AJNR

Multicenter trial of gadoteridol, a nonionic gadolinium chelate, in patients with suspected head and neck pathology.

G H Zoarski, R B Lufkin, W G Bradley, Jr, A E Flanders, D R Gale, S E Harms, V M Haughton, S E Joy, E Kanal and L Rosa

AJNR Am J Neuroradiol 1993, 14 (4) 955-961
http://www.ajnr.org/content/14/4/955

Multicenter Trial of Gadoteridol, a Nonionic Gadolinium Chelate, in Patients with Suspected Head and Neck Pathology

Gregg H. Zoarski,[1,13] Robert B. Lufkin,[1] William G. Bradley, Jr.,[2] Adam E. Flanders,[3] Daniel R. Gale,[4] Steven E. Harms,[5] Victor M. Haughton,[6] Stephen E. Joy,[7] Emanuel Kanal,[8] Louis Rosa,[9] Val M. Runge,[10] John M. Talbot,[11] and William T.C. Yuh[12]

PURPOSE: To evaluate the safety and efficacy of gadoteridol as an MR contrast agent in patients with suspected head and neck pathology. **METHODS:** One hundred thirty-three adult patients were studied with MR at 12 clinical trial sites before and after the intravenous administration of 0.10 mmol/kg gadoteridol. After enrollment, patients underwent a complete physical examination. Patient monitoring included vital signs, laboratory tests, and recording of the incidence and duration of adverse events. To evaluate efficacy, postcontrast T1-weighted images were compared with precontrast T1- and T2-weighted images. Investigators having clinical information evaluated 129 studies for efficacy; two readers blinded to clinical information subsequently evaluated 122 studies using the same criteria as the investigators. **RESULTS:** Eight patients (6.0%) experienced mild adverse events possibly or probably related to contrast administration, all of which resolved without treatment. Two clinically significant laboratory abnormalities considered related or possibly related to the administration of gadoteridol were reported in two patients. Enhancement of pathology was seen in 82.9% of cases evaluated by investigators at the study site and in 78.7% of cases subsequently evaluated by the blinded readers. Postcontrast images were judged by investigators to provide additional diagnostic information over precontrast images in 68.9% of studies. The additional diagnostic information available on postcontrast studies most often consisted of improved visualization of pathology and better definition of lesion borders. The use of this information might have contributed to a change in patient diagnosis in 18.6% of the cases evaluated by the investigators and in 16.4% of the cases reviewed by the blinded readers. **CONCLUSIONS:** Preliminary results show gadoteridol to be a safe and efficacious contrast agent for enhanced MR study of extracranial and extraspinal head and neck pathology.

Index terms: Contrast media, paramagnetic; Contrast media, nonionic; Efficacy studies

AJNR 14:955–961, Jul/Aug 1993

Magnetic resonance (MR) imaging is useful for identifying and defining pathology of the head and neck region (1–3). MR has been indicated for imaging the oropharynx, the floor of the mouth

Received January 15, 1992; revision requested March 31, received August 10, and accepted August 31.

This paper was presented at the 29th Annual Meeting of the American Society of Neuroradiology, Washington, DC, June 9–14, 1991.

[1] Department of Radiological Sciences, University of California, Los Angeles, CA 90024.

[2] Department of Radiology, Long Beach Memorial Hospital, Long Beach, CA 90806.

[3] Department of Radiology, Thomas Jefferson University Hospital, Philadelphia, PA 19107.

[4] Department of Diagnostic Radiology, Boston VA Medical Center, Boston, MA 02130.

[5] Department of Radiology, Baylor University Medical Center, Dallas, TX 75246.

[6] Department of Radiology, Medical College of Wisconsin, Milwaukee, WI 53226.

[7] Department of Radiology, University of Rochester, Rochester, NY 14642.

[8] Department of Radiology, University of Pittsburgh, Pittsburgh, PA 15213.

[9] Division of Neurosurgery, Georgetown University Hospital, Washington, DC 20007.

[10] Department of Radiology, University of Kentucky, Lexington, KY 40536.

[11] Department of Radiology, Oregon Health Sciences University, Portland, OR 97201.

