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Cranial MR Imaging with Gd-DTPA in Neonates and Young Infants: Preliminary Experience¹

Gadopentetate dimeglumine (gadolinium diethylenetriaminepentaacetic acid [DTPA]) was prospectively administered to 15 consecutive neonates and young infants (less than 6 weeks old) referred for routine cranial magnetic resonance (MR) imaging. The goals of the study were (a) to provide preliminary safety and efficacy data concerning the use of this drug in neonates and (b) to determine whether the patterns and time course of normal contrast material enhancement were similar to those seen in older children and adults. Gd-DTPA-enhanced MR images revealed significant abnormalities not seen on the MR images obtained before administration of contrast material in four (27%) of 15 patients. The adult dose (0.1 mmol/kg) provided bright enhancement of normal intracranial structures. Because of significantly reduced glomerular filtration and renal clearance rates in newborns, vivid contrast enhancement of normal structures was seen to persist for several hours after injection. A prolonged window of time for imaging may therefore exist for neonates and young infants.

Index terms: Brain, MR studies, 10.1214 • Gadolinium • Magnetic resonance (MR), contrast enhancement • Magnetic resonance (MR), in infants and children

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THE utility and safety of gadopentetate dimeglumine (gadolinium diethylenetriaminepentaacetic acid [DTPA]) as an adjunct to cranial magnetic resonance (MR) imaging has been thoroughly documented in both children (1-4) and adults (5-16). Its use in neonates and young infants remains largely uninvestigated, however, because patients younger than 2 years were purposely excluded from the initial Magnevist (gadopentetate dimeglumine [Gd-DTPA]; Berlex Imaging; Cedar Knolls, NJ) clinical trials. We therefore designed a prospective study to provide preliminary safety and efficacy data on the administration of Gd-DTPA to neonates and young infants. We particularly sought to study the patterns, time course, and duration of contrast material enhancement seen when the adult dose was administered to neonates.

SUBJECTS AND METHODS

The subjects comprised 15 consecutive newborns and young infants (less than 6 weeks old) referred for routine cranial MR imaging during a 6-month period. They ranged in age from 1 day to 6 weeks (median age, 8 days) (Table 1). Ten patients were the product of term gestations, while the other five were born between 35 and 38 menstrual weeks. All patients were studied after informed consent was obtained from a parent or guardian and with institutional review board approval.

Each patient was evaluated by a neonatologist immediately before and within 1 day after MR imaging; and the following routine laboratory tests also were performed: blood leukocyte count; hematocrit, serum creatinine, and blood urea nitrogen determinations; and urinalysis. Patients older than 2 weeks were sedated with orally administered chloral hydrate (50 mg/kg). All patients were monitored continuously with a pulse oximeter during imaging. A radiology resident and a neonatal intensive care nurse observed each patient during and after MR imaging.

Table 1
MR Imaging in 15 Neonates and Young Infants Who Received Gd-DTPA

Case/ Age(d)/ Sex	MR Findings/ Diagnosis
1/1/M*	Angiomatous malformation (variant of Sturge-Weber syndrome)
2/2/M*	Ventriculitis and subdural empyema
3/5/F	Chiari II malformation
4/5/M	Normal
5/6/F	Chiari II malformation
6/8/M*	Meningitis
7/9/F	Germinal matrix hemorrhage
8/9/M*	Cephalhematoma
9/12/M	Cerebellar hypoplasia
10/15/M	Normal
11/17/F	Intracranial hemorrhage
12/28/M*	Encephalitis
13/34/F	Intracranial hemorrhage
14/41/F	Normal
15/42/M	Schizencephalic porencephaly

* In these cases, abnormal contrast enhancement was noted.

All MR images were obtained with a 1.5-T imager (Picker International; Highland Heights, Ohio). Before contrast material administration, T2-weighted axial images were routinely obtained with a long spin-echo protocol similar to that recommended by Nowell et al (17). Specific imaging parameters included a repetition time of 3,500 msec, an echo time of 120 msec, a section thickness of 5 mm with a 0.5-mm intersection gap, an image acquisition matrix of 192 X 256, and a field of view of 20 cm. The number of signals averaged was 1. A gradient-moment-nulling technique (motion artifact suppression technique [MAST, Picker]) also was used to reduce intracranial phase-shift artifacts (18).

