

CASE REPORT

Overdosage of intrathecal gadolinium and neurological response

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Introduction

Gadopentetate dimeglumine (gadolinium complexed with diethylenetriamine pentaacetic acid; Gd-DTPA) is the most commonly used contrast agent in magnetic resonance imaging (MRI). It has been proven safe for intravenous administration in routine clinical practice (at dose of 0.1 mmol/kg), although it has been shown to cause a number of systemic adverse effects, of which nausea or vomiting and headache are most commonly observed with a frequency ranging from 0.26–0.42%.¹

Intrathecal administration of Gd-DTPA (MR cisternography or myelography) is useful in a number of pathophysiological conditions, such as the assessment of communication or obstruction of cerebrospinal fluid (CSF) pathways, spontaneous or acquired CSF fistula evaluation, or the study of the dynamics of gadolinium diffusion,^{2–4} although this may introduce a higher incidence of headache, nausea, and vomiting in the lower dose (0.18–0.36 $\mu\text{mol/g}$ brain) in humans.^{3–11} Relatively severe behavioural changes, neurological alterations, and seizure activity have been reported at doses of 5–15 $\mu\text{mol/g}$ brain in animal experiments.^{12–14} The best balance between potential Gd-DTPA toxicity and MR myelographic quality in humans is extremely difficult to determine, and high doses (or accidental overdose) of Gd-DTPA in humans have never been reported.

The present study reports a case in which a patient underwent a MR myelography and in

the process inadvertently received a high dose of intrathecal Gd-DTPA (approximately 5.35 $\mu\text{mol/g}$ brain), that was approximately 30 times the recommended dosage used in humans, and roughly equivalent to the lowest dose that could cause severe neurotoxicity in animals. Clinical manifestation, MR image characteristics, and rescue procedures are emphasized and discussed.

Case report

A 34-year-old woman was admitted to our hospital on 15 January 2007 with left upper limb dyskinesia caused by a traumatic injury 3 weeks previously. At admission, neurological examinations indicated hypoesthesia and paralysis of the left upper limb. She was diagnosed with brachial plexus injury and was admitted to the hospital for surgical correction.

Myelography was performed 1 day after admission. Fifteen millilitres of Gd-DTPA (500 $\mu\text{mol/ml}$ or 5.35 $\mu\text{mol/g}$ brain) was inadvertently administered intrathecally at a speed of approximately 7.8 ml/min through a lumbar puncture. The patient immediately complained of headache, accompanying nausea, and vomiting. She became comatose approximately 1 h after the incident, and additionally had an outbreak of systemic seizures. Treatment was immediately initiated, with the patient receiving a high dose of intravenous methylprednisolone (1 g/day) for 7 days. Chlorpromazine 50 mg and phenergan 50 mg were given intravenously for 2 days, after which naloxone 4 mg was given intravenously for 7 days. A catheter was placed into the lumbar cisterna to drain CSF with a speed of 0.3–0.5 ml/min.

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Her CSF analysis revealed 2640.3 mg/l protein, 5.1 mmol/l glucose, 105.4 mmol/l chloride, and a normal cell count on the day of the incident.

Brain MRI using a 3.0 T machine was performed on day 6 after the injection. The signals in CSF cisterns and cerebral sulci on fluid-attenuated inversion recovery (FLAIR) images (Fig. 1a) and T1-weighted images (Fig. 1b) were prominently increased, especially in the posterior part of the cerebrum. Generalized enhancement of the cerebral cortex and marked enhancement in the deep parieto-occipital white matter was seen in T1-weighted images (Fig. 1b). The enhanced white matter contained hyperintense linear structures, indicating penetration of Gd-DTPA into the deep parenchyma via the perivascular spaces (Fig. 1b). T2-weighted images showed

slightly increased signals in the corona radiata and centrum semiovale (Fig. 1c). Diffusion-weighted imaging ($b = 1000 \text{ s/mm}^2$) depicted abnormal hyperintense signals in the right insular cortex, bilateral thalamus, basal ganglia, and corona radiata (Fig. 1d), and apparent diffusion coefficient (ADC) maps illustrated low signal in the cerebellum, brainstem, basal ganglia, and cerebral cortex, indicating widespread cerebral oedema (Fig. 2a). MR angiography (MRA) showed significant vasospasm in branches of the middle, anterior, and posterior cerebral arteries (Fig. 3a).