[12] Department of Radiology, University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

[13] Address reprint requests to G.H. Zoarski, MD, Department of Radiology, University of Maryland Hospital, 22 South Greene Street, Baltimore, MD 21201.

AJNR 14:955–961, Jul/Aug 1993 0195-6108/93/1404–0955

and tongue base (4), the larynx (5), the parapharyngeal space (2), and the nasopharynx (6). The use of gadolinium-based contrast agents in MR of the head and neck has further improved the sensitivity of MR in these regions (5–8). Previous studies have also demonstrated the clinical utility of contrast–enhanced MR in the evaluation of benign extraaxial tumors such as meningiomas, acoustic neuromas, and neurofibromas (9–13).

Gadoteridol, a low osmolal, nonionic gadolinium chelate, is a new MR contrast agent currently undergoing clinical trials in the United States, Europe, and Japan. The safety and efficacy of gadoteridol for MR imaging of central nervous system pathology in adults have been demonstrated previously in phase II and phase III clinical trials (14–17). The phase IIIB open-label, multicenter study presented here was undertaken to evaluate the safety and efficacy of gadoteridol-enhanced MR in a select population of adult patients with suspected extracranial and/or extraspinal head and neck pathology.

Materials and Methods

One hundred forty adult patients (older than 18 years of age) with suspected extracranial and/or extraspinal head and neck pathology were enrolled in this study at 12 participating institutions. Study protocol and consent forms were reviewed and approved by the Institutional Review Board at each site, and informed consent was obtained from each study participant. Pregnant or lactating women, patients with hemolytic anemia, and patients with known sensitivity to MR contrast media were excluded from the study.

After enrollment in the study, a comprehensive medical history was obtained for each patient. Patients were given a thorough physical examination, including vital signs and laboratory tests before the administration of gadoteridol. Vital signs were monitored within 24 hours before contrast injection, immediately precontrast, immediately postcontrast, and at 2 and 24 hours postcontrast. A complete physical examination including laboratory studies was also performed at 24 hours postcontrast. Laboratory tests included: a complete blood count with differential cell count; mean red blood cell volume and platelet count; serum assays for glucose, creatinine, urea nitrogen, calcium, phosphorus, uric acid, total cholesterol, albumin, total protein, alkaline phosphatase, serum glutamic oxaloacetic transaminase, lactate dehydrogenase, serum glutamic pyruvic transaminase, γ-glutamyl transpeptidase, total bilirubin, sodium, potassium, and chloride; iron studies for transferrin, iron-binding capacity, serum iron, and serum ferritin; clotting function as determined by prothrombin time and partial thromboplastin time; and urinalysis for pH, specific gravity, protein, glucose, blood, ketones, casts, white blood cells, red blood cells, crystals, bacteria, and epithelial cells.

The reporting of adverse events included the time of onset, duration, and severity of any adverse event, including significant changes in vital signs or laboratory values. The probable cause of each adverse event was determined by the investigator, and the event was classified as possibly, probably, or remotely related to contrast administration or as undetermined in its relationship to contrast administration. Investigators were given guidelines to determine the significance of any abnormal postcontrast laboratory value. These values were repeated until they normalized or returned to baseline, unless the investigator determined them to be unrelated to contrast administration.

Patients were evaluated by MR imaging before and within 1 hour after the intravenous administration of 0.10 mmol of gadoteridol per kilogram of body weight. Gadoteridol (ProHance; Squibb Diagnostics, Princeton, NJ) was supplied in 20-mL vials as a sterile, aqueous solution for intravenous injection. Each vial contained a formulation of (per milliliter) 0.5 mmol of gadoteridol, 0.01 mmol of Tris, and 0.00025 mmol of calteridol calcium. The Tris buffer was added to maintain pH at 7.4; the calcium salt of the ligand was added to act as a scavenging agent for the uncomplexed gadolinium ion, Gd^{3+}.

