AJNR

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AJNR Am J Neuroradiol 1990, 11 (3) 537-540
http://www.ajnr.org/content/11/3/537

Hemodynamic Effects of Gd-DTPA Administered via Rapid Bolus or Slow Infusion: A Study in Dogs

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The hemodynamic effects of rapid (10 sec) versus slow (1 min) IV injection of Gd-DTPA were compared in normal, pentobarbital-anesthetized mongrel dogs. Hypertonic mannitol and isotonic saline were used as equiosmotic and equivolumetric controls. Two dose levels of Gd-DTPA were administered: 0.1 mmol/kg and 0.5 mmol/kg, corresponding to dose volumes of 0.2 and 1.0 ml/kg, respectively. The rapid injection of a high dose (0.5 mmol/kg) produced a transient decrease in arterial blood pressure (21 mm Hg, $p < .001$), which returned to control values within 1 min after the injection. Slow IV infusion at this high dose had no statistically significant hemodynamic effects. There were no statistically significant effects of the lower dose (0.1 mmol/kg) administered as a bolus or by infusion, nor of the saline or osmotic control solutions.

These results suggest that acute hemodynamic effects of Gd-DTPA are not observed at clinically relevant doses and the vasodilation observed at a higher dose may result from a direct action of the contrast agent.

***AJNR* 11:537–540, May/June 1990**

Gd-DTPA is a relatively new contrast agent for MR imaging. It is distributed in extracellular water and has been most extensively studied in disease states, such as lesions within the CNS, where dysfunction of diffusion barriers provides a clear indication of disease [1–3]. Rapid imaging techniques have been developed that allow Gd-DTPA to provide contrast enhancement in other tissues, such as the liver, where such diffusion barriers do not exist [4]. Optimal contrast with these techniques requires that the contrast agent be administered rapidly; however, the hemodynamic safety of such a rapid injection of Gd-DTPA has not been addressed. Therefore, we conducted a study to investigate the hemodynamic effects of Gd-DTPA administered as a rapid IV injection (10 sec) and to compare these effects with the effects observed when Gd-DTPA is administered at a slower rate (1 min). The two doses of Gd-DTPA chosen for study represent a usual clinical dose (0.1 mmol/kg) and a dose that is five times the usual clinical dose (0.5 mmol/kg). Since hemodynamic effects could be the result of rapid changes in local osmolarity or volume, the effects of administration of a hyperosmotic solution (mannitol solution with the same osmolarity as the Gd-DTPA solution) or transient volume changes (isotonic saline administration) were also studied and compared with the effects in animals receiving Gd-DTPA.

Received July 26, 1989; revision requested September 23, 1989; revision received November 9, 1989; accepted November 15, 1989.

Presented at the annual meeting of the Society of Magnetic Resonance in Medicine, San Francisco, August 1988.

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0195–6108/90/1103–0537

Materials and Methods

Mongrel dogs, unselected as to sex, weighing 10–20 kg were anesthetized with sodium pentobarbital (30 mg/kg, IV), intubated, and mechanically ventilated at a rate of 12 cycles/min and a tidal volume of 20 ml/kg/cycle. Left ventricular (LV) pressure was measured by means of a fluid-filled polyethylene catheter introduced into the left carotid artery and positioned in the left ventricle. Correct placement in the left ventricle was assured by monitoring the pressure waveform of the advancing catheter. This catheter was used to

monitor LV systolic pressure, LV end diastolic pressure, and the maximum rate of LV pressure development (LV dp/dt). Central venous pressure was monitored by means of a fluid-filled polyethylene catheter inserted into the left jugular vein and advanced to the level of the superior vena cava. Arterial blood pressure (systolic, diastolic, and mean) was monitored by a fluid-filled polyethylene catheter inserted in the right femoral artery and advanced to the level of the abdominal aorta. The right femoral vein was cannulated for the administration of fluids or drug. A lead II ECG was monitored throughout the experiment by means of needle electrodes.

