patients with intracranial tumors showed favorable results at an IV injected dose of 0.1 mmol/kg [4–12]. Since the LD_{50} for Gd-DTPA determined in several species after IV injection is about 10 mmol/kg body weight [2] a safety factor of about 100 can be assumed. By comparison, the safety factor of iodinated contrast agents such as the well-known diatrizoates was determined to be about 10, depending on the injection volume and the iodine concentration [14]. Gd-DTPA dosages below 0.1 mmol/kg may also be effective for contrast enhancement, which, in turn, would further increase safety. On the other hand, the high safety factor of more than 100 allows for the use of higher doses of Gd-DTPA for possibly improved detection and characterization of lesions. Both aspects were evaluated in the present brain tumor study with Gd-DTPA injections in a dose range of 0.025–0.2 mmol/kg. The intraindividual rather than the interindividual study design was chosen because of better comparability and higher reliability of intraindividual data and because fewer patients are necessary to generate such data.

In a brain-tumor study of 15 patients it was shown that tumor tissue displays marked enhancement 5 min after IV injection of 0.1 mmol of Gd-DTPA/kg without significant further changes for at least 45 min after injection [13]. Although the time–SI curves of individual tumors differed somewhat from the curve of median values given in Figure 9, these time-course data are principally in keeping with data published by Graif et al. [15]. With 0.1 mmol of Gd-DTPA/kg and with the SE 1500/44 sequence they found SI increases in seven low-grade primary lesions about 22 min after injection. Slight decreases were observed with a second measurement at 50 min after injection. In metastatic lesions ($n = 4$) further enhancement was displayed at about 60 min after injection when compared with the preceding measurement (SE 1500/44) at about 40 min. Total postcontrast investigation time in our present study, however, was only 42 min (Fig. 1). The time-course data reported by Graif et al. [15] are compatible with the data of Schörner et al. [13], which served to set up the design of our present study.

It was assumed for tumor tissue that each of the three injections produced time–SI curves similar to those obtained after a single injection of 0.1 mmol of Gd-DTPA/kg. On the basis of the aforementioned course of the time–SI curve, the SI increases in tumor tissue after the second and third injections were regarded to be in the range of maximum SI values obtainable at the respective dose levels. The SI increases measured in enhancing tumor tissue after the second and third injections, therefore, can be attributed predominantly to the additive effect of additional Gd-DTPA dose fractions and not to delayed SI enhancement from previous dose fractions.

SI in MR does not show a linear dependence on the concentration of Gd-DTPA. When Gd-DTPA is given the SI changes are governed by the combined effect of a shortening of both T1 and T2 relaxation times [16–18]. At a given pulse sequence T1 shortening results in an increase of SI, whereas