Multiplanar (axial, coronal, and sagittal) T1-weighted MR images were obtained before and after the administration of Gd-DTPA. Specific imaging parameters varied slightly with the plane of imaging

Abbreviations: DTPA = diethylenetriaminepentaacetic acid, ECV = extracellular fluid volume, GFR = glomerular filtration rate.

and included a repetition time of 500–700 msec, an echo time of 20 msec, a section thickness of 5–6 mm, an image acquisition matrix of 256 × 256, a field of view of 20 cm, and two signals averaged. Identical imaging parameters and imager attenuator settings were maintained for corresponding pre- and postcontrast sets of images.

All patients received intravenous injections of Gd-DTPA (Magnevist) after the precontrast MR image was obtained. All patients received the recommended adult dose (0.1 mmol/kg), and imaging was resumed within 5–10 minutes following injection. The multiplanar postcontrast study took approximately 15 minutes to complete. Two patients were also imaged during an additional 4-hour period to evaluate the duration of contrast enhancement in normal structures.

Measurements of signal intensities in selected structures (dura mater, white matter, choroid plexus, cavernous sinus, pituitary gland, and scalp fat) were performed with use of a region-of-interest cursor and conventional imaging software. The percentage of contrast enhancement was calculated in a manner similar to that described by Kilgore et al (10):

$$\% \text{ enhancement} = \frac{(\text{post SI}/\text{post ST}) - (\text{pre SI}/\text{pre ST})}{(\text{pre SI}/\text{pre ST})}$$

where SI indicates signal intensity of the tissue of interest and ST indicates signal intensity of the standard or reference tissue, here taken to be white matter (shown by Kilgore et al not to enhance).

On completion of each study, the pre- and postcontrast images were reviewed by a neuroradiologist experienced with high-field-strength pediatric MR imaging and the use of Gd-DTPA in older children and adults. Observations concerning the patterns of contrast enhancement of normal structures were carefully recorded, together with the abnormal patterns of enhancement seen in cases of brain disease. The pre- and postcontrast findings were then analyzed together with the medical history to determine the role Gd-DTPA enhancement played in the detectability and characterization of lesions.

RESULTS

All 15 infants tolerated the administration of Gd-DTPA with no detectable change in their clinical status or physical examination findings. Similarly, no significant alterations were noted in blood chemistry or hematologic findings.

The patterns and locations of contrast enhancement seen in the infants were qualitatively similar to those reported in adults (10). Intense contrast enhancement was noted in areas outside the blood-brain barrier: pituitary gland, pineal body, cavernous sinus-

