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Gadopentetate Dimeglumine–Enhanced MR of the Brain: Clinical Utility and Safety in Patients Younger than Two Years of Age

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PURPOSE: To evaluate the clinical utility and safety of gadopentetate dimeglumine as a contrast agent for MR of the brain in patients younger than 2 years of age. **METHODS:** In 125 consecutive patients younger than 2 years of age, MR images obtained before and after gadopentetate dimeglumine administration (0.1 mmol/kg) were independently and prospectively evaluated. After interpreting the unenhanced T1- and T2-weighted images, we rated the utility of contrast administration in each patient as not helpful, helpful, or essential for formulation of the radiologic diagnosis. Ratings were categorized both on the basis of the referring clinical diagnoses and on the basis of a radiologic diagnosis that was established from the clinical history and from the findings on the precontrast and postcontrast T1- and T2-weighted images. Patients' vital signs were recorded, and general medical status was observed for 120 minutes after gadopentetate dimeglumine administration. **RESULTS:** In no case did gadopentetate dimeglumine permit detection of lesions when precontrast T1- and T2-weighted images were normal. In only 4 of 125 patients were postcontrast images considered essential for establishing the radiologic diagnosis. Abnormal contrast enhancement was radiologically helpful in 20 of 125 patients. Lack of enhancement was considered helpful in 22 of 125 patients. No adverse clinical events or clinically important trends in vital signs were observed after contrast administration. **CONCLUSION:** The indiscriminate use of contrast agents in the MR imaging of patients younger than 2 years of age is not warranted. Appropriate decisions regarding the use of gadopentetate dimeglumine can be based on the findings in unenhanced T1- and T2-weighted images and on the referring clinical diagnosis.

Index terms: Magnetic resonance, in infants and children; Contrast media, paramagnetic; Brain, magnetic resonance

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The efficacy of gadopentetate dimeglumine administration for magnetic resonance (MR) of the brain has been evaluated in numerous studies of adults (1–4) and in pediatric patients older than 2 years of age (1, 2, 5–20). Although the diagnostic accuracy of MR can be improved by the use of intravenous contrast material in selected adults and older children, the benefit of contrast administration for routine imaging in younger children has not been as extensively investigated.

References to the utility of gadopentetate dimeglumine for MR of the brain are limited to fewer than 100 patients younger than 2 years of age (2, 5–18, 20–24). In many of these reports pediatric and adult patients are combined, with specific age groups not categorized. Despite this limited experience, initial impressions regarding gadopentetate dimeglumine use have emerged. In 65 children studied by Elster et al, contrast administration was considered helpful in 8 (ages not stated), with all 8 having central nervous system tumors (9). Enhancing lesions were not found in any child with a normal precontrast study (9). Baierl et al studied 40 children, including 15 between 1 and 6 years of age (6). More precise lesion characterization was reported in the 30 patients who had positive findings, most of

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whom had central nervous system neoplasms (6) In 15 infants younger than 6 weeks of age (8) gadopentetate dimeglumine administration modified the diagnosis in 4 patients, 3 of whom had infections (meningitis, ventriculitis, or encephalitis), with one having an angiomatoid malformation. In 11 other separate reports, 22 children younger than 2 years of age received gadopentetate dimeglumine for evaluation of brain neoplasms (11, 14, 15, 20, 22), Sturge-Weber syndrome (16, 21, 24), cerebral hemorrhage (13), trilateral retinoblastoma (23), and subdural empyema (18). Contrast administration generally has been considered helpful in all patients. In seven patients younger than 2 years of age contrast administration was described as helpful for characterization of pituitary gland morphology (5).

The purposes of this study were to characterize further the clinical utility of gadopentetate dimeglumine administration for MR of the brain in subjects younger than 2 years of age and to develop a rational strategy for the use of MR contrast agents in patients of this age group. We wished to describe how often and for which clinical indications enhanced images are helpful for the interpretation of MR studies and to estimate the frequency with which entirely normal precontrast T1- and T2-weighted images are associated with the occurrence of abnormal contrast enhancement. We also wished to determine the clinical safety of gadopentetate dimeglumine administration to patients of this age group.