The CSF was continuously drained for 6 days. The CSF analysis was normal on day 7. She regained consciousness on day 8 after the myelography.

The patient's heart rate, blood pressure, and blood oxygen saturation levels were checked

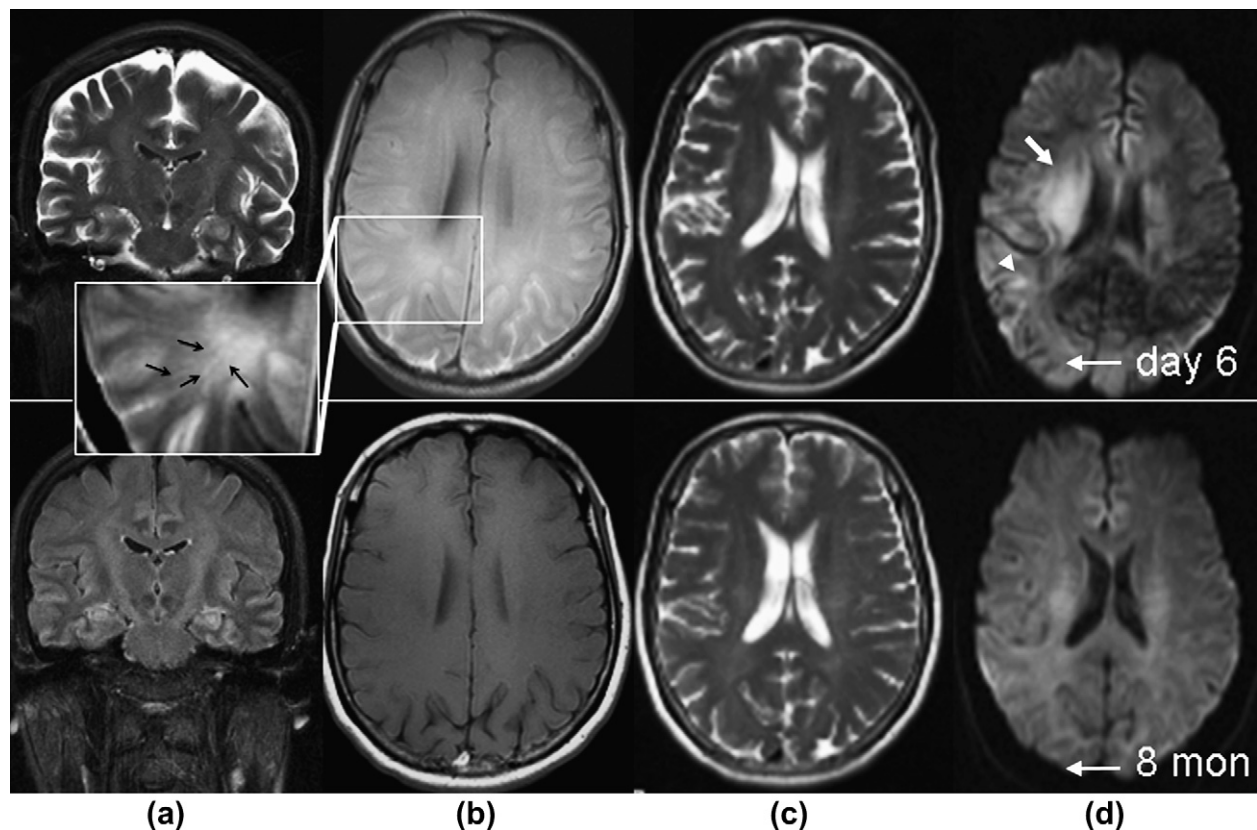


Figure 1 MR images showing abnormalities on day 6 and change over time after the intrathecal Gd-DTPA injection. (a) Coronal FLAIR images through the inter-peduncular cistern show prominent CSF enhancement on day 6 after the injection, and the cerebral cortex (including hippocampus) and deep white matter remain relatively enhanced after 8 months. (b–d) Axial MR images through the body of the lateral ventricle. (b) T1-weighted images show diffused sulcal CSF enhancement, and marked parieto-occipital white matter enhancement on day 6 after the injection. Linear hyperintense signals (black arrows) in the enlarged image indicate the penetration of Gd-DTPA into the deep white matter through the perivascular spaces. After 8 months, signal intensities are significantly reduced in the cerebral cortex and deep white matter. (c) T2-weighted images are essentially normal in both the day 6 and 8 months follow-up images, except for slightly increased intensities in the deep white matter of the corona radiata. (d) Diffusion-weighted images ($b = 1000 \text{ s/mm}^2$), obtained on day 6 after intrathecal overdosing of Gd-DTPA, show hyperintense signals in the corona radiata (arrow), and right posterior temporal lobe (arrowhead), indicating possible ischaemic changes. However, the follow-up images at 8 months show only slightly increased signal in those regions.

