Determination of Electron Spin Relaxation Time of the Gadolinium-Chealted MRI Contrast Agents by Using an X-band EPR Technique

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Purpose: To determine the electronic spin relaxation times, T_{1e}, of three commercially available Gd-chelated MR contrast agents, Gd-DTPA, Gd-DTPA-BMA and Gd-DOTA, using Electron Paramagnetic Resonance(EPR) technique.

Material and Methods: The paramagnetic MR contrast agents, Gd-DTPA(Magnevist), Gd-DTPA-BMA(OMNISCAN) and Gd-DOTA(Dotarem), were used for this study. The EPR spectra of these contrast agents, which were prepared 2:1 methanol/water solution, were obtained at low temperatures, from -160℃~-20℃. The glassy-state EPR spectra for these contrast agents were then fitted by the simulation spectra generated with different zero-field splitting (ZFS) parameters by a computer simulation program 'GEN', which generates the EPR powder spectrum using a given ZFS in 3×3 tensor. Finally, the spin relaxation times of the contrast agents were then determined from the T_{2e}, D, and E values of the best simulation spectra using the McLachlan's theory of average relaxation rate.

Results: The electronic transverse spin relaxation times, T_{2e}'s, of Gd-DTPA, Gd-DTPA-BMA and Gd-DOTA were 0.113ns, 0.147ns and 1.81ns respectively. The g-values were 1.9737, 1.9735 and 1.9830 and the electronic spin relaxation times, T_{1e}'s, were 18.70ns, 33.40ns and 1.66μs, respectively.

Conclusion: The results of these studies reconfirm that the paramagnetic MR contrast agents with larger ZFS parameters should have shorter T_{1e}'s. Among three contrast agents used for this study, Gd-DOTA chelated with cyclic ligand structure shows better electronic property then the others with linear structure. Thus, it is concluded that the exact determination of ZFS parameters is the important factor in evaluating relaxation enhancement effect of the agents and in developing new contrast agents.

Introduction

The MRI contrast agents, chelated with the paramagnetic metals have attracted much attention due mainly to their wide applications and diagnostic values in the clinical environment. The gadolinium (which is referred to as Gd from this point) is widely used as the paramag-

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netic metal of choice in most of present commercial MRI agents, because Gd has 7 unpaired electrons and thus has large magnetic moment. However, Gd itself is very toxic and needs to be chelated with polyamino polycarboxylic ligands as in DTPA and DTPA-BMA to eliminate the toxicity of Gd. Consequently, this paramagnetic Gd ion inside the human body gives disturbance to the local magnetic field, shortening the T_1 relaxation time of the tissue. This is important because the image intensity in ^1H MRI, which is largely composed of the NMR signal from the tissue water protons, is strongly dependent on the nuclear relaxation times. Therefore, the Gd-based MR relaxation agents can change the MR image intensity and improve the contrast between the normal and diseased tissue. However, the various correlation times associated with these Gd ions, which eventually influence the relaxivity of the proton in the hydrogen atom, have not been clarified yet. Here, the relaxivity is defined as the change of relaxation time per millimolar concentration. The relaxivity of the proton is known to be affected(2) mainly by the electron spin relaxation time, T_{1e}, the rotational correlation time, τ_R, and the residence lifetime of coordinated waters, τ_M, as well as other factors. The goal of contrast agents is to increase the relaxivity of the proton in tissue water to provide better MR image contrast, suitable for diagnostic purposes. Thus, shortening the T_1 relaxation times of water protons is more favorable. However, the correlation times mentioned above are correlated with one another, which makes the problem more complex. Consequently, it is essential to measure each correlation time separately.

