

# Characteristics of Gadolinium-DTPA Complex: A Potential NMR Contrast Agent

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**Chelation of the rare-earth element gadolinium (Gd) with diethylenetriaminepentaacetic acid (DTPA) results in a strongly paramagnetic, stable complex that is well tolerated in animals. The strongly paramagnetic gadolinium complex reduces hydrogen-proton relaxation times even in low concentrations (less than 0.01 mmol/L). The pharmacokinetic behavior of intravenously delivered Gd-DTPA is similar to the well known iodinated contrast agents used in urography and angiography; excretion is predominately through the kidneys with greater than 90% recovery in 24 hr. The intravenous LD<sub>50</sub> of the meglumine salt of Gd-DTPA is 10 mmol/kg for the rat; in vivo there is no evidence of dissociation of the gadolinium ion from the DTPA ligand. The combination of strong proton relaxation, in-vivo stability, rapid urinary excretion, and high tolerance favors the further development and the potential clinical application of gadolinium-DTPA as a contrast enhancer in magnetic resonance imaging.**

Recent developments in nuclear magnetic resonance (NMR) technology have led to a new and extremely promising diagnostic technique, proton NMR tomography. Using a suitable radiofrequency pulse sequence (saturation-recovery, inversion-recovery, or spin-echo), it is possible to obtain images of high quality that often aid in the characterization of pathologic processes, especially within the brain [1-10]. Differentiation of tissue from normal is provided when a distinction exists between the spin-lattice and/or spin-spin relaxation times of a lesion and those of surrounding normal tissues. Other factors that influence signal intensity, such as hydrogen-proton concentration and proton motion, seem to play a lesser role than relaxation times in most cases.

If differences in relaxation times between contiguous healthy and pathologic tissues are only insignificant, or even identical, differentiation is impossible by NMR tomography [11]. Diagnosis is made more difficult by the fact that relaxation times of various malignant and benign lesions or normal tissue may overlap [12]. Another feature of NMR imaging that may be regarded as a disadvantage in comparison with conventional imaging techniques is that the NMR image does not provide a direct measurement of organ function [11].

Recent investigations indicate that paramagnetic compounds used as NMR contrast agents may augment the diagnostic yield from NMR tomography by enhancing the contrast between magnetically similar but histologically dissimilar tissues and by providing a direct measure of organ function [13-19]. Alternatively, continued development of NMR technology and the use of sophisticated computer-assisted analyses may render contrast agents unnecessary.

To date, experiments with NMR contrast agents have focused on three different types of paramagnetic substances. The first type belongs to the group of nitroxyl stable-free radicals; these compounds, containing one unpaired electron, have been shown to be relatively stable, to be well tolerated in experimental animals, and to decrease proton relaxation times [19]. Transition elements and rare-earth elements constitute the second major group of paramagnetic substances with

Received July 7, 1983; accepted after revision November 14, 1983.

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**AJR 142:619-624, March 1984**  
 0361-803X/84/1423-0619

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potential as NMR contrast agents. Considerable attention has focused on the bivalent manganese ion ( $Mn^{2+}$ ), which owes its high degree of paramagnetism to five unpaired electrons [20]. Due to the potential of the  $Mn^{2+}$  ion to undergo spontaneous oxidation leading to a change or loss of paramagnetic properties and because of prolonged retention within the liver, the in-vivo possibilities may be limited. A third class of paramagnetic compounds is represented by molecular oxygen, which is paramagnetic by virtue of two unpaired electrons with parallel spins that do not cancel. Oxygen used as a NMR contrast agent has the disadvantage that within an organism, the molecule may rapidly lose its paramagnetic properties (e.g., in the formation of diamagnetic oxyhemoglobin) [21].

The general aim was to find a compound that remained stable in vivo, had a powerful influence on proton relaxation times, but was free of toxic effects in doses appropriate for contrast enhancement in vivo. Moreover, it was essential that the compound undergo tissue-specific or, at least, compartment-specific distribution in the living organism.