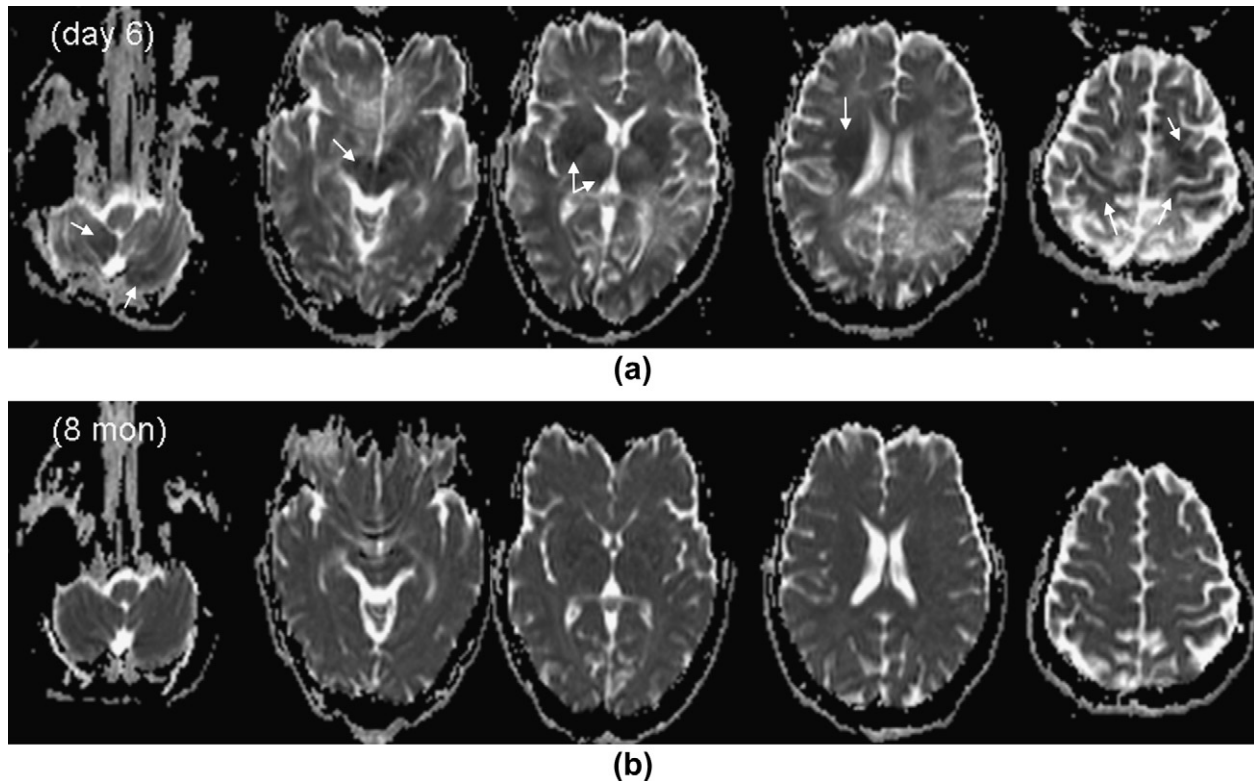


Figure 2 (a) Axial ADC map obtained on day 6 after the injection, reveals hypointense signals scattered in the cerebellum, brainstem, basal ganglia, corona radiata, and cerebral cortex (arrows), indicating restricted diffusion, which returned to normal diffusion after 8 months (b).

during her hospitalization. Standard blood biochemistry was studied before and after the intrathecal Gd-DTPA injection. The study included glucose concentration, creatine level, liver enzyme concentration, creatine phosphokinase level, lipase level, lactate dehydrogenase concentration, haemoglobin level, and red, white and platelet cell counts. Results of the biochemistry studies were within the normal range.

Except for the signs of the left brachial plexus injury, her physical examination was normal. Her higher nervous system activities, including orientation, memory, and comprehension were good. She was discharged on day 22 after the intrathecal Gd-DTPA myelography.

In her first follow-up (approximately 2 months after the myelography), she had no significant complaints. Repeated brain MRI demonstrated similar enhancement on the surface of cerebral parenchyma on T1-weighted and FLAIR images, but to a much lesser extent than directly after the incident and CSF analysis was clear. ADC maps had also returned to normal.