Before contrast administration, T1- and T2-weighted spin-echo images of the region of interest were obtained. Postcontrast T1-weighted scans were obtained in the same plane as precontrast scans, with identical section thickness, spacing, and matrix size. Images were evaluated for efficacy by an unblinded reader at the institution where they were acquired. Evaluation criteria included the diagnostic quality of the images, the presence or absence of enhancement of pathology on postcontrast sequences, the degree of enhancement of pathology, and an assessment of whether additional diagnostic information was available on postcontrast images. Readers also specified the nature of any additional information provided by contrast administration. The studies were subsequently evaluated by one of two neuroradiologists who were blinded to patient history and identity, physical examination, laboratory data, and presumptive and final diagnosis. These blinded readers used the same image evaluation criteria as the unblinded readers.

Recommended methods of confirming the postcontrast MR diagnosis included the following: computed tomography, biopsy, surgery, endoscopy, or a second unenhanced and enhanced MR study.

Results

Of 140 patients initially enrolled in the study, 6 were later excluded because of claustrophobia or a clinical condition. An MR system malfunction prevented the completion of another study. The final study population of 133 patients included 74 men and 59 women, ranging in age from 19 to 76 years, with a mean age of 53 ± 15 years. A variety of MR imaging instruments ranging in field strength from 0.3 to 1.5 T was used throughout the 12 participating institutions. The volume