Gadolinium (Gd), a rare-earth element the ion of which ( $Gd^{3+}$ ) has seven unpaired electrons, also has an unusually strong hydrogen-proton spin-lattice relaxation effect (fig. 1) [20]. The gadolinium ion has been used as a paramagnetic proton-relaxation probe in NMR biochemical studies [22]. Because of poor tolerance for unaltered gadolinium ions, a means of detoxification is necessary for in-vivo administration [23]. Since the atoms of the rare-earth elements do not form stable, covalent bonds with organic molecules, the paramagnetic Gd ion might be detoxified by complexation. Gadolinium is known to form stable chelates with ethylenediaminetetraacetic acid (EDTA) and diethylenetriaminepentaacetic acid (DTPA); the formation constants ( $\log k$ ) for Gd-EDTA and Gd-DTPA are 17 and 22–23, respectively [24]. Our study examines the in-vivo stability, pharmacokinetics, and toxicity of Gd-DTPA and compares it with Gd-EDTA and gadolinium chloride.

## Materials and Methods

Gadolinium chelates were synthesized by incubation of  $Gd_2O_3$  (Auer-Remy, Hamburg, W. Germany) and the corresponding ligands. The synthesis of Gd-DTPA is an example. A suspension of 43.5 g of  $Gd_2O_3$  and 94.5 g of DTPA in 1.2 L water was stirred, while being heated to 90°C to 100°C, for 48 hr. The undissolved material was then filtered off, and the filtrate was evaporated until dry.

The addition of N-methylglucamine yielded water-soluble salts of the gadolinium chelates, ethylenediaminetetraacetic acid (Gd-EDTA) and diethylenetriaminepentaacetic acid (Gd-DTPA) as described in the published patent application [25]. A 0.5 mol/L solution of dimeglumine-Gd-DTPA has an osmotic pressure of 49.8 atm (1.94 osmol/kg) and a viscosity of 2.9 mPa.s measured at 37°C by vapor-pressure osmometry and capillary viscosimetry, respectively. Free gadolinium ions were not detectable (below 0.01%) by use of xylenol orange as indicator [26]. Aqueous gadolinium chloride and diatrizoate (Angiografin [corresponds to Angiovist]) were used as reference solutions.

### Proton Relaxation Effects

The effects of the paramagnetic compounds on proton relaxation times were measured in aqueous solutions at 20 MHz (0.47 T) using

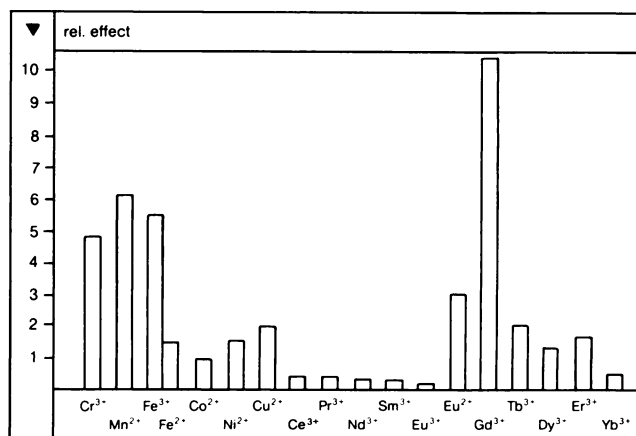


Fig. 1.—Influence of paramagnetic ions on proton spin-lattice relaxation time [20].

a pulse NMR spectrometer (Minispec pc 20, Bruker, Karlsruhe, W. Germany) for inversion-recovery and Carr-Purcell-Meiboom-Gill pulse sequences.

### Tolerance

The acute intravenous tolerance ( $LD_{50}$ ) of test solutions was evaluated by administration of different volumes of each agent directly into the tail veins of rats. Outbred male and female rats (strain: Wistar-Han-Schering) weighing 90–110 g were given a single intravenous injection at one of two to four dose levels; three to six animals were given each dose. The injection rate was 2 ml/min and the rats were observed for 7 days after the injection. The concentration of test solution was 0.5 mol/L Gd-DTPA, 0.1 mol/L  $GdCl_3$  and Gd-EDTA, or 306 mg l/ml for diatrizoate. The amount of compound producing 50% mortality ( $LD_{50}$ ) was determined by interpolation from the results of different dose levels. A 0.5 mol/L solution of  $Na_3Ca$ -DTPA (Heyl, W. Germany), a chelating drug used to treat heavy-metal poisoning, was also tested for  $LD_{50}$  as a comparison.

