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Neurotoxic Effects of Gadopentetate Dimeglumine: Behavioral Disturbance and Morphology after Intracerebroventricular Injection in Rats

D. E. Ray, J. B. Cavanagh, C. C. Nolan, and S. C. R. Williams

PURPOSE: To determine the neurotoxic potential of gadopentetate dimeglumine in an animal model that allowed the agent to avoid the blood-brain barrier. Gadopentetate dimeglumine is known to produce functional changes when injected into the cerebrospinal fluid, and we hypothesized that such changes might be associated with morphologic damage. **METHODS:** Conscious rats, surgically prepared with a lateral ventricular cannula, were given a slow injection of gadopentetate dimeglumine into the lateral ventricle, and behavioral and neuropathologic changes were noted. **RESULTS:** Gadopentetate dimeglumine produced signs of acute neurotoxicity over several hours (stereotyped movements and myoclonus), medium-term signs over several days (ataxia and tremor), and neuropathologic changes over 24 hours, with reactive changes persisting for 42 days. All of the above were dose-dependent over the range of 2.5 to 15 $\mu\text{mol/g}$ brain. The lowest dose producing morphologic or behavioral changes was 5 $\mu\text{mol/g}$ brain. Iso-osmotic, isovolumetric injections of sucrose produced no such effects. Focal lesions occurred within the thalamus, brain stem, and spinal cord, with necrosis of glia, loss of myelin, and, usually, sparing of neurons and nerve fibers. Persisting ataxia was always associated with brain stem or spinal cord lesions. **CONCLUSION:** Intraventricular administration of contrast medium allows toxicity to be evaluated in areas such as the spinal cord that are not accessible by osmotic opening. While it is unlikely that these toxic effects would be seen at the doses used for clinical imaging by the intravenous route, gadopentetate dimeglumine clearly has some neurotoxic and neuropathologic potential. Although the acute excitation could be attributed to a transiently high local concentration of the agent at the injection site, the lesions were widely distributed through the brain and spinal cord and may reflect a region-specific neurotoxic action, possibly related to central pontine myelinolysis.

Index terms: Contrast media, paramagnetic; Contrast media, toxicity; Animal studies

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Gadopentetate dimeglumine (gadolinium complexed with diethylenetriamine pentaacetic acid [DTPA]), is a magnetic resonance (MR) imaging contrast agent widely used in clinical medicine. Although inorganic gadolinium salts are toxic, producing an acute anticoagulant effect that slowly develops into lethargy and re-

spiratory depression (1, 2), organic gadolinium chelates have produced few complications in clinical use for MR imaging enhancement of normal and abnormal brain structures (3, 4, 5) owing to the protective effect of chelation: intravenous gadopentetate dimeglumine is 20 times less toxic to rats than is unconjugated gadolinium chelates (6).

Studies involving osmotic opening of the blood-brain barrier in dogs have, however, suggested that gadopentetate dimeglumine can cause seizures and morphologic damage (7), but even well-controlled and reversible osmotic opening can of itself cause morphologic damage (8), creating difficulties in interpretation. Gadopentetate dimeglumine is also known to be capable of stimulating brain tissue metabo-

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lism at concentrations that might be reached in areas of blood-brain barrier damage (9), and the German Federal Health Office has drawn attention to the possibility that it may cause seizures in children younger than 2 years old (10). The toxicity of gadopentetate dimeglumine has been evaluated by Weinmann et al (5), who used the intracisternal route, but these workers carried out no neuropathologic investigations. Hence, we studied the neuropathologic potential of gadopentetate dimeglumine using the intraventricular route, which allows evaluation uncomplicated by potential vascular damage and also allows potential access to all parts of the central nervous system (CNS).