Among the various correlation times, the electron spin relaxation time(T_{1e}) is related to the zero field splitting (ZFS) of Gd and can be measured by EPR. Since electron spin has much higher resonance frequency (normally GHz) than nuclear spin, the EPR technique is required to measure electronic properties of a paramagnet such as T_{1e} directly. Although there is no comprehensive theory for the electron spin relaxation of metal ions in the solution, the collisions between the chelate and the solvent water molecules are suggested to induce a transient zero-field splitting in the spin levels of Gd ions. Consequently, this ZFS significantly affects the behavior of spin relaxation time. The complexes with larger ZFS parameters are known to have shorter T_{1e}s and thus smaller values of relaxivity(2). Therefore, in developing the new contrast agents, it is important to find the ZFS parameters more precisely. Several methods(3-4) have been introduced in determining both the ZFS parameters and T_{1e} of Gd ions in the Gd-based contrast agents, using the NMR and EPR techniques.

In this study, we obtained the EPR spectra of Gd electrons from the contrast agents of Gd(DTPA), Gd(DTPA-BMA), and Gd(DOTA) by using an X-band EPR technique. From these spectra, we determined the transverse relaxation time and g-factor of Gd ions. Using these values, the ZFS parameters could be obtained by simulating the EPR spectra using the computer program GEN(5). Finally, the spin relaxation time, T_{1e}, was determined using the McLachlan' s theory of average relaxation rate.

Theory

Paramagnetic contrast agents increase the longitudinal proton relaxation rate, 1/T1, through the inner-sphere mechanism resulting from a chemical exchange of the water molecule between the primary coordination site of the Gd ion and the bulk water :

$$\frac{1}{T_1} = \frac{P_M q}{T_{1M} + \tau_M} \qquad [1]$$

where q is the number of coordinated protons per metal ion, P_M is the mole fraction of metal ion, T_{1M} is the relaxation time of the bound water protons, and τ_M is the residence life time of the bound water. T_{1M} is given by so-called Solomon-Bloembergen theory as

$$\frac{1}{T_{1M}} = \frac{2}{15}\left(\frac{\gamma_I g \beta}{\gamma^3}\right)^2 S(S+1)\left(\frac{7\tau_C}{(1+\omega_S^2\tau_C^2)} + \frac{3\tau_C}{(1+\omega_I^2\tau_C^2)}\right) + \frac{2}{3}S(S+1)\left(\frac{A}{\hbar}\right)^2\left(\frac{\tau_e}{(1+\omega_S^2\tau_C^2)}\right) \qquad [2]$$

where γ_I is the proton gyromagnetic ratio, g is the electronic g-factor, β is the Bohr magneton, r is the proton-metal ion distance, S is the total electron spin of the metal ion, ω_S and ω_I are the electronic and proton Lamor frequencies, respectively, and $A/\hbar$ is the electron-nuclear hyperfine coupling constant. The correlation times τ_C and τ_e are defined as follows:

$$\frac{1}{\tau_C} = \frac{1}{T_{1e}} + \frac{1}{\tau_M} + \frac{1}{\tau_R}$$

$$\frac{1}{\tau_e} = \frac{1}{T_{1e}} + \frac{1}{\tau_M} \qquad [3]$$

where τ_R is the rotational correlation time for the entire agent-proton complex, τ_M is, as above mentioned, the residence lifetime of the bound protons, and T_{1e} is the electronic spin relaxation time. From the eq. [2] and [3], we can see that the electronic spin relaxation time is one of the parameters to determine the longitudinal proton relaxation time.

Materials and Methods

The commercial products of brand names of Magnevist, OMNISCAN, and Dotarem were used as samples of Gd-DTPA, Gd-DTPA-BMA, and Gd-DOTA, respectively. In all of these compounds, the amount of 0.5 mol/l of each Gd chelate was used for this study. The EPR spectrum cannot be obtained by directly using these solutions, since a high concentration of Gd causes the dipole-dipole broadening of the spectra. Thus, the 5% solution was made by diluting them with a solution of methanol/water(2 to 1 in volume).

We used the EPR apparatus (model JES-TE300, manufactured by JEOL) whose frequency range covers 8.8 to 9.6 GHz, thus called X-band EPR. The temperature at the sample region was controllable between -170℃ and 100℃. The EPR spectra were obtained by sweeping the magnetic field from zero to 6000 Gauss at the fixed microwave frequency around 9.2254 GHz, which needed controlling since the resonance condition was slightly temperature dependent.

