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Transfer Index of MR Relaxation Enhancer: A Quantitative Evaluation of MR Contrast Enhancement

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To clarify the effects of Gd-DTPA on biological water, we examined the effects of the compound on spin-lattice relaxation rate with various concentrations of gelatin solutions. The results indicate that the effects on relaxation rate of Gd-DTPA in biological water fundamentally correspond to those in aqueous solution. To evaluate the distribution of Gd-DTPA in tissues, we introduced a transfer index that represents the product of tissue-blood ratio of Gd-DTPA and the ratio of extracellular volume of a tissue based on the above findings. The index depends neither on dose of the compound nor on Larmor frequency. The clinical significance of the index was studied in patients with brain tumors. The indexes varied from 0.038 to 0.51, depending on the biological characteristics of the tumors.

The transfer index may be used in the quantitative evaluation of MR relaxation enhancement, which may be applied to monitoring therapeutic efficacy and to estimating tissue perfusion.

Recent clinical experiences with MR imaging have shown a rather low specificity for the recognition of pathology in contrast with a high sensitivity for the detection of lesions [1]. Gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA) is the first practical contrast agent for MR that is expected to improve diagnostic capability. Although the clinical usefulness of Gd-DTPA has been generally acknowledged, in particular for the CNS [1–3], it is not so clear how and to what extent the relaxation rates for biological tissues are changed when the compound is administered.

This study was designed to examine comparatively the spin-lattice relaxation-rate effects of Gd-DTPA on different substances, such as gelatin solutions, blood samples, and in vivo brain lesions. In this paper we stress that the principal effects of Gd-DTPA on proton spin-lattice relaxation rates for tissues are the same as those on rates for aqueous solutions, and propose the concept of a transfer index, which may play a role in featuring the characteristics of biological tissues.

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Rationale of Behavior of Gd-DTPA in Biological Water and the Transfer Index

It is well known that the relation between the proton spin-lattice relaxation rate and the Gd-DTPA concentration in aqueous solutions is expressed by the following equation [4, 5]:

$$R1' = k \cdot C + R1 \quad (1)$$

where R1 is the intrinsic relaxation rate for distilled water and R1′ is the relaxation rate for the solution at C mmol/l of Gd-DTPA. The value of k represents the relaxivity of Gd-DTPA, influenced by the chemical environment of Gd-DTPA in a solution as well as by Larmor frequency [6].

Biological water is divided into two components, free and bound (hydrated) water, according to the theory of a two-component fast-exchange model [7–9]. In general, the free water fraction occupies the major part of biological water and its

relaxation rate is much smaller than that for bound water. Free water is regarded as being equal to distilled water in nature [7, 9], so that the effects of Gd-DTPA on free water relaxation rates should be the same as those on distilled water relaxation rates. Although the effects of the compound on bound water relaxation rates should differ from those on distilled water relaxation rates, the effects may be inadequate to distinguish them from the effects on free water relaxation rates owing to the much higher relaxation rates for bound water [5, 7, 10].

From the above, one can see that relaxation-rate changes in biological water due to Gd-DTPA should be derived from the changes in relaxation rate for the free water. This means that equation (1) can be applied to biological water. Changes in relaxation rate for plasma should be given as follows:

$$R1p' = k \cdot Cp + R1p \quad (2)$$

where R1p is the intrinsic relaxation rate for plasma and R1p′ is the plasma relaxation rate at the concentration of Cp mmol/1 of water in plasma. The value of k, the relaxivity of Gd-DTPA for biological water, should be equal to that for aqueous solutions [4, 11].

Since Gd-DTPA never enters cells [4, 11], the effects of the compound on whole blood are considered to be a combination of those on plasma and blood cells. Accordingly, the following equation [7] is applicable to predict relaxation rate for blood after administration of the compound:

$$R1b = (1 - h) \cdot R1p + h \cdot R1c \quad (3)$$

where R1b is the relaxation rate for whole blood and R1c is the relaxation rate for red blood cells; h is hematocrit. Because no difference in relaxation rate for red blood cells is expected before or after administration of Gd-DTPA, the whole blood relaxation rate (R1b′) at the concentration of Cp mmol per plasma water can be expressed by the following equation derived from equations (2) and (3):

$$R1b' = k \cdot (1-h) \cdot Cp + R1b \quad (4)$$

If the tissue relaxation rate is represented by the summation of relaxation rates in cellular and extracellular space in a same manner as blood in equation (3), the following equation is obtained for biological tissue:

$$R1t' = k \cdot f \cdot Ct + R1t \quad (5)$$

where R1t and R1t′ are the respective relaxation rates for tissue before and after Gd-DTPA administration and f is the ratio of volume of extracellular space to total tissue volume; Ct is the Gd-DTPA concentration of mmol/l of extracellular water.