Materials and Methods

One hundred fifty-six patients younger than 2 years of age underwent 171 MR studies without and with contrast administration. Patients were selected prospectively on the basis of age, willingness of a parent to give informed consent for contrast administration, and absence of severe renal dysfunction. The study was approved by our institutional review board. MR imaging at 1.5 T used precontrast T2-weighted axial, T1-weighted sagittal, and T1-weighted coronal or axial images. Imaging parameters varied with age and plane of imaging. T1-weighted spin-echo sequences were obtained before and after contrast administration (500–567/16–20/1–4 [repetition time/echo time/excitations], 128 × 256 or 192 × 256 matrix). T2-weighted sequences were obtained before contrast administration (2500–3500/90–160/1, 256 × 256 matrix). All sequences used a 16- to 20-cm field of view. Patients received intravenous gadopentetate dimeglumine (Magnevist, Berlex, Wayne, NJ), 0.1 mmol/kg of body weight, as slow intravenous infusions. T1-weighted images were obtained 5 to 10 minutes later.

MR images were interpreted by two neuroradiologists (O.P.E. and J.A.B.) to whom the referring clinical histories were available. Precontrast and postcontrast images were evaluated independently, with postcontrast images graded as radiologically helpful or not helpful using the following criteria.

1. Was an abnormal structure seen on the following sequences:
   a. T2-weighted images?
   b. T1-weighted images before contrast?
   c. T1-weighted images after contrast?
2. Did gadopentetate dimeglumine facilitate lesion visualization?
3. Did gadopentetate dimeglumine obscure lesion visualization?
4. Did gadopentetate dimeglumine assist by:
   a. improving border resolution?
   b. improving conspicuity?
   c. visualization of internal morphology of the lesion?
   d. distinguishing tumor from edema?
5. Did gadopentetate dimeglumine:
   a. disclose findings not seen on precontrast images?
   b. increase confidence in diagnosis?
   c. alter patient treatment?
   d. resolve possible artifacts?
6. Did gadopentetate dimeglumine assist in defining the number of lesions?

Contrast administration was considered helpful if it led to the detection of a mass or lesion not identified in the precontrast image, if it clarified the margins, size, or nature of an abnormality, or if it provided functional information about disease activity by assessment of integrity of the blood-brain barrier. Lack of enhancement was considered radiologically helpful if it demonstrated integrity of the blood-brain barrier around a lesion and was occasionally considered helpful in excluding certain specific lesions. Contrast administration was considered helpful in all cases of suspected neoplastic, infectious, or endocrine disorders, regardless of whether there was any abnormal enhancement.

Patient charts and MR requisition forms were reviewed and the referring diagnoses or clinical problems tabulated (Table 1). A radiologic diagnosis was formulated after reviewing all images (Table 2). Patients were then divided into eight groups based on whether the precontrast images were normal or abnormal, whether there was abnormal contrast enhancement, and whether contrast administration was considered helpful (Tables 1 and 2). It was noted also whether contrast material was simply helpful (based on the criteria enumerated above) or whether it was considered essential for establishing the MR diagnosis.

The association between qualitative factors, such as helpful or not helpful and normal or abnormal precontrast images, was assessed using Fisher's Exact Test (25). Exact binomial 95% confidence intervals (CIs) were constructed around the estimated percent with a given characteristic using the STATA statistical package (Computing Resource Center, Santa Monica, Calif).

TABLE 1: Referring diagnoses: correlation with MR findings before and after contrast administration in 125 patients younger than 2 years of age

Referring diagnosis	n	Normal Precontrast T1- and T2-weighted Imates				Abnormal Precontrast T1- and T2-weighted Images			
		No Abnormal Enhancement		Abnormal Enhancement		No Abnormal Enhancement		Abnormal Enhancement	
		Helpful	No help	Helpful	No help	Helpful	No help	Helpful	No help
Seizures	32		14			3	10	3	2
Developmental delay	15		3			1	9	1	1
Large head	13		2			2	6	1	2
Seizures and infection	12	5					2	5	
Neurological deficit	9		7				2		
Congenital malformation?	8		3				3	2	
Endocrine disorder?	6	3				3			
Bleeding?	5		1				1	3	
Brain neoplasm?	5	1				2		2	
Phacomatosis?	4		2				1	1	
Seizures, focal	4						3	1	
Trauma	4						2		2
Hypotonia	3		2				1		
Infection	3	1				1		1	
Hypoxic or anoxic episode	2		1				1		
Total	125	10	35			12	41	20	7

