AJNR

Rapid bolus injection of gadopentetate dimeglumine: absence of side effects in normal volunteers.

F K Kashanian, H A Goldstein, R F Blumetti, W L Holyoak, F P Hugo and M Dolker

AJNR Am J Neuroradiol 1990, 11 (5) 853-856
http://www.ajnr.org/content/11/5/853

Rapid Bolus Injection of Gadopentetate Dimeglumine: Absence of Side Effects in Normal Volunteers

Franciska K. Kashanian[1]
Harold A. Goldstein
Rosemary F. Blumetti
Wayne L. Holyoak
Frank P. Hugo
Michael Dolker

The safety and tolerance of gadopentetate dimeglumine 0.1 mmol/kg when injected at a bolus rate (10 ml/15 sec; four times the recommended rate) was studied in 12 normal men between the ages of 20 and 36 years. Each of the subjects received a single injection of either gadopentetate dimeglumine (0.2 ml/kg) or a placebo (normal saline, 0.2 ml/kg), followed by a 7-day washout and a single injection of the alternative treatment (six subjects per sequence). Measurement parameters included blood pressure, pulse rate, ECG, cardiographic rhythm strips, hematology and blood chemistry evaluations, physical examinations, and adverse drug experiences. Variations of ≥ ± 15 mm Hg in diastolic blood pressure and ≥ ± 15 beats per min in heart rate were observed in some subjects after injection of either gadopentetate dimeglumine or the placebo, but no clinically significant changes from baseline were observed for any parameter. Post-gadopentetate dimeglumine results were not significantly different statistically from post-placebo results. No adverse experiences were reported for any subject.

It is concluded that gadopentetate dimeglumine is safe and well tolerated when administered to normal men at a rapid injection rate of 10 ml/15 sec.

***AJNR* 11:853–856, September/October 1990**

Gadopentetate dimeglumine is an imaging agent intended for IV administration to selected patients undergoing MR imaging. It is available for use with MR in adult and pediatric patients to provide contrast enhancement and to facilitate visualization of intracranial lesions and lesions in the spine and associated tissues.

In the clinical studies previously conducted in the United States, gadopentetate dimeglumine 0.1 mmol/kg was administered at an injection rate of approximately 10 ml/min. Analysis of data obtained from these trials showed that gadopentetate dimeglumine had an acceptable safety profile. However, it may be desirable to administer the drug at a bolus rate when using MR to evaluate such tissues as the liver or kidney [1, 2].

This study was therefore designed to evaluate the safety and tolerance of gadopentetate dimeglumine 0.1 mmol/kg when administered to normal subjects at a bolus injection rate of 10 ml/15 sec, which is four times the rate stated in the package insert for Magnevist (Berlex Laboratories, Wayne, NJ) injection.

Materials and Methods

Subjects and Drugs

This was a double-blind, randomized, crossover, placebo-controlled study. Enrollment in the study was limited to subjects who fulfilled the following criteria: normal as determined by medical history, physical examination, ECG, and laboratory tests; between 18 and 75 years old; less than 100 kg body weight; had not had an organ transplant; had not received any medications within 24 hr of participation; had not received any investigational drugs within 30 days; had not received iodinated contrast agents within 7 days; agreed to remain in the

Received July 26, 1989; revision requested September 23, 1989; revision received April 12, 1990; accepted April 18, 1990.

Presented at the annual meeting of the American Society of Neuroradiology, Orlando, March 1989.

[1] All authors: Berlex Laboratories, Inc., 300 Fairfield Rd., Wayne, NJ 07470. Address reprint requests to F. Kashanian.

0195-6108/90/1105-0853

testing facility for 24 hr after each injection; and gave written informed consent.

Gadopentetate dimeglumine (0.5 mol/l concentration) was provided as a sterile, stable, clear, colorless aqueous solution in 20-ml vials. Each ml contained 469.01 mg gadopentetate dimeglumine, 0.39 mg meglumine, 0.15 mg diethylenetriamine pentaacetic acid, and water for injection. A placebo was provided as a sterile solution of 0.9% sodium chloride in 30-ml vials.

