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Gadolinium as a CT Contrast Agent: An Experimental Study for the Effects of Injection Parameters in the Rabbit Brain Model[1]

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Purpose: We wanted to investigate the use of gadolinium based contrast agent (Gd-DTPA) for computed tomography (CT), and we also wanted to assess the effects of valuable injection parameters on enhancement in an experimental rabbit brain model.

Materials and Methods: *In vitro*, attenuation measurements of serial dilutions of Gd-DTPA and iopromide were compared. In five rabbits, single level dynamic gadolinium-enhanced brain CT studies were obtained using different injection parameters. A comparison CT scan after iopromide administration was performed. The time-attenuation curves of the brain vessel and parenchyma were obtained and the magnitude of enhancement (Hmax) and the time to peak enhancement (Tmax) were analyzed.

Results: *In vitro*, the attenuation coefficient of undiluted Gd-DTPA (2,578 HU) was higher than that of iopromide (1,761 HU) at equimolar concentrations. In 5 rabbits, the time-attenuation curve demonstrated a distinct pattern with peak enhancement only in the brain vessel, but not in the brain parenchyma. There was increasing linear relationship between the injection rate of Gd-DTPA and Hmax, and a declining linear relationship with Tmax. The higher the concentration of Gd-DTPA, the higher Hmax was, but no significant difference was found for the Tmax. Higher volumes of Gd-DTPA revealed a higher Hmax and a delayed Tmax.

Conclusion: Enhancement of the brain parenchyma on gadolinium-enhanced CT is minimal, while enhancement of the brain vessels is distinctive. The most important factor affecting Hmax of the vessel is the concentration of the contrast medium and the most important factor affecting Tmax of the vessel is volume of the contrast medium. The gadolinium-based contrast agent may be an reasonable alternative contrast agent for brain CT, and especially in cerebral vessels, and it may also be advantageous for brain parenchyma of those patients with BBB dysfunction.

Index words : Gadolinium
Computed tomography (CT), contrast media
Computed tomography (CT), experimental

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Gadolinium (Gd)-based contrast agents have a proven utility in MR imaging and they have gained wide-spread use in modern medicine (1). Gd is characterized by a high atomic number and Gd's pharmacokinetics are similar to those of iodine, the latter of which is widely used as a CT contrast agent. In contradistinction to the iodinated contrast agents, Gd-based contrast solutions have been well tolerated by patients in the clinical setting with only a few serious side effects being reported in the world literature (2). Given the chemical similarities of Gd and iodine coupled with a lack of associated side effects, the utilization of Gd-based contrast agents in conjunction with CT could prove useful for some applications.

The purpose of this study is to investigate the use of a Gd-based contrast agent in conjunction with CT by evaluating the effects of differing combinations of injection parameters for the contrast agent including the injection rate, concentration and volume for contrast enhanced CT.

Materials and Methods

In Vitro

We performed an in vitro study to determine the relative CT attenuation coefficient of gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA) (0.5 mmol Gd/mL, Magnevist, Schering, Berlin, Germany), and it was compared with that of the iodinated contrast agent iopromide (2.5 mmol I/mL, Ultravist, Schering, Berlin, Germany). Serial dilutions were made by adding each agent in multiples of 1 mL to normal saline solution up to a total volume of 10 mL in test tubes. Each test tubes' contents was then used for scanning rabbit brains with the HiLight Advantage system CT scanner (General Electric Medical System, Milwaukee, Wisconsin, U.S.A.) using 120 kVp, 120 mA and 5-mm collimation for all the scans. Twenty attenuation measurements were obtained from approximately 1 mm^2 square regions of interest (ROI)s, and Hounsfield unit (HU)s were used for the attenuation coefficient. Linear regression analysis was then performed.

In Vivo

The imaging protocol was reviewed and approved by the institution's Animal Studies Internal Review Board. Five rabbits weighting 2.4 - 2.6 kg each (mean weight: 2.5 kg) were anesthetized with an intramuscular injection of ketamine hydrochloride that was administered prior to each imaging session (35 mg/kg). An intravenous line was placed in an ear vein for each of 8 to 9 imaging sessions, and these sessions were temporally separated by 2 days to allow for complete biological clearance of the contrast material. In the first imaging session, CT scans of the brain prior to the administration of any contrast agent were obtained using the following parameters: 120 kVp, 120 mA, 3 mm collimation and a 10 cm field of view. This was followed by a single level, dynamic Gd-enhanced monophasic CT study performed at 5 second-intervals beginning 10 seconds after the IV administration of the contrast agent for a total duration of 2 minutes. On each day of imaging, different combinations of the following parameters were tested and these are listed in Table 1: rate of injection (0.2 mL/sec and 0.4 mL/sec), concentration of contrast (0.25 mmol/mL and 0.5 mmol/mL) and volume of contrast administered (5 mL and 10 mL). In the final imaging session, a single level, dynamic iopromide enhanced monophasic CT study was performed in rabbit No. 1 for comparison.