Methods

Intraventricular Injection

Rats were prepared for intraventricular injection by implantation of a sterile supradural guide tube over the left lateral ventricle 7 to 10 days before injection by a modification of the method of Goodrich et al (11). Under sodium pentobarbitone anesthesia, a 0.35-mm-diameter (30-gauge) stainless steel needle was advanced into the left lateral ventricle 1 mm lateral and 1 mm caudal to the bregma by using a stereotaxic device. The needle was previously fitted with a 5-mm-long, 0.6-mm-diameter (23-gauge) outer guide tube held 4 mm from the tip by a fixed stop. Pressure in the needle was maintained at 20 cm saline to prevent blockage, and penetration of the lateral ventricle was confirmed by the sudden fall in back pressure, which was then reduced to zero. When the needle was in place, the outer guide tube remained just above the surface of the dura. Two 1.2-mm-diameter (12BA gauge) stainless steel screws were then threaded into the skull on either side of the guide tube and the whole assembly firmly fixed in place with dental acrylic (Austen Dental Products Ltd, Harrow, England). Once the acrylic was set, the needle was withdrawn from the ventricle, leaving the outer guide tube in place. The guide tube was then temporarily closed with a 5-mm-long stainless steel stylet, and the rat allowed to recover consciousness.

Preparatory to making the injections, the rats were anesthetized with isoflurane and placed in a restraining hammock (Alice King Chatham Medical Arts, Hawthorne, Calif); the stylet was then removed and a sterile injection needle (identical to that used during implantation) manually inserted into the implanted guide tube. The rat was then allowed to recover consciousness and the injection was made by displacement from a length of sterile PE10 tubing (A. R. Horwell, London, England) using a saline-filled microliter syringe. The injection was made at a constant rate of 2 μ L/min, and mixing between the injectant and the displacing saline was prevented by a 1- μ L air gap. A delay of 2 minutes was allowed after the end of the injection before the needle was withdrawn and the stylet

replaced. The rat was then removed from the restraining hammock and placed in its home cage, where it was closely observed for at least 2 hours. Some initial experiments were made in unrestrained rats not placed in the hammock. Animals were allowed to survive for a period ranging from 4 hours to 42 days after injection, during which they were observed daily.

Animals

Male F344 rats (8 to 10 weeks old) weighing 200 g to 250 g were used for all experiments. Rats were bred at the Toxicology Unit and maintained in individual plastic cages with ad libitum access to pelleted 41B diet (Labsure, Poole, England) and tap water.

Chemicals

Magnevist injection was obtained from the manufacturer (Schering AG). The solution consists of a sterile 0.5-mol/L aqueous solution of the di-*N*-methylglucamine salt of the gadolinium chelate of DTPA (469 mg/mL). Sucrose (Sigma Chemical Co) was dissolved in distilled water at a concentration of 418 g/L and passed through a sterile 0.4- μ m filter before injection. The osmolality of both solutions was 1.96 osm/kg water.

Motor Disturbances

Rats were assessed daily for the severity of ataxia and muscle weakness according to the following 10-point scale: 1 = body sways when walking; 2 = legs extended or splayed when walking; 3 = slow to pick up hind legs when walking; 4 = clear signs of hind limb weakness; 5 = occasionally drags a leg when walking; 6 = hind legs splayed out behind body; 7 = some additional forelimb weakness; 8 = cannot lift 350 g with forelimbs; 9 = difficult to right body; and 10 = unable to right body. Any rats sufficiently incapacitated to be unable to feed or drink were humanely killed within 12 hours, and all animal procedures conformed to United Kingdom Home Office animal welfare requirements.

Histology

Rats were killed by perfusion through the ascending aorta with 10% formalin, 2% acetic acid fixative while under deep ether anesthesia. Perfusion was continued for 12 minutes at a pressure of 100 to 120 mm mercury, and was preceded by a 1-minute flush with heparin and saline to remove blood according to the method of Brown and Brierley (12). The head was then stored for 2 to 24 hours in fixative at 4°C before the brain was removed. The brain and cervical spinal cord were divided into five coronal blocks, dehydrated, embedded in wax, cut into 10- μ m step serial (1 in 20) sections, stained with hematoxylin and eosin, and examined by light microscopy. Additional selected sections were stained with Luxol fast blue/cresyl

TABLE 1: Frequency of behavioral disturbances in rats after injection of sucrose and gadopentetate dimeglumine at varying doses