Neural tolerance was assessed by intracisternal injection in male and female rats. The amounts of each compound producing 50% morbidity ( $ED_{50}$ ) (lack of motor coordination or epileptoid fit) and 50% mortality ( $LD_{50}$ ) were determined by interpolation from the results of four to 10 dose levels, each administered to 10 animals [27].

Because the in-vivo tolerance of contrast media correlates with the hydrophobicity, the partition coefficients of Gd-DTPA and diatrizoate were determined in a n-butanol-buffer mixture at pH 7.6 [28]. In order to establish whether Gd-DTPA causes some of the side effects known from radiographic contrast media the potential influence of Gd-DTPA and diatrizoate on the complement system was measured using the method of activation described by Mützel et al. [29].

### Pharmacokinetics

Pharmacokinetic studies were performed with  $^{153}Gd$ -labeled compounds:  $^{153}GdCl_3$  (382 MBq/mg Gd, Amersham, England) was added to a 0.25 mol/L solution of unlabeled  $GdCl_3$ ;  $^{153}Gd$ -labeled Gd-DTPA was prepared by incubation of  $^{153}GdCl_3$  and DTPA. On the basis of molar concentrations, the amount of DTPA was 10% higher than the amount of the radioactive material; pH was adjusted to 7.2 by addition of N-methylglucamine. A small amount of this solution of high specific

activity (high radioactivity but low Gd concentration) was mixed with 0.5 mol/L of unlabeled Gd-DTPA. The specific activity of the resulting solution, used for the study of excretion and organ distribution, was 2 MBq/mmol; for blood- and plasma-level studies, an activity of 0.15 MBq/mmol was used. Free gadolinium was not detectable (below 0.01%) by means of thin-layer chromatography or xylenol orange as indicator [26]. The  $^{153}\text{Gd}$  activity was measured with the aid of a gamma scintillation counter (Compu Gamma 1282, LKB/Wallac, Finland).

Renal and fecal excretions were analyzed for 7 days after intravenous administration of 0.5 mmol/kg radiolabeled Gd-DTPA or 0.25 mmol/kg radiolabeled  $\text{GdCl}_3$  in five male rats (140–160 g). In another experiment using five rats, serial blood, urine, and plasma concentrations of Gd-DTPA were determined for 3 hr after intravenous injection of 0.5 mmol/kg. For each time point, blood was taken from three to five animals. Half-lives of Gd-DTPA disappearance were then calculated for blood, plasma, and urine from levels of radiolabel; values were based on computer calculation using an open one-compartment model [30]. Gadolinium concentrations in kidney, liver, and spleen and the amount of gadolinium remaining in the organism were determined 7 days after injection.

## Results

### Proton Relaxation Effects of Gadolinium Compounds

The free gadolinium ion ( $\text{Gd}^{3+}$ ) and the two gadolinium chelates produced distinct effects on the T1 and T2 relaxation times of hydrogen protons in aqueous solutions (table 1); increases in the concentration of these paramagnetic agents resulted in a decrease in both T1 and T2 relaxation times. A straight-line relation was observed between concentration and the reciprocal value of relaxation times in the range of 0–1 mmol/L. Chelation with either EDTA or DTPA reduced the paramagnetic properties of nonchelated gadolinium. The proton relaxation times of demineralized water were reduced by half with about 50  $\mu\text{mol/L}$  gadolinium chloride and about the same amount of Gd-EDTA, but almost 80  $\mu\text{mol/L}$  was required to achieve the same proton relaxation effect with Gd-DTPA.