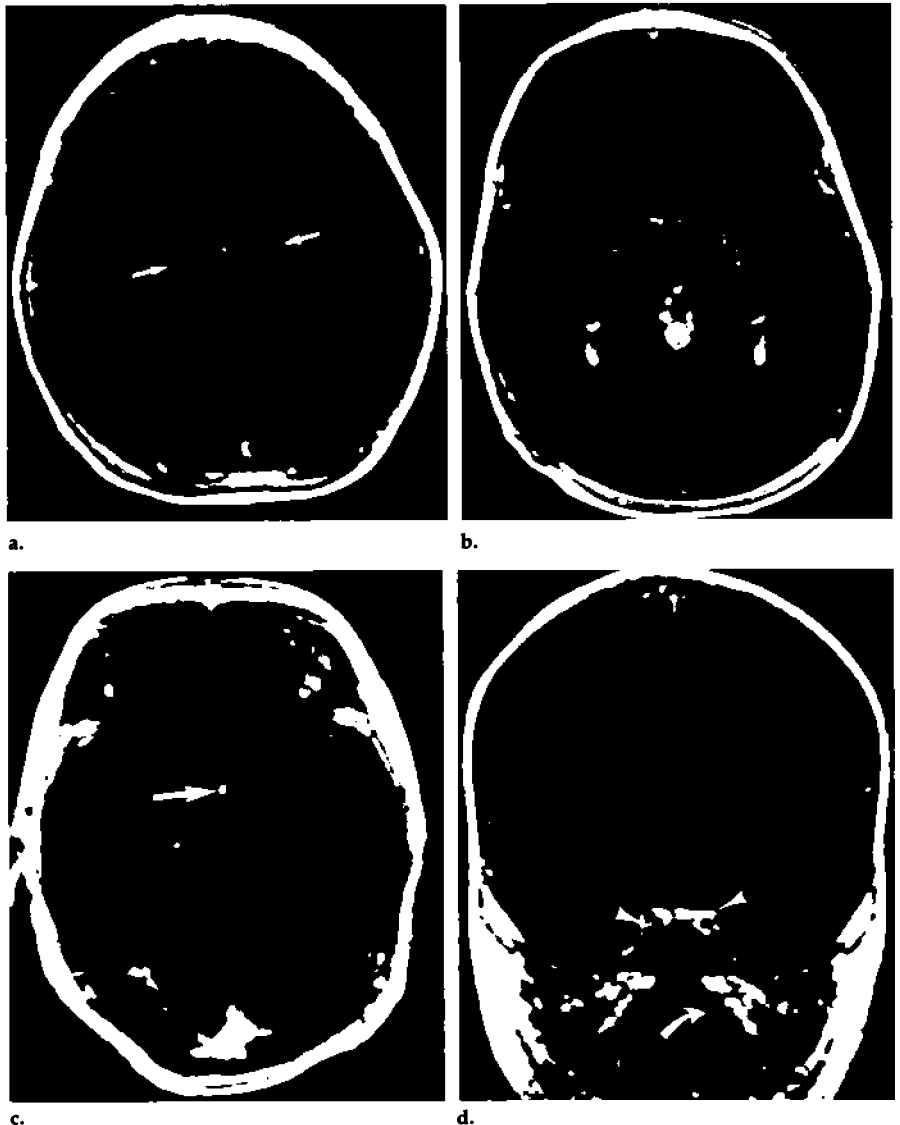


Figure 1. Normal intracranial enhancement with Gd-DTPA in neonates is similar to that seen in adults. (a) Subependymal veins are prominent (arrows). (b) The choroid, pineal body, and deep veins are enhanced. (c) Prominent enhancement of the infundibulum (arrow) and tentorial vessels is noted. (d) Bright enhancement of the cavernous sinuses (arrowheads) and enhancement of the nasopharyngeal mucosa (curved arrow) are also observed.

es, infundibulum, choroid plexus, dura, major dural sinuses, nasopharyngeal mucosa, and smaller cortical veins (Fig 1). In two premature infants, enhanced subependymal veins along the margins of the lateral ventricles were noted to be slightly more prominent than is normally seen in adults, which may relate to the relatively larger size of these vessels and greater vascularity of the ependymal and subependymal regions in the premature infant (19,20).

Enhancing lesions were encountered in five (33%) of 15 patients (Table 1). In four of these patients, contrast enhancement significantly modified the diagnosis made before administration of contrast-material (Figs 2,3); in the fifth patient, contrast enhancement was incidentally

noted at the margin of a cephalhematoma (Fig 4).

The images of two infants obtained 4 hours after injection demonstrated marked persistent contrast enhancement in normal structures (Fig 5). Serial measurements revealed an approximately 50% decrease in the level of contrast enhancement during this 4-hour period for most structures (Fig 6). Even with this absolute reduction in enhancement signal intensity, however, vivid contrast enhancement of many normal structures was still visually striking.

DISCUSSION

The pharmacokinetics of intravenously administered Gd-DTPA have been well studied in adults (21–23).