The EPR spectra were obtained at various temperatures from -160℃ to -20℃ to see the temperature dependence of the spectrum. From the EPR spectra obtained, we determined the ZFS parameters by using the GEN program, which basically generated the EPR spectra given ZFS parameters in a tensor. Since the sample is highly diluted, the g-factor is safely assumed to be isotropic, and in addition, the hyperfine interaction can be also ignored. Thus, the hamiltonian could be simplified, as shown in Eq. 4 below. The ZFS parameters were determined by simulating the EPR spectra with the GEN program using this hamiltonian of Eq. 4. The simulation was performed with the use of a computer, IBM RS/6000 Model 320H, at the EPR Research Center of the University of Illinois at Urbana-Champaign.

Results

The hamiltonian of the paramagnetic ion system under the magnetic field is expressed as

$$H = \vec{\beta H} \cdot \overleftrightarrow{g} \cdot \vec{S} + D\{S_z^2 - \frac{1}{3}S^2\} + E\{S_x^2 - S_y^2\} \qquad [4]$$

where H is the local magnetic field, β is the Bohr magneton, g is a dimensionless constant(g-value) that determines the magnetic dipole moment, D and E are the ZFS parameters that determine the energy levels with zero magnetic field, and S_x, S_Y, and S_z are the spin operator components about x, y, and z axis, respectively. The first term of this equation represents the effect of Zeeman splitting, and the second and third terms show the effects of ZFS. Here, the values of D and E determine the strength of ZFS. Bloembergem and Morgan' s

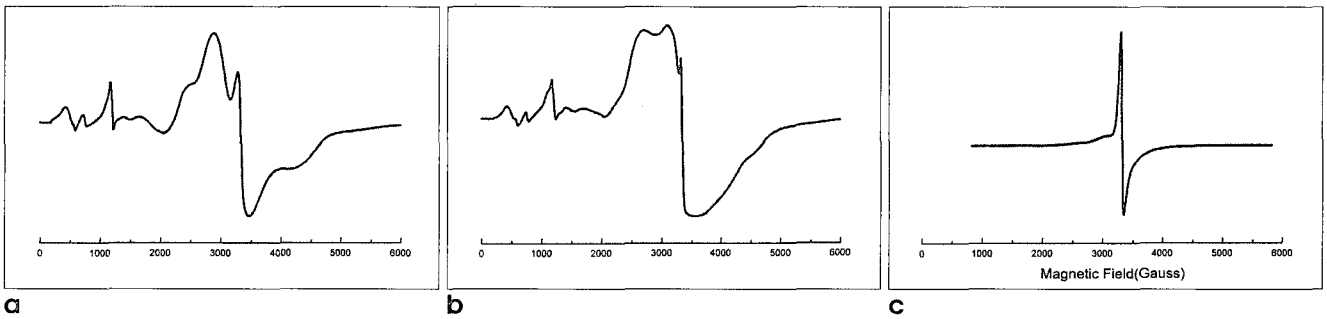

Fig. 1. The EPR spectra of three contrast agents at a temperature of -160℃. The spectrum of Gd-DOTA(Fig.1c) shows the symmetrical behavior, differently from those of Gd-DTPA(Fig. 1a) and Gd-DTPA-BMA(Fig.1b). These EPR spectra were obtained with following conditions; RF Power 1.99 mW, Modulation Frequency 100kHz, Time Constant 0.1 sec, and Amplitude 40(Fig.1a, Fig.1b) and 2(Fig.1c).