Injectant	Type of Disturbance					
	Circling*	Myoclonus		Biting§	Ataxia/Weakness	
		Focal†	Generalized‡		Same Day	at 24 h
Sucrose						
40 μ L	0/4	0/4	0/4	0/4	0/4	0/4
60 μ L	2/2	0/2	0/2	0/2	2/2	0/2
Gadopentetate dimeglumine						
10 μ L (2.5 μ mol/g brain)	0/4	0/4	0/4	0/4	0/4	0/4
15 μ L (3.3 μ mol/g brain)	0/4	0/4	0/4	0/4	0/4	0/4
20 μ L (5 μ mol/g brain)	2/4	1/4	0/4	0/4	4/4	0/4
40 μ L (10 μ mol/g brain)	17/23	20/23	1/23	0/23	23/23	18/20
60 μ L (15 μ mol/g brain)	3/3	3/3	3/3	3/3	3/3	3/3

* Seen over 10 to 100 minutes, midpoint of 42 ± 2.5 minutes after start of injection.

† Seen over 11 to 100 minutes, midpoint of 38 ± 2.6 minutes.

‡ Seen over 32 to 42 minutes, midpoint of 38 ± 1.8 minutes.

§ Seen over 25 to 76 minutes, midpoint of 41 ± 3.8 minutes.

|| Seen over 24 to 144 hours, midpoint of 65 ± 4.5 hours.

fast violet, Glee's and Marsland's silver method, periodic acid-Schiff, or Perls's method for iron.

MR Imaging

A single anesthetized rat was prepared for MR imaging by using a slightly modified nonmagnetic injection system. This involved substitution of an in-dwelling silica tube for the stainless steel injection needle, and sterile wooden plugs for the stainless steel retaining screws. Conventional T1-weighted MR images (900/34/2 [repetition time/echo time/excitations]) were collected at a temporal resolution of 8 minutes over the first 3 hours and subsequently at 24 hours after injection using a 4.7-T, 33-cm bore Sisco (Varian Associates, Palo Alto, Calif) system. Twelve contiguous 1.7-mm-thick transverse sections were collected at an in-plane resolution of 150 μ m using conventional hardware capable of generating magnetic field gradients of 10 mT/m. In addition, the perfusion-fixed heads of two animals, one 4 days after injection of 40 μ L gadopentetate dimeglumine and one sucrose control animal, were examined postmortem.

Results

Behavioral Changes

The nature and time course of behavioral changes are summarized in Table 1. Control sucrose injections at 40 or 60 μ L produced a hunched posture and rapid respiration for up to 5 minutes after injection. After injection of 60 μ L sucrose, rats also showed transient circling behavior and were reluctant to walk for 2 to 3 hours. With 20 μ L gadopentetate dimeglumine (5 μ mol/g brain), but not with 10 or 15 μ L, variably clockwise or counterclockwise circling

behavior developed, as did transient intermittent myoclonic twitching of the dorsal neck and back muscles, suggestive of focal seizure activity. At 40 μ L (10 μ mol/g brain), a degree of ataxia was also seen, which ranged in severity from grade 1 to grade 10, and began 28 to 220 minutes after injection and lasted for up to 8 days. The mean time of onset of grade 2 or greater ataxia was 64 ± 14 minutes. By 24 hours the overall mean ataxia score fell to 3.2. A further sign was a fine muscular tremor that began 1 to 2 days after dosing, varied in peak severity from mild to moderately incapacitating, involved all palpable muscle groups, and was seen both at rest and during activity. At 60 μ L gadopentetate dimeglumine (15 μ mol/g brain), rats showed similar but more severe signs, plus stereotyped sniffing and biting shortly after the injection. No tonic seizures were seen at any time and respiration was not visibly compromised. One rat died spontaneously between 8 and 22 hours after injection, and was thus not available for morphologic study.

Changes in Body Weight

Rats injected with 40 μ L sucrose showed a normal pattern of weight gain, but animals given 60 μ L transiently lost 10 to 15 g. Gadopentetate dimeglumine at 20 μ L produced a modest, transient weight loss of not more than 10 g, but at 40 and 60 μ L, weight losses were in the region of 30 to 40 g, with gradual recovery over 10 to 20 days.