Attenuation coefficients were measured at the square ROI's approximately 1 mm^2 at the brain vessels and at the central and peripheral portion of the parenchyma for each scan during each time interval. Time-attenuation curves of the brain vessels and parenchyma were obtained for each scan at each level, and the magnitude of enhancement (Hmax) and the time to peak enhancement (Tmax) were both analyzed.

The ANOVA test was used to analyze the contrast enhancement as defined by the attenuation coefficients in the different combinations of injection parameters for

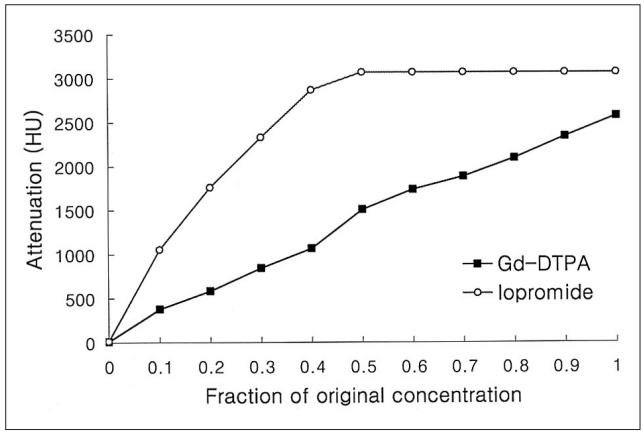


Fig. 1. Attenuation coefficients for different fractions of the original concentration of Gd-DTPA and iopromide in vitro. The attenuation coefficient of undiluted Gd-DTPA (2,578 HU) corresponded to that of iopromide diluted to 0.33 times the original concentration.

the Gd-DTPA, as well as analyzing as their comparison with the data for iopromide.

Results

In Vitro

Figure 1 demonstrates the attenuation coefficients for the different concentrations of Gd-DTPA and iopromide that we tested during the in vitro study. Gd-DTPA shows a linear relationship between the attenuation coefficient and the concentration while the attenuation of iopromide plateaus after a 0.5 dilution of the original concentration. The attenuation coefficient of undiluted Gd-DTPA was 2,578 HU, and this corresponded to that of iopromide when it was diluted to 0.33 times the original concentration. The attenuation coefficient of undiluted Gd-DTPA (2,578 HU) was 14% higher than that of iopromide (1,761 HU) diluted to an equimolar concentration (0.5 mmol Gd/mL = an iopromide dilution factor of 0.2).

In Vivo

In 5 rabbits, the time-attenuation curves of the brain parenchyma showed contrast enhancement in all injection combinations that ranged from 20 to 40 HU with no demonstrable peak. On the contrary, the time-attenuation curves of the brain vessels demonstrated a distinct pattern with a peak attenuation coefficient ranging from 40 to 138 HU (Fig. 2). Altering the combinations of injection parameters had a significant impact on contrast enhancement of the brain vessels. Therefore, the contrast enhancement effects of altered injection parameters were analyzed only for the brain vessels with Gd-DTPA (Table 1).

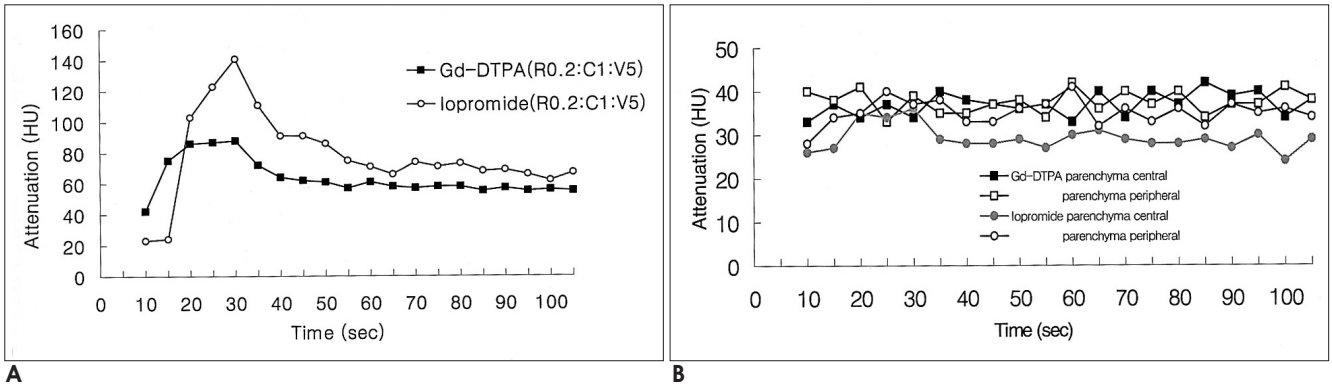
Contrast enhancement effect by injection rate