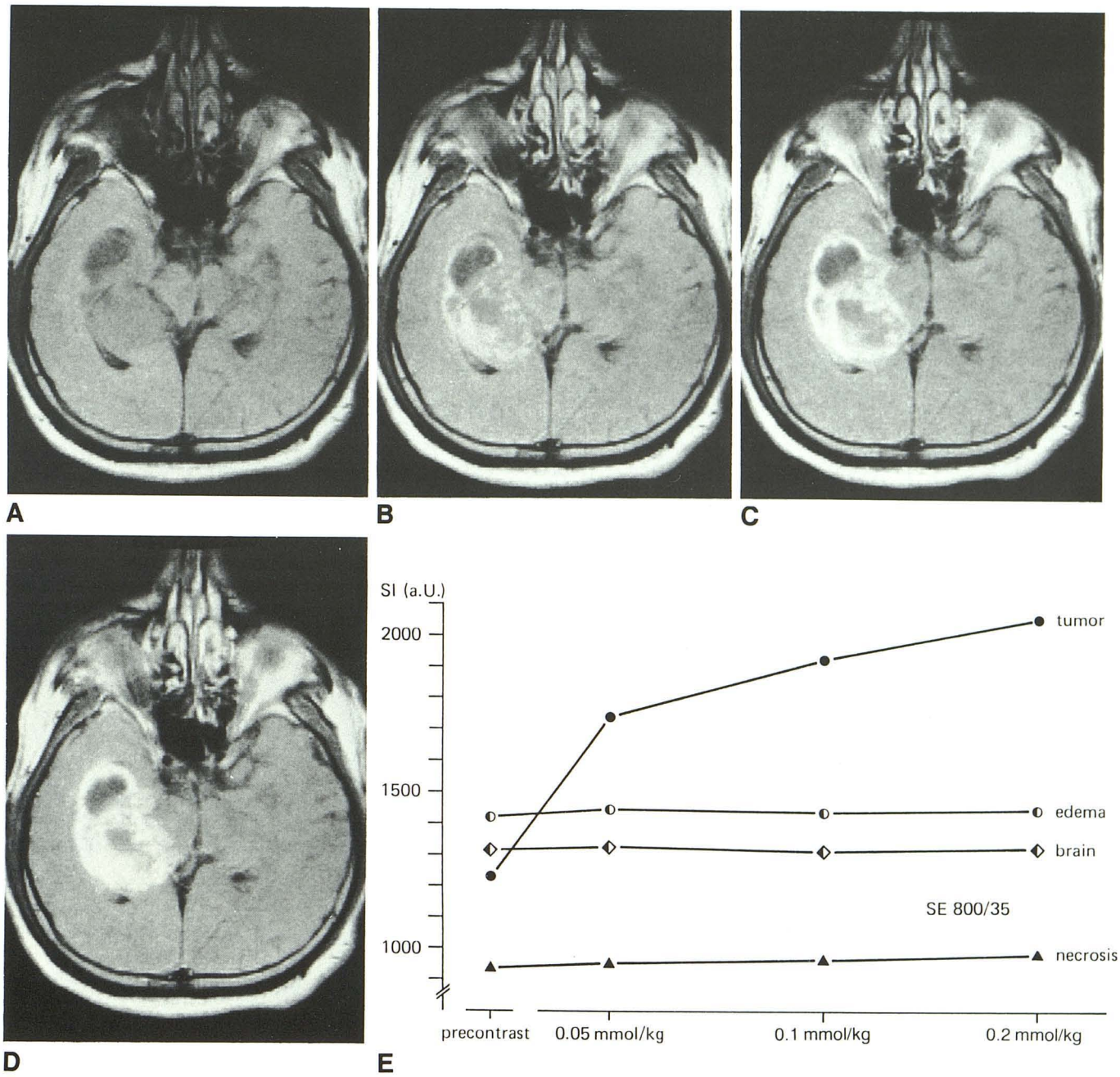

Fig. 5.—Case 7: 42-year-old man with presumed right temporal glioblastoma. SE 800/35 images.

***A*, Before enhancement. Compression of ventricle, effacement of sulci, and shift of midline structures, as well as large hypointense area, suggest mass in right medial temporal lobe.**

***B*, 0.05 mmol of Gd-DTPA/kg. Moderate increase in signal intensity displays areas of disturbed blood-brain barrier in large region with inhomogeneous signal intensity and poorly defined margins.**

***C*, 0.1 mmol of Gd-DTPA/kg. Good demarcation of garland-shaped tumor with "necrotic" tissue.**

***D*, 0.2 mmol of Gd-DTPA/kg. Adjacent to medial margin of tumor, additional small area of enhancement is seen in region that at lower dose levels was not identified as enhancing tumor tissue.**

***E*, Signal-intensity (SI) values of tumor tissue, "necrotic" tissue, edema, and normal brain. Signal intensity of edema was measured on adjacent section obtained by multislice technique. Signal-intensity values are in arbitrary units (a.U.).**

T2 shortening decreases SI. Up to a certain concentration of Gd-DTPA the T1 effect continues to increase SI. At higher concentrations, however, the T1 effect levels off and the influence of a shortened T2 predominates attenuating SI. This is caused by rapid dephasing of spins in the x-y plane, which in turn results in loss of signal at the time of sampling, even at short TE intervals.