### Tolerance

For gadolinium chloride and Gd-EDTA, half of the animals investigated died after a dose of less than 1 mmol/kg (table 2). Gd-DTPA demonstrated a considerably better tolerance; for this chelate, the  $\text{LD}_{50}$  was 10 mmol/kg. For comparison, the  $\text{LD}_{50}$  was 18 mmol/kg for the iodinated radiographic contrast agent, diatrizoate, corresponding to about 7 g l/kg. For Gd-DTPA and diatrizoate administrations, the animals died within the first 3 hr. For Gd-EDTA and  $\text{GdCl}_3$ , some animals died several days after administration, implying a different form of toxicity.

Animals receiving subarachnoidal administrations of  $\text{GdCl}_3$  and Gd-EDTA displayed a poorer tolerance than that shown for Gd-DTPA and diatrizoate (table 3). Tolerance to free gadolinium ions was lowest of all gadolinium agents for the intracisternal route. In the case of  $\text{GdCl}_3$ , the values of the  $\text{ED}_{50}$  and  $\text{LD}_{50}$  were virtually identical, meaning that minor neurotoxic effects were immediately followed by severe and

TABLE 1: Relation of Proton Relaxation Rates and Concentrations of Paramagnetic Agents

Agent	Relaxation Rate
<b>GdCl<sub>3</sub>:</b>	
T1	$T1^{-1} (\text{sec}^{-1}) = 0.49 + 9.09 \times C$
T2	$T2^{-1} (\text{sec}^{-1}) = 0.65 + 10.3 \times C$
<b>Meglumine-Gd-EDTA:</b>	
T1	$T1^{-1} (\text{sec}^{-1}) = 0.44 + 6.89 \times C$
T2	$T2^{-1} (\text{sec}^{-1}) = 0.55 + 8.19 \times C$
<b>Dimeglumine-Gd-DTPA:</b>	
T1	$T1^{-1} (\text{sec}^{-1}) = 0.39 + 4.52 \times C$
T2	$T2^{-1} (\text{sec}^{-1}) = 0.50 + 5.66 \times C$

Note.—Influence of concentration, C (mmol/L), of gadolinium compounds on the T1 and T2 relaxation times of hydrogen protons of water at 20 MHz. Values were calculated using regression analyses of the relation  $1/T$  vs. C in concentration range 0–1 mmol/L.

TABLE 2: Acute Lethal Toxicity

Agent	Dose (mmol/kg)	No. Deaths/ No. Rats	Interpolated $\text{LD}_{50}$ (mmol/kg)*
Meglumine diatrizoate	12	0/4	18
	20	1/4	
	28	4/4	
$\text{GdCl}_3$	0.3	0/5	0.5
	0.45	2/5	
	0.6	5/5	
Meglumine-Gd-EDTA	0.3	2/3	0.3
	1.2	5/5	
	2.5	0/4	
Dimeglumine-Gd-DTPA	7.5	0/4	10
	12.5	4/4	
	1	0/6	
$\text{Na}_3\text{Ca-DTPA}$	2	2/6	5
	4	0/6	
	6	6/6	

\*  $\text{LD}_{50}$  in male and female rats (90–110 g) after intravenous injection (2 ml/min).

lethal toxicity. The overall best neural tolerance was observed for gadolinium chelated with DTPA; for Gd-DTPA, the values of the  $\text{LD}_{50}$  were 10 times higher than  $\text{ED}_{50}$  values with both routes of neural administration.

Both Gd-DTPA and diatrizoate are very hydrophilic substances. Partition coefficients ( $\log P$ ) of  $-2.7$  and  $-1.3$  were measured for the gadolinium chelate and the iodinated contrast agent, respectively. However, the butanol-buffer partition coefficient of Gd-DTPA is about 25 times smaller than that of the iodinated compound.

The in-vitro investigation of complement activation showed that 50% of plasma complement remained at a diatrizoate concentration of 0.4 mol/L. In the case of Gd-DTPA, practically no influence on the complement system was detected; 50% activation required 2.5 mol/L.