At the 6 and 8 months follow-up examinations after the intrathecal overdosing of Gd-DTPA she was in good condition without complaints. MR imaging

was also repeated at these two visits, and slight cortical enhancement still remained (Fig. 1a); white matter intensities were slightly increased in the corona radiata on T2-weighted images (Fig. 1c) and diffusion-weighted images (Fig. 1d); no necrotic lesions were seen; and ADC maps (Fig. 2b) and MR angiography appeared normal (Fig. 3b).

Discussion

A severe neurotoxic response after an intertheal or intraventricular injection of Gd-DTPA has been related to a higher dose in animal models,^{13,14} in which 5–15 $\mu\text{mol/g}$ brain could produce severe neurological alterations, including ataxia, weakness, delayed tremor, or stereotyped behavior.¹³ Seizures have been reported at a rate of up to 25% at doses of 4–5 $\mu\text{mol/g}$ brain.^{13,15} Impaired grip strength, lack of coordination, and persistent limb paresis would likely be evident at doses of 15–18 $\mu\text{mol/g}$ brain.¹³ Histopathological changes, such as loss of oligodendroglia, hypertrophy of astrocytes, formation of eosinophilic granules, have been observed in the brainstem, thalamus, and spinal cord at a dose of 5 $\mu\text{mol/g}$ brain in animal