TABLE 2: Radiologic diagnoses: correlation with MR findings before and after contrast administration in 125 patients younger than 2 years of age

Radiologic diagnosis	n	Normal Precontrast T1- and T2-weighted Imates				Abnormal Precontrast T1- and T2-weighted Images			
		No Abnormal Enhancement		Abnormal Enhancement		No Abnormal Enhancement		Abnormal Enhancement	
		Helpful	No help	Helpful	No help	Helpful	No help	Helpful	No help
Normal	44	9	35						
Congenital malformation	17					3	9	4	1
Hydrocephalus	15					4	10		1
Ischemia or infarct	8						3	5	
Delayed myelination	8						8		
Infection or inflammation	7					1	1	5	
Low brain volume	6						5		1
Neoplasm	5					2		3	
Bleeding	4						2	2	
Subdural fluid collection	4								4
Phacomatosis	2					1		1	
Metabolic disorder	1						1		
Trauma	1						1		
Undetermined	3	1				1	1		
Total	125	10	35			12	41	20	7

All 171 studies were included in the evaluation of safety and patient response to gadopentetate dimeglumine administration. Blood pressures, pulse rates, respiration rates, and general tolerances were measured before injection (baseline) and at 30, 60, 90, and 120 minutes after gadopentetate dimeglumine administration. Adverse events were documented on the case report form. Univariate repeated-measures analysis of variance (26) was used to test the null hypothesis that mean values for heart rate, respiration rate, and blood pressure were each equal across the timetable periods of baseline to 2 hours after contrast. The Greenhouse-Geisser adjustment was used on this method to take into account that the same patient had several measurements over time (27).

Results

One hundred seventy-one MR studies were performed on 156 patients before and after intra-

venous gadopentetate dimeglumine administration. Forty-six studies were excluded from the efficacy evaluation portion of this protocol, because they were limited to the spine (16 of 46) or to the face and neck (4 of 46), or because they were follow-up studies of patients already included in this study (15 of 46). Nine of the 46 studies were excluded because they did not show enhancement of structures that normally should enhance after contrast administration, indicating that a full dose of contrast material had not been injected successfully. Two of the 46 studies were excluded because of motion artifact. The utility of postcontrast MR imaging was evaluated in the remaining 125 patients. Patient ages follow (median was 9.2 months; mean, 9.7 months).

Age (Months)	Number of Patients
0–3	34
3–6	12
6–9	16
9–12	18
12–15	12
15–18	11
18–21	11
21–24	11
Sum (0–24)	125

When evaluating the study population as a whole it was noted that precontrast MR studies of the brain were normal in 45 of 125 patients (36%). Among these 45 patients none had abnormal enhancement on the postcontrast images (Tables 1 and 2). This was statistically significant ($P < .001$) when compared with the occurrence of abnormal enhancement in 27 of 80 patients with abnormal precontrast images. Within this group of 45 patients the administration of gadopentetate dimeglumine was considered of diagnostic help in excluding underlying abnormality in 10, as described below. In the 80 patients who demonstrated abnormalities on precontrast T1- and/or T2-weighted images, abnormal enhancement was diagnostically helpful in 20 and was not helpful in 7. Among the entire group of 125 patients, lack of abnormal enhancement was demonstrated in 98 (78%). This lack of enhancement was considered helpful in 22 (22%) of 98 and of no help in 76 (78%) of 98. This tendency that lack of abnormal enhancement was not helpful was statistically significant ($P < .001$). In only 4 of 125 patients (95% CI = 0.9%–8%) were postcontrast images considered essential. Overall, abnormal contrast enhancement was radiologically helpful in 20 of 125 patients (95% CI = 10%–24%). Lack of enhancement was considered helpful in 22 of 125 patients (95% CI = 11%–25%).