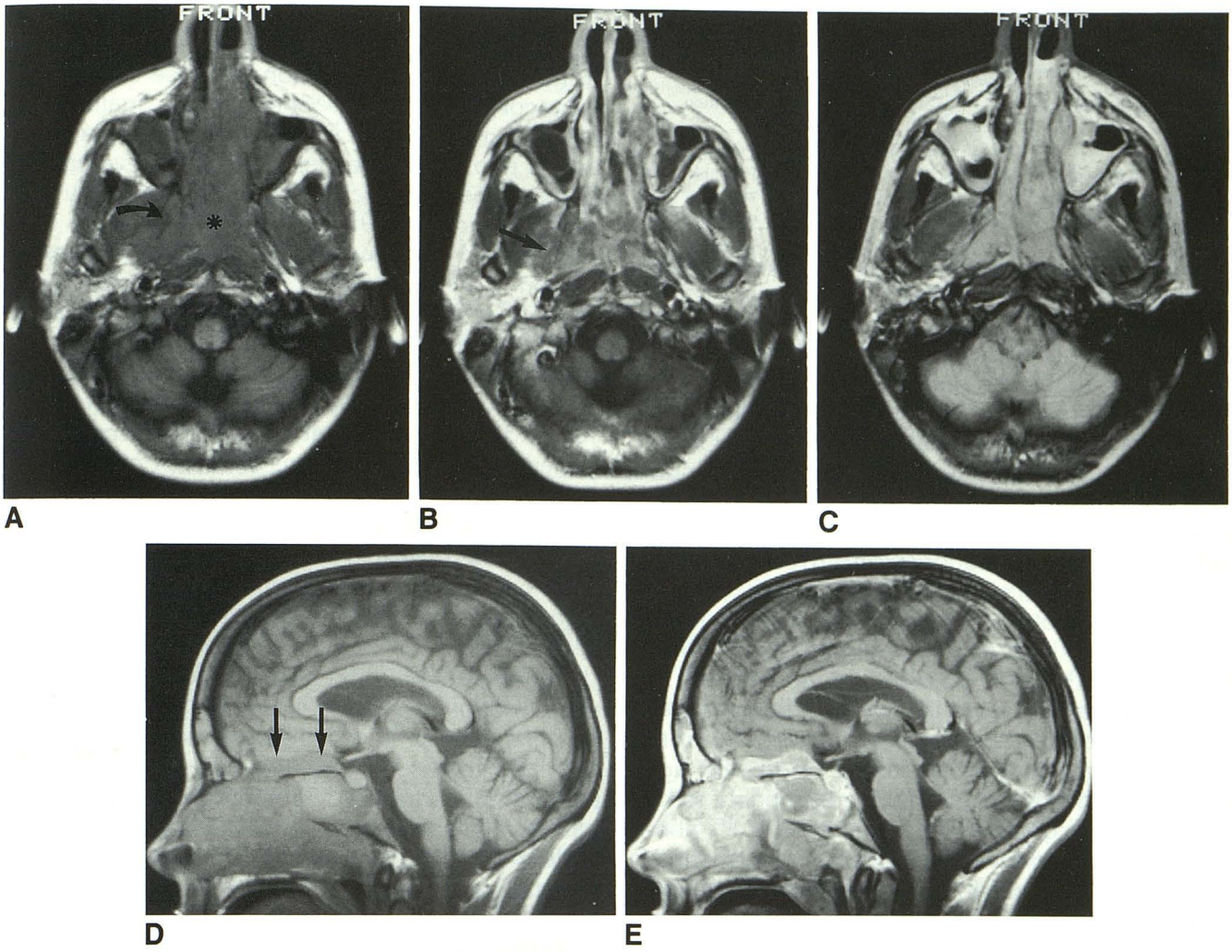

Fig. 1. Nasopharyngeal and nasal cavity mass in a patient with acquired immunodeficiency syndrome suspected of having sinusitis. A biopsy revealed immunoblastic lymphoma.

A, Axial T1-weighted image reveals a large nasal and nasopharyngeal mass (*asterisk*); however, the relationship of the mass to the adjacent pterygoid muscles (*curved arrow*) is unclear.

B, Axial T1-weighted image after gadoteridol injection shows enhancement of the mass with invasion of the pterygoid muscles on the right (*arrow*).

C, Axial proton density-weighted image without contrast confirms findings.

D, Sagittal T1-weighted precontrast image suggests possible intracranial involvement of the tumor in the region of the cribiform plate (*arrows*).

E, Intracranial extension of the tumor is confirmed by the marked enhancement on the sagittal T1-weighted image after gadoteridol injection.

of contrast administered at a dose of 0.10 mmol/kg ranged from 6.4 to 27.0 mL with a mean volume of 13.9 mL; the rate of contrast administration varied from 1 mL/min to bolus (at the discretion of the investigator).

Primary patient diagnoses (postcontrast) included a benign or malignant neoplasm in 97 patients, an inflammatory or infectious process in 11 patients, and a normal study or postoperative changes in 23 patients. The postcontrast MR diagnosis was confirmed within eight weeks before or after participation in the study for 86 (86 of 133, 64.7%) of the patients completing the study.

Eight adverse events considered by the investigator to be possibly or probably related to contrast administration were reported in eight patients (eight of 133, 6.0%) (Table 1). All of these events were considered to be mild in severity, and all resolved spontaneously without residual effects. The most common adverse event was nausea, which occurred in three patients (three

TABLE 1: Adverse events possibly or probably related to contrast administration

Adverse Event	No. of Patients (%)	Intensity	Relation
Nausea	3/133 (2.3%)	Mild	Probably
Itching, watery eyes	2/133 (1.5%)	Mild	Probably
Small, solitary hive	1/133 (0.8%)	Mild	Probably
Diarrhea	1/133 (0.8%)	Mild	Possibly
Metallic taste	1/133 (0.8%)	Mild	Possibly

Note.—In the judgment of the investigator.

of 133, 2.3%). There were no clinically significant changes in vital signs recorded in this study.

At 24 hours after contrast administration, investigators reported a total of 41 abnormal laboratory values in 19 patients. Two of these abnormal values in two patients were judged by the investigator at the site involved to be related or to have a possible relationship to the injection of gadoteridol (two of 133, 1.5%). One patient showed an elevation in γ-glutamyl transpeptidase from 56 to 74 IU/L (normal range, 0 to 65 IU/L), which was thought possibly to be related to contrast administration. A second patient experienced a decrease in iron levels in serum from 151 to 22 μg/dL (normal range, 50 to 180 μg/dL), which the investigator judged probably to be related to the gadoteridol injection. All 41 laboratory values returned to baseline or normalized on follow-up except for the decreased iron level in serum in one patient. (Values at 6, 13, and 22 days were 28, 42, and 22 μg/dL, respectively.) This patient received iron supplements for a previously undetected iron-deficiency anemia.