Hemodynamic data were acquired with the aid of an on-line computer. LV, arterial, and venous pressure waveforms were collected and digitized over a 5-sec period (i.e., one complete respiratory cycle) and averaged to form one data point. The sampling frequency was 200 Hz for the blood pressure and 400 Hz for the left ventricular pressure trace. LV dp/dt was determined on-line using a moving average technique, which set the slope at each point equal to the difference (slope) between the two adjacent points. Preliminary studies showed that this sampling and analysis protocol, which at a heart rate of 120 bpm averages data for 10 cardiac cycles, obviated any problems with data collection via fluid-filled catheters and allowed accurate comparison between left ventricular and aortic pressures. Mean blood pressure was calculated for each cardiac cycle as the arithmetic mean of the pressures recorded at each time point during that cycle. Heart rate was determined electronically from the pressure waveforms and confirmed manually from the ECG tracings. In addition, the appearance of any ectopic beats was recorded.

The Animal Care facility of Berlex Laboratories is fully accredited by the American Association of Laboratory Animal Care and all studies were conducted according to the NIH guidelines for the care of laboratory animals.

Study Design

Thirty animals were allocated to six treatment groups ($n = 5$/group) by the use of a computer-generated randomization scheme. Each group received two dose levels of test compound, approximately 45 to 60 min apart, at one rate of administration. The six groups were as follows: (1) isotonic saline control (bolus administration over 10 sec); (2) isotonic saline control (infusion over 1 min); (3) Gd-DTPA (bolus); (4) Gd-DTPA (infusion); (5) hyperosmotic control (bolus); and (6) hyperosmotic control (infusion).

After surgical preparation, animals were allowed to equilibrate for at least 30 min, during which time hemodynamic parameters were monitored to assure their stability prior to drug administration. Animals in the "bolus" groups received injections by hand over a 10-sec time period. Animals in the "infusion" groups received injections over 1 min by means of a calibrated syringe pump (Medrad Electronics, Pittsburgh, PA). After administration of the first dose, data were collected at 0.5, 1, 2, 5, 10, 15, 30, and 45 min. The second dose was given after the data for the 45-min time point had been collected or after stabilization of parameters. Because of uncertainties about carryover effects, all animals were tested in the order of increasing dose.

Drug Administration

Gd-DTPA (gadopentetate dimeglumine) (Magnevist injection, lot #63121, Berlex Laboratories, Inc., Wayne, NJ) was supplied in vials as a 0.5 mol/l solution, corresponding to an osmolality of 1.94 Os/kg H_2O. Gd-DTPA is a clear, colorless aqueous solution that contains the di-*N*-methylglucamine salt of diethylenetriamine pentaacetic acid (DTPA) in a concentration of 0.5 mol/l (0.5 mmol/ml). The solution also includes 0.39 mg/ml of meglumine and 0.15 mg/ml DTPA. The desired doses to be administered were 0.1 and 0.5 mmol/kg; thus, the 0.5 mol/l solution was given, undiluted, at a volume of 0.2 and 1.0 ml/kg. Isotonic saline (0.9% NaCl) and hyperosmotic mannitol were also administered at a volume of 0.2 and 1.0 ml/kg. The mannitol solution was made by dissolving 166.69 g of mannitol (USP grade) in 500 ml of deionized water. The resulting solution had an osmolality of approximately 1.94 Os/kg H_2O.

Statistical Analysis

Univariate analyses of variance (ANOVA) were performed on each of eight cardiovascular parameters. Homogeneity of the six groups was tested by comparing the baseline means ($t = 0$ min) with a one-way ANOVA. Tests for treatment effects were performed at each postbaseline time point, where the criterion variable was change from baseline. These data were analyzed by using a repeated-measures ANOVA in which dose (0.2 ml/kg or 1.0 ml/kg) was repeated on each dog. Simple main effects were tested within each dose level by using Scheffe's F-test ($k = 6$). This test was based on an error term (MSE within cell) in which we pooled the variation due to dogs within sequence and the variation due to the interaction between dose and dogs within sequence. The degrees of freedom associated with this error term were adjusted according to Satterthwaite [5].