When looking at specific diagnostic groups of the study population, we noted that among 32 patients with the referring diagnosis of generalized seizures, lack of abnormal enhancement increased our confidence that there was no underlying neoplasm in 3 patients. One patient had a cerebellopontine angle cyst, one patient had tuberous sclerosis and ventriculomegaly, and the third patient had a lesion in the left frontal lobe. In three other patients enhancement of the cortex was helpful in establishing the diagnosis of infarction. Two of these patients were neonates, in whom high brain water content can potentially obscure the visualization of regions of infarction unassociated with hemorrhage. Enhancement in three patients with subdural fluid collections was not helpful in establishing the diagnosis. In four patients with focal or partial complex seizures, one showed abnormal contrast enhancement. This patient, at 1 month of age, had evidence of tuberous sclerosis on the MR study. Contrast enhancement was considered helpful by showing enhancement of several subependymal nodules and as a baseline for future study.

In 12 patients with the referring diagnosis of generalized seizures, fever, and suspected central nervous system infection, 5 showed abnormal enhancement. Four of these patients had encephalitis, and one had an incidental finding of a cerebellar hemangioma. Enhancement increased lesion conspicuity, and its pattern helped exclude abscess formation. In seven patients with no abnormal enhancement, five had normal MR studies, one had low brain volume, and one had brain edema. Gadopentetate dimeglumine administration was credited as being useful in all seven cases because we thought it was important to see that there was no abnormal enhancement of brain or meninges. Despite this absence of meningeal enhancement, two of the seven patients had cerebrospinal fluid pleocytoses consistent with meningitis, although bacterial and virus cultures of blood and cerebrospinal fluid remained negative. Three other patients were treated with antiviral and/or antibacterial medication for several days after the normal MR examinations. In these patients there was no laboratory confirmation of infection.

Three patients had clinical signs of meningitis or suspected congenital cytomegalovirus infection. No signs of intracranial infection were detected on the MR studies. In two patients a lack

of enhancement was scored as helpful and an indicator that there was no acute infection, but this was probably misleading. In one patient with subdural effusions and no meningeal enhancement, cultures from blood and cerebrospinal fluid grew *Hemophilus influenzae*. The second patient with lack of enhancement was a 2-month-old infant with a history of a proved herpes simplex meningitis 3 weeks earlier, which had been treated with antiviral agents. Although clinical symptoms were those of recurrent meningitis, and cerebrospinal fluid demonstrated recurrent pleocytosis, cultures were negative.

Of the 13 patients referred for evaluation of large head size, 10 had no abnormal enhancement. Three patients showed abnormal enhancement: one with a brain infarct, and two with enhancement of the meninges. Enhancement was helpful in one patient with infarction, indicating that the lesion was subacute in duration. Abnormal meningeal enhancement in two patients was considered not helpful, indicating suspected meningeal irritation in one patient and outlining an otherwise recognized subdural fluid collection in the other. Among nine patients with fixed focal neurologic deficits none showed abnormal enhancement.

Eight patients were evaluated for suspected congenital anomalies of the brain. In two patients abnormal enhancement helped delineate an epidermoid tumor in the frontal skull base and helped exclude the presence of a neoplasm associated with a hemorrhagic cyst in the sylvian fissure. Lack of enhancement was not helpful in the remaining six patients. Of the five patients with suspected intracerebral bleeding, three had abnormal parenchymal enhancement near the hemorrhages, which was considered helpful, and two showed no abnormal enhancement. In two patients, abnormal enhancement made obvious adjacent regions of cerebral infarction. In the third, enhancement of the meninges allowed the separation of a subdural hematoma from an associated intraparenchymal bleeding.

In five children with suspected central nervous system neoplasms, imaging after gadopentetate dimeglumine administration provided increased confidence that there were no metastases or recurrent neoplasms or was helpful for tumor characterization. Six children were referred for MR because of endocrine dysfunction. All had normal pituitary glands and hypothalamic regions on MR before and after contrast. In all cases, lack of abnormal enhancement was characterized as helpful. Of four patients with suspected phacomatosis, two had abnormalities on the MR studies. One of them was a 5-month-old infant with an enhancing neoplasm along the petrous ridge and cavernous sinus, which extended to the orbital apex. Contrast administration was considered essential in diagnosing the area of the cavernous sinus involved by the tumor. The other patient had a mild hydrocephalus.