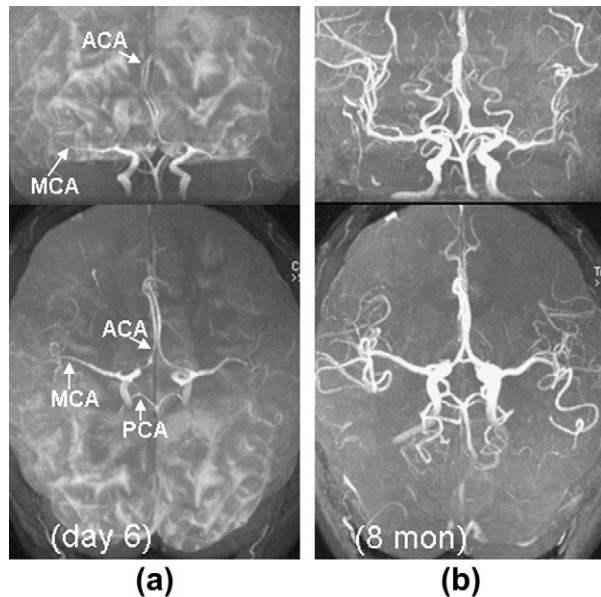


Figure 3 MR angiograms in the anterior–posterior view (top), and 30° caudal to the anterior–posterior view (bottom). (a) MR angiogram obtained on day 6 after the injection reveals an overall significant angiographic vasospasm in the anterior (ACA), middle (MCA), and posterior (PCA) cerebral arteries, demonstrated with either tapering or narrowing of the proximal segments and poor visualization in the distal segments. The patchy, cloud-like high-signal areas, which appear more prominent in the posterior portion of the brain, are the Gd-DTPA contrast agent that has diffused into the CSF spaces. (b) MR angiogram obtained 8 months after the intrathecal Gd-DTPA injection illustrates normal appearance and flow in all major cerebral arteries and no Gd-DTPA enhancement in the CSF spaces.

models.^{13,14} Relatively high doses could also cause an increase in CSF pressure and CSF protein concentration.⁷ In contrast, behavioural and morphological changes were not seen when the dose of intraventricular Gd-DTPA was less than 3.3 $\mu\text{mol/g}$ brain.^{7,13}

Several pilot and multicentre studies in humans have shown no clinical evidence of acute or chronic biological, behavioural, and significant gross neurological abnormalities after low-dose intrathecal injection of Gd-DTPA at concentrations of 0.5–1.0 ml (500 mmol) or 0.18–0.36 $\mu\text{mol/g}$ brain.^{9,10,16} The lower end of this range (0.18 $\mu\text{mol/g}$ brain) was about 30 times less than the 5 $\mu\text{mol/g}$ brain, which is the lowest dose shown to bring on toxic central nervous system (CNS) alterations in animal models.^{13,14}

In the present case, the total volume of intrathecal Gd-DTPA of 15 ml (500 mmol/ml) (about 5.35 $\mu\text{mol/g}$ brain) injected through the lumbar puncture was coincidentally similar to the lowest

dose that causes severe CNS alterations in animals^{13,14} or 30 times over the usual dose used in humans.^{10,16} However, the patient's response to that dose of intrathecal Gd-DTPA was much more intense than the reactions reported in animal studies. The patient not only immediately presented with headache, nausea, and vomiting, involuntary stereotyped movement and episodic systemic seizures, and increased CSF protein concentration, but also coma, which has never been reported in toxicity studies even in animal models.

The osmotic pressure of gadopentetate dimeglumine is about 1940, which is roughly six to seven times the plasma osmotic pressure in humans.¹⁷ The contrast agent should be mixed with the patient's native CSF (1:5 to 1:10) before subarachnoid injection. The mixture should then be slowly injected, at a rate of approximately 1 ml/min. By diluting the contrast agent and slowly injecting the dose into the subarachnoid space, hyperosmolar toxic effects should be clearly diminished.¹⁶ In the present patient, 15 ml Gd-DTPA (500 $\mu\text{mol/ml}$ or 5.35 $\mu\text{mol/g}$ brain), which was not diluted with the patient's native CSF, was injected intrathecally, at a speed of approximately 7.8 ml/min through lumbar puncture. Excitation of highly concentrated Gd-DTPA and the high-speed of administration likely played a major role in producing most of neurotoxic symptoms that the patient experienced, particularly loss of consciousness.

In this case, MRI provided crucial information, which may help to illustrate other mechanisms of neuropathophysiological processes in response to the high dose of Gd-DTPA. Severe vasospasm of all major cerebral arteries was a unique finding revealed by the MRA, and likely resulted from the hypertonic nature of Gd-DTPA (Fig. 3a).