A higher injection rate of Gd-DTPA resulted in a higher Hmax and a shorter Tmax at constant concentration and volume. For example, in rabbit No. 1 with a constant concentration (0.5 mmol/mL) and volume (10 mL), the Hmax was 88 HU for an injection rate of 0.2 mL/sec and 138 HU for an injection rate 0.4 mL/sec ($p < 0.01$),

Table 1. Magnitude of Peak Enhancement and Time to Peak Enhancement in the Brain Vessels of Five Rabbits

	R 0.2 - V 5				R 0.4 - V 5				R 0.2 - V 10				R 0.4 - V 10			
Rabbit	C 1		C 1/2		C 1		C 1/2		C 1		C 1/2		C 1		C 1/2	
	Hm	Tm	Hm	Tm	Hm	Tm	Hm	Tm	Hm	Tm	Hm	Tm	Hm	Tm	Hm	Tm
No. 1 Iop	141	30														
No. 1 Gd	88	30	62	25	113	15	85	15	88	40	63	55	138	25	91	25
No. 2 Gd	47	30	40	20	74	15	51	20	59	30	57	25	75	25	57	25
No. 3 Gd	57	25	47	25	73	20	59	20	74	45	62	55	117	30	95	30
No. 4 Gd	75	25	55	25	77	20	55	15	90	50	69	50	88	30	64	30
No. 5 Gd	56	20	50	20	60	20	50	30	70	55	61	50	112	30	77	30

Note. R: injection rate (mL/sec), V: volume (mL), C: fraction of original concentration, Hm [Hmax]: magnitude of peak enhancement, Tm [Tmax]: time to peak enhancement, Iop: Iopromide, Gd: gadopentetate dimeglumine



A B

Fig. 2. Comparison of the time-attenuation curves for Gd-DTPA and iopromide in the brain vessel (**A**) and in the brain parenchyma (**B**) for rabbit No. 1.

A. Significant vascular enhancement and a similar time to peak enhancement of Gd-DTPA compared to iopromide. R: injection rate (mL/sec), C: fraction of original concentration, V: volume (mL).

B. There was no significant parenchymal enhancement and no magnitude of peak enhancement by both contrast medias.

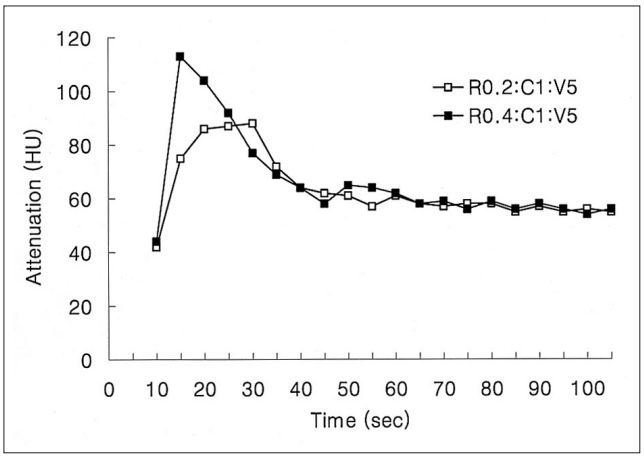


Fig. 3. Contrast enhancement effects of injection rate for Gd-DTPA with constant concentration and volume in rabbit No. 1 brain vessel. Time-attenuation curves show an increase in Hmax with the increase in injection rate, and the higher injection rate results in the shorting of Tmax. R: injection rate (mL/sec), C: fraction of original concentration, V: volume (mL).