In our study higher dose levels always resulted in higher SI

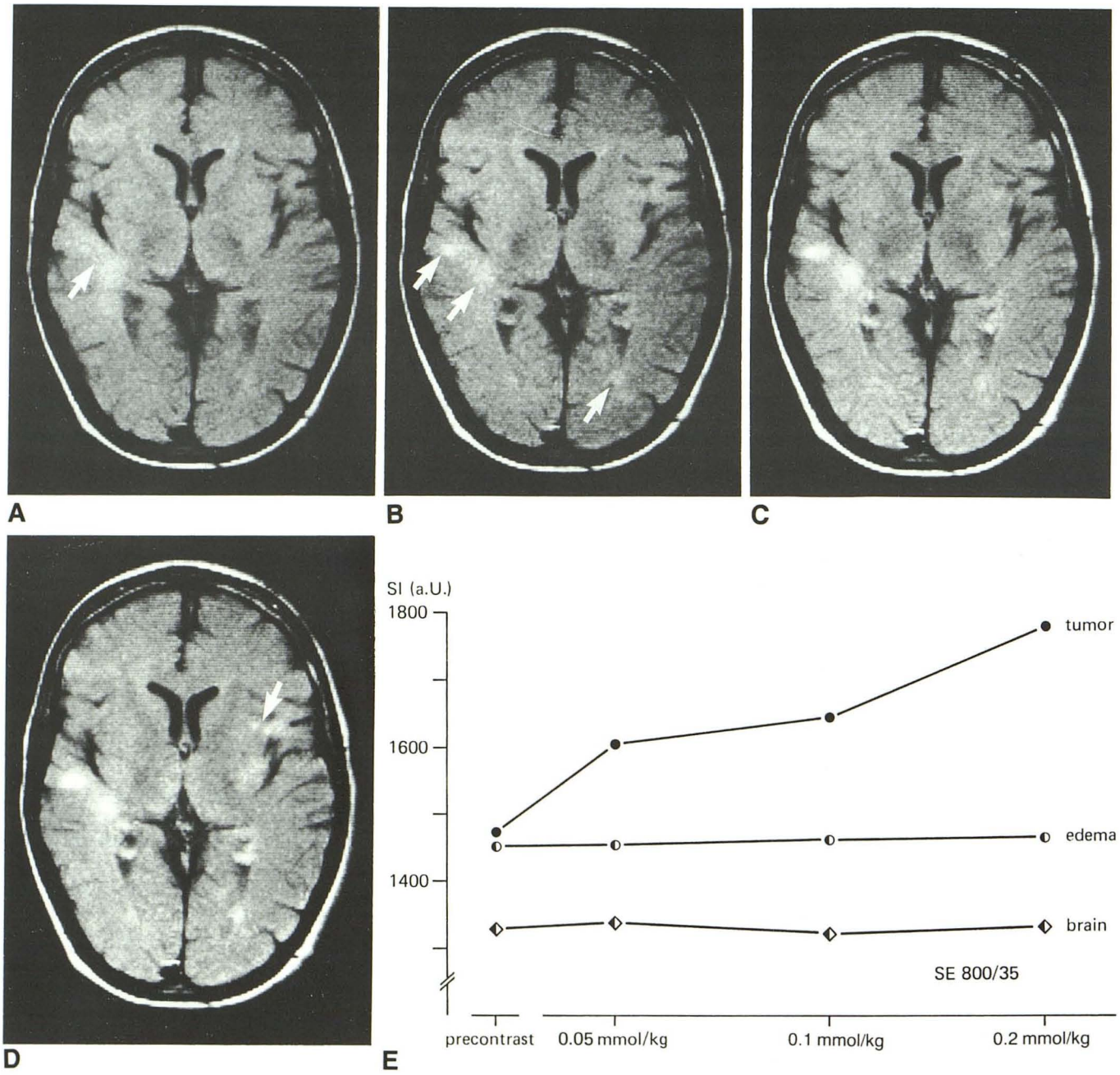

Fig. 6.—Case 8: 45-year-old woman with presumed multiple metastases. SE 800/35 images.

***A*, Before enhancement. Asymmetry in signal intensity of right vs left postsylvian region caused suspicion of lesion. Area of edema (*arrow*) was seen on T2-weighted precontrast scan.**

***B*, 0.05 mmol of Gd-DTPA/kg. Three poorly defined areas show slight enhancement in signal intensity (*arrows*).**

***C*, 0.1 mmol of Gd-DTPA/kg. The three small areas have increased in signal intensity. Two lesions in right postsylvian region show improved demarcation.**

***D*, 0.2 mmol of Gd-DTPA/kg. All three areas of enhancement show further increase in signal intensity and are now well demarcated relative to surrounding tissue. Two additional lesions are seen (*arrow*).**

***E*, Signal-intensity (SI) values of tumor tissue, edema, and normal brain. Signal-intensity values of tumor tissue are arithmetic mean of three lesions. Values are in arbitrary units (a.U.).**

values of tumor tissue, suggesting tissue concentrations of Gd-DTPA compatible with predominantly T1 effect. The increasing T2 effect, however, produced less dramatic rises in dose–SI curves at higher doses. With total doses of both 0.1 and 0.2 mmol Gd-DTPA/kg the summary curves showed a steeper increase in SI values after the first injection than after the second and third administration of Gd-DTPA (Figs. 4 and 8). A similar interdependence of SI values and T2 effect with increasing dose levels was measured after 0.3 mmol/kg in a canine brain tumor (Figs. 10 and 11).