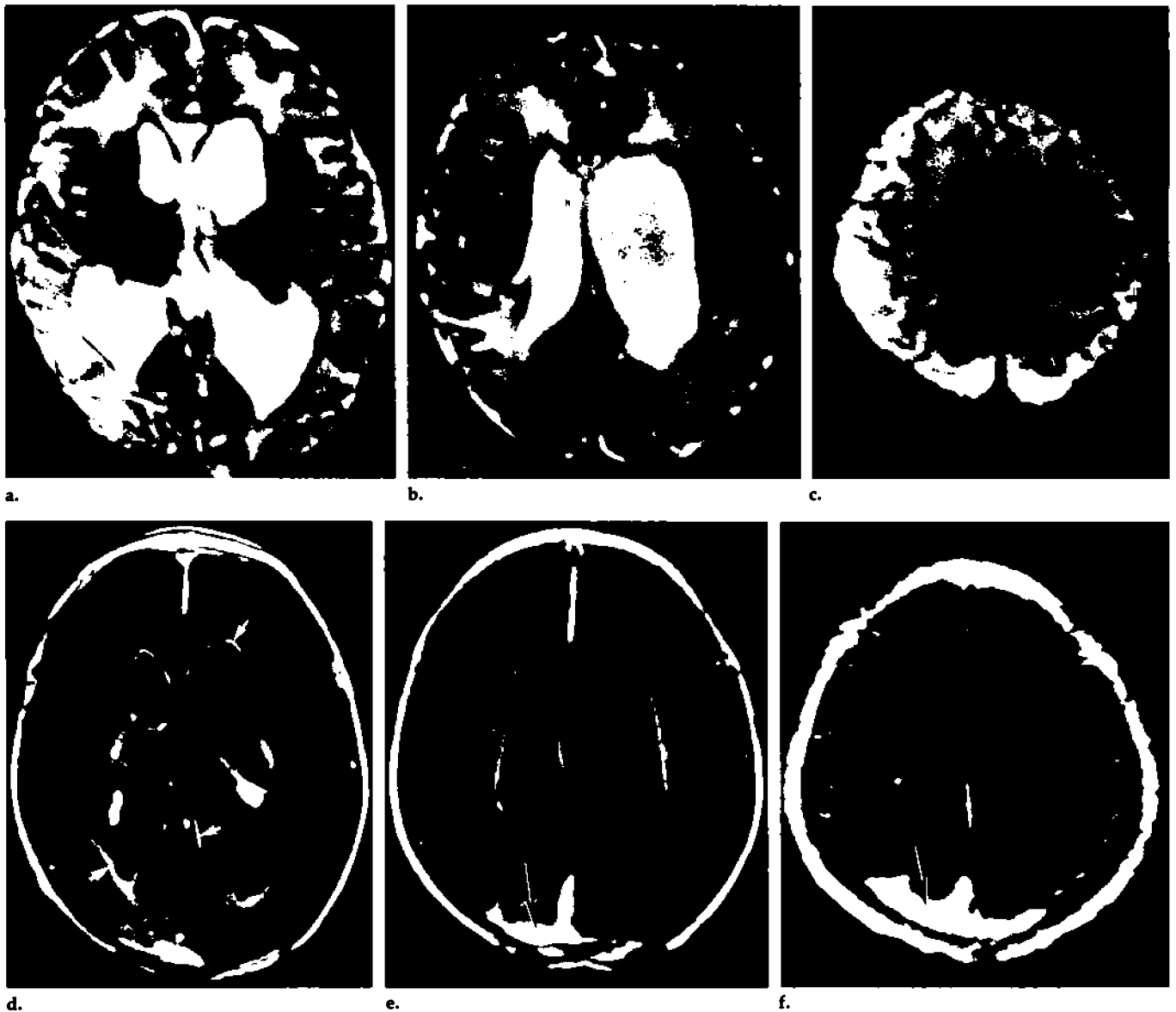


Figure 2. MR images of a 36-week-old infant with *Haemophilus influenzae* sepsis. (a-c) Precontrast T2-weighted axial images show only hydrocephalus. (d) Marked ventriculitis (arrows) is noted on this postcontrast T1-weighted image. (e, f) More cephalically, an enhanced subdural effusion or empyema (arrow) is seen.



Figure 3. MR image of an 8-day-old term infant suspected to have viral meningitis. Precontrast images were normal, but this postcontrast coronal image demonstrates diffuse meningeal enhancement.

On injection, the meglumine salt completely dissociates from the gadopentetate complex. No detectable biotransformation or decomposition occurs. The gadopentetate complex rapidly diffuses into the extracellular compartment of the body, with a volume of distribution almost identical to the extracellular fluid volume (ECV). Gd-DTPA is exclusively eliminated in the urine and has a clearance rate similar to that of substances that are subject to glomerular filtration alone.