In the 171 MR studies on 156 pediatric patients, vital signs measured during 120 minutes after gadopentetate dimeglumine injection demonstrated no overall trends that were of clinical significance, and most changes were less than ± 20%. We obtained a borderline significant result for heart rate (Greenhouse-Geisser F statistic = 2.59, $P = .0451$). There seemed to be a trend of gradual decline in mean heart rate from the baseline to 1 hour after contrast injection and then a gradual increase in heart rate from 1 to 2 hours after contrast injection. Deteriorating neurologic function after gadopentetate dimeglumine injection was not documented, and no instances of immediate or delayed allergic reactions were recorded.

Discussion

To our knowledge, descriptions of the use of gadopentetate dimeglumine as a contrast agent for MR of the brain in patients younger than 2 years of age are limited. The current study expands these observations and attempts to provide a basis for the formulation of a rational strategy for the use of MR contrast agents in this age group. Patient considerations and economic imperatives require that specific medical indications govern decisions regarding the use of contrast agents. The three agents currently available, essentially identical in price at just more than $100 per routine adult dose, represent a significant portion of the cost of MR imaging. Information routinely available that may assist in decisions regarding contrast use in this age group may include MR findings on unenhanced T1- and T2-weighted images and a knowledge of the referring clinical diagnosis.

Among 45 patients in this study who had normal precontrast T1- and T2-weighted images, none demonstrated abnormal enhancement or abnormal findings on postcontrast images (Tables 1 and 2). This finding indicates a low overall sensitivity for gadopentetate dimeglumine in demonstration of abnormality in children younger

than 2 years of age when precontrast T1- and T2-weighted images of the brain are normal. Among these 45 patients it was our impression that a lack of abnormal enhancement was in itself helpful in 10 because it provided greater confidence that the results were truly normal. Such judgments regarding the usefulness of a lack of enhancement are, however, subjective. They are entwined with patient history, with the spectrum of diseases reasonably being considered, and with both the level of experience and the confidence of the radiologist interpreting the study (2, 4). Based on this absence of altered sensitivity for the detection of MR abnormality after administration of gadopentetate dimeglumine in patients with normal unenhanced T1- and T2-weighted images, consideration may be given either to not using contrast agents in such situations or to selective use of contrast agents depending on the clinically suspected diagnosis.

Defining the utility of contrast administration based on referring clinical diagnosis was more difficult because of the small number of patients in each clinical category. Sixteen categories were defined based on information contained in the requisitions and/or from consultations with the referring physicians. The largest single group of patients in the current series had referring diagnoses of seizure disorders. In this group abnormal contrast enhancement was helpful in 3 of 32 patients (95% CI = 2%–25%). In an additional 3 of 32 patients lack of contrast enhancement was considered helpful, so the contrast administration was found to be helpful one way or another in a total of 6 of 32 patients (95% CI = 7%–36%).

To increase patient sample size on the basis of primary suspected diagnosis, 26 patients with suspected intracranial infections (without or with seizures), neoplasms, or endocrine disorders were combined. Among older patients with these disorders contrast agents generally have been considered useful for image interpretation. Similar observations have been made in patients younger than 2 years of age (5, 6, 8–10, 14, 15, 18, 20, 22, 23). Among this group, 8 of 26 had abnormal enhancement, and 18 of 26 demonstrated a lack of abnormal enhancement. No patient with a normal precontrast study demonstrated abnormal enhancement. Based on our bias from experience with older patients with these disorders, image interpretation in all of these patients was considered to benefit from contrast administration. The assumption that the lack of contrast enhancement would be helpful in the exclusion of infection or neoplasm proved, however, incorrect in 1 of 5 patients with neoplasms and in 5 of 15 patients with suspected infections. The absence of abnormal meningeal enhancement does not seem to be a sensitive indicator of the lack of cerebrospinal fluid pleocytosis and apparent meningitis.