TABLE 2: Frequency of morphologic changes in rats after injection of sucrose and gadopentetate dimeglumine at varying doses

Injectant	Thalamus	Hypothalamus	Superior Olivary Nuclei	Medulla	Spinal Cord	All Areas
Sucrose						
40 μ L	0/2	0/2	0/2	0/2	0/2	0/2
60 μ L	0/2	0/2	0/2	0/2	0/2	0/2
Gadopentetate dimeglumine						
10 μ L (2.5 μ mol/g brain)	0/4	0/4	0/4	0/4	0/4	0/4
15 μ L (3.3 μ mol/g brain)	0/4	0/4	0/4	0/4	0/4	0/4
20 μ L (5 μ mol/g brain)	1/4	0/4	0/4	0/4	0/4	1/4
40 μ L (10 μ mol/g brain)	8/17	1/17	13/17	2/17	6/17	17/17
60 μ L (15 μ mol/g brain)	2/2	1/2	2/2	2/2	2/2	2/2

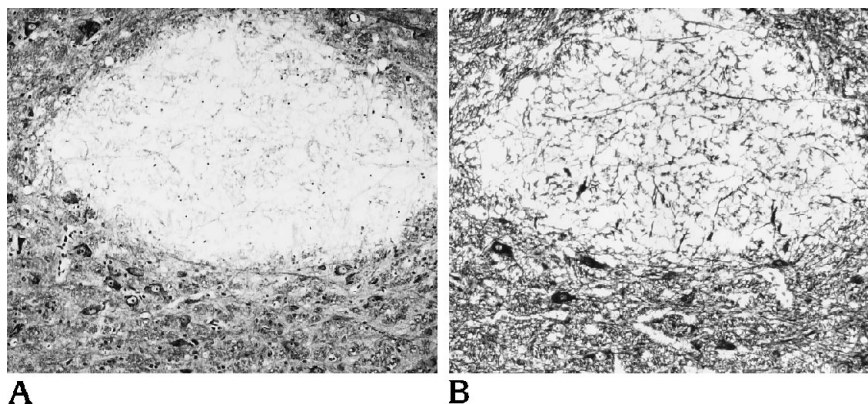
Morphologic Findings

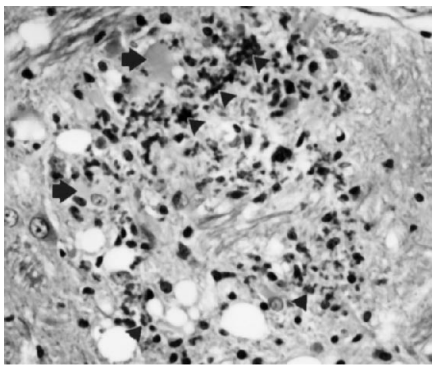
Nonspecific changes.—In all but one animal the small injection needle track was associated with evidence of slight hemorrhage and local damage to the corpus callosum. The ventricles were often slightly enlarged, and there was occasionally a slight depression on the surface of the neocortex in the area beneath the fixing screws, with thickening and increased cellularity of the overlying pia-arachnoid. These changes were seen in both sucrose control animals and gadopentetate dimeglumine-injected rats. In one of the animals that received 20 μ L of gadopentetate dimeglumine and survived 42 days, an empty cyst, 100 μ m in diameter, was seen in the white matter of the corpus callosum and adjoining subcortical white matter. The cyst was presumed to represent the site of a failed lateral ventricle penetration. This animal showed no other morphologic changes.

Gadopentetate dimeglumine.—The results are summarized in Table 2. All affected rats given 20 to 60 μ L of gadopentetate dimeglumine showed changes of dose-related severity but of the same general nature in all regions.

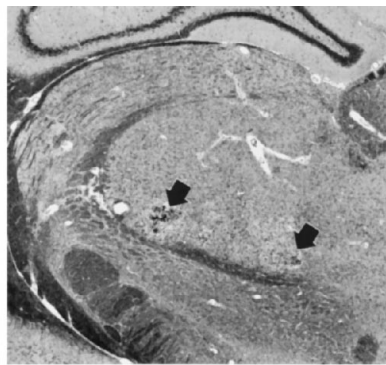
The early changes seen 24 hours after the intraventricular infusion (three animals) consisted of sharply circumscribed foci of loss of oligodendroglia and astroglia, with accompanying disintegration of myelin sheaths in these foci (Fig 1A). Axons running through the lesions were usually spared (Fig 1B), but occasionally in the larger foci neurons also showed some necrotic changes. Vessels in these lesions were apparently unaltered and no hemorrhages were seen in any of them. There were no alterations in the vessels of the choroid plexus, either. Five days after injection (two animals) the lesions showed a marked increase in the number of microglia/macrophages and hyperplasia of astrocytes (as shown in Fig 2), as well as hypertrophy of small vessels within the lesions. Essentially the same changes of a tissue repair nature were present in the lesions at 10 days (two animals), 14 days (two animals), 21 days (one animal), 28 days (two animals), 35 days (two animals), and 42 days (four animals), except that at these stages there was the appearance of fine eosinophilic granules (2 to 5 μ m in diameter) in the neuropil of the healing lesion