Results

No statistically significant differences were noted among any of the six treatment groups for any of the parameters measured during the predrug period (Table 1). Neither the isotonic control (saline) nor the hypertonic control (mannitol) had any statistically significant hemodynamic effect when administered in either volume (0.2 or 1 ml/kg) or at either rate

TABLE 1: Baseline Hemodynamic Measurements in All Animals

	Systolic Blood Pressure (mm Hg)	Diastolic Blood Pressure (mm Hg)	Mean Blood Pressure (mm Hg)	Heart Rate (bpm)	Left Ventricular EDP (mm Hg)	Left Ventricular dp/dt (mm Hg/sec)	Central Venous Pressure (mm Hg)
Saline bolus	127 ± 6	85 ± 5	98 ± 5	123 ± 12	3.8 ± 0.7	2573 ± 177	2.6 ± 0.4
Saline infusion	125 ± 8	86 ± 6	98 ± 7	115 ± 6	4.0 ± 1.7	2560 ± 188	2.8 ± 0.5
Mannitol bolus	137 ± 9	93 ± 10	107 ± 9	120 ± 14	6.4 ± 1.3	2913 ± 250	2.4 ± 0.5
Mannitol infusion	142 ± 9	94 ± 6	109 ± 7	114 ± 12	5.2 ± 0.6	2967 ± 188	2.4 ± 0.4
Gd-DTPA bolus	137 ± 11	90 ± 6	105 ± 8	126 ± 8	5.0 ± 1.1	3121 ± 647	2.0 ± 1.1
Gd-DTPA infusion	133 ± 9	90 ± 6	103 ± 7	109 ± 12	5.6 ± 1.1	2315 ± 319	2.2 ± 0.7

Note.—Each value represents the mean ± SEM of five dogs for hemodynamic data acquired before the first dose of test compound. Baseline data before the second dose were not significantly different. EDP = end diastolic pressure.

TABLE 2: Hemodynamic Effects of Gd-DTPA in Normal, Pentobarbital-Anesthetized Dogs (n = 5)

Time* (min)	0.1 mmol/kg Gd-DTPA				0.5 mmol/kg Gd-DTPA			
	Heart Rate (bpm)	Left Ventricular EDP (mm Hg)	Left Ventricular dp/dt (mm Hg/sec)	Central Venous Pressure (mm Hg)	Heart Rate (bpm)	Left Ventricular EDP (mm Hg)	Left Ventricular dp/dt (mm Hg/sec)	Central Venous Pressure (mm Hg)
A. Bolus Injection								
0.5	126 ± 9	3.2 ± 1.3	2907 ± 478	1.8 ± 0.8	129 ± 8	4.0 ± 1.0	2869 ± 336	2.8 ± 0.8
1.0	124 ± 9	3.4 ± 1.0	2954 ± 528	2.0 ± 0.8	125 ± 9	4.6 ± 0.8	3048 ± 400	2.6 ± 0.8
5.0	123 ± 8	4.8 ± 0.8	3012 ± 543	2.2 ± 0.8	122 ± 9	6.0 ± 1.1	2933 ± 437	2.4 ± 0.7
10.0	123 ± 8	5.2 ± 1.1	3096 ± 573	2.0 ± 0.8	119 ± 9	5.2 ± 1.1	3087 ± 390	1.8 ± 1.0
45.0	122 ± 9	3.8 ± 1.3	2850 ± 392	1.6 ± 0.8	116 ± 14	4.2 ± 1.2	2814 ± 525	1.6 ± 1.0
B. Infusion								
0.5	108 ± 11	6.0 ± 1.2	2467 ± 249	2.2 ± 0.7	118 ± 12	6.2 ± 1.7	2396 ± 305	2.2 ± 0.9
1.0	109 ± 11	6.4 ± 1.2	2297 ± 270	2.0 ± 0.7	119 ± 12	6.4 ± 1.7	2503 ± 288	2.2 ± 0.9
5.0	109 ± 12	6.2 ± 1.1	2328 ± 295	1.8 ± 0.8	116 ± 13	5.4 ± 1.4	2351 ± 254	2.2 ± 0.9
10.0	106 ± 12	6.2 ± 1.2	2322 ± 304	2.0 ± 0.8	113 ± 15	6.0 ± 2.0	2354 ± 218	1.8 ± 0.7
45.0	123 ± 17	5.8 ± 1.5	2543 ± 284	1.8 ± 0.8	113 ± 19	6.0 ± 2.4	2141 ± 239	2.0 ± 1.1