Each of 12 subjects was randomly assigned to either group 1 or group 2 (six subjects per group). The subjects in group 1 received a single IV injection of gadopentetate dimeglumine (week 1), and after a 7-day washout period, they each received a single IV injection of the placebo (week 2). The subjects in group 2 received a placebo in week 1 and gadopentetate dimeglumine in week 2. Subjects did not receive concomitant medication(s); meals (standard or special, if necessary) were provided. Intake of fluids was not restricted.

In order to maintain investigator blinding to the IV drug between week 1 and week 2, tamper-resistant seals were supplied, and a third party (i.e., not the principal investigator or study personnel who obtained vital signs or adverse drug experiences) prepared the study drug for injection.

To calculate the amount of contrast medium to be administered, each subject was weighed before each injection. The undiluted gadopentetate dimeglumine or the placebo was injected IV at 10 ml/15 sec (the maximum injection period was 24–25 sec). After each injection, a 5-ml saline flush was administered over a period of 8 sec to ensure complete injection.

Safety Measurements and Observations

For all safety measurements and observations, the initial baseline was defined as the 24-hr time interval prior to first study drug administration (week 1). All baseline parameters were reestablished for week 2 during the 24-hr time interval prior to administration of the study drug. Evaluations were performed as follows: (1) Medical history at the initial baseline. (2) Physical examination at each baseline and 24 hr after each injection. (3) ECGs: a 12-lead ECG was obtained within 24 hr before each injection (weeks 1 and 2) and 24 hr after each injection. (4) Cardiographic rhythm strips were obtained immediately before each injection, immediately after each injection, and at 2, 5, 10, 15, 30 min, and 2–4 hr after each injection. (5) Vital signs: after the subject had remained supine for at least 5 min, systolic and diastolic brachial blood pressures and pulse rate were obtained during each baseline physical examination and immediately before each (week 1 and week 2) drug administration. (Systolic and diastolic brachial blood pressures were obtained in the opposite arm from the arm used for injection. The same arm was used for all measurements. Pulse rate was obtained from the cardiographic rhythm strip.) Postinjection (week 1 and week 2), supine systolic and diastolic brachial blood pressures, and pulse rate were obtained immediately after each injection, and at 2, 5, 10, 15, and 30 min, 2–4 hr, and 24 hr after each injection. (6) Hematology specimens were obtained at each baseline and 24 hr after each injection (week 1 and week 2) for hematocrit, hemoglobin, RBC, WBC, and differential. (7) Blood chemistry specimens were obtained at each baseline and 24 hr after each injection (week 1 and week 2) for BUN, creatinine, LDH, SGOT, SGPT, alkaline phosphatase, total bilirubin, indirect bilirubin (if total bilirubin was within normal limits, indirect bilirubin was not required), and iron. Serum iron and total bilirubin were also evaluated at 2–4 hr after each injection. (8) Adverse drug experiences: indirect questioning techniques were used for collection of information.

Statistical Methods

1. Sample Size Considerations

The study was designed for 12 subjects in order to achieve an 80% chance (alpha < 5%) of detecting the following mean changes from baseline (assuming the mean changes from baseline for placebo are zero):

Variable	Units	Mean Change	Assumed Standard Deviation (σ)
Systolic BP	mm Hg	±25	±12
Diastolic BP	mm Hg	±15	±8
Pulse rate	bpm	±15	±8

Note. Assumed σ was based on the observed SD of the change from baseline in previously conducted clinical trials.

2. Clinical Variables

The primary clinical variables to assess the safety and tolerance of gadopentetate dimeglumine in the population under study were cardiographic rhythm strips, vital signs, and adverse drug experiences. Secondary variables were hematology, hepatic and renal functions, and serum iron. The criterion variable was the change from preinjection in each of the primary variables for each period.

Analyses of the vital sign data (systolic and diastolic blood pressures and pulse rate) were performed using a procedure proposed by Patel [3].

Pretests were performed to establish the validity of testing treatment differences. The hypotheses tested were (a) pretreatment values are equal in the two periods, (b) treatment carryover effects are equal in the two sequences, and (c) there is no treatment-by-period interaction.