Fig 1. Histopathologic sections in rats 24 hours after intraventricular infusion of 20 to 40 μ L of gadopentetate dimeglumine show focal loss of myelin in the medulla (Luxol fast blue and cresyl fast violet stains, A) and preservation of axons in the same lesion (Marsland, Glees, and Erikson silver stain, B; magnification $\times 180$).





2



3

Fig 2. Small eosinophilic granules (*arrow-heads*) and reactive astrocytes (*arrows*) are seen in a thalamic lesion at 28 days after injection (hematoxylin and eosin stain; magnification $\times 600$, coronal section).

Fig 3. Cellular thalamic lesions (*arrows*) are seen at 42 days after injection (Luxol fast blue and cresyl fast violet stains; magnification $\times 35$).

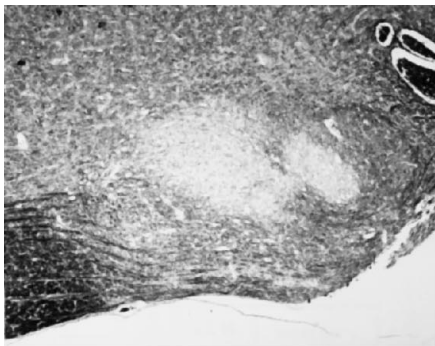
(Fig 2). These fine granules appeared to coalesce with advancing time and in those animals killed at 42 days they were readily visible as irregular brightly eosinophilic masses of up to 50- μ m diameter (Fig 3), that stained positively with the periodic acid-Schiff reaction, suggesting a probable content of glycoproteins. No mineralization of these bodies was detected, but the use of acetic acid fixative may have impaired any detection of this. These bodies were more apparent in the thalamic lesions than elsewhere.

The distribution of the lesions is summarized in Table 2. In animals given the two higher doses, lesions were usually symmetrical, and most commonly lay in the superior olivary nuclei (Fig 4) and in the ventrolateral nuclei of the thalamus (Fig 5). Spinal cord lesions were seen at both the lumbar and cervical levels, usually at the gray matter-white matter junction (Fig 6). Isolated lesions were also occasionally seen in

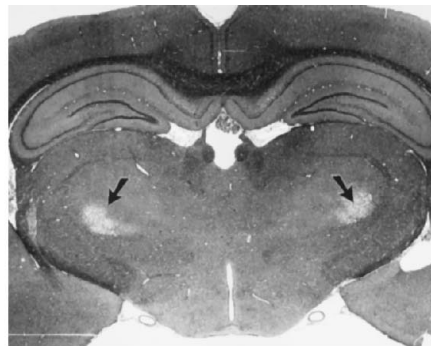
the facial, trigeminal, and vestibular nuclei, and in the hypothalamus.

MR Imaging

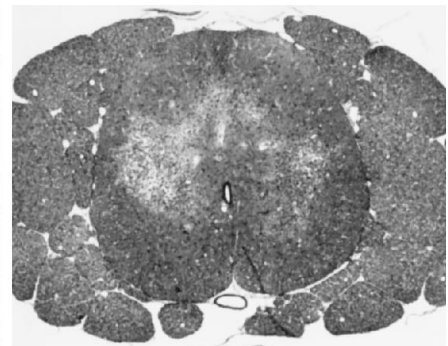
MR image enhancement showed that the injected gadopentetate dimeglumine mixed rapidly through the ventricular system, reaching the third ventricle within 40 minutes of the start of the injection. Marked enhancement was seen unilaterally along the injection needle track and weak enhancement bilaterally at the base of the lateral ventricles (Fig 7). Enhancement of the ventricular space was still visible at 24 hours (Fig 8), but no significant enhancement of brain tissue was visible at this time, either by T1 or conventional T2 imaging. Similarly, a prolonged scan of a fixed postmortem brain 4 days after injection showed enhancement of the ventricular spaces, but not of deeper brain tissue. Subsequent histologic examination of this brain



4



5



6

Fig 4. Large vacuolar superior olivary lesion is present at day 1 after injection (Luxol fast blue and cresyl fast violet stains; magnification $\times 68$).