In adult volunteers, the pharmacokinetics of intravenously administered Gd-DTPA conforms closely to a classic two-compartment open model, with a mean elimination half-life of approximately 1.5 hours (21). To our knowledge, however, no corresponding pharmacokinetic study of

Gd-DTPA has been performed in infants or children. Nevertheless, it is relatively easy to make reasonable estimates of the half-life of Gd-DTPA injected into neonates. These estimates are based on three broad assumptions that have been shown to be true in adults: (a) that the diffusion time of Gd-DTPA from blood to the ECV is small compared with its elimination half-life, (b) that the volume of distribution of Gd-DTPA approximates the extracellular fluid space, and (c) that Gd-DTPA is totally cleared by glomerular filtration.

For substances that fit these assumptions (eg, Gd-DTPA or inulin), the elimination half-life ($T_{1/2}$) can easily be calculated as follows (24,25): $T_{1/2} = (ECV \times 0.693) / GFR$, where the ECV is the volume of distribution, GFR is the glomerular filtration rate

or renal clearance, and 0.693 is approximately the natural logarithm of 2. Extensive measurements are available for ECV and GFR at various points during the neonatal period (24-32). It is therefore possible to estimate the elimination half-life of Gd-DTPA injected into infants of various ages (Table 2). As shown in Table 2, the expected half-life of Gd-DTPA is greater than 6 hours in the full-term newborn and may be significantly higher in the premature infant. By age 6-8 weeks, however, the mean elimination half-life approaches the adult value of 1.5 hours. This marked age dependency of the half-life of Gd-DTPA results from differences in the relative volumes of distribution and GFRs between neonates and adults.

The quantity and distribution of body water change markedly throughout fetal development and infancy (24,26,29,30). In the 3rd fetal month, total-body water represents about 94% of the body weight (29). As gestation progresses, the amount of total-body water per kilogram declines, reaching approximately 78% of body weight by term. Characteristic changes also occur in the partition of body water between the intracellular and extracellular spaces. The ECV decreases from 60% of body weight during the 5th fetal month to about 45% at term.

After birth, the amount of total-body water per kilogram continues to decrease, due at least in part to a contraction of the ECV (29,30). This mobilization of extracellular fluid may be the result of improved renal function, as little significant change occurs in intracellular water content during this same period. By 3 months of age, the ECV falls to approximately 31% of body weight. By age 3 years, the adult range of ECV (20%-25%) is reached.

The approximately two-fold larger ECV fraction in neonates compared with adults holds immediate relevance for the administration of intravascular contrast material and all drugs. Renal excretion rates aside, the twofold larger relative ECV in neonates means that infants in whom Gd-DTPA is injected on a dose per kilogram basis will have a blood Gd-DTPA concentration of only one-half that in adults following equilibration. This fact argues against using a lower dose per kilogram in infants compared with adults, even though the serum half-life is prolonged. We therefore continue to use and recommend a dose of 0.1 mmol/kg for in-