relaxation theory(6) suggests that the Gd ions should have four separated T_{1e}s. However, the obtained EPR spectra show a broad behavior, which does not give the separated T_{1e}s. Thus, our experimental spectra are more realistic by analyzing them with the theory of average relaxation rates, suggested by McLachlan(7). From this theory, we can obtain the expressions of T_{1e} and T_{2e} for S=7/2 system, which is the case of Gd ions, as

$$\frac{1}{T_{1e}} = \frac{36}{5}\left(D^2+\frac{E^2}{3}\right)\left(\frac{2\tau_v}{(1+\omega_0^2\tau_v^2)}+\frac{8\tau_v}{(1+4\omega_0^2\tau_v^2)}\right) \quad [5]$$

$$\frac{1}{T_{2e}} = \frac{36}{5}\left(D^2+\frac{E^2}{3}\right)\left(3\tau_v+\frac{5\tau_v}{(1+\omega_0^2\tau_v^2)}+\frac{2\tau_v}{(1+4\omega_0^2\tau_v^2)}\right) \quad [6]$$

where ω_0 and τ_v represent the Larmor frequency and the correlation time associated with ZFS interaction, respectively. Here, the values of D and E are determined by simulating the EPR spectra with the GEN program.

The shape of the spectrum is assumed to be of a Lorentzian type,thus the relation between T_{2e} and $\Delta\omega$ is simplified as

$$T_{2e} = \frac{2}{\sqrt{3}\Delta\omega} \quad [7]$$

We see in Eq. 7 that the value of T_{2e} can be obtained from the peak width, $\Delta\omega$, of the spectrum by considering the fact that EPR spectrum is the first derivative of absorption curve. The value of τ_v can be calculated from Eq. 6 with the values of D, E, and T_{2e}. Finally, the value of T_{1e} is determined from Eq. 5. The values of various parameters for the contrast agent samples, determined by using the above procedures, are summarized in Table 1.

The EPR spectra of Gd-DTPA, Gd-DTPA-BMA, and Gd-DOTA at a temperature of -160℃ are shown in Fig. 1. Here, the sample temperature was lowered to this temperature by injecting liquid nitrogen into the sample region. Then, the liquid nitrogen evaporates in the sample region and gives cooling power to lower the sample temperature. At this low temperature, the Gd ions in the frozen solution are in a glassy state, which satisfies the condition to give the powder spectrum of EPR, and thus gives a suitable condition for the use of the GEN program: We also obtained the EPR spectra in a wide range of temperatures, from -160℃ to -20℃, to see the temperature dependence of EPR spectra. Here, the sample temperature was controlled by changing the rate of injection of liquid nitrogen via a temperature controller.

The temperature dependence of EPR spectra is nicely seen in Fig. 2. In this figure, the peaks of EPR spectra reduce gradually as the temperature increases, and eventually disappears above -20℃. This behavior reflects the fact that as the temperature increases, the sample departs from a glassy state and gradually becomes a liquid state.

This is clearly seen by comparing the EPR spectrum at -160℃ with that at -20℃, where the EPR spectrum at -160℃ shows a typical powder-like pattern, while the spectrum at -20℃ shows a typical liquid-like pattern.

Table 1. The g-factor, the ZFS Parameters, and the Relaxation Times, Determined from the EPR Spectra and GEN Program, are Summarized in This Table

	g	D (MHz)	E (MHz)	T_{2e} (ns)	τ_v (ns)	T_{1e} (ns)
Gd-DTPA	1.9737	1250	257	0.113	0.255	18.70
Gd-DTPA-BMA	1.9735	1010	280	0.147	0.296	33.40
Gd-DOTA	1.9830	200	87	1.81	0.60	1660