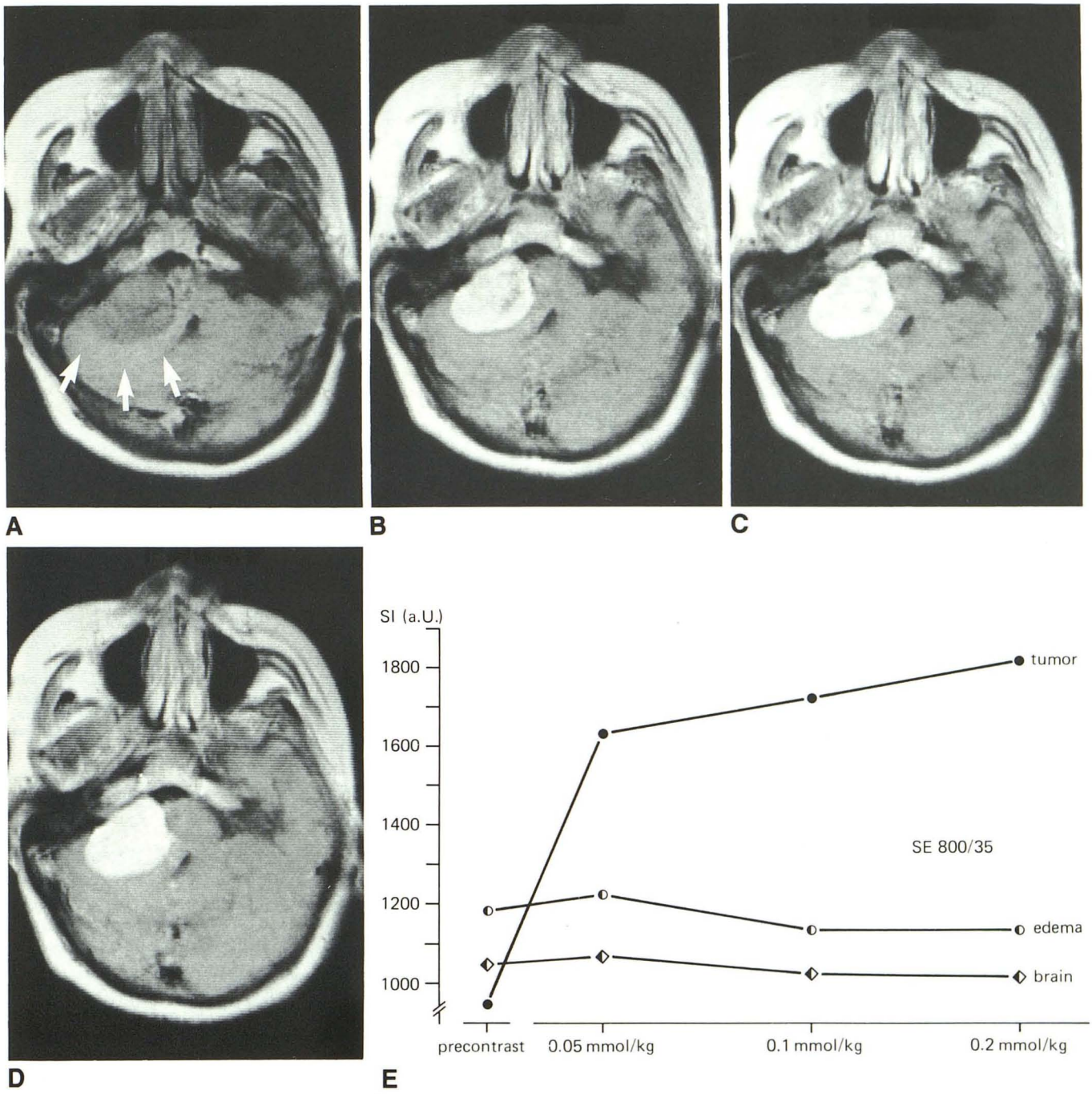

Fig. 7.—Case 9: 67-year-old woman with right acoustic neuroma. SE 800/35 images.

***A*, Before enhancement. Well-defined area of decreased signal intensity in cerebellopontine angle. Compression and displacement of fourth ventricle. Area of edema (*arrows*) was identified on T2-weighted precontrast scan.**

***B*, 0.05 mmol of Gd-DTPA/kg. Strong contrast enhancement with very good demarcation of tumor margins, whereas tumor itself shows some inhomogeneities in signal intensity.**

***C*, 0.1 mmol of Gd-DTPA/kg. Moderate increase in signal intensity. Tumor now displays more homogeneous signal intensity, but there is no further diagnostic information.**

***D*, 0.2 mmol of Gd-DTPA/kg. A slight increase in signal intensity is seen, but no change in tumor demarcation.**

***E*, Signal-intensity (SI) values of tumor tissue and normal brain. Signal-intensity values are in arbitrary units (a.U.).**

With regard to diagnostic yield the dose of 0.2 mmol/kg showed two lesions in a patient with multiple metastases that had not been detected at a dose level of 0.1 mmol Gd-DTPA/kg. Three other lesions in the same patient were shown to better advantage after the third injection (Fig. 6D). In a glioblastoma, contrast enhancement in a small additional portion was observed at a dose level of 0.2 mmol Gd-DTPA/kg as compared with 0.1 mmol/kg (Fig. 5D). These findings had no

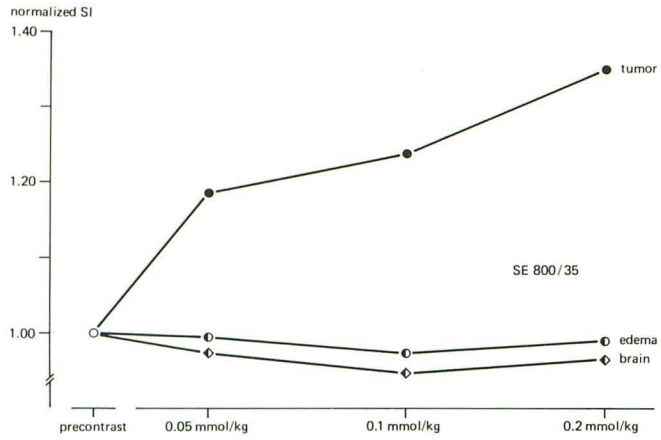

Fig. 8.—Dose-dependent changes in signal intensity (SI) on SE 800/35 images (TR = 800 msec, TE = 35 msec) measured in tumor tissue and normal brain in five patients (cases 7–11). Perifocal edema was detected in three patients and tumor "necrosis" in only one. Data for tumor "necrosis" are not in curve. Signal-intensity values are normalized to precontrast measurements.