* Minutes after the end of the injection. Data from intermediate time points were not different from those shown.
Note.—EDP = end diastolic pressure.

of administration (bolus or infusion) (data not shown). Gd-DTPA had no statistically significant effect on heart rate, LV end diastolic pressure, LV dp/dt, or central venous pressure with any of the injection or dosing regimens tested (Table 2).

Administration of the usual clinical dose of Gd-DTPA (0.1 mmol/kg) had no statistically significant effect on LV systolic pressure or on aortic blood pressure with either of the injection regimens tested (Fig. 1). The high dose of Gd-DTPA (0.5 mmol/kg) had no statistically significant effect on LV systolic pressure or on aortic blood pressure when it was infused over 1 min (Fig. 1). However, the rapid (10 sec) injection of the high dose caused a small but statistically significant decrease in LV and aortic systolic pressures, and in aortic diastolic and, consequently, mean pressures (Fig. 1). Within 30 sec of the end of the injection, systolic aortic pressure decreased from 144 to 125 mm Hg ($p < .001$) and diastolic pressure decreased from 97 to 75 mm Hg ($p < .001$). Mean arterial pressure fell from 112 to 91 mm Hg ($p < .001$). Blood pressure recovered rapidly and was not significantly different from control at the 1-min measurement (Fig. 1) or thereafter.

Approximately 50% of the animals studied had some degree of ectopic activity, consisting of isolated premature ventricular contractions (PVCs) at a rate of 1 to 2 per 10 min during the baseline period. This ectopic activity began after the introduction of the LV pressure catheter and thus represents local irritation of the endocardial surface by the catheter. The frequency and rate of PVCs was not affected by any of the treatment or dosing regiments tested (Gd-DTPA saline, or mannitol, by bolus injection or 1-min infusion), and no new arrhythmias were seen.

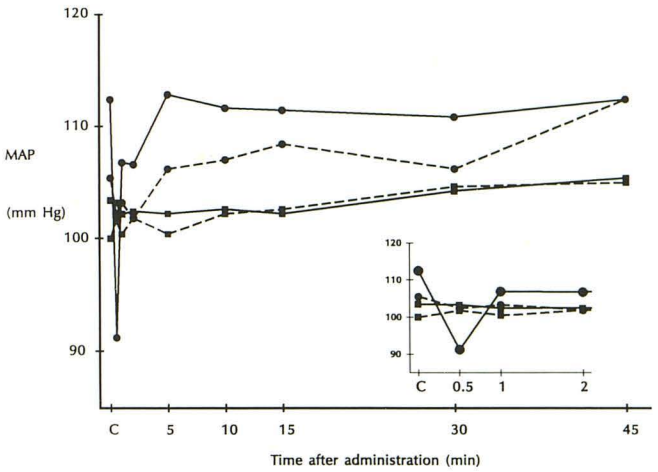

Fig. 1.—Effect of Gd-DTPA on mean arterial pressure (MAP) in pentobarbital-anesthetized dogs. The effect of Gd-DTPA when administered by bolus (*circles*) or by infusion (*squares*) was evaluated over time. Only the bolus administration of the high dose (0.5 mmol/kg) of Gd-DTPA had a statistically significant effect on mean blood pressure, and this was only statistically significant at the 0.5-min observation point. Each point represents the mean response from five dogs; standard errors have been omitted for clarity. *Dotted lines* show the data from the low dose (0.1 mmol/kg); *solid lines*, the high dose (0.5 mmol/kg). The inset shows the results for the first 2 min after administration on an expanded time base for clarity.

