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Brain Nuclear Magnetic Resonance Imaging Enhanced by a Paramagnetic Nitroxide Contrast Agent: Preliminary Report

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Contrast-enhancing agents for demonstrating abnormalities of the blood-brain barrier may extend the diagnostic utility of proton nuclear magnetic resonance (NMR) imaging. "TES," a nitroxide stable free radical derivative, was tested as a central nervous system contrast enhancer in dogs with experimentally induced unilateral cerebritis or radiation cerebral damage. After intravenous injection of TES, the normal brain showed no change in NMR appearance, but areas of disease demonstrated a dramatic increase (up to 45%) in spin-echo intensity and a decrease in T_1 relaxation times. The areas of disease defined by TES enhancement were either not evident on the nonenhanced NMR images or were better defined after contrast administration. In-depth tests of toxicity, stability, and metabolism of this promising NMR contrast agent are now in progress.

Contrast-enhancing pharmaceutical agents may extend the diagnostic capabilities of nuclear magnetic resonance (NMR) imaging. Paramagnetic substances tested as NMR contrast agents include the ions of manganese and iron and nitroxide stable free radicals (NSFRs) [1, 2]; all have been shown to decrease proton relaxation times, namely T_1 and T_2 [3]. Thus, paramagnetic substances enhance contrast differences between those tissues containing the contrast agent and magnetically similar tissues without it.

In separate reports we have described the relative advantages and disadvantages of various methods to manipulate NMR contrast [2, 4] and the potential to directly evaluate renal function in experimental animals using NSFRs as urographic NMR contrast agents [2, 5].

NSFRs are a group of synthetic, strongly paramagnetic organic compounds that for two decades have been used as "spin labels" for in vitro biologic studies [6]. A water-soluble piperidinyl NSFR derivative, "TES," is rapidly excreted into the urine after intravenous administration, an excretion pattern useful for NMR urographic studies [2, 5]. TES demonstrates additional properties suggesting promise as a clinically useful NMR contrast agent; these include chemical stability of solutions over a broad range of pH and temperature, limited in vivo metabolism, and broad chemical versatility [2, 6]. The ability to chemically attach TES to a variety of biomolecules, drugs, and particles may permit the synthesis of tissue-

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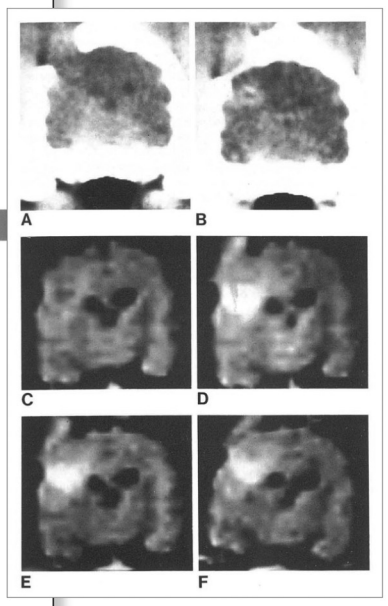

Gadolinium as a Contrast Agent for NMR

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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^{-3} 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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