Fig 5. Bilateral vacuolar lesions (*arrows*) of the ventrolateral thalamus are seen at 21 days (hematoxylin and eosin stain; magnification $\times 14$).

Fig 6. Asymmetric cellular lesions in the gray matter of the caudal spinal cord are seen at 5 days (hematoxylin and eosin stain; magnification $\times 110$).

Fig 7. Series of three transverse T1-weighted MR images (900/34) acquired before (*bottom*) and 3 hours after intraventricular administration of 20 μ L gadopentetate dimeglumine (*middle*), and a difference image (*middle* – *bottom*) (*top*). In *top* image, note the highlighted bilateral enhancement of the ventral cortex (arrows).

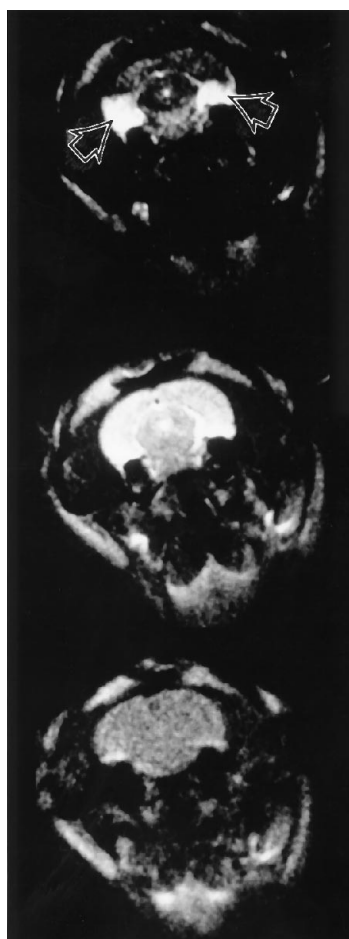
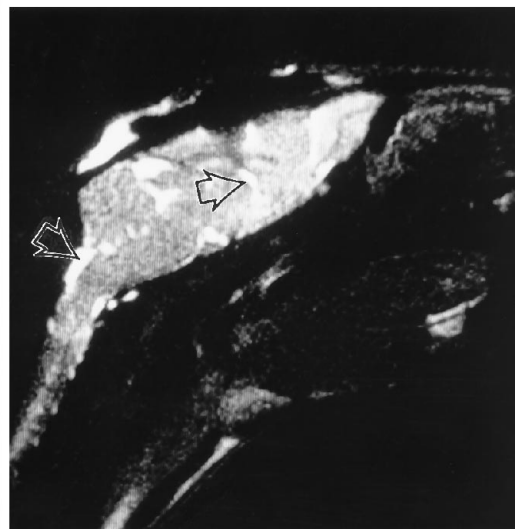


Fig 8. Parasagittal MR image of a rat head 24 hours after injection of 20 μ L gadopentetate dimeglumine shows enhancement of the ventricular and cisternal space (arrows).



showed lesions typical of the rest of the gadopentetate dimeglumine series.

Discussion

These results show that gadopentetate dimeglumine has the potential to produce severe motor disturbances associated with widely disseminated lesions in the CNS of rats after intraventricular administration at doses of 5 to 15 μ mol/g brain. Persisting ataxia and weakness was the most prominent sign of poisoning, consistent with the distribution of lesions in the spinal cord and medulla. The lesions in the ventral thalamus and superior olives would not be expected to produce obvious motor signs, as these are essentially sensory projection nuclei. Tremor was the last motor sign to develop at 1 to 3 days, although this was not associated with the appearance of new lesions in motor areas. The transient myoclonus and stereotyped behavior produced by gadopentetate dimeglu-

mine were probably the result of nonspecific local excitation, similar to that seen after injection of ionized iodinated contrast agents into the cerebrospinal fluid of humans and animals (13). This is consistent with our demonstration of early MR image enhancement at the site of the injection. Transient circling was produced by both gadopentetate dimeglumine and the highest dose of sucrose, and may have resulted from an osmotic action.