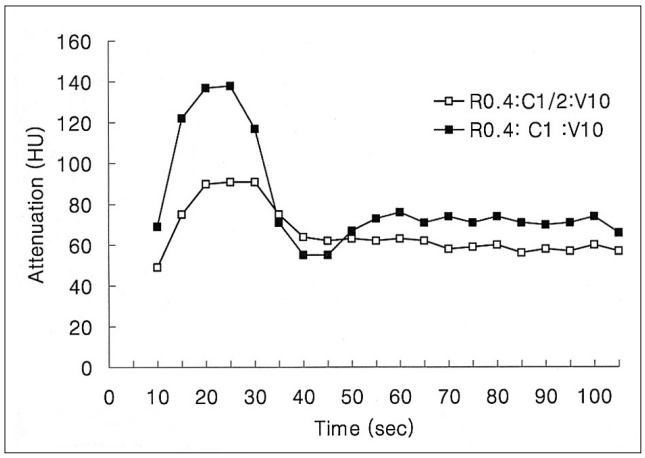
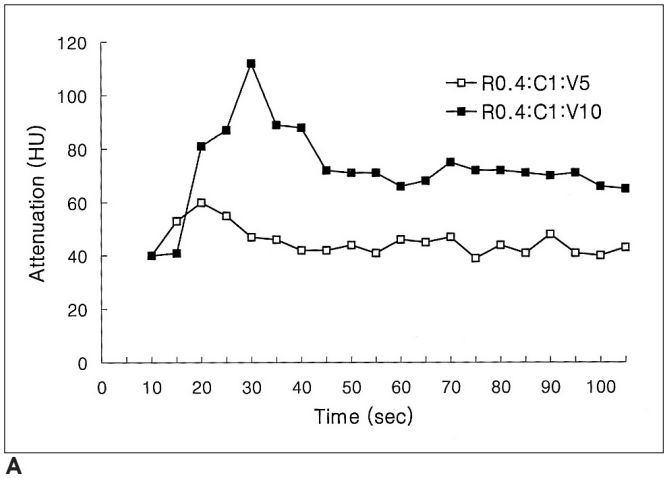


Fig. 4. Contrast enhancement effects of concentration for Gd-DTPA with a constant injection rate and volume in rabbit No. 1 brain vessels. Time-attenuation curves show a higher Hmax with a higher concentration and there was no significant difference in Tmax with change of the contrast concentration. R: injection rate (mL/sec), C: fraction of original concentration, V: volume (mL).



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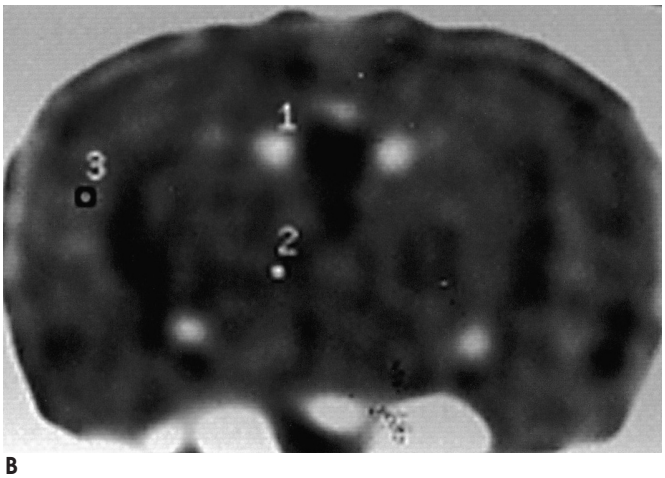

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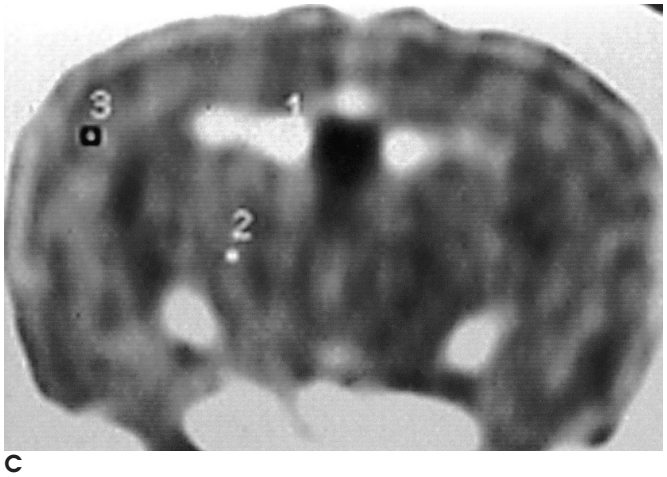


C

Fig. 5. Contrast enhancement effects of volume for Gd-DTPA with a constant injection rate and concentration in rabbit No. 5. **A.** Higher volume of the Gd-DTPA reveals a higher Hmax and longer Tmax. R: injection rate (mL/sec), C: fraction of original concentration, V: volume (mL). Postcontrast CT scans with an injection volume of 5 mL (**B**) and 10mL (**C**). Note the more intense enhancement of the vessel (1) with a higher injection volume, while there is little difference in the enhancement of the parenchymas (2, 3).

and the Tmax was 40 sec and 25 sec, respectively ($p <$ 0.0001) (Fig. 3).