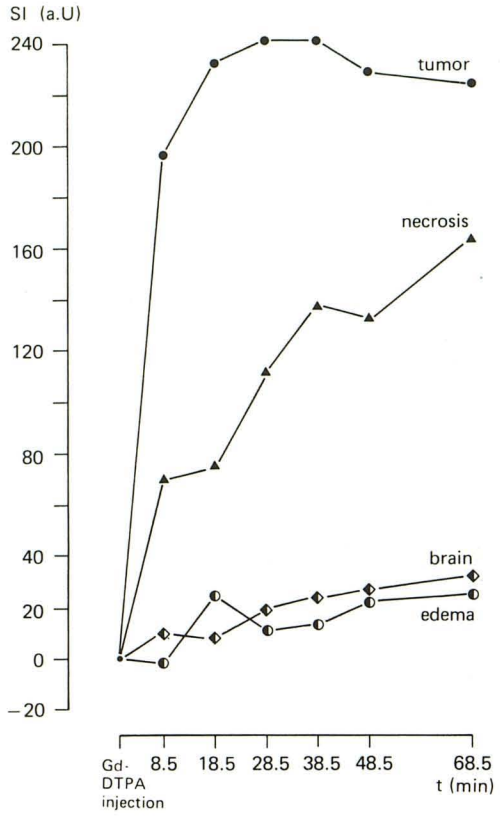

Fig. 9.—Time-dependent changes in image contrast in 15 patients with intracranial tumors. Differences between pre- and postcontrast signal-intensity (SI) values are calculated for tumor, "necrotic" tissue, edema, and normal brain. Differences in signal intensity are given as median values. t = time. (Adapted from [13].)

impact on patient management in these two cases; however, they may have clinical impact in selected cases. In the other three cases in group 2 (0.2 mmol Gd-DTPA/kg), even when an SI increase was measured, the area of enhancement did not change. Thus, for routine administration, no justifiable reasons for doses higher than 0.1 mmol Gd-DTPA/kg emerged from our study.

The other objective of our study was to determine whether the dose of 0.1 mmol/kg could be reduced without loss of diagnostic information. In six cases (cases 1–6) contrast-enhanced MR was performed with 0.025 mmol of Gd-DTPA/kg. Only in case 6 (pituitary adenoma) was contrast-enhanced MR at 0.025 mmol/kg diagnostically useful, showing tumor extension. In this case the tumor could already be delineated before injection of Gd-DTPA. After injection of 0.025 mmol of Gd-DTPA/kg the increase in SI resulted in increased contrast between tumor and adjacent structures with further improvement of differentiation between both. However, with respect to therapy planning, Gd-DTPA did not contribute indispensable information in this case.

In all 11 cases, contrast-enhanced MR was performed with a dose of 0.05 mmol Gd-DTPA/kg. In addition to the pituitary adenoma, a glioblastoma (Fig. 2) and an acoustic neuroma (Fig. 7) could be delineated at this dose level. Both tumors were hypointense on precontrast SE 800/35 scans and therefore were differentiable from surrounding tissue.

As with the dose level of 0.05 mmol/kg all 11 cases in groups 1 and 2 were evaluated with 0.1 mmol/kg. In eight of the 11 cases this dose was indispensable for diagnostic images. Our results, therefore, strongly suggest that 0.1 mmol Gd-DTPA/kg rather than lower doses are required for brain-tumor imaging.

To assess the validity of our results for short TR/short TE SE pulse sequences, an experimental study was performed in one brain-tumor–bearing dog. After precontrast SE 800/35 and SE 500/16 images had been obtained, a total dose of 0.3 mmol Gd-DTPA/kg was IV injected according to the fractionated incremental dose regime (Fig. 1, 0.1 mmol/kg with each injection). Pre- and postcontrast imaging was performed with the pulse sequences SE 500/16 (5 min postinjection) and SE 800/35 (8 min postinjection) with single signal averaging in order to meet the experimental protocol for dose administration (Fig. 1). Generally, a greater SI increase of enhancing tumor tissue was found with SE 500/16 as compared with SE 800/35 (Figs. 10E and 11E). The SI difference (contrast) between enhancing tumor tissue and normal brain after injection of 0.1 mmol/kg, however, was greater with SE 800/35. According to the quantitative results of this experiment a somewhat higher dose of contrast medium was necessary to obtain a comparable contrast between enhancing tumor tissue and normal brain with SE 500/16. Visual evaluation of SE 500/16 and SE 800/35 images supported the quantitative results (Figs. 10 and 11).