Tests for treatment differences were declared statistically significant if $p < .05$. Analyses were performed at each time point, with no adjustment made for multiple tests performed over time.

Results

Subjects and Drug Dosage

Twelve normal male subjects completed the study and provided valid data for the analyses. The dosage of gadopentetate dimeglumine used in this study was 0.2 ml/kg (0.1 mmol/kg) of body weight; the placebo was also administered at 0.2 ml/kg of body weight. No concurrent illnesses or use of concomitant medication were reported; there were no abnormalities or changes from baseline in physical examinations. Descriptive statistics for the subjects and mean volumes and ranges of drug administered are shown in Table 1.

Safety and Tolerance

1. Electrocardiograms (ECGs) and Cardiographic Rhythm Strips

No abnormalities or changes from baseline were reported for 12-lead ECGs or for the overall evaluations of cardiographic rhythm strips. Results of the analyses of pulse rates

TABLE 1: Subject Information and Volume of Gadopentetate Dimeglumine Administered

	Mean (SD)	Range
Age (years)	26 (±5)	20–36
Weight (kg)		
GD*	71 (±7)	56–81
Placebo	71 (±8)	54–84
Volume (ml)		
GD	14.0 (±1.5)	10.7–16.2
Placebo	14.0 (±1.4)	10.8–16.1

* GD = gadopentetate dimeglumine.

(which were obtained from the rhythm strips) are described in the following section.

2. Vital Signs

With respect to the sample size, the observed standard deviations in vital signs parameters were equal to or lower than the assumed values; therefore, the power expected for this study was met or exceeded.

Tests of the statistical hypotheses yielded no statistically significant results ($p > .05$). Statistical analyses of the measured parameters showed that there were no pretreatment differences between the two sequence groups. Treatment carryover effects were equal in the two sequences. In general, there was no treatment-by-period interaction.

Graphs of the mean changes from baseline for systolic blood pressure, diastolic blood pressure, and pulse rate are shown in Figures 1, 2, and 3. There were no clinically significant changes or trends in change from baseline in any of these parameters.

3. Adverse Experiences

There were no adverse experiences reported in this study.

4. Laboratory Evaluations (Hematology and Chemistry)

Hematologic evaluations were obtained at baseline and at 24 hr after each injection in all 12 subjects. There were a few values outside the specified normal ranges for these parameters, but there were no clinically significant changes or trends in change from baseline for any hematologic evaluation.

Chemistry evaluations were obtained at baseline and 24 hr after each injection in all 12 subjects. Additional evaluations for total bilirubin and serum iron were made at 2–4 hr after each injection in all 12 subjects. No clinically significant trends or changes from baseline were observed.

Transient elevations in serum iron were observed in some subjects following both gadopentetate dimeglumine and placebo injections; however, most values remained within normal limits, and no value was considered clinically significantly abnormal. No subject had a total bilirubin value outside the normal range.

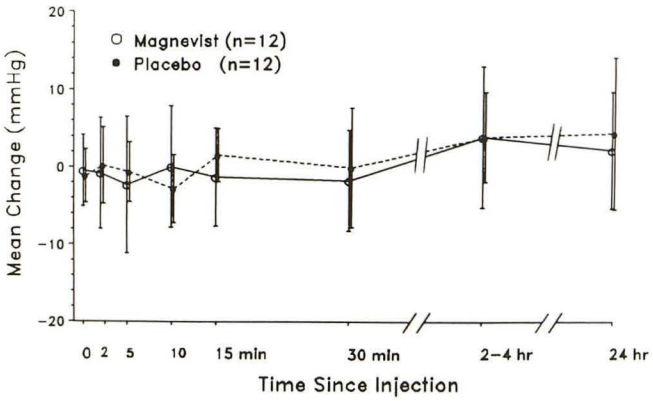

Fig. 1.—Mean changes (± SD) in supine systolic blood pressure (mm Hg). Time 0 is immediately after injection. Placebo means are offset in time.