Equation (5), derived from the above assumption, corresponds well to the results of Strich et al. [12]. Therefore, the equation can be used for brain lesions and various other tissues (but not for normal brain tissue), although the assumption has not yet been proved.

Concerning the contribution of Gd-DTPA to both compartments of tissue and blood, the following equation is derived from equations (4) and (5), indicating the tissue-blood ratio of the compound administered:

$$f \cdot Ct/Cp = (1-h) \cdot \Delta R1t/\Delta R1b$$

$$(\Delta R1t = R1t' - R1t;\ \Delta R1b = R1b' - R1b) \quad (6)$$

The left side of the equation, represented as the product of the tissue-blood ratio of the compound (Ct/Cp) and the ratio of extracellular volume (f), can be readily derived from the values of relaxation rates, which can be quantitatively obtained as shown in the right side of the equation. We propose this value, calculated by equation (6), as the transfer index of Gd-DTPA intravenously administered for each biological tissue, which should vary with state of tissue perfusion, blood-tissue permeability, edema, and many other pathologic conditions. Ct/Cp will be changed by tissue perfusion and blood-tissue permeability; the value of f will be changed by edematous state. This index ought to be independent of both the dose of the compound and the Larmor frequency. The time at which the index is measured after administration of the compound will cause the implications of the index to vary, since the time dependence of Ct/Cp will be changed by local cerebral blood flow mainly in the early and late stages by the vascular architecture of a tissue, blood-tissue permeability, and so on.

Materials and Methods

Measurements of proton spin-lattice relaxation times (T1) were taken in a series of gelatin solutions containing various concentrations of Gd-DTPA as well as in patients with brain tumors. In clinical observations the values of T1 were examined comparatively before and after Gd-DTPA administration. The values of in vitro and in vivo relaxation rates were measured at 2.12 MHz (0.047 T) utilizing Fonar QED 80-alpha with the progressive saturation method (90° $-\tau$ $-$90°) and the field focusing technique. Thirteen values of τ, ranging from 25 to 2000 msec, were used to accumulate FID signals. In each value of τ seven FID signals were accumulated for noise reduction. Values of T1 were calculated from 13 signal intensities. Absolute uncertainty in measurement of T1 (standard deviation) was around 5%. Details of the method have been given elsewhere [13].

Gelatin Solution Series

Five concentrations of Gd-DTPA solution, containing 0.031, 0.31, 0.50, and 2.0 mmol/l, were prepared by dilution of 0.5 mol/l Gd-DTPA solution* with distilled water. Weighed gelatin† was mixed with each of the above Gd-DTPA solutions to make five kinds of solutions, with 10, 20, 30, 40, and 50 wt%. This solution series, which consisted of 25 kinds of concentrations of gelatin and Gd-DTPA, was used to measure in vitro values of relaxation times. The values obtained were compared with the intrinsic relaxation times for gelatin without Gd-DTPA.

Clinical Observation

Ten patients with brain tumors and brain abscess were studied to measure in vivo relaxation times for brain tissues. Relaxation times for the regions of interest in the tissues of brain tumors, peritumoral

* Shering AG, Berlin, West Germany.
† Wako Pure Chemical Industries, Ltd., Osaka, Japan.

edema, and normal white matter were measured, respectively, before and after IV administration of 0.10 mmol/kg of Gd-DTPA every 60 sec up to 30 min. The sites of relaxation-time measurements were determined from MR images as well as from CT findings.

In each measurement of brain relaxation rates, venous blood samples were collected in heparinized bottles before and 5, 10, 15, and 30 min after administration of the compound. Each 4 ml of blood sample were used to measure relaxation time by the same MR system with an original coil that was designed to measure relaxation times for small materials after all measurements of brain relaxation times. Relaxation times for blood samples were measured at 21°C and their changes were corrected to be the values at 37°C by the relaxivity of Gd-DTPA at 37° C (7.0 $mmol^{-1} \cdot sec^{-1}$).

