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Gadolinium as a Contrast Agent for NMR

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Gadolinium chloride ($GdCl_3$) was studied as a contrast agent for nuclear magnetic resonance. This rare-earth element dramatically alters proton resonance (paramagnetic moment = 10.8 Bohr magnetons). Acute toxicity was determined by intravenous injections in mice; mean lethal dose was 100–200 mg of $GdCl_3 \cdot 6\ H_2O$/kg. Changes in T_1 of plasma, kidney, liver, and brain of mice and rats were measured after intravenous injections of $GdCl_3$ solution at a concentration of 60 mg gadolinium metal/kg. The apparatus used was a WH 270 Brucker with a field of 63 kG. The T_1 was found to be significantly decreased in plasma, kidney, and liver.

Contrast media may be used for three different purposes: (1) to differentiate normal from pathologic tissue, (2) to characterize pathologic tissue, and (3) to characterize physiologic or pathologic phenomena. Contrast media that can theoretically be used in nuclear magnetic resonance (NMR) can be divided into three general groups: (1) products that can be detected directly by their gyromagnetic moment, such as fluorine, phosphorus, and sodium; (2) products that modify photon density, such as alcohol and glucose; and (3) products that modify the resonance of protons, such as free radicals and paramagnetic ions. We are particularly interested in paramagnetic ions and the modifications they can produce to the spin-lattice relaxation time (T_1) [1]. We chose to study gadolinium, a rare-earth element that possesses the highest paramagnetic moment, 10.8 Bohr magnetons [2].

Materials and Methods

First, we measured the toxicity of gadolinium in 19–20 g female Swiss mice (1 IOPS strain) by intravenous injections of 20 or 30 g/L gadolinium chloride ($GdCl_3$) solutions [3–5]. The median lethal dose (LD_{50}) for $GdCl_3$ was 100–200 mg $GdCl_3 \cdot 6\ H_2O$/kg (table 1). From a theoretic standpoint, a concentration of 60 mg of gadolinium metal/kg corresponding to 0.4×10^{-3} mol/L (molecular weight of gadolinium <156) should produce a significant modification of the T_1 process in tissues because the T_1 of water changes from 2.3 sec to 16×10^{-2} sec for a concentration of 0.4×10^{-3} mol/L. Therefore, we decided to study the modifications of the T_1 process by $GdCl_3$ at concentrations of about 60 mg gadolinium metal/kg, representing the approximate LD_{50}.

We used a Brucker WH 270 NMR apparatus. This apparatus is equipped with a cryomagnet with a magnetic field strength of 65 kG, the frequency for analyzing the proton is 270 MHz, and the field homogeneity is 10^{-9} for a volume of 1 cm^3. We traced the changes in $^1/T_1$ responses as a function of increasing concentrations of gadolinium in water. When graphed, this function has a slope of 12.8 sec^{-1}/mmol/L solution. We also traced the $^1/T_1$ responses as a function of increasing concentrations of gadolinium in plasma (fig. 1). The response of plasma is quite different from water, since the slope of the function is 7.4 sec^{-1}/mmol of gadolinium/L plasma. When gadolinium was added to blood, the effect was masked. It is very probable that in blood gadolinium forms complexes with blood proteins that mask the paramagnetic effect.

We analyzed specimens taken from animals for modifications of T_1 of different organs.

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TABLE 1: **Determination of Intravenous Toxicity of Gadolinium Chloride Solutions in Mice**

Solution: Dose (mg/kg)	No. of Animals that Died/No. Studied
20 g/L:	
100	1/10
200	7/10
500	10/10
30 g/L:	
50	0/10
100	2/10
150	10/10
200	10/10

Note.—The injection speed was 2 ml/min. The LD_{50} of g/L $GdCl_3$ was estimated at 200 mg/kg, which contains about 0.75 mmol gadolinium metal/kg. The LD_{50} of 30 g/L $GdCl_3$ was 100–150 mg/kg.

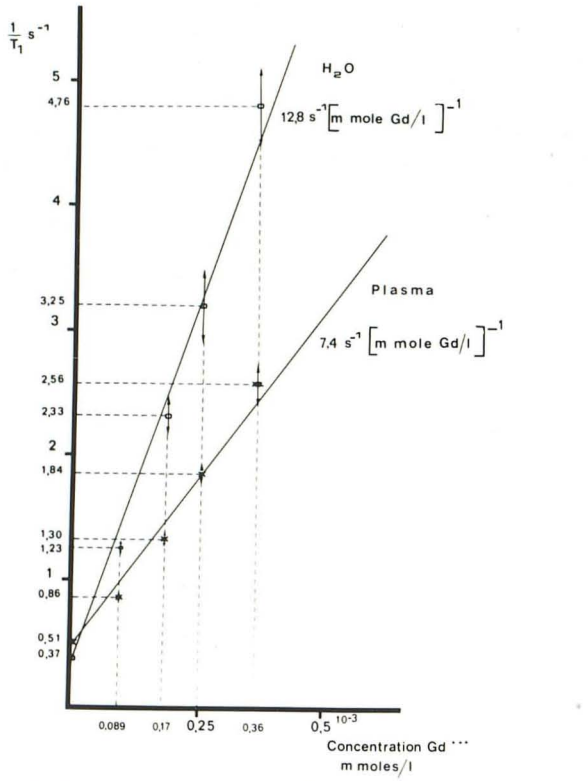

Fig. 1.—Graph of $^1/T_1$ in relation to Gd^{+++} concentrations in water and in plasma.

The specimens were taken 15 min after intravenous injection of a $GdCl_3$ solution at a concentration of 70 mg gadolinium metal/kg (table 2).

Results and Discussion

In mice, an injection of $GdCl_3$ at a concentration of 70 mg gadolinium metal/kg produced a significant modification of T_1 of the liver, changing it from 0.49 to 0.124 sec. The same concentration in the rat produced the following modifications: the T_1 of plasma changed from 1.76 to 0.9 sec; the T_1 of the kidney changed from 0.59 to 0.39 sec; the T_1 of the liver changed from 0.43 to 0.11 sec; and the T_1 of the brain changed from 0.79 to 0.87 sec. In the brain, there was no significant modification of T_1. It is probable that gadolinium did not diffuse through the blood-brain barrier and that the relatively small cerebral blood volume (5%) was insufficient to produce a measurable difference in the T_1 relaxation time of the whole brain. In the kidney, the variation of T_1 is significant but not very pronounced, whereas the liver T_1 is reduced by a factor of 3–4. A diffusion in the extracellular spaces as well as a fixation of gadolinium in the reticuloendothelial system may account for this pronounced effect. Capture by the reticuloendothelial system has been described for other rare-earth elements, such as lanthanum, but not for gadolinium.

TABLE 2: **Effects of Gadolinium on T_1 Times of Several Organs in Rats**

	T_1 Times (in msec) by Organ			
	Plasma	Kidney	Liver	Brain
T_1 control	176 ± 20	59 ± 6	43 ± 5	79 ± 8
T_1 Gd^{+++}	90 ± 10	39 ± 4	11 ± 2	87 ± 9

Note.—Samples were taken 15 min after injection of Gd^{+++}.

These measurements were carried out only at 15 min after injection. Other more delayed measurements are necessary to study the behavior of the blood-brain barrier in relation to Gd^{+++} and to study Gd^{+++} concentrations in the blood and the liver. It is possible that a redistribution later occurs. These preliminary results are encouraging and will be pursued. We will try to perfect the formation of complexes with gadolinium to reduce toxicity while conserving its paramagnetic properties.

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