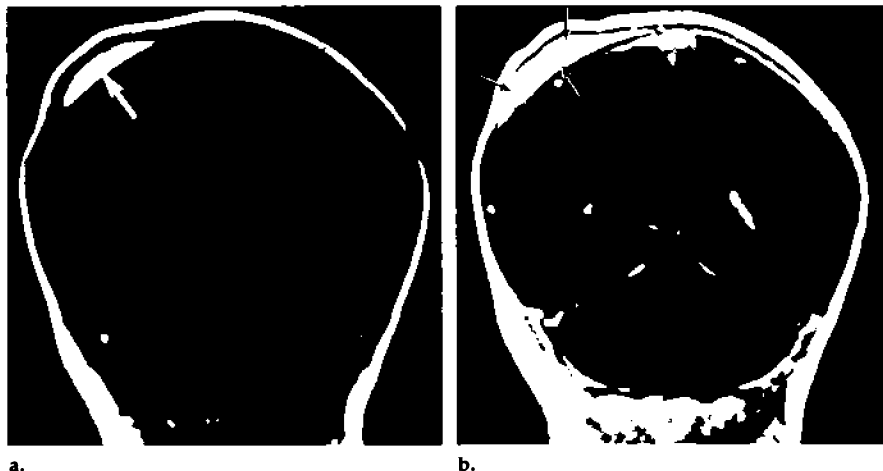


Figure 4. MR image of an infant with a 5-day-old cephalhematoma. (a) Precontrast coronal T1-weighted image shows high signal intensity from methemoglobin within the hematoma (arrow). (b) Postcontrast image shows enhancement, incidentally noted around the margins of this lesion (arrows).

Table 2
Predicted Elimination Half-Life of Gd-DTPA by Infant Age

Infant Age (wk)	ECV (L)	GFR (mL/min)	Calculated Half-Life (hr)
Newborn			
Premature (36 wk)	1.2	1.5	9.2
Term (40 wk)	1.4	2.5	6.5
2	1.5	5.0	3.5
4	1.6	9.0	2.1
6	1.7	12.0	1.6
Adult	16.0	120.0	1.5

Note.—Values are based on data from references 24-32.

fants until further data are available.

The second important difference between infants and adults concerning contrast material concerns the maturation of renal function. GFR is approximately 0.5 mL/min in premature infants of less than 34 weeks gestation, while term newborns have a GFR of about 2.5 mL/min (26,31,32). There is a sharp postnatal increase in GFR, which doubles by 2 weeks of age (27,28). When corrected for body surface area, GFR reaches adult values by approximately 1-2 years of age. Hemodynamic and morphologic changes seem to be responsible for this rapid maturation of renal function: a decrease in renal vascular resistance, an increase in effective filtration pressure, and an increase in glomerular permeability and filtering area (26). Renal tubular function also is immature in the neonate, resulting in a limited renal concentrating ability. This effect limits the visualization of the renal collecting system on excretory urograms obtained during the first few weeks of life. Because Gd-DTPA is apparently eliminated totally by glomerular filtration, however, tubular maturity does not play a role in its prolonged half-life.

Knowledge of the prolonged half-life of Gd-DTPA in neonates and young infants may be useful in certain clinical circumstances. For example, a sedated infant who awakes during Gd-DTPA infusion may be removed from the imager, resedated, and reimaged within 1-2 hours with no need for injection of additional contrast material. Alternatively, if only a postcontrast study is desired, the infant may be sedated and undergo Gd-DTPA infusion while still in the neonatal care unit, followed by nonurgent MR imaging.

Our preliminary analysis concerning the half-life of Gd-DTPA in neonates contains several unproved assumptions that await further experimental verification. It is not known whether the diffusion time of Gd-DTPA from blood to the extracellular space is the same in neonates and adults. We do not know whether other significant modes of Gd-DTPA excretion exist in neonates, such as into the gastrointestinal tract or biliary system. To our knowledge, no pharmacokinetic studies exist of Gd-DTPA in human infants or immature animals. Nevertheless, it is clear that the half-life of Gd-DTPA is signifi-