Four studies were excluded from image evaluation because they did not entirely conform to the imaging protocol. The remaining 129 cases were evaluated by an unblinded reader at the institution of origin. Enhancement of pathology after contrast administration was noted in 107 of these cases (107 of 129, 82.9%). The enhancement was judged as "slight" in 28 patients (26.2%) and "marked" in 79 patients (73.8%). In 89 patients (68.9%), the postcontrast MR examination was judged to provide additional diagnostic information when compared with the precontrast study (Table 2). Additional information available in those 89 cases was most often classified by investigators as improved lesion visualization (in 67 patients, 75.3%) and better definition of lesion borders (in 66 patients, 74.2%) (Fig. 1). In 24 cases (18.6%), additional information available postcontrast contributed to a change in patient diagnosis.

Of the 129 studies evaluated by unblinded readers, an additional seven cases were excluded from the blinded evaluation because of imaging protocol violations or poor diagnostic quality. The remaining 122 cases were randomly assigned to one of two blinded readers for further evaluation. Enhancement of pathology was noted by the blinded readers in 96 of these cases (96 of 122, 78.7%) and provided additional diagnostic information in 57 cases (46.7%). In 20 of these cases (20 of 57, 35.1%), the blinded readers determined that this additional information would have resulted in a change in patient diagnosis (16.4% of the 122 cases evaluated). In four cases (four of 122, 3.3%), postcontrast T1-weighted images revealed one or more lesions not seen on precontrast T1- or T2-weighted images. In three cases, these additional lesions were discovered in the intracranial region.

Discussion

Gadopentetate dimeglumine (Gd-DTPA) was approved for enhanced MR imaging of the central nervous system in adults in June 1988 (18–20) and later for use in imaging of the spine and in pediatric patients (21). Several other gadolinium-based MR contrast agents have subsequently undergone clinical trials in the United States, Europe, and Japan. These include gadoterate meglumine (22), gadodiamide (23, 24), and gadoteridol (14–17). Each of these agents is a paramagnetic Gd^{3+} chelate possessing imaging properties similar to those of Gd-DTPA; however, the various agents have different chemical structures and physical properties that may affect their safety profiles.

Osmolality, ionicity, and chemical stability are features of contrast agents that may compromise patient safety and limit clinical usefulness. In a recent study of radiographic contrast agents involving over 300,000 patients, Katayama et al (25) concluded that "nonionic contrast media significantly reduce life-threatening adverse drug reactions to contrast media at all levels of risk. . ." Nonionic MR contrast media such as gadoteridol may provide an additional margin of safety over the currently used ionic formulation, especially in debilitated patients or in patients with cardiovascular compromise. A 0.5 mmol/L solution of gadoteridol possesses approximately one third the osmolality of a similar solution of Gd-DTPA (640 versus 1940 mOsmol/kg). Available experience suggests that a lower osmolal MR agent

TABLE 2: Additional diagnostic information gained after contrast administration

Type of Additional Diagnostic Information	% of Cases with Additional Diagnostic Information[a] (n = 89)		% of All Evaluable Cases in Study Population[a] (n = 129)	
	Unblinded % (n = 89)	Blinded % (n = 57)	Unblinded % (n = 129)	Blinded % (n = 122)
Additional information postcontrast	100 (89)	100 (57)	68.9 (89)	46.7 (57)
Improved visualization of lesions	75.3 (67)	64.9 (37)	51.9 (67)	30.3 (37)
Improved definition of lesion borders	74.2 (66)	59.6 (34)	51.2 (66)	27.9 (34)
Improved lesion detection	44.9 (40)	14.0 (8)	31.0 (40)	6.6 (8)
Improved disease classification	25.8 (23)	24.6 (14)	17.8 (23)	11.5 (14)
Increased number of lesions visualized	11.2 (10)	1.8 (1)	7.8 (10)	<1 (1)
Improved detection of tumor recurrence	4.5 (4)	5.3 (3)	3.1 (4)	2.5 (3)

[a] More than one category was selected for some patients.

may be safely administered at doses two to three times greater than the currently approved dose for Gd-DTPA (0.10 mmol/kg) without compromising patient safety (26–28). Because the free gadolinium ion (Gd^{3+}) and free ligand are both poorly tolerated in vivo, the safety of gadolinium chelates also depends on the kinetic stability of the ligand-metal ion complex. In vitro tests have shown gadoteridol to be more stable than Gd-DPTA in the presence of endogenously available ions (29), and recent research with liposomal gadolinium complexes has shown macrocyclic gadolinium complexes, such as gadoteridol and gadoterate meglumine, to be more stable in vivo than linear complexes, such as Gd-DTPA (30, 31).