Gd-DTPA was well tolerated by all patients up to a dose level of 0.2 mmol/kg. Noteworthy is the complete absence of drug-related heat, pain, nausea, vomiting, urticaria, etc., which are sometimes associated with the administration of iodinated contrast media. Extensive laboratory testing in all

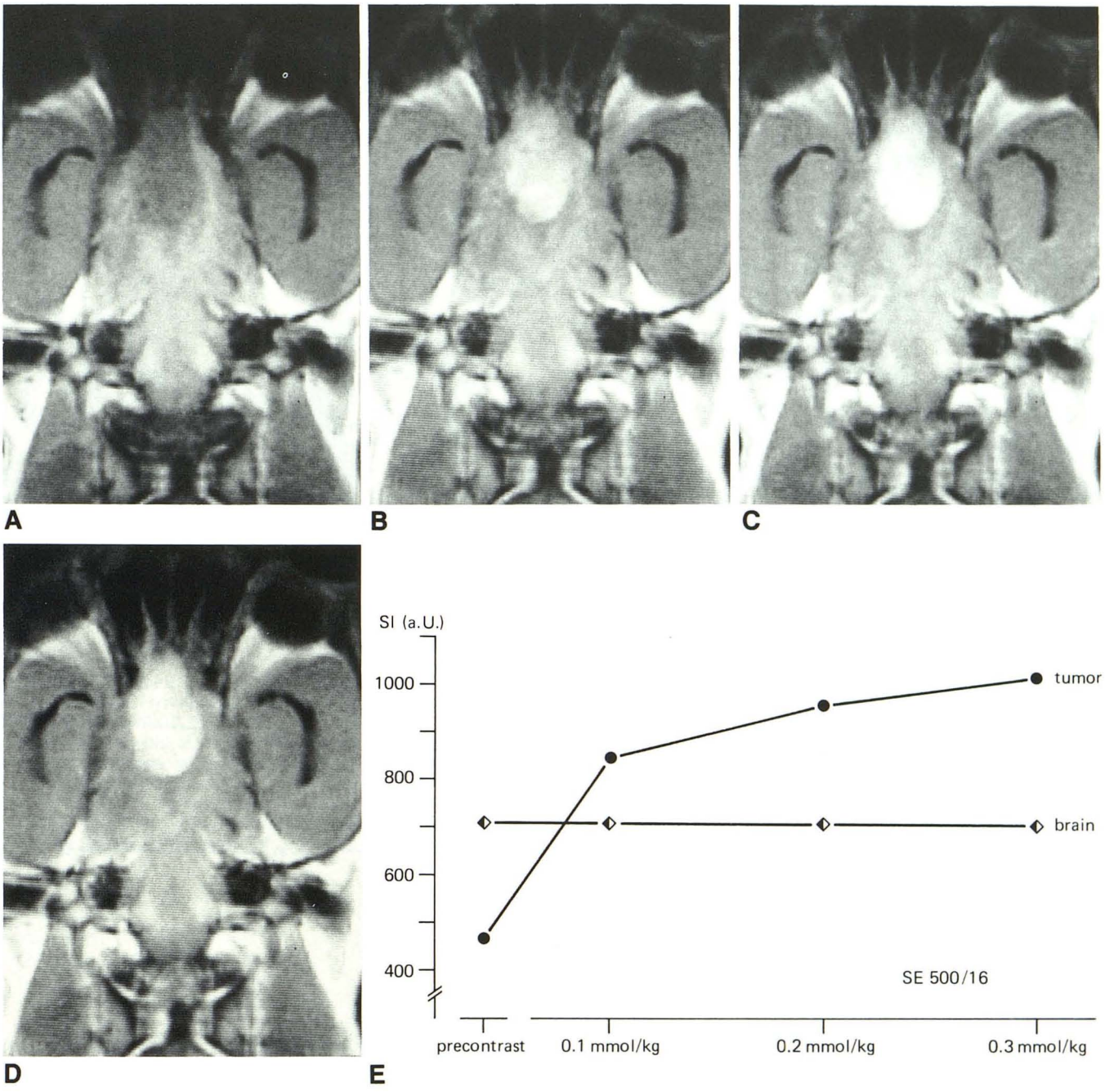

Fig. 10.—Canine brain. Tumor suspected clinically because of history of repeated seizures. SE 500/16 images. Examination was done according to protocol in Figure 1, except total dose was 0.3 mmol of Gd-DTPA/kg.

***A*, Before enhancement. Area of low signal intensity is displayed in rhinencephalic region of brain.**

***B*, 0.1 mmol of Gd-DTPA/kg. Signal-intensity increase within tumor tissue with fair demarcation.**

***C*, 0.2 mmol of Gd-DTPA/kg. Slight increase of tumor signal intensity and good demarcation of enhancing tumor.**

***D*, 0.3 mmol of Gd-DTPA/kg. Slightly increasing contrast enhancement in tumor tissue.**

***E*, Signal-intensity (SI) values of tumor tissue and normal brain. Signal-intensity values are in arbitrary units (a.U.).**

patients showed only slight transient elevations of serum iron in some patients, which usually lasted for only 24 hr and was in no case observed to persist after 48 hr. This has been reported by other investigators also, but has been found to be of no clinical relevance [19, 20].