Discussion

The hemodynamic effects of rapid (10 sec) bolus administration of two doses of Gd-DTPA were compared with the hemodynamic effects of Gd-DTPA administered at a slower rate (1-min infusion). In addition, the effects of Gd-DTPA administration (either bolus or infusion) were compared with an equivalent volume or an equivalent osmotic solution given in a similar manner so as to adequately assess the direct effects of Gd-DTPA unrelated to volume or osmotic effects. The choice of examining the effects of Gd-DTPA in a model that utilizes closed-chest, pentobarbital-anesthetized dogs was made because the closed-chest preparations would mimic the clinical setting better than the corresponding open-chest models. Also, the closed-chest preparations would not be associated with overt sympathetic stimulation, which often occurs during open-chest surgical maneuvers. Anesthetized dogs were chosen rather than conscious dogs because of the decreased variability associated with any experimental

measurements. In addition, since anesthesia blunts compensatory hemodynamic reflex mechanisms, any adverse effects produced by a compound would tend to be magnified and easily measured under these conditions.

The only statistically significant effects seen were those observed for Gd-DTPA given as a bolus injection at a dose of 0.5 mmol/kg. Bolus injection of this dose produced transient decreases in indices of peripheral arterial resistance (LV systolic pressure and systolic, diastolic, and mean arterial [aortic] blood pressures). The decreases seen in blood pressure were statistically significantly different from their volume and osmotic controls only when measured 30 sec after administration. The average decrease in mean arterial pressure during this transient period was 21 mm Hg, which is of little biological significance over this interval. All other variables measured (LV dp/dt, LV end diastolic pressure, central venous pressure, heart rate, and the frequency of ectopic activity) were unaffected. Bolus injection of the clinically used dose of Gd-DTPA (0.1 mmol/kg) produced no statistically significant changes when compared with the volume and osmotic controls. Clinically, Gd-DTPA has been reported to cause a decrease in blood pressure in a small percentage of patients [6]. This decrease in blood pressure, which may be reflected in the results seen in the present study only for the high dose administered as a bolus, is rarely of clinical significance.

The bolus administration of the high dose of Gd-DTPA transiently decreased arterial blood pressure, which was unrelated to volume or osmotic effects. The decrease in blood pressure seen is most likely a direct result of Gd-DTPA on the peripheral vascular resistance vessels rather than a direct effect on the contractility of the myocardium, since LV dp/dt was not significantly affected, nor were central venous pressure or LV end diastolic pressure, indices of ventricular filling, significantly altered. A central effect of Gd-DTPA cannot be ruled out, but this seems unlikely because of the rapid onset and very short duration of the response. The X-ray contrast agents iohexol and diatrizoate sodium have been shown to release prostacyclin in patients [7]. Although the mechanism of the vasodilator response to Gd-DTPA is not known, a transient release of prostacyclin would be entirely consistent with the effects seen. The very short duration of the vasodilator effect may also suggest that high concentrations of Gd-DTPA release endothelium-derived relaxing factor.

In conclusion, bolus administration of Gd-DTPA at a dose of 0.1 mmol/kg was not associated with any significant changes in hemodynamic parameters or ectopic activity and should be well tolerated in patients. Bolus administration of Gd-DTPA at a dose of 0.5 mmol/kg produced a very transient decrease in arterial pressure without affecting indices of cardiac contractility or ectopic activity. It seems unlikely that this effect will be clinically significant in hemodynamically stable patients. Clinical administration of Gd-DTPA as a 1-min infusion at either the 0.1 or 0.5 mmol/kg dose should be well tolerated in all patients.

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