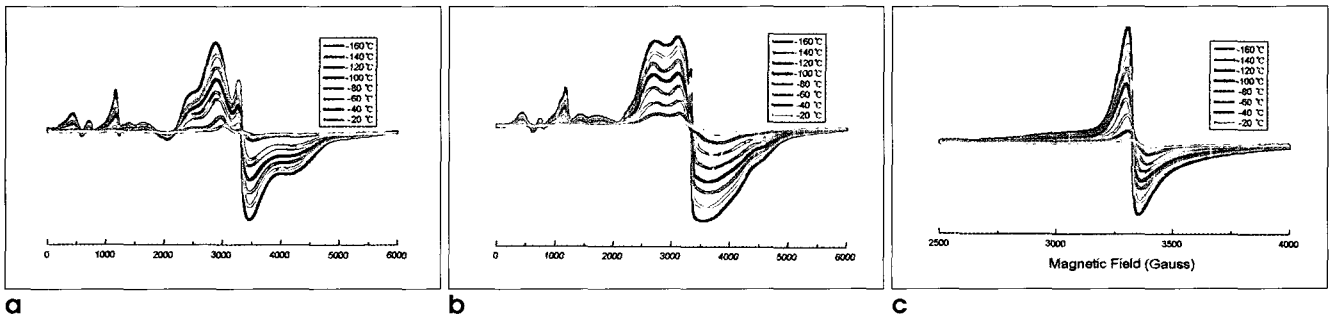

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Fig. 2. The temperature dependence of EPR spectra of three contrast agents, Gd-DTPA(Fig. 2a), Gd-DTPA-BMA(Fig.2b) and Gd-DOTA(Fig.2c). Note that the peaks of EPR spectra reduce gradually as the temperature increases, and eventually disappears at -20℃.

The difference between these two spectral patterns can be explained by considering the following fact: the Gd-chelates, which are relatively stationary but randomly oriented at low temperatures, start to tumble rapidly as the temperature increases. This rapid tumbling motion results in the disappearance of peaks in the spectrum, since due to this tumbling motion, the sample becomes isotropic and thus all the orientation-dependent terms in the spin hamiltonian have their average values finally go to zero.

In Fig. 2, we can see a continuous change from a glassy(powder) spectrum to a spectrum affected by the tumbling motion, as the temperature increases. These spectra suggest that Gd-chelates in the methanol/water solution start to show liquid characteristics around -20℃.

The contrast agents are used at the temperature of the human body. Hence, the relaxation times at this temperature are required for use in practical applications. However, the EPR spectra at this temperature cannot provide the informations on zero field splitting, which are necessary to determine relaxation time, due to motion averaging effect as shown in Fig. 2. In the previous study using fluorescence spectroscopy, however, it was found that the ZFS symmetry for Eu^{3+} is virtually unchanged between liquid and frozen state. Since both Eu^{3+} and Gd^{3+} are rare earth S-state ions, it seems to be assumed that ZFS symmetry of frozen state for Gd^{3+} is not much different from that of liquid solution. Therefore, although T_{1e} itself is temperature dependent, ZFS symmetry of frozen state may be same as that of liquid solution at human body temperature. Temperature dependence of T_{1e} may stem from the τ_v, which represents the characteristic frequency of collisions between the chelate and solvent molecules to induce a transient ZFS of the spin levels. Unfortunately, there is no comprehensive theory for detailed temperature dependence of this parameter τ_v yet.

We can also see in Fig. 2 that the spectrum of Gd-DOTA is somewhat different from those of Gd-DTPA and Gd-DTPA-BMA, in that the Gd-DOTA' s spectrum shows a symmetrical shape. This is because the Gd-DOTA has a ring structure in the chemical bond, as shown in Fig. 3c, and thus the electrons in Gd ions experience the same crystal field in all directions, which re-