In the 99 patients in whom the referring diagnoses were other than infection, neoplasm, or endocrine disorder, abnormal enhancement was observed in 18 (95% CI = 11%–27%). The abnormal enhancement was considered helpful in 11 of 99 (95% CI = 6%–19%). In an additional 7 of 99 patients lack of abnormal enhancement was considered helpful; so the administration of contrast was considered helpful one way or the other in 18 of 99 patients (95% CI = 11%–27%).

In our opinion postcontrast MR images are helpful for the evaluation of patients with known brain neoplasms or clinically suspected neoplasms. Contrast administration may be useful to exclude tumors, if the precontrast images are normal, or may assist in the characterization and staging of the neoplasms. Gadopentetate dimeglumine is unreliable, however, for the identification of tumor margins, because there is often microscopic infiltration beyond the margin of enhancement (28).

Postcontrast images were essential for image interpretation in only 4 of the 125 patients included in this study (95% CI = 0.9%–8%). Refinement of the radiologic diagnosis after contrast administration does not necessarily translate into a change in clinical management. Decisions regarding patient management are only indirectly dependent on the results of imaging studies, and the relevance of imaging studies to patient management is difficult to define. In the four patients in whom we found contrast-enhanced sequences to be essential for the radiologic diagnoses, the information provided did not alter treatment of any patient. Two of these four patients had cerebral infarcts after heart surgery; one had neurofibromatosis with a neurinoma in the cavernous sinus demonstrated only on the postcontrast images; and the fourth, who had seizures and fever, demonstrated abnormal enhancement of the caudate nucleus and of the meninges. This fourth patient was on antibacterial medication before and after the MR study.

The potential for lesion obscuration after administration of gadopentetate dimeglumine has been discussed (4). In our material no such occurrence was encountered. In one patient, how-

ever, a subdural hematoma, which was high in signal intensity on T1-weighted images, was less conspicuous on postcontrast sequences.

Based on the lack of enhancement of structures that normally enhance on postcontrast images, patients in 9 of the 171 studies (5%) did not receive proper intravenous doses of gadopentetate dimeglumine. A similar occurrence was noted by Hudgins et al in 7 of 58 (18%) pediatric patients (14). We speculate that the contrast may have been injected subcutaneously.

Among patients studied in this series, no adverse reactions were recorded. We did not observe irritability, emesis, systematic change in vital signs, or signs of allergic or anaphylactic reaction. We had no report of adverse reactions after the 2-hour observation of the patients in the MR unit. Because glomerular filtration rate corrected for body surface area has not reached adult levels, the estimated mean elimination half-life of gadopentetate dimeglumine is approximately 6.5 hours in term newborn infants and 9.2 hours in preterm infants of 36 weeks gestation, versus 1.5 hours in healthy adults (8). A weakness of the present study of possible adverse reactions was that laboratory analysis of the blood or urine was not a part of the protocol. Other studies have concluded that gadopentetate dimeglumine in a dose of 0.1 mmol/kg is safe in children younger than 2 years of age (1, 8, 9, 22, 29) and in children older than 2 years (1, 3, 9, 19, 30, 31). There are, to our knowledge, no reports of serious side effects of gadopentetate dimeglumine in children younger than 2 years of age.

Patient selection in this study reflected this institution's function as a tertiary neonatal, neurosurgical, and pediatric neurology referral center. The data we present may apply only to our particular patient population. In a population with a higher prevalence of brain tumors or metastases, the useful yield after administration of gadopentetate dimeglumine most likely would be higher. In a large outpatient population of patients with less specific neurologic symptoms, the utility of routine gadopentetate dimeglumine administration may be significantly lower. In our experience, normal precontrast findings showed a significant association with absence of abnormal contrast enhancement ($P < .0001$). None of the 45 of 125 patients with normal precontrast findings had abnormal contrast enhancement. The indiscriminate use of contrast agents in the MR imaging of patients younger than 2 years of age is not warranted. Appropriate decisions regarding the use of gadopentetate dimeglumine can be based on the findings of unenhanced T1- and T2-weighted images and on the referring clinical diagnosis.

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