### Pharmacokinetics

At 5 min after intravenous injection of 0.5 mmol/kg Gd-DTPA into the rats, about 10% of the dose could be detected in the whole blood volume. The blood concentration subsequently decreased with a half-life of about 20 min (fig. 2). Gd-DTPA apparently did not penetrate the cell membrane of

TABLE 3: Tolerance after Intracisternal Administration in Rats

Agent	Dose* (mmol/kg)	No. Reactors	No. Deaths	ED <sub>50</sub>	LD <sub>50</sub>
Meglumine diatrizoate	4	1	NE	11 (8-15)	55 (44-67)
	8	2	NE		
	13	5	NE		
	17	7	NE		
	21	10	NE		
	32	NE	1		
	42	NE	3		
	63	NE	6		
	84	NE	8		
	128	NE	10		
GdCl <sub>3</sub>	3	3	NE	6 (4-8)	8 (7-10)
	4	3	0		
	6	5	2		
	8	7	6		
Meglumine-Gd-EDTA	17	10	10	12 (4-8)	23 (19-27)
	8	2	NE		
	16	7	1		
	27	NE	6		
Dimeglumine-Gd-DTPA	32	10	9	74 (49-112)	650 (544-800)
	17	0	NE		
	33	3	NE		
	67	4	NE		
	133	7	NE		
	198	9	NE		
	417	NE	1		
	617	NE	5		
	833	NE	8		
1233	NE	9			

Note.—NE = Not evaluated; numbers in parentheses are 95% confidence intervals.  
\* n = 10 per dose.

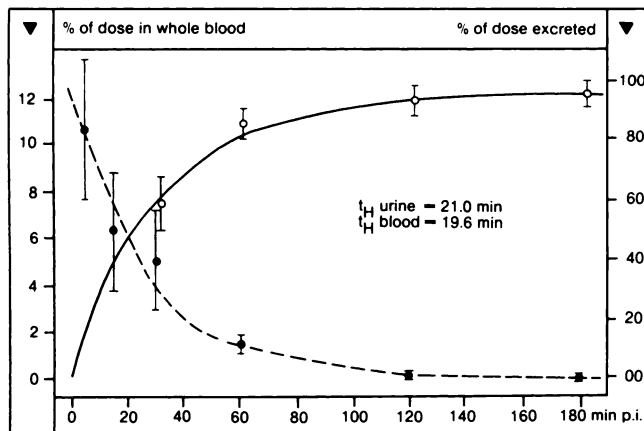


Fig. 2.—Blood level and urinary excretion of <sup>153</sup>Gd-DTPA after intravenous injection of 0.5 mmol/kg in five male rats (140–160 g body weight).

blood cells; the concentration in plasma remained 1.6 times higher than in blood over 2 hr of observation.

A half-life of about 20 min was observed for renal excretion up to 3 hr after injection. By 3 hr, more than 80% of the compound had been excreted from the organism in urine (table 4). By 7 days after intravenous injection, a total of 90% of the dose had been recovered in the urine and another 7%

TABLE 4: Excretion and Tissue Distribution after Intravenous Injection of <sup>153</sup>Gd-DTPA in Rats

Gd-DTPA	Time after Dose (days)*	% of Administered Dose
<b>Excreted:</b>		
Urine	0–3 hr	87.6 ± 1.9
	0–1	89.2 ± 2.6
	0–7	89.7 ± 2.7
Feces	0–1	5 ± 3.5
	0–7	7.4 ± 4.5
<b>Residual:</b>		
Liver	7	0.08 ± 0.01
Spleen	7	0.01
Kidney	7	0.1 ± 0.03
Remaining body	7	0.21 ± 0.05
<b>Total recovery</b>	7	<b>97.5 ± 3.0</b>

Note.—Data from injection of 0.5 mmol/kg <sup>153</sup>Gd-DTPA in five male rats weighing 140–160 g.

\* Time given in days unless indicated otherwise.

was recovered in the feces. Less than 0.3% of the given dose was found in the organism, with 0.08% of the dose being detected in the liver and 0.1% in the kidneys.