These factors may be responsible for the apparent improvement in the safety profile of the newer agents as compared with Gd-DTPA. The overall incidence of adverse effects in this study (6.0%) compares favorably with the reported incidence of adverse events with Gd-DTPA (19.9%) in 1068 patients enrolled in US clinical trials (32). A recent postmarketing survey on the safety profile of Gd-DTPA in a worldwide patient population (33) showed a lower percentage of adverse events than that reported in US clinical trials; however, adverse events are less rigorously monitored in such trials than in controlled clinical trials. Although there have been no reports of severe adverse reactions with gadoteridol to date, investigators have reported several such reactions with Gd-DTPA (32, 34). Three patients in our series (2.3%) experienced mild nausea after the injection of gadoteridol, a figure higher than that reported (1.2%) in a previous trial involving 411 patients (16), but similar to that reported in clinical trial with Gd-DTPA (1.5 to 1.9%) (32). All adverse events in this study were graded as mild and resolved completely without intervention.

The patients in this study did not demonstrate the pattern of transient increases in levels of iron or bilirubin in serum seen in 23% of the patients at 2 to 4 hours after the injection of 0.10 mmol of Gd-DTPA per kilogram (32). The tendency of Gd-DTPA to cause transient increases in iron levels in serum has been described by Niendorf and Seifert (35), who propose that temporary elevations in iron and bilirubin levels in serum that occur after the administration of Gd-DTPA may be due to a slight hemolysis "of no recognizable clinical significance." Three patients in this study exhibited a *decrease* in iron levels in serum at 24 hours after contrast administration (three of 133, <1%). In two of these cases, the decrease was considered to be unrelated to contrast administration, and iron levels in serum normalized or returned to baseline on follow-up. In the third case, the investigator initially determined that the decrease in iron levels in serum was probably related to contrast administration. However, this patient (who underwent a surgical resection within 24 hours after contrast administration) subsequently received iron supplements for a previously undetected iron-deficiency anemia.

Overall, a strong correlation can be seen between the unblinded and the blinded readers for the presence of enhancement: postcontrast enhancement was seen in 82.9% of cases evaluated by investigators and in 78.7% of cases reviewed by the blinded readers. Unblinded and blinded readers also concurred on the percentage of cases

in which additional information would have contributed to a change in patient diagnosis (18.6 and 16.4%, respectively). A discrepancy can be seen, however, between the two readings regarding the presence of additional diagnostic information. Postcontrast studies were felt to yield more diagnostic information than precontrast studies in 68.9% of cases evaluated by unblinded investigators, but in only 46.7% of cases evaluated by the two blinded readers. Investigators with full access to clinical data may have been in a better position to interpret the significance of the presence or absence of postcontrast enhancement of pathology. For both unblinded and blinded readers, the nature of the additional diagnostic information most often noted was "improved visualization" of pathology (unblinded, 67/89, 75.2%; blinded, 37/57, 64.9%) or better "definition of lesion borders" (unblinded, 66/89, 74.2%; blinded, 34/57, 59.6%) (Table 2). These results compare favorably with those reported in a summary of US clinical trial experience with Gd-DTPA, in which improved visualization of extracranial lesions of the head and neck was seen in 41% of patients studied (7).

In three of the four cases in which postcontrast T1-weighted images demonstrated additional lesions not seen on precontrast T1- or T2-weighted images, the additional lesions were discovered in the intracranial region. These cases included multiple cerebral metastases in one patient and postoperative changes surrounding the optic nerve in another. In the third patient, gadoteridol administration demonstrated the extension of a mucoepidermoid carcinoma to the petroclival fissure and petrous apex. The fourth case involved postcontrast detection of an intradural extension from a bone neoplasm in the upper cervical region. These cases highlight another important role of contrast injection in patients with suspected head and neck pathology: to demonstrate pathology that is separate from, or has extended from, the primary region of interest. In appropriate cases, such as those with an expected perineural spread of malignancy, the use of a contrast agent may be routinely indicated.