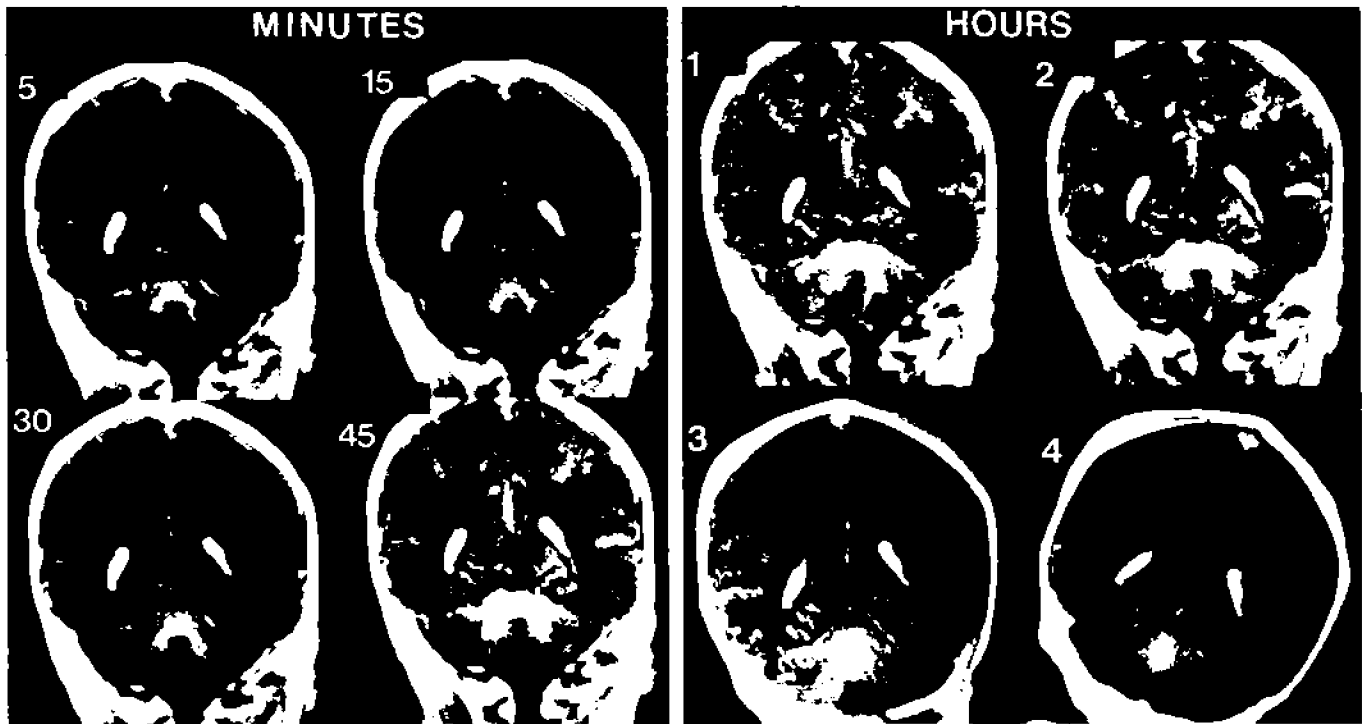


Figure 5. Sequential postcontrast MR images in a neonate born at 37 weeks gestation. No visually apparent difference during the first 2 hours can be noted. At 3 and 4 hours, contrast enhancement remains remarkably bright but is slightly diminished.

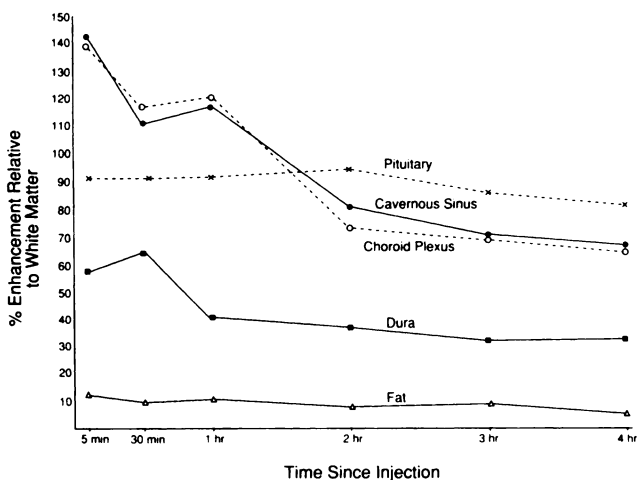


Figure 6. Percentage of enhancement of various intracranial structures versus time since injection for the same patient as in Figure 5.

cantly prolonged in neonates compared with that in adults, which may impact the Gd-DTPA dosage and timing of imaging relative to contrast material administration.

In conclusion, our preliminary study indicates that Gd-DTPA may be useful for evaluating intracranial lesions in neonates and young infants, especially those suspected to have intracranial infections. Because of the prolonged half-life of Gd-DTPA in neonates and young infants, an expanded window of time for postcontrast MR imaging may therefore be possible. The safety and efficacy of this agent, however, must still be proved in much larger clinical trials. Until that time, cautious and selec-

tive use of Gd-DTPA is still advised in this age group. ■

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