By 7 days after intravenous injection of radiolabeled GdCl<sub>3</sub>, only 2% of the dose had been excreted. The major portion was discovered in the liver and spleen, about 60% being in the liver and 25% in the spleen (table 5).

**TABLE 5: Excretion and Tissue Distribution after Intravenous Injection of  $^{153}\text{GdCl}_3$  in Rats**

GdCl <sub>3</sub>	Time after Dose (days)*	% of Administered Dose
<b>Excreted:</b>		
Urine	0-3 hr	0.05
	0-1	0.07
Feces	0-7	0.1 ± 0.0
	0-1	0.6 ± 0.4
	0-7	2.1 ± 0.5
<b>Residual:</b>		
Liver	7	56.1 ± 8.9
Spleen	7	25.3 ± 3.7
Kidney	7	0.6 ± 0.1
Remaining body	7	16.3 ± 2.3
Total recovery	7	100.6 ± 8.9

Note.—Data from injection of 0.25 mmol/kg  $^{153}\text{GdCl}_3$  in five male rats weighing 140–160

g.

\* Time given in days unless indicated otherwise.

## Discussion

Of all elements, gadolinium has the strongest influence on T1 relaxation times of hydrogen protons (fig. 1) [20]. This powerful proton-relaxing effect of gadolinium can be attributed to a complex interplay of several factors including a strong magnetic moment, long electron-spin-relaxation time, isotropy of g-tensors, rotational tumbling time, configuration and mobility of molecules of hydration, and proximity of hydrogen nuclei to the paramagnetic center [31, 32]. Chelating gadolinium to EDTA or DTPA reduces, but far from eliminates, gadolinium's strong influence on proton T1 and T2 relaxation.

The coordination number of  $\text{Gd}^{3+}$  is estimated to be 9 or 10 [22, 33]. Thus, using DTPA with eight coordination sites as a chelation ligand, only eight of gadolinium's nine or 10 possible coordination sites could be filled. This leaves at least one or two sites open for fast-exchanging water protons to approach closely to the paramagnetic center of the complex. Proton relaxation enhancement is directly proportional to the number of available coordination proton ligands per paramagnetic ion. Thus gadolinium complexes (Gd-DTPA and Gd-EDTA), compared with the nonchelated gadolinium species, would be predicted to have reduced proton relaxation effects on water molecules. This prediction was supported by our experimental results. To obtain the same influence on proton relaxation as that achieved with the free gadolinium ion, the concentration of Gd-DTPA must be about twice as high.

The complexation of gadolinium with EDTA produced little or no improvement in tolerance compared with gadolinium chloride. Whether the chemotoxicity of the entire complex itself or a dissociation of the gadolinium ion from the EDTA ligand within the body caused the effect is not clear. It may be that the Gd-EDTA stability constant of about  $10^{17}$  is insufficient to prevent the interaction of free gadolinium ions with high-affinity binding sites of enzymes. DTPA binds gadolinium several magnitudes more tightly ( $\log k = 22$ ) than EDTA [24]. Gd chelation with DTPA does, in fact, produce a compound with much improved tolerance. The  $\text{LD}_{50}$  is higher

than that of  $\text{Na}_3\text{Ca-DTPA}$ , which is a complexing agent used as an antidote for heavy-metal poisoning in man.

The acute intravenous tolerance ( $\text{LD}_{50}$ ) of Gd-DTPA in rats is in the range of that of the most commonly used radiographic contrast agent, diatrizoate. The neural tolerance of Gd-DTPA is several times better than for diatrizoate. A high neural tolerance is particularly advantageous if a compound may pass the blood-brain barrier.

According to the hypothesis of Lasser (Lang et al. [34]), activation of the complement system by radiographic contrast media is correlated to certain of their untoward anaphylactoid reactions. Gd-DTPA, a very poor activator of the complement system, would not be expected to produce such adverse reactions.