Conclusions

In this phase III clinical trial, gadoteridol, at a dose of 0.10 mmol/kg body weight, was found to be a safe and efficacious MR contrast agent for use in the evaluation of extracranial and/or extraspinal head and neck pathology. The low rate of adverse events (6%) and the demonstrated diagnostic utility of gadoteridol (enhancement of pathology noted in 78.7% of cases evaluated by blinded readers) confirm the safety and clinical utility of this agent. The degree to which the favorable physicochemical properties of gadoteridol will result in a demonstrable safety advantage over higher osmolal or ionic agents or those using linear ligands will need to be evaluated in a larger patient population. Complementary advances in MR imaging techniques and magnetopharmaceutical development will likely result in more sensitive and specific protocols for MR imaging of head and neck pathologies.

Acknowledgment

We thank Julien Keesing and Alison Heinrichs for their invaluable help in preparing the manuscript.

References

1. Mafee MF, Campos M, Raju S, et al. Head and neck: high field magnetic resonance imaging versus computed tomography. *Otolaryngol Clin North Am* 1988;21:513–546
2. Lloyd GA, Phelps PD. The demonstration of tumours of the parapharyngeal space by magnetic resonance imaging. *Br J Radiol* 1986; 59:675–683
3. Lufkin RB, Hanafee WN. Magnetic resonance imaging of the head and neck. *Invest Radiol* 1988;23:162–169
4. Kassel EE, Keller MA, Kucharczyk W. MRI of the floor of the mouth, tongue, and oropharynx. *Radiol Clin North Am* 1989;27:331–350
5. Phillips CD, Spencer BG, Newton RL, Levine PA. Gadolinium-enhanced MRI of tumors of the head and neck. Head Neck 1990;12: 308–315
6. Crawford SC, Harnsberger HR, Lufkin RB, Hanafee WN. The role of gadolinium-DTPA in the evaluation of extracranial head and neck mass lesions. *Radiol Clin North Am* 1989;27:219–242
7. Robinson JD, Crawford SC, Teresi LM, et al. Extracranial lesions of the head and neck: preliminary experience with Gd-DTPA-enhanced MR imaging. *Radiology* 1989;172:165–170
8. Vogl T, Bruning R, Grevers G, Mees K, Bauer M, Lissner J. MR imaging of the oropharynx and tongue: comparison of plain and Gd-DTPA studies. *J Comput Assist Tomogr* 1988;12:427–433
9. Breger RK, Papke RA, Pojunas KW, Haughton VM, Williams AK, Daniels DL. Benign extraaxial tumors: contrast enhancement with Gd-DTPA. *Radiology* 1987;163:427–429
10. Haughton VM, Rimm AA, Czervionke LF, et al. Sensitivity of Gd-DTPA-enhanced MR imaging of benign extraaxial tumors. *Radiology* 1988;166:829–833
11. Daniels DL, Millen SJ, Meyer GA, et al. MR detection of tumor in the internal auditory canal. *AJNR: Am J Neuroradiol* 1987;8:249–252
12. Curati WL, Graif M, Kingsley DP, Niendorf HP, Young IR. Acoustic neuromas: Gd-DTPA enhancement in MR imaging. *Radiology* 1986; 158:447–451
13. Millen SJ, Daniels DL, Meyer GA. Gadolinium-enhanced magnetic resonance imaging in temporal bone lesions. *Laryngoscope* 1989; 99:257–260
14. Pollei SR, Atlas S, Drayer B, et al. Preliminary experience with a new low osmolar, nonionic gadolinium preparation in patients with intra-