In conclusion, with the pulse sequence of SE 800/35, the doses of 0.025 and 0.05 mmol Gd-DTPA/kg are insufficient to produce unambiguous tumor visualization. The dose of 0.1 mmol Gd-DTPA/kg is recommended as a diagnostic dose in MR of intracranial tumors. In selected cases a dose of 0.2

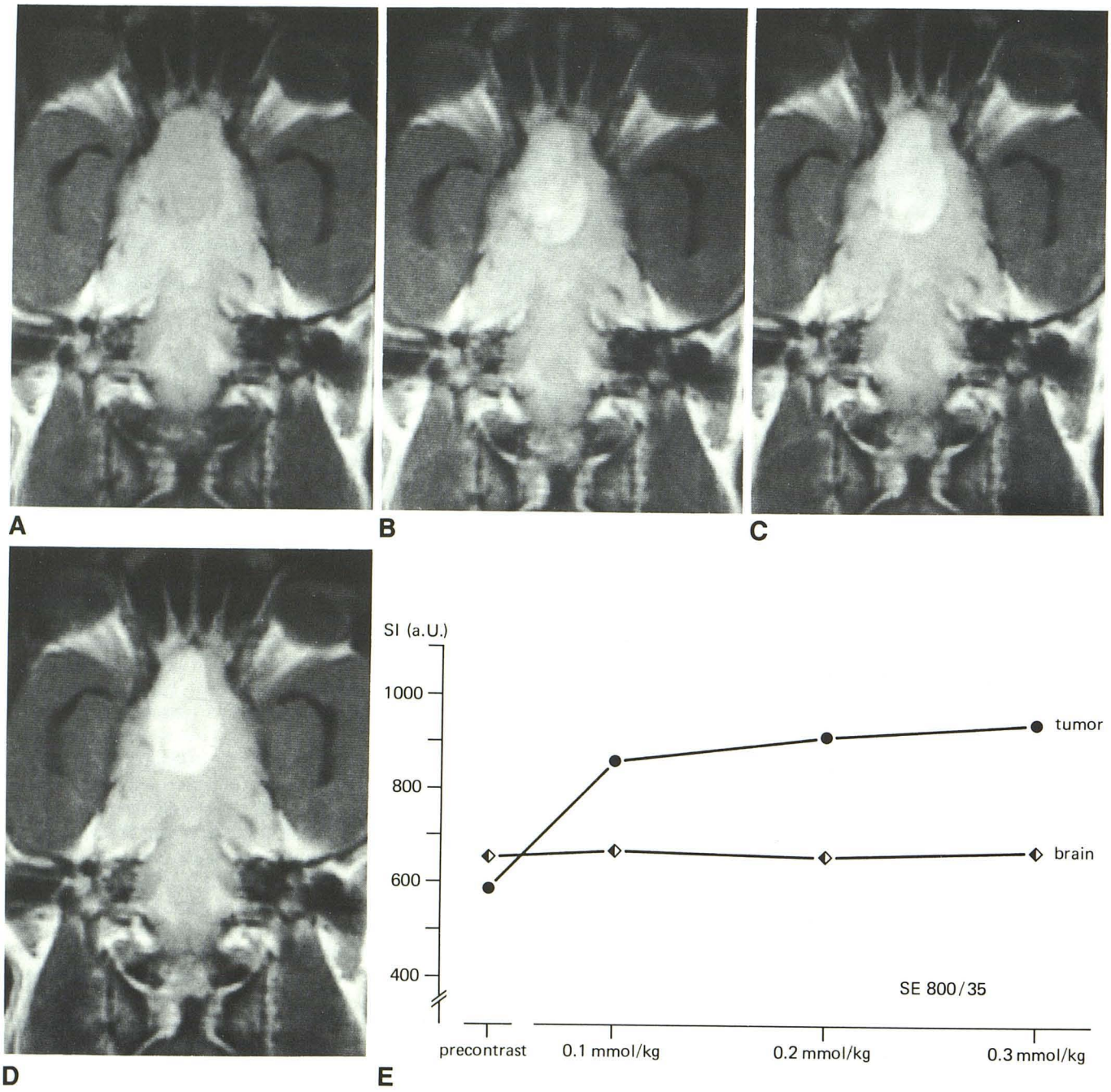

Fig. 11.—Same canine as in Figure 10 studied at SE 800/35. Examination was done according to protocol in Figure 1, but total dose was 0.3 mmol of Gd-DTPA/kg and scanning was performed 8 min after injection.

***A*, Before enhancement. Poorly defined area of slightly hypointense signal intensity in rhinencephalic region.**

***B*, 0.1 mmol of Gd-DTPA/kg. Increase in signal intensity provides fair demarcation relative to surrounding tissue.**

***C*, 0.2 mmol of Gd-DTPA/kg. Further contrast enhancement and good demarcation of enhancing tumor.**

***D*, 0.3 mmol of Gd-DTPA/kg. Slight increase in signal intensity.**

***E*, Signal-intensity (SI) values of tumor tissue and normal brain. Signal-intensity values are in arbitrary units (a.U.).**

mmol Gd-DTPA/kg may yield additional information and can be given safely.

In the meantime the evaluated optimum dose of 0.1 mmol Gd-DTPA/kg has proven to be appropriate for clinical purposes, also for more T1-weighted sequences, with a shorter TR (TR ≤ 500 msec) and shorter TE (TE ≤ 30 msec) yielding comparable and good diagnostic results [6–8, 20–23].