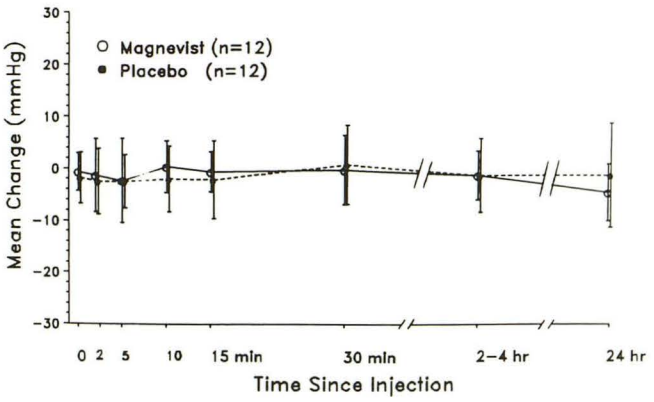

Fig. 2.—Mean changes (± SD) in supine diastolic blood pressure (mm Hg). Time 0 is immediately after injection. Placebo means are offset in time.

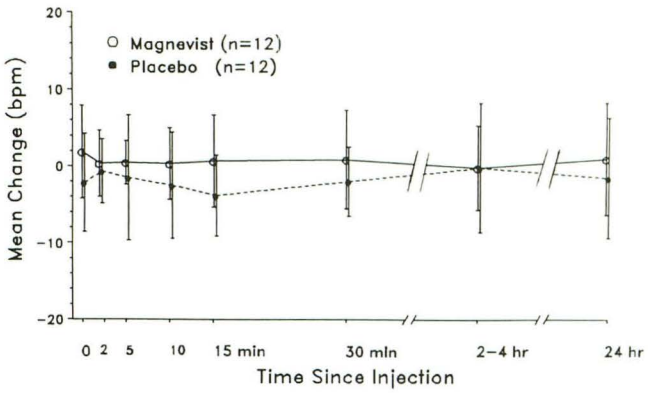

Fig. 3.—Mean changes (± SD) in supine pulse rate (bpm). Time 0 is immediately after injection. Placebo means are offset in time.

Discussion

In controlled clinical trials in the United States, gadopentetate dimeglumine 0.1 mmol/kg was studied in more than 1000 adult patients with suspected CNS lesions who were undergoing MR; reports have appeared in the literature describing some of these patients [4–10]. In these trials, gadopentetate dimeglumine was administered at a rate of approximately 10 ml/min (the rate stated in the package insert). However, it may be desirable to inject gadopentetate dimeglumine at a bolus rate when using MR to evaluate tissues in areas other than the CNS, such as the liver or kidney.

In a study that used a rat model of experimentally induced pyogenic liver abscesses, gadopentetate dimeglumine was administered at a bolus rate, using a fast spin-echo sequence [1]. Gadopentetate dimeglumine increased the conspicuity of the hepatic abscess by rim enhancement of the abscess wall, whereas unenhanced T1- and T2-weighted MR images showed no specific morphologic features that could be used to distinguish intrahepatic abscesses from metastases. In another study, which was performed in rabbits, fast imaging techniques with bolus administration of gadopentetate dimeglumine were used to determine the normal appearance of dynamic enhanced renal MR images [2]. In this study, a reproducible three-phase renal enhancement pattern was observed. Since the enhancement pattern depends on an intact urinary concentrating mechanism, it could have clinical appli-

cation in a wide range of disorders, such as pyelonephritis, obstruction, and drug nephrotoxicity.

In the U.S. clinical studies of the CNS in which the 10 ml/min injection rate was used, analysis of physical and neurologic examination results, laboratory data obtained up to 48 hr after drug administration, and reports of adverse experience have shown that gadopentetate dimeglumine has an acceptable safety profile [11]. Several patients developed hypotension or signs suggestive of possible hypotension after drug administration, usually within 25–85 min after injection; however, the relationship of hypotension to gadopentetate dimeglumine administration in humans is uncertain.