cranial tumors (abstract). Berkeley, CA, SMRM Book of Abstracts, 1990;2:645
15. Runge VM, Gelblum DY, Pacetti ML, et al. GD-HP-DO3A in clinical MR imaging of the brain. *Radiology* 1990;177:393–400
16. Runge VM, Bradley WG, Brant-Zawadzki MN, et al. Clinical safety and efficacy of gadoteridol: a study in 411 patients with suspected intracranial and spinal disease. *Radiology* 1991;181:701–709
17. DeSimone D, Morris M, Rhoda C, et al. Evaluation of the safety and efficacy of gadoteridol injection (a low osmolal magnetic resonance contrast agent): clinical trials report. *Invest Radiol* 1991;26: S212–S216
18. Weinmann HJ, Brasch RC, Press WR, Wesbey GE. Characteristics of gadolinium-DTPA complex: a potential NMR contrast agent. *AJR: Am J Roentgenol* 1984;142:619–624
19. Brant-Zawadzki M, Berry I, Osaki L, Brasch R, Murovic J, Norman D. Gd-DTPA in clinical MR of the brain: 1. intraaxial lesions. *AJNR: Am J Neuroradiol* 1986;7:781–788
20. Berry I, Brant-Zawadzki M, Osaki L, Brasch R, Murovic J, Newton TH. Gd-DTPA in clinical MR of the brain: 2. extraaxial lesions and normal structures. *AJNR: Am J Neuroradiol* 1986;7:789–793
21. Powers TA, Partain CL, Kessler RM, et al. Central nervous system lesions in pediatric patients: Gd-DTPA enhanced MR imaging. *Radiology* 1988;169:723–726
22. Parizel PM, Hendrik RD, Gheuens J, et al. Gadolinium-DOTA enhanced MR imaging of intracranial lesions. *J Comput Assist Tomogr* 1989;13:378–385
23. Greco A, McNamara MT, Lanthiez P, Quay SC, Michelozzi G. Gadodiamide injection: nonionic gadolinium chelate for MR imaging of the brain and spine—phase II-III clinical trial. *Radiology* 1990;176: 451–456
24. Sze G, Brant-Zawadzki M, Haughton VM, et al. Multicenter study of gadodiamide injection as a contrast agent in MR imaging of the brain and spine. *Radiology* 1991;181:693–699
25. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. *Radiology* 1990;175:621–628
26. Yuh WTC, Fisher DJ, Engelken JD, et al. MR evaluation of CNS tumors: dose comparison study with gadopentetate dimeglumine and gadoteridol. *Radiology* 1991;180:485–491
27. Yuh WTC, Engelken JD, Muhonen MG, Mayr NA, Fisher DJ, Ehrhardt JC. Experience with high-dose gadolinium imaging in the evaluation of brain metastases. *AJNR: Am J Neuroradiol* 1992;13:335–345
28. Runge VM, Kirsch JE, Burke VJ, et al. High dose gadoteridol in MR imaging of intracranial neoplasms. *J Magn Reson Imaging* 1992;2: 9–18
29. Tweedle MF, Hagan JJ, Kumar K, Mantha S, Chang CA. Reaction of gadolinium chelates with endogenously available ions. *Magn Reson Imaging* 1991;9:409–415
30. Fritz T, Unger E, Wilson-Sanders S, Ahkong QF, Tilcock C. Detailed toxicity study of liposomal gadolinium-DTPA. *Invest Radiol* 1991; 26:960–968
31. Unger EC, Fritz TA, Tilcock C, New TE. Clearance of liposomal gadolinium: in vivo decomplexation. *J Magn Reson Imaging* 1991;1: 689–693
32. Goldstein HA, Kashanian FK, Blumetti RF, Holyoak WL, Hugo FP, Blumenfield DM. Safety assessment of gadopentetate dimeglumine in U.S. clinical trials. *Radiology* 1990;174:17–23
33. Niendorf HP, Dinger JC, Haustein J, Cornelius I, Alhassan A, Clauss W. Tolerance data of Gd-DTPA: a review. *Eur J Radiol* 1991;13: 15–20
34. Weiss KL. Severe anaphylactoid reaction after IV Gd-DTPA. *Magn Reson Imaging* 1990;8:817–818
35. Niendorf HP, Seifert W. Serum iron and serum bilirubin after administration of Gd-DTPA-dimeglumine: a pharmacologic study in healthy volunteers. *Invest Radiol* 1988;23:S275–S280