The combination of gadolinium with DTPA reduces the toxicity of the two separate components, gadolinium and DTPA [35]. This is reflected in the pharmacokinetic behavior after intravenous administration of Gd-DTPA compared with gadolinium chloride. Whereas the gadolinium ion is largely retained by the organism, in particular in the liver and spleen, Gd-DTPA leaves the body within the first few hours after intravenous injection. Compared with  $\text{GdCl}_3$ , there is no retention of gadolinium in liver and spleen. There seems to be no dissociation of gadolinium from the Gd-DTPA complex within the body.

The short (20 min) half-life of Gd-DTPA in blood and urine and the predominate renal elimination suggest that the compound has very little if any interaction within the body. The stable ratio of concentrations between plasma and blood and the fate of Gd-DTPA in the organism lead us to postulate that this complex is distributed exclusively extracellularly. The very high hydrophilicity, the charge, and the rather large molecular weight of Gd-DTPA (about 550) probably account for its exclusion by biologic barriers such as cell membranes. Gd-DTPA would be expected to remain within the extracellular space and not to penetrate the normal blood-brain barrier.

From the pharmacokinetic and in-vitro proton relaxation data for Gd-DTPA, we predict that an in-vivo dose of 0.1–0.5 mmol/kg would produce a significant tissue enhancement on NMR images. This predicted diagnostic dose is  $1/100$  to  $1/20$  of the observed  $\text{LD}_{50}$  dose, a wide margin of safety. Independent from our study, Fobben and Wolf [36] have called attention to Gd-DTPA as a potential NMR myocardial contrast agent and noted an absence of cardiotoxicity.

In summary, our results indicate that Gd-DTPA is an agent capable of strong proton relaxation enhancement with relatively high in-vivo tolerance. This hydrophilic complex is rapidly excreted, predominately in the urine, and apparently does not dissociate in vivo. These characteristics favor the use of Gd-DTPA as an NMR contrast enhancer.

## REFERENCES

- Partain CL, James AE, Watson JT, Price RR, Coulam CM, Rollo FD. Nuclear magnetic resonance and computed tomography. *Radiology* 1980;136:767–770
- Young IR, Burl M, Clarke GJ, et al. Magnetic resonance properties of hydrogen: imaging the posterior fossa. *AJR* 1981;