A study in anesthetized mongrel dogs was conducted in which gadopentetate dimeglumine (0.1 mmol/kg and 0.5 mmol/kg) was administered at a bolus rate (over 10 sec) and at a 1-min rate [12]. The 0.1 mmol/kg dose had no effects on the measured hemodynamic parameters at either rate of injection; however, the 0.5 mmol/kg dose injected at the bolus rate produced a transient decrease in LV systolic pressure and in systolic, diastolic, and mean arterial blood pressures. These transient decreases were only statistically significant from the values for the controls (isotonic saline and mannitol) at 30 sec after administration, and did not affect indexes of cardiac contractility or the appearance of ectopic activity. Because it appeared unlikely that a dose of 0.1 mmol/kg of gadopentetate dimeglumine administered at a bolus rate would have clinically significant effects in hemodynamically stable subjects or patients, the study described in this report was conducted in normal subjects to evaluate the safety and tolerance of gadopentetate dimeglumine (0.1 mmol/kg) when administered at a bolus injection rate of 10 ml/15 sec.

This double-blind, randomized, crossover, placebo-controlled study showed that there were no clinically significant changes or trends in change from baseline in blood pressures or pulse rate after bolus injection of gadopentetate dimeglumine. There were no clinically significant changes from baseline in any of the ECG or laboratory parameters; none of the subjects reported any adverse experiences. The results obtained after injection of gadopentetate dimeglumine were not significantly different statistically from the results obtained after injection of the placebo.

It is concluded that gadopentetate dimeglumine 0.1 mmol/kg, when administered to normal male subjects at a bolus rate of 10 ml/15 sec, is safe and well-tolerated.

ACKNOWLEDGMENT

The authors thank Diane Blumenfield for her assistance in preparing this manuscript.

REFERENCES

1. Weissleder R, Saini S, Stark DD, et al. Pyogenic liver abscess: contrast-enhanced MR imaging in rats. *AJR* **1988**;150:115–120
2. Choyke PL, Frank JA, Girton ME, et al. Dynamic Gd-DTPA-enhanced MR imaging of the kidney: experimental results. *Radiology* **1989**;170:713–720
3. Patel HI. Use of baseline measurements in the two-period crossover design. *Commun Stat Theor Meth* **1983**;12:2693–2712
4. Russell EJ, Geremia GK, Johnson CE, et al. Multiple cerebral metastases: detectability with Gd-DTPA-enhanced MR imaging. *Radiology* **1987**;165:609–617
5. Berry I, Brant-Zawadzki M, Osaki L, Brasch R, Murovic J, Norman D. Gd-DTPA in clinical MR of the brain: 1. intraaxial lesions. *AJNR* **1987**;147:1223–1230
6. 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* **1987**;147:1231–1235
7. Stimac GK, Porter BA, Olson DA, Gerlach R, Genton M. Gadolinium-DTPA-enhanced MR imaging of spinal neoplasms: preliminary investigation and comparison with unenhanced spin-echo and STIR sequences. *AJNR* **1988**;9:839–846
8. Sze G, Abramson A, Krol G, et al. Gadolinium-DTPA in the evaluation of intradural extramedullary spinal disease. *AJNR* **1988**;9:153–163, *AJR* **1988**;150:911–921
9. Sze G, Krol G, Zimmerman RD, Deck MD. Malignant extradural spinal tumors: MR imaging with Gd-DTPA. *Radiology* **1988**;167:217–223
10. Russell EJ, Schaible TF, William D, et al. Multicenter double-blind placebo-controlled study of gadopentetate dimeglumine as an MR contrast agent: evaluation in patients with cerebral lesions. *AJNR* **1989**;10:53–63, *AJR* **1989**;152:813–823
11. Goldstein HA, Kashanian F, Blumetti RF, Holyoak W, Hugo F, Blumenfield DM. Safety assessment of gadopentetate dimeglumine in United States clinical trials. *Radiology* **1990**;174:17–23
12. Sullivan ME, Goldstein HA, Sansone KJ, Stoner SA, Holyoak WL, Wiggins JR. Hemodynamic effects of Gd-DTPA administered via rapid bolus or slow infusion: a study in dogs. *AJNR* **1990**;11:537–540