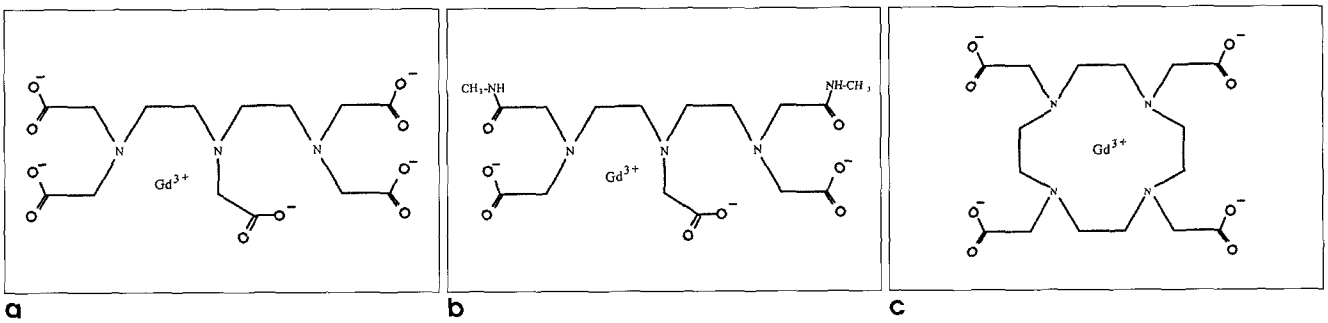

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Fig. 3. The molecular structure of Gd-DTPA(Fig.3a), Gd-DTPA-BMA(Fig.3b), and Gd-DOTA(Fig.3c). The Gd-DOTA has a ring structure in the chemical bond, different from those of the other two contrast agents, an ionic linear Gd-DTPA and a non-ionic linear Gd-DTPA-BMA.

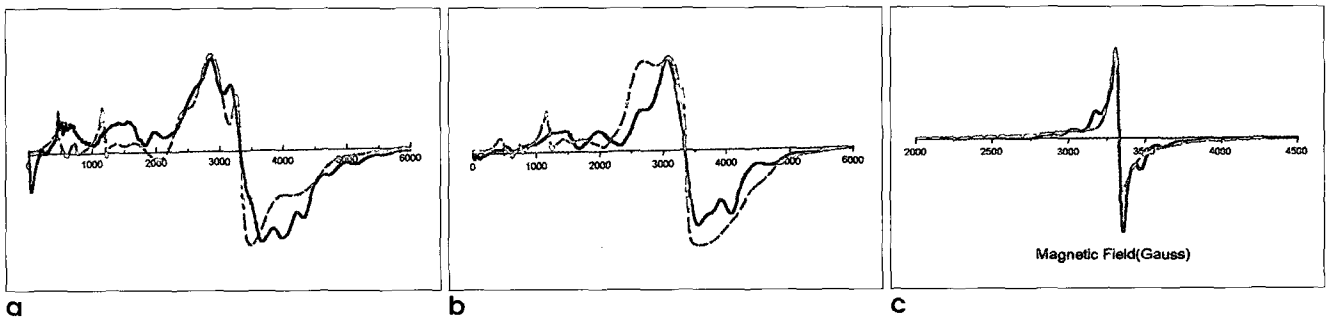

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Fig. 4. The comparison between the simulated EPR spectra (solid lines) and the experimental ones (dotted lines) obtained from Gd-DTPA(Fig. 4a), Gd-DTPA-BMA(Fig. 4b), and Gd-DOTA(Fig. 4c) at a temperature of -160℃. The resonance frequencies and resonance peaks are seen to coincide quite well. Note that these simulated results are quite good, compared with those obtained in similar experiments.

sults in the symmetrical spectrum. This highly symmetrical shape of the EPR spectrum in Gd-DOTA suggests that the Gd ions in this contrast agent have small ZFS parameters. This behavior in Gd-DOTA is found to agree very well with the result of NMRD (Nuclear Magnetic Relaxation Dispersion) measurements[8]. Furthermore, the ring structure makes the resonance frequency region narrower and the resonance peak higher than those of Gd-DTPA and Gd-DTPA-BMA, which is clearly seen in Fig. 4 (Note in this figure that the peak height in Gd-DOTA spectrum is not drawn to scale for the sake of clarity). Consequently, the values of D and E for Gd-DOTA become smaller than those of Gd-DTPA and Gd-DTPA-BMA, which result in a larger value of T_{1e} of Gd-DOTA, as shown in Table 1.