- 137:895-901
3. Pykett IL. NMR imaging in medicine. *Sci Am* **1982**;246:78-88
  4. Taveras JM. Nuclear magnetic resonance imaging. *AJR* **1982**;139:406-407
  5. Bydder GM, Steiner RE, Young IR, et al. Clinical NMR imaging of the brain: 140 cases. *AJR* **1982**;139:215-236
  6. James AE, Partain CL, Holland GN, et al. Nuclear magnetic resonance imaging: the current state. *AJR* **1982**;138:201-210
  7. Margulis AR. Nuclear magnetic resonance imaging: the present status. *J Can Assoc Radiol* **1983**;33:131-136
  8. Bydder GM, Steiner RE. NMR imaging of the brain. *Neuroradiology* **1982**;23:231-240
  9. Young IR, Randell CP, Kaplan PW, James A, Bydder GM, Steiner RE. Nuclear magnetic resonance (NMR) imaging in white matter disease of the brain using spin-echo sequences. *J Comput Assist Tomogr* **1983**;7:290-294
  10. El Yousef SJ, Alfidri RJ, Duchesneau RH, et al. Initial experience with nuclear magnetic resonance (NMR) imaging of the human breast. *J Comput Assist Tomogr* **1983**;7:215-218
  11. Brasch RC. Method of contrast enhancement for NMR imaging and potential application. *Radiology* **1983**;147:781-788
  12. Davis PL, Kaufman L, Crooks LE, Miller TR. Detectability of hepatomas in rat livers by nuclear magnetic resonance imaging. *Invest Radiol* **1981**;16:354-359
  13. Lauterbur PC, Mendonça-Dias MH, Rudin AM. Augmentation of tissue water proton spin-lattice relaxation rates by in vivo addition of paramagnetic ions. *Front Biol Energ* **1978**;1:752-759
  14. Young IR, Clarke GJ, Bailes DR, Pennock JM, Doyle FH, Bydder GM. Enhancement of relaxation rate with paramagnetic contrast agents in NMR imaging. *CT* **1981**;5:543-547
  15. Brady TJ, Goldman MR, Pykett IL, et al. Proton nuclear magnetic resonance imaging of regionally ischemic canine heart: effect of paramagnetic proton signal enhancement. *Radiology* **1982**;144:343-347
  16. Brasch RC, Nitecki ED, Brant-Zawadzki MN, Enzmann D, Tozer TN. "NSFR": NMR contrast agents for the CNS. Presented at the Symposium Neuroradiologicum, Washington, DC, October **1982**
  17. Runge VM, Stewart RG, Clanton JA, James AE, Partain CL. Paramagnetic NMR contrast agents: potential oral and intravenous agents. *Radiology* **1983**;147:789-791
  18. Goldman MR, Brady TJ, Pykett IL, et al. Quantification of experimental myocardial infarction using nuclear magnetic resonance imaging and paramagnetic ion contrast enhancement in excised canine hearts. *Circulation* **1982**;66:1012-1016
  19. Brasch RC, London DA, Wesbey GE, et al. Nuclear magnetic resonance study of a paramagnetic nitroxide contrast agent for enhancement of renal structures in experimental animals. *Radiology* **1983**;147:773-779
  20. Pople JA, Schneider WG, Bernstein HJ. *High-resolution nuclear magnetic resonance*. New York: McGraw-Hill **1959**:209
  21. Pauling L, Coryell CD. The magnetic properties and structure of hemoglobin, oxyhemoglobin and carbonmonoxyhemoglobin. *Proc Natl Acad Sci* **1936**;22:210-216
  22. Reuben J. Gadolinium (III) as a paramagnetic probe for protons relaxation studies of biochemical molecules. *Biochemistry* **1971**;10:2834-2838
  23. Arvela P. Toxicity of rare-earth. *Progr Pharmacol* **1979**;2:71-114
  24. Moeller T. *Gmelin Handbuch der anorganischen Chemie: rare earth elements, part D1*. Berlin: Springer-Verlag, **1980**
  25. Gries H, Rosenberg D, Weinmann HJ. Patent application DE-OS 3129906 A 1; **1981**
  26. Schwarzenbach G, Flaschka H. *Die komplexometrische Titration*. Stuttgart: Ferdinand Enke, **1965**:161-163
  27. Siefert HM, Press WR, Speck U. Tolerance to iohexol after intracisternal, intracerebral and intraarterial injection in the rat. *Acta Radiol [Suppl]* (Stockh) **1980**;362:77-81
  28. Levitan H, Rapoport SI. Contrast media: quantitative criteria for designing compounds with low toxicity. *Acta Radiol [Diagn]* (Stockh) **1976**;17:81-92
  29. Mützel W, Siefert HM, Speck U. Biochemical-pharmacologic properties of iohexol. *Acta Radiol [Suppl]* (Stockh) **1980**;362:111-115
  30. Poland H, Woloszczak R. A program library for computing models in pharmacokinetics. *Int J Biomed Comput* **1980**;2:115-128
  31. LaMar GN, Horrocks WD, Holm RH. *NMR of paramagnetic molecules: principles and application*. New York: Academic, **1973**:1-85
  32. James TL. *Nuclear magnetic resonance in biochemistry*. New York: Academic, **1975**:179
  33. Dwek RA. *Nuclear magnetic resonance (N.M.R.) in biochemistry*. Oxford: Clarendon, **1973**:174-284
  34. Lang JH, Lasser EC, Kolb WP. Activation of the complement system by x-ray contrast media. *Invest Radiol* **1976**;11:303-308
  35. Catsch A. Zur Toxikologie der Diaethylentriamine Pentaessigsäure. *Naunyn Schmiedebergs Arch Pharmacol* **1964**;246:316-329
  36. Fobben E, Wolf G. Gadolinium DTPA—a potential NMR contrast agent: effects upon tissue proton relaxation and cardiovascular function in the rabbit. Presented at the annual meeting of the Association of University Radiologists, Mobile, March **1983**