Restricted diffusion scattered in the cerebellum, brainstem, thalamus, corona radiata, and cerebral cortex on diffusion-weighted images suggested the existence of widespread cerebral oedema or pre-ischaemic abnormalities,¹⁸ which most likely related to the severe vasospasm of all major cerebral arteries. Additionally, Gd-DTPA accumulated in the extracellular space of the brain tissue resulting in the hyper-osmolarity of the extracellular space. Therefore, there may be an osmotic gradient between the extracellular space and the blood circulation, with the higher osmolarity of the extracellular spaces of the brain tissue attracting fluid from the blood circulation, which could also contribute to the formation of the cerebral oedema.

This case also demonstrates that there is no CSF–brain barrier with regard to Gd-DTPA, as diffusion of the Gd-DTPA into the cerebral grey

matter was evident on the T1-weighted and FLAIR images. This is consistent with previous findings in an animal study.¹³ Interestingly, Gd-DTPA can also penetrate into the cerebral deep white matter through the perivascular spaces, as linear hyperintense signals were demonstrated on T1-weighted images running from the superficial to the periventricular area (Fig. 1b). This provides evidence *in vivo* to support the idea that the perivascular space is a channel for CSF–brain exchanges.¹⁹

The free gadolinium ion (Gd^{3+}), of which the coordination number is estimated to be 9 or 10, is a highly toxic substance.^{17,20} Using DTPA with eight coordination sites as a chelation ligand, the combination of gadolinium with DTPA reduces the toxicity of the two separate components, gadolinium and DTPA.²¹ DTPA binds gadolinium several magnitudes more tightly ($\log K = 22$) than do other chelation ligands, such as ethylenediaminetetraacetic acid.²² In the present patient, no biological, behavioural, or significant gross neurological changes were seen in the follow-up studies at 3, 6, and 8 months after the incident. All cerebral arteries returned to normal. Although diffuse, slightly enhanced cerebral parenchyma was still visible in FLAIR images 8 months after the injection, no necrotic lesions were seen. Therefore, there seems to be no dissociation of gadolinium from the Gd-DTPA complex within the brain tissues of the patient.

The prompt continuous CSF draining through a catheter placed into the lumbar cisterna should be regarded as a life-saving procedure for this patient. The use of methylprednisolone also likely assisted in the patient regaining consciousness after the intrathecal Gd-DTPA injection. Glucocorticoid (methylprednisolone) has been used widely in patients with closed-head injuries or brain tumours to prevent and help reverse brain oedema.

In conclusion, there is a growing body of literature in relation to the use of intrathecal Gd-DTPA in the investigation of CSF leaks and the study of CSF flow dynamics. The fact that this approach has not been approved worldwide underlines the potential problems and lack of research regarding safety and tolerance in humans. The present case indicates that humans might be less tolerant to intrathecal Gd-DTPA than animals, suggesting that low-dose intrathecal or intracisternal application of Gd-DTPA in humans, as have been used by others, is a wise choice. The patient fully recovered without disability in the follow-up studies at 8 months after the injection, which indicates that Gd^{3+} that is chelated to DTPA appears very stable.