Weinmann et al (5) have also reported seizures or lack of motor coordination after intracisternal administration of gadopentetate dimeglumine to rats. The median effective dose for acute effects was 74 μ mol/kg, with a median lethal dose of 650 μ mol/kg. (These values are incorrectly given as mmol/kg in the original publication; H-J. Weinmann, personal communication.) This median effective dose would correspond to approximately 4 μ mol/g brain, a value that agrees well with our observation of 25% seizures at 5 μ mol/g brain. A similar me-

dian lethal dose value of 529 $\mu\text{mol/kg}$ (approximately 50 $\mu\text{mol/g}$ brain) was reported by Adams et al (14). These workers also found impaired grip strength, incoordination, and persistent hind limb paresis at 150 $\mu\text{mol/kg}$ (18–15 $\mu\text{mol/g}$ brain), which agrees well with our findings. The incoordination showed an early phase reversing over 2 hours, and a late phase developing over 4 to 96 hours, but the late tremor seen in our animals was not reported. At 50 and 100 $\mu\text{mol/kg}$, only transient incoordination was seen, this lowest dose corresponding to 5–6 $\mu\text{mol/g}$ brain. Both Adams et al (14) and Weinmann et al (5) used the same injection concentration as that used in our investigation, but neither reported any histologic observations. Our results are also consistent with the findings of Roman-Goldstein et al (7) in that these authors found acute excitation and brain lesions at 0.1 to 0.2 mmol/kg gadopentetate dimeglumine using the different model of intravenous administration in dogs with osmotic barrier disruption. However, the dogs showed seizures after a much longer latency period (0 to 19 days) than that seen in the present study, and the corresponding neuropathologic damage was reported as largely hemorrhagic infarcts. This latter finding may have been caused by an interaction with the vascular effects of the osmotic opening. The lesion topography also differed from that seen in the present study, but this was not unexpected, as an osmotic opening does not allow access to the brain stem or spinal cord, where most of our lesions were seen. In another study, there were no adverse behavioral effects in Rhesus monkeys given a cumulative dose of 30 $\mu\text{mol/kg}$ gadopentetate dimeglumine via the cisterna magna (15). This dose is equivalent to approximately 4 $\mu\text{mol/g}$ brain, but anesthesia was used throughout, and the follow-up period was not specified.

The initial cellular targets of the gadopentetate dimeglumine lesion are difficult to define precisely at the level of the light microscope, but the lesions appear to be primarily nonneuronal and, because loss of oligodendrocytes and a reduction in astrocytic number were evident at 24 hours, glial cells appeared particularly at risk. The lesion distribution was multifocal and variable, although some regions, such as the superior olives and spinal cord, were frequently involved while others, such as the hippocampus, cerebellar cortex, and neocortex,

were spared. This topography clearly does not parallel that which would be expected by simple diffusion from the cerebrospinal fluid, since areas distant from any ependymal or pial surface, such as the thalamus (Fig 5), were regularly involved while superficial structures were spared. This distribution contrasts with that of the astrocytic and myelinolytic lesions seen in rats after intraventricular injection of methotrexate (16), or the oligodendrocytic lesions seen after intracisternal injection of ethidium bromide (17), which were both local to the injection site. In our study, successful injection of gadopentetate dimeglumine produced local damage in only one animal, which consisted of largely bilateral hippocampal lesions confined to the H1 region. Thus, intraventricular administration can provide an effective means of delivering gadopentetate dimeglumine to the intact CNS without producing artifactual local damage at the injection site.