Results

Changes in Relaxation Times Associated with Concentrations of Gd-DTPA and Gelatin

Table 1 indicates the relaxation times (T1) obtained from various concentrations of gelatin and Gd-DTPA. Changes in T1 values were found to be inversely proportional to concentrations of gelatin and Gd-DTPA. Contribution of Gd-DTPA to T1 values was outstanding in high ranges of intrinsic T1 value compared with the low ranges of T1: the intrinsic T1 value of 552 msec measured in 10% gelatin solutions was reduced to 164 msec at 0.5 mmol/l of Gd-DTPA concentration, whereas the T1 value of 52 msec in 50% gelatin solution was reduced to only 44 msec at the same concentration of Gd-DTPA.

The measured T1 values for various gelatin solutions with Gd-DTPA corresponded closely to the T1 values calculated by equation (1) from the intrinsic T1 values without Gd-DTPA. The value of 7.7 $mmol^{-1} \cdot sec^{-1}$ was used for the value of k in equation (1), which was determined as the relaxivity of Gd-DTPA in distilled water at 21°C. Figure 1 shows a plot of measured T1 values against calculated T1 values. Good agreement is demonstrated between calculated and measured relaxation times, although there is a small amount of deviation of T1, possibly owing to measurement errors at smaller T1 ranges.

In Vivo T1 Changes Before and After Gd-DTPA Administration and Transfer Indexes in Patients with Brain Tumors

In all cases of brain tumors, no significant differences in T1 values were noted for normal white matter and peritumoral tissues either before or after IV administration of Gd-DTPA. In contrast, relaxation times for the lesion sites of the brain tumors changed consistently, attaining maximum values of relaxation rates (1/T1) within 15 min after Gd-DTPA administration. In blood samples, the value of relaxation rates moved more rapidly and reached the maximum about 5 min after injection. An illustrative example of the changes in relaxation rate is shown in Figure 2.

Table 2 shows the T1 values for the sites of brain tumors before and 5 min after Gd-DTPA administration and the transfer indexes calculated from those values. Transfer indexes varied from 0.038 to 0.51. In meningiomas, the transfer index varied in the same range, and an exclusively high value was found in a case of meningioma (case 4) that invaded the paranasal sinuses and was judged by pathology to be sarcomatous. A case of glioma (case 5) showed the value of 0.11 in the transfer index. In metastatic tumors the indexes varied from 0.049 to 0.25. The metastatic tumor (case 9), whose index was 0.25, grew rapidly.

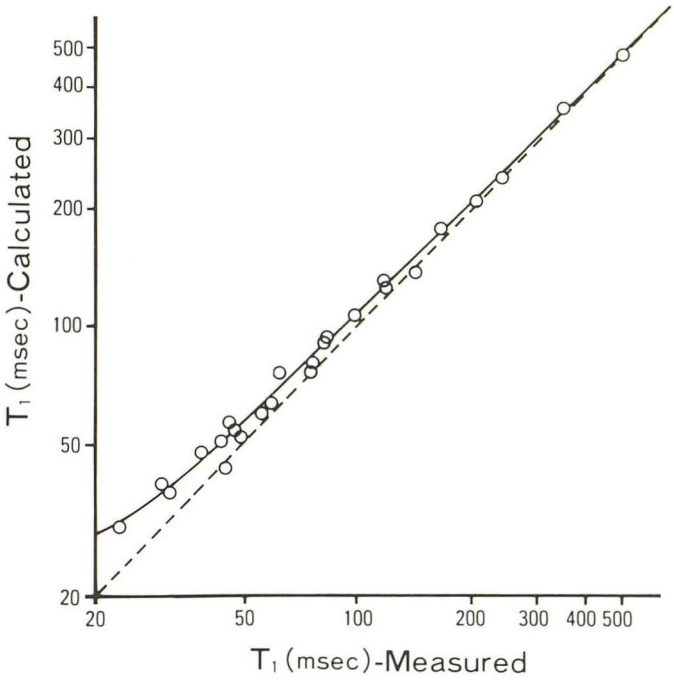

Fig. 1.—Logarithmic plot of measured T1 versus calculated T1 for gelatin and Gd-DTPA solution. *Solid line* represents curve best fit to the data; it shows good agreement with *dotted line*, which expresses perfect agreement.

TABLE 1: Values of In Vitro T1 with Different Gelatin and Gd-DTPA Concentrations

Gelatin Concentration (%)	Gd-DTPA Concentration (mmol/l)					
	0	0.031	0.13	0.5	1.0	2.0
10	552 ± 15*	490 ± 10	342 ± 9	164 ± 6	97 ± 5	55 ± 2
20	255 ± 5	236 ± 9	202 ± 5	116 ± 4	83 ± 3	46 ± 2
30	141 ± 7	140 ± 6	118 ± 2	81 ± 3	61 ± 3	38 ± 1
40	82 ± 4	75 ± 6	74 ± 2	58 ± 6	45 ± 5	30 ± 2
50	52 ± 5	49 ± 6	43 ± 2	44 ± 5	31 ± 3	23 ± 3

* T1 values expressed in msec ± SD.