Contrast enhancement effect by injection concentration

With a constant injection rate and constant volume of Gd-DTPA, Hmax was significantly increased by increasing the concentration of Gd-DTPA from 0.25 mmol/mL to 0.5 mmol/mL ($p < 0.0001$), but no significant difference was found for the Tmax ($p > 0.01$) (Fig. 4).

Contrast enhancement effect by injection volume

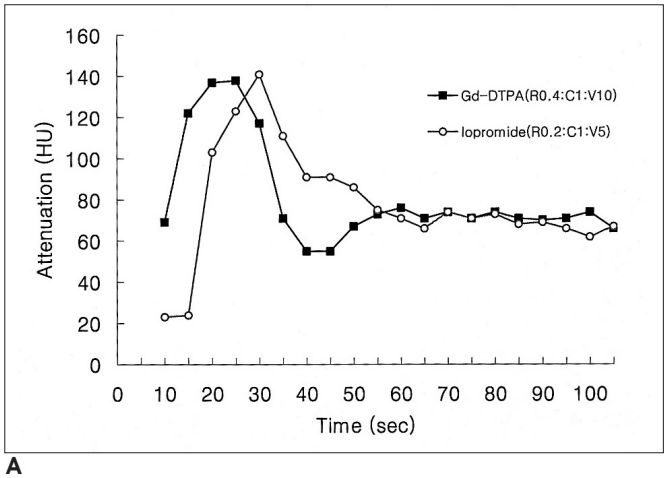
A higher volume of Gd-DTPA revealed a higher Hmax and a delayed Tmax. In rabbit No. 5, with a constant injection rate (0.4 mL/sec) and concentration (0.5 mmol/mL), the Hmax was 60 HU and 112 HU ($p < 0.01$) and the Tmax was 20 sec and 30 sec ($p < 0.0001$), respectively, with the injection volume of 5 mL and 10 mL (Fig. 5).

Contrast enhancement effect comparison of Gd-DTPA and iopromide

The highest Hmax and the shortest Tmax were established by an injection of Gd-DTPA at a rate of 0.4 mL/sec, a concentration of 0.5 mmol/mL, and a constant volume. Particularly, 10 mL volume of Gd-DTPA demonstrated the most similar spectrum height and pattern to the time-attenuation curve of iopromide ($p < 0.01$) (Fig. 6).

Discussion

Gd is one of the lanthanide series of rare-earth ions and its chelation with DTPA results in a strongly paramagnetic, stable complex. Of all rare-earth elements, it has the strongest influence on T1 relaxation times of hydrogen protons. This characteristic of Gd has resulted in its widespread use as a contrast agent for MR imaging (3, 4). The atomic number and k-edge of Gd (64 and 53 keV, respectively) is higher than of iodine (54 and 33 keV, respectively). Because it also attenuates x-rays like iodine, one may expect a theoretical increase in attenuation when using Gd with CT. The higher k-edge of Gd results in decreased low-energy filtration and thus, there



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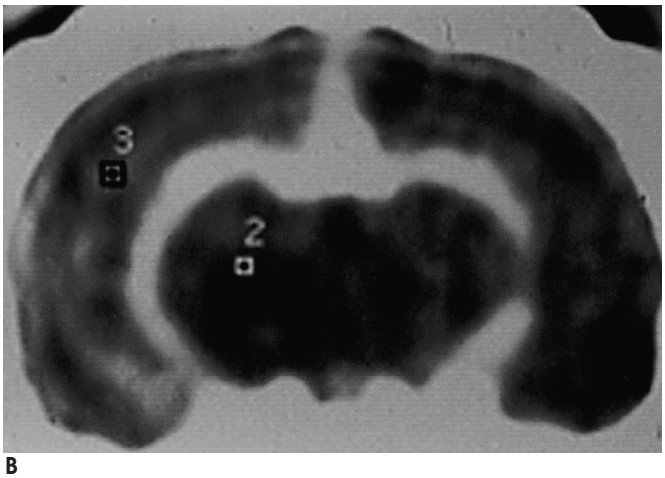