The quantitative distribution of intracerebroventricularly injected gadopentetate dimeglumine is not known, but a widespread distribution of the hydrophilic antimetabolite 5-aminolevulinic acid was seen after a similar injection protocol (19). Similarly, the tissue dose of gadopentetate dimeglumine received by the brain in clinical practice is unknown, and will vary with region and individual disease state, but the threshold intraventricular dose range of 10 μmol per rat used in this study is half of the entire conventional intravenous imaging dose of 0.1 mmol/kg (20 μmol per rat). Brain tissue levels in areas without a functional blood-brain barrier might approach peak plasma levels that, from a study of rabbits given intravenous gadopentetate dimeglumine (9), would be 1.2 $\mu\text{mol/g}$ after a dose of 0.1 mmol/kg. This is four times lower than the threshold dose found in the present study. Were gadopentetate dimeglumine uptake similar to that of doxorubicin hydrochloride seen after intracarotid injection in rats or dogs after osmotic disruption (18), brain concentrations after 0.1 $\mu\text{mol/kg}$ would be 0.045 $\mu\text{mol/g}$ (rat data) or up to 0.9 $\mu\text{mol/g}$ (dog data). These values correspond to 110 and 5.5 times less than the threshold dose used in the present study.

The lesions produced in the CNS by the intraventricular infusion of gadopentetate dimeglumine have close similarities to the human condition of central pontine myelinolysis. This condition was noted in rehydrated alcoholic and

malnourished subjects (20), a rapid change in plasma osmolarity being the essential feature of the pathogenesis of the brain lesions (21). The condition has been produced by manipulation of plasma sodium levels in rats, dogs, and rabbits (22–26), and involves lesions in the brain stem and the thalamus essentially similar to those reported here. Unfortunately, the spinal cord was apparently not examined in any of these animal studies. As with the gadopentetate dimeglumine-induced lesions, the changes vary from partial to complete tissue necrosis, with most lesions, however, not advancing beyond death of oligodendroglia and astrocytes with associated myelin loss. Topographically, they are usually found where white matter and gray matter are intermixed, typically in the pons and possibly in the dorsal columns of the spinal cord (27). The similarity of the two lesions suggests that the gadopentetate dimeglumine lesion also may have been induced by an osmotic or ionic imbalance between the inside and outside of brain cells. Although the osmolarity of the gadopentetate dimeglumine injectant (1.96 osm/kg water) was 6.9 times that of plasma, sucrose at the same high osmolarity did not produce similar effects. Iso-osmotic sucrose was chosen as the control injectant because, like gadopentetate dimeglumine, it contained no sodium ions and would be expected to diffuse away from the injection site only gradually. Sucrose is, however, nonionic, which leaves the possibility of damage being a nonspecific toxic effect of a high-ionic-strength injectant.

The zinc chelating action of the DTPA used in gadopentetate dimeglumine might conceivably play a role in the pathogenesis of the lesions. At 50 $\mu\text{mol/L}$, DTPA has a selectivity for gadolinium over zinc by a factor of 6310, but values for this selectivity parallel toxicity across a range of gadolinium chelators (28, 29). Hence, free-brain zinc might displace some gadolinium from the chelator resulting in either gadolinium toxicity or zinc depletion. Total brain zinc ranges from 170 to 260 $\mu\text{mol/L}$, with chelatable zinc levels being at least 30% lower owing to protein binding (30), although gadopentetate dimeglumine-sensitive regions, such as the superior olivary nuclei and thalamic nuclei, are not high in zinc content compared with other brain regions (31, 32) (G. Danscher, personal communication). Oligodendrocytes are, however, known to have a high zinc content, and it has been suggested that the copper chelator

cuprizone may cause demyelination via zinc chelation (33). Cuprizone lesions show morphologic similarities to those produced by gadopentetate dimeglumine, although the topography differs in both rats (34) and mice (35), which may reflect different biodistribution after systemic and intraventricular administration.

The overall conclusion of this study is that gadopentetate dimeglumine has a low but finite neurotoxic potential when injected directly into the cerebrospinal fluid, and an unexpected degree of regional specificity in producing lesions distant from the site of injection. Because modern contrast-enhanced dynamic MR imaging can involve larger cumulative doses of gadolinium chelates, this finding may be of importance; but before we can understand the nature and specificity of this neurotoxicity, we need to investigate the mechanism of lesion production by making comparisons with related agents given by the same route and at a range of ionic strengths. Our findings also emphasize the need to develop better toxicologic models, which allow quantifiable access of potentially harmful agents to the CNS.

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