Discussion

Several investigators have mentioned the excellent efficacy of Gd-DTPA for discriminating between the characteristics of various tissues and pathologies [1–3, 14–16]. Use of this contrast enhancer is actually opening a new aspect of MR capability in tissue characterization, particularly in diagnosing brain tumors and distinguishing them from edematous processes. In most investigations, however, the authors discussed only whether a lesion was enhanced in MR imaging and slighted the quantitative estimation of contrast enhancement. It is expected that quantitative evaluation of the enhancement of tissues or lesions will give us further information about their pathologic characteristics [16].

Such a quantitative study of the effects of an enhancer can be readily done by measurement of T1 values or signal intensity for tissues before and after administration of Gd-DTPA. The data of T1 and signal intensity present difficulties in clinical evaluation for various reasons, such as T1 differences in individuals and in tissues, varieties of Larmor frequencies used, and variations in dose of the compound administered. For actual application to clinical practice, a universal index is needed that is never influenced by the above factors. From the fundamental observations on gelatin solutions, the changes in the relaxation rates were found to be well represented in a manner similar to those in aqueous water within the dose range of Gd-DTPA in clinical usage. The present results indicate that the effects of Gd-DTPA on biological water principally originated in the free water fraction of the system. Accordingly, such evidence can be readily applied to deal with the changes in relaxation rates for biological water, such as in plasma, and extracellular water in tissues.

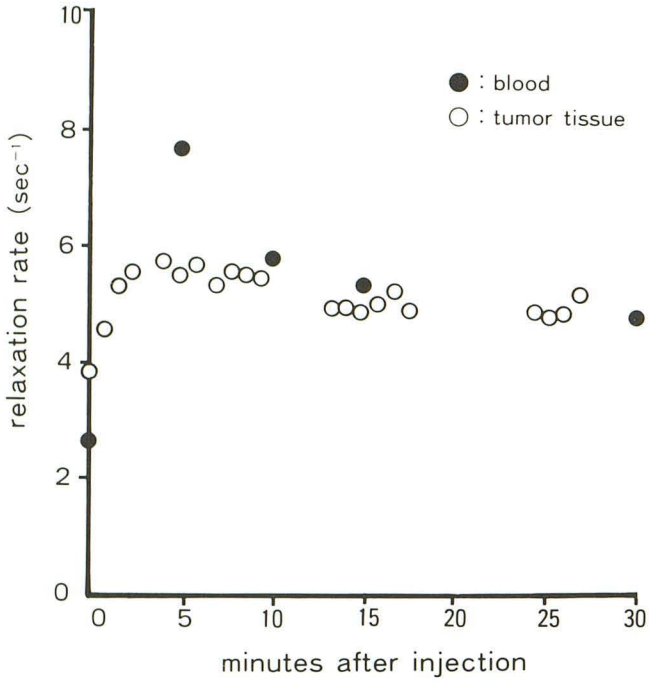

Fig. 2.—Time courses of relaxation rates for blood and metastatic tumor (case 9 in Table 2).

The transfer index, proposed as $(1-h)\cdot \Delta R1t/\Delta R1b$ in the present study, represents the product of the tissue-blood ratio of the compound and the ratio of extracellular volume. The index will be varied by tissue perfusion, blood-tissue permeability, edema, and many other pathologic conditions. Furthermore, this index possesses important features as a universal parameter for evaluation of MR enhancement, since the values attained are independent not only of differences in Larmor frequency but also of the given dose of the contrast enhancer.

Variability and validity of the transfer index in biological organs were examined and are shown in Table 3, extrapolated from the data published by Wolf and Fobben [17], in which in vitro T1 for various rabbit tissues were determined after Gd-DTPA administration. There is significant variability in the transfer indexes among tissues, ranging from 0.08 to 2.7. Markedly high index values are seen in the renal medulla and cortex, 2.7 and 1.4, respectively, probably owing to high accumulation of Gd-DTPA in the organ. Relatively high values of the index found in pancreas and heart may be due to their high tissue perfusion.