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References

1. Tardy B, Guy C, Barral G, et al. Anaphylactic shock induced by intravenous gadopentetate dimeglumine. *Lancet* 1992; **339**:494.
2. Tali ET, Ercan N, Kaymaz M, et al. Intrathecal gadolinium (gadopentetate dimeglumine)-enhanced MR cisternography used to determine potential communication between the cerebrospinal fluid pathways and intracranial arachnoid cysts. *Neuroradiology* 2004; **46**:744–54.
3. Munoz A, Hinojosa J, Esparza J. Cisternography and ventriculography gadopentetate dimeglumine-enhanced MR imaging in pediatric patients: preliminary report. *AJNR Am J Neuroradiol* 2007; **28**:889–94.
4. Jinkins JR, Williams RF, Xiong L. Evaluation of gadopentetate dimeglumine magnetic resonance cisternography in an animal model: preliminary report. *Invest Radiol* 1999; **34**:156–9.
5. Di Chiro G, Knop RH, Girton ME, et al. MR cisternography and myelography with Gd-DTPA in monkeys. *Radiology* 1985; **157**:373–7.
6. Di Chiro G, Girton ME, Frank JA, et al. Cerebrospinal fluid rhinorrhea: depiction with MR cisternography in dogs. *Radiology* 1986; **160**:221–2.
7. Skalte IO, Tang GJ. Magnetic resonance imaging contrast media in the subarachnoid space: a comparison between gadodiamide injection and gadopentetate dimeglumine in an experimental study in pigs. *Invest Radiol* 1997; **32**:140–8.
8. Siebner HR, Grafin von Einsiedel H, Conrad B. Magnetic resonance ventriculography with gadolinium DTPA: report of two cases. *Neuroradiology* 1997; **39**:418–22.
9. Zeng Q, Xiong L, Jinkins JR, et al. Intrathecal gadolinium-enhanced MR myelography and cisternography: a pilot study in human patients. *AJR Am J Roentgenol* 1999; **173**:1109–15.
10. Jinkins JR, Rudwan M, Krumina G, et al. Intrathecal gadolinium-enhanced MR cisternography in the evaluation of clinically suspected cerebrospinal fluid rhinorrhea in humans: early experience. *Radiology* 2002; **222**:555–9.
11. Aydin K, Guven K, Sencer S, et al. MRI cisternography with gadolinium-containing contrast medium: its role, advantages and limitations in the investigation of rhinorrhoea. *Neuroradiology* 2004; **46**:75–80.
12. Toney GM, Chavez HA, Ibarra R, et al. Acute and subacute physiological and histological studies of the central nervous system after intrathecal gadolinium injection in the anesthetized rat. *Invest Radiol* 2001; **36**:33–40.
13. Ray DE, Cavanagh JB, Nolan CC, et al. Neurotoxic effects of gadopentetate dimeglumine: behavioral disturbance and morphology after intracerebroventricular injection in rats. *AJNR Am J Neuroradiol* 1996; **17**:365–73.
14. Ray DE, Holton JL, Nolan CC, et al. Neurotoxic potential of gadodiamide after injection into the lateral cerebral ventricle of rats. *AJNR Am J Neuroradiol* 1998; **19**:1455–62.
15. Weinmann HJ, Press WR, Gries H. Tolerance of extracellular contrast agents for magnetic resonance imaging. *Invest Radiol* 1990; **25**:s49–50.
16. Tali ET, Ercan N, Krumina G, et al. Intrathecal gadolinium (gadopentetate dimeglumine) enhanced magnetic resonance myelography and cisternography. *Invest Radiol* 2002; **37**:152–9.

17. Kanal E, Shellock FG, Talagala L. Safety consideration in MR imaging. *Radiology* 1990;**176**:593–606.
18. Schaefer PW, Grant PE, Gonzalez RG. Diffusion-weighted MR imaging of the brain. *Radiology* 2000;**217**:331–45.
19. Rennels ML, Gregory TF, Blaumanis OR, et al. Evidence for a “paravascular” fluid circulation in the mammalian central nervous system, provided by the rapid distribution of tracer protein throughout the brain from the subarachnoid space. *Brain Res* 1985;**326**:47–63.
20. Reuben J. Gadolinium(III) as a paramagnetic probe for protons relaxation studies of biochemical molecules. *Biochemistry* 1971;**10**:2834–8.
21. CaTsch A. Zur Toxikologie der Diaethylentriamine Pentaessigsaeure. *Naunyn Schmiedebergs Arch Pharmacol* 1964;**246**:316–29.
22. Weinmann HJ, Brasch RC, Press WR, et al. Characteristics of gadolinium DTPA complex: a potential NMR contrast agent. *AJR Am J Roentgenol* 1984;**142**:619–24.