The simulated EPR spectra (solid lines) of three contrast agents are shown in Fig. 4, superimposed with the experimental ones (dotted lines) at low temperature. The discrepancy between the experimental spectra and the simulated ones may result from the use of the site independent parameters of D and E for the Gd ions in the computer simulation process. Broadbeck and Iton[9] pointed out that due to the random variations of local interactions in the glassy material, the asymmetrical broad values of D and E might be necessary for the correct calculations of EPR spectrum - in this glassy material. The simulation program adapted in our study was designed to give only constant values of D and E, regardless of the position of Gd ions. Further modifications of the program resolving this problem are in progress. However, we can see in Fig. 4 that the resonance frequencies and peaks in the experimental and simulated spectra are seen to coincide quite well. This indicates that the ZFS parameters obtained from the simulation are well within the major population of the broad distribution of these parameters. We should also note that these simulated results are quite good, compared with those obtained in similar experiments(10).

Conclusion

The efficiency of paramagnetic MR agents is in part determined by the electron spin relaxation of Gd ions, which are related to zero field splitting. In this study, we obtained the X-band EPR spectra of Gd(DTPA), Gd(DTPA-BMA), and Gd(DOTA) and determined the spin relaxation time by applying these spectra to the computer simulation program GEN. From our results, we found that the ZFS parameters were important factors to determine spin relaxation times. The agents, Gd-DTPA and Gd-DTPA-BMA, with larger ZFS parameters were found to have shorter T_{1e}s whereas Gd-DOTA, with smaller ZFS has longer T_{1e}.

In conclusion, it is important to know the electron spin relaxation time of the paramagnetic MR agent to understand the agent' s action more clearly and also to provide a valuable information in developing new contrast agents.

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대한자기공명의과학회지 4:27-33(2000)

EPR을 통한 상자성 자기공명 조영제의 전자스핀 이완시간의 결정

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목적: 전자 상자성 공명(Electron Paramagnetic Resonance, EPR)을 사용하여, 현재 상용되고 있는 세가지 상자성 자기공명 조영제, Gd-DTPA, Gd-DTPA-BMA, Gd-DOTA의 전자스핀 이완시간 T_{1e}를 결정하고자 한다.

대상 및 방법: 본 연구에 사용된 상자성 자기공명 조영제는 Gd-DTPA(Magnevist), Gd-DTPA-BMA(OMNISCAN), Gd-DOTA(Dotarem)이다. 이들 자기공명 조영제들은 2:1 부피 비율의 메탄올과 물의 혼합용액에 희석하여 저온의 glassy상태에서 EPR 스펙트럼을 얻었으며, 또한 주어진 영 자기장 갈라지기(zero-field splitting, ZFS)변수를 3×3 텐서량으로 계산하는 컴퓨터 시뮬레이션 프로그램 'GEN' 을 사용하여, 이들 조영제들에 대한 각각 다른 ZFS변수를 가지는 시뮬레이션 스펙트럼을 만들었다. 이 결과들과 McLachlan의 평균이완율 이론을 적용하여 전자스핀 이완시간이 결정되었다.

결과: 상자성 자기공명 조영제 Gd-DTPA, Gd-DTPA-BMA, Gd-DOTA의 전자 횡축 스핀이완시간(T_{2e})은 각각 0.113ns, 0.147ns, 1.81ns, g-value는 1.9737, 1.9735, 1.9830, 전자스핀 이완시간(T_{1e})는 18.70ns, 33.40ns, 1.66μs로 결정되었다.

결론: 실험 결과로부터 상자성 자기공명 조영제의 ZFS변수가 클수록 짧은 전자스핀 이완시간 T_{1e}를 가진다는 일반적인 사실을 재 확인할 수 있었다. 본 연구에 사용된 3가지 자기 공명 조영제들 중에는 화학적으로 환상구조 배위자를 갖는 Gd-DOTA가 가장 긴 전자스핀 이완시간 T_{1e}를 가지는 것으로 나타나서 일반적으로 환상구조 배위자를 갖는 조영제들이 선상구조 배위자를 갖는 조영제에 비해 전자적인 성질은 우수한 것으로 나타났고 결론적으로 상자성 조영제가 물분자의 자기이완시간에 미치는 영향을 평가하고 고효율 상자성 자기 공명 조영제 개발에는 정확한 ZFS변수 결정이 매우 중요하다는 것을 알 수 있었다.

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