It is reasonable to assume that in pathologic central nervous tissues the values of the transfer index must be influenced by the mode and extent of blood-brain barrier disturbances as well as by the state of tissue perfusion. As represented in the

TABLE 2: Differences in Relaxation Times and Rates for Brain Lesions Before and After Gd-DTPA Administration, and Their Transfer Indexes

Case No.	Type of Brain Lesion	T1	T1′	ΔR1t	ΔR1b	Hct	Transfer Index
1	Meningioma	376	236	1.58	26.0	0.376	0.038
2	Meningioma	281	202	1.39	16.5	0.384	0.052
3	Meningioma	323	254	0.840	5.52	0.371	0.096
4	Meningioma	311	152	3.36	4.40	0.334	0.51
5	Glioblastoma	391	293	0.855	4.54	0.439	0.11
6	Metastasis	991	652	0.53	6.97	0.352	0.049
7	Metastasis	369	335	0.275	3.43	0.328	0.054
8	Metastasis	353	275	0.795	9.25	0.367	0.054
9	Metastasis	263	179	1.79	4.57	0.356	0.25
10	Abscess	349	246	1.20	3.39	0.242	0.27

Note.—T1 = relaxation time for brain lesion before Gd-DTPA administration (msec); T1′ = relaxation time for brain lesion after Gd-DTPA administration (msec); ΔR1t = relaxation rate difference in tissue (sec^{-1}); ΔR1b = relaxation rate difference in blood (sec^{-1}); Hct = hematocrit.

TABLE 3: MR Relaxation Rates and Transfer Indexes for Various Rabbit Tissues

Tissue	R1	R1′	Transfer Index
Renal medulla	2.67	21.3	2.7
Renal cortex	4.83	13.9	1.4
Pancreas	5.71	7.75	0.30
Heart	3.57	5.02	0.22
Lung	3.22	4.44	0.18
Skeletal muscle	4.59	5.78	0.18
Liver	5.85	6.90	0.15
Spleen	3.85	4.44	0.08
Blood	1.75	5.92	–

Note.—R1 = relaxation rate before Gd-DTPA administration (sec^{-1}); R1′ = relaxation rate 15 min after Gd-DTPA administration (sec^{-1}) (value of hematocrit is assumed to be 0.40. Utilized values are derived from the data from Wolf and Fobben [17]).

study, the index observed in various brain lesions ranged from 0.038 to 0.51. High index values were found in active and invasive tumors in meningioma and metastatic tumor compared with other tumors of the same kind. The capsule of a brain abscess had a relatively high index value, namely, 0.27. A rather low index value for the glioblastoma may be due to radiation therapy.

Obviously, there is no simple correlation between pathologic malignancy of tumors and the degree of Gd-DTPA shift into tumors, because blood-tissue permeability of Gd-DTPA or blood-brain barrier breakdown in tumorous tissues depends not only on the growth states but also on the differences in tissue origin such as extra- or intraaxial structures. This transfer index, however, has an outstanding significance in quantitative evaluation on the enhancing effects of the contrast agent.

Figure 2 indicates that the transfer index will depend significantly on the time the value is measured. The values of transfer index described in the present study were calculated from the T1 values attained 5 min after Gd-DTPA administration. Because of rather rapid renal excretion of Gd-DTPA [4], utilization of the value at the earlier phase is considered to be more reliable for estimation of blood-tissue distribution. Such immediate values also may be a good marker for indicating the state of the tissue perfusion [12]. The index measured in later phase may reflect vascular architecture, and so on. Thus, we may be able to obtain further information about a lesion from two or more values of the index measured at various times after Gd-DTPA administration.

For the calculation of the transfer index, sampling of blood is required as an unavoidable procedure. It is also necessary to measure in vivo T1 values as accurately as possible. Measurement errors of transfer index will be four times as large as those of T1 according to mathematical estimation. In spite of these complexities in methodology, the evidence is convincing that application of this transfer index to evaluate the degree of enhancement in MR opens possibilities for discriminating tumor characteristics. Furthermore, the present studies indicate that this index may also be used for estimating tissue perfusion and sensitivities to tumor therapies, although further investigations are needed to clarify such issues.

In conclusion, the relaxation rate effects of Gd-DTPA on various solutions depend essentially only on the concentration of the compound in the solutions. On the basis of our findings, we introduce the transfer index of Gd-DTPA for MR. The index depends on the tissue-blood ratio of Gd-DTPA concentration and on the volume of extracellular fluid. The value proposed depends neither on the dose of the compounds nor on Larmor frequency. Therefore, the index should by useful as a universal parameter for MR that depends on pathologic changes in biological tissues. The index may be used to evaluate local blood flow of tissues, blood-tissue permeability, the effects of therapy on tumors, and malignancy of tumors.

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