ACKNOWLEDGMENTS

We thank Renate Kentenich, Jochen Kasbohm, and Hossein Zolfaghari for technical assistance; Martina Licht for help in manuscript preparation; and Dr. Schwartz-Porsche for Figures 10 and 11.

REFERENCES

1. Brasch RC, Weinmann HJ, Wesbey GE. Contrast-enhanced NMR imaging: animal studies using gadolinium-DTPA complex. *AJR* **1984**;142:625–630
2. Weinmann HJ, Brasch RC, Press WR, Wesbey GE. Characteristics of gadolinium-DTPA complex: a potential NMR contrast agent. *AJR* **1984**;142:619–624
3. Laniado M, Weinmann HJ, Schörner W, Felix R, Speck U. First use of Gd-DTPA/dimeglumine in man. *Physiol Chem Phys Med NMR* **1984**;16: 157–165
4. Schörner W, Felix R, Laniado M, et al. Prüfung des kernspintomographischen Kontrastmittels Gadolinium-DTPA am Menschen: Verträglichkeit, Kontrastbeeinflussung und erste klinische Ergebnisse. *ROFO* **1984**;140:493–500
5. Schörner W, Felix R, Claussen C, et al. Kernspintomographische Diagnostik von Hirntumoren mit dem Kontrastmittel Gadolinium-DTPA. *ROFO* **1984**;141:511–516
6. Claussen C, Laniado M, Kazner E, Schörner W, Felix R. Application of contrast agents in CT and NMR: their potential in imaging of brain tumors. *Neuroradiology* **1985**;27:164–171
7. Claussen C, Laniado M, Schörner W, et al. The use of gadolinium-DTPA in magnetic resonance imaging of glioblastomas and intracranial metastases. *AJNR* **1985**;6:669–674
8. Felix R, Schörner W, Laniado M, et al. Brain tumors: MR imaging with gadolinium-DTPA. *Radiology* **1985**;156:681–688
9. Runge V, Schörner, W, Niendorf HP, et al. Initial evaluation of gadolinium-DTPA for contrast-enhanced magnetic resonance imaging. *Magnetic Resonance Imag* **1985**;3:27–35
10. Carr DH, Brown J, Bydder GM, et al. Intravenous chelated gadolinium as a contrast agent in NMR imaging of cerebral tumours. *Lancet* **1984**;1: 484–486
11. Carr DH, Brown J, Bydder GM, et al. Gadolinium-DTPA as a contrast agent in MRI: initial clinical experience in 20 patients. *AJR* **1984**;143: 215–224
12. Bydder GM, Kingsley DPE, Brown J, Niendorf HP, Young IR. MR imaging of meningiomas including studies with and without gadolinium-DTPA. *J Comput Assist Tomogr* **1985**;9:690–697
13. Schörner W, Laniado M, Niendorf HP, Schubert C, Felix R. Time-dependent changes of image contrast in brain tumors after gadolinium-DTPA. *AJNR* **1986**;7:1013–1020
14. Wolf GL, Burnett KR, Goldstein EJ, Joseph PM. Contrast agents for magnetic resonance imaging. In: Kressel HY, ed. *Magnetic resonance annual 1985*. New York: Raven, **1985**:247
15. Graif M, Bydder GM, Steiner RE, Niendorf HP, Thomas DGT, Young IR. Contrast-enhanced MR imaging of malignant brain tumors. *AJNR* **1985**;6:855–862
16. Brasch RC. Work in progress. Methods of contrast enhancement for NMR imaging and potential applications. *Radiology* **1983**;147:781–788
17. Runge VM, Clanton JA, Lukehart CM, Partain CL, James AE. Paramagnetic agents for contrast-enhanced NMR imaging: a review. *AJR* **1983**; 141:1209–1215
18. Niendorf HP, Semmler W, Laniado M, Felix R. Some aspects of the use of contrast agents in magnetic resonance imaging. *Diagn Imag Clin Med* **1986**;55:25–36
19. Bradley WG, Brant-Zawadzki M, Brasch RC, et al. Initial clinical experience with Gd-DTPA in North America: MR contrast enhancement of brain tumors (abstract). *Radiology* **1985**;157(P):125
20. Runge VM, Price AC. Gd-DTPA: an i.v. contrast agent for MRI investigation of intracranial neoplastic disease. Presented at the annual meeting of the American Society of Neuroradiology, San Diego, January **1986**
21. Laniado M, Niendorf HP, Schörner W, Felix R. Spin-echo and inversion-recovery sequences for gadolinium-DTPA-enhanced MRI of intracranial tumors. *Acta Radiol* **1986**;369:469–471
22. Brant-Zawadzki M, Berry I, Osaki L, Brasch R, Murovic J, Norman D. Gd-DTPA in clinical MR of the brain: 1. Intraaxial lesions. *AJNR* **1986**;7:781–788
23. Berry I, Brant-Zawadzki M, Osaki L, Brasch R, Murovic J, Newton TH. Gd-DTPA in clinical MR of the brain: 2. Extraaxial lesions and normal structures. *AJNR* **1986**;7:789–793