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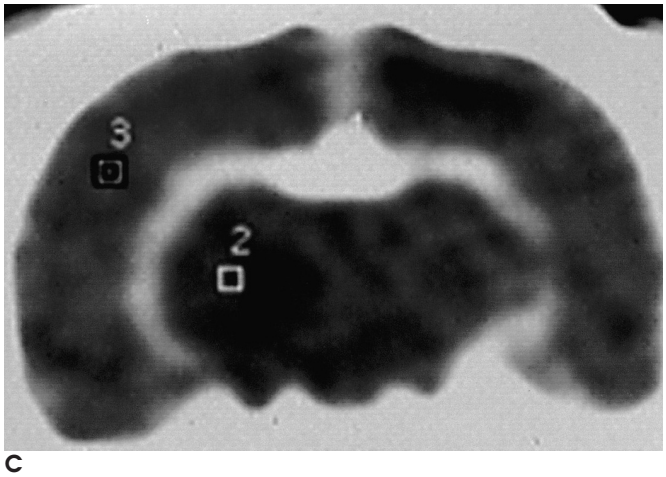

C

Fig. 6. A. Graphs show the most satisfactory vascular enhancement with Gd-DTPA at a dose of 2 mmol/kg and an injection rate of 0.4 mL/sec compared to iopromide at a dose of 5 mmol/kg and an injection rate of 0.2 mL/sec. R: injection rate (mL/sec), C: fraction of original concentration, V: volume (mL). This injection protocol for Gd-DTPA, among the combinations of injection parameters, shows the most similar pattern with iopromide. Postcontrast CT scans with Gd-DTPA (**B**) and iopromide (**C**) reveal a similar degree of vascular and parenchymal enhancement.

is less beam-hardening artifact when using Gd than when using iodine (5).

Considering the molar concentration of Gd in manufactured Gd-DTPA (0.5 mol Gd/L) and that of iodine in iopromide (2.5 mol I/L), Gd-DTPA contains one-fifth the Gd compared to that of iodine in iopromide. On an equimolar basis, Gd produces more attenuation than iodine and greater contrast (6 - 8), and in our study the attenuation of Gd-DTPA was 14% higher than that of iopromide at equimolar concentrations. This supports the data of Gierada and Bae (6), which demonstrated that the attenuation of Gd-DTPA, as compared to iodinated contrast, was 50% higher when used for CT. In our study, the injection rate of 0.4 mL/sec and dose of 2 mmol/kg showed satisfactory enhancement of the brain vessels of rabbits, and a similar pattern was noted for the time-attenuation curve as compared to those qualities of iopromide.

The atoms of the rare-earth elements form stable, covalent bonds with organic molecules and they are detoxified by combination. Gd-DTPA is a complex of Gd covalently bonded to DTPA and the combination of Gd with DTPA reduces the toxicity of the two separate components, Gd and DTPA (4). There is no dissociation of Gd from the Gd-DTPA complex within the body. The half-life of Gd-DTPA is short (20 min) in blood and urine, and it's rapidly excreted predominantly in the urine. This suggests that the compound has very little if any reaction within the body (9, 10). This complex is exclusively distributed extracellularly and it is hydrophilic in nature. This feature, coupled with its charge and the rather high molecular weight, accounts for its inability to cross biologic barriers such as cell membranes. Gd-DTPA would be expected to remain within the extracellular space and not penetrate the normal blood-brain barrier (BBB) (3, 11). These pharmacokinetic properties are likely to account for the suboptimal enhancement of the brain parenchyma compared to the cerebral vasculature in our study, and our findings are consistent with the findings of Gierada and Bae (6). In their study, the intense enhancement of vascular structures including the aorta and lower pulmonary arteries was noted along with the suboptimal enhancement of hepatic or renal parenchyma in pigs.

Anaphylactoid reactions to the contrast media are induced by activation of the complement system. According to Lasser's hypothesis (12), Gd-DTPA is a poor activator of the complement system and it would not be expected to produce such adverse reactions. Three times the standard dose (0.1 mmol/kg) is commonly used in MR angiography where it has been used as an alternative contrast agent to iodinated contrast agent. In the setting of angiography, neither the high dose nor its utilization in patient populations with risk factors that precludes iodine-based contrast administration (i.e. renal failure) has proven to be problematic (13 - 16).

The effects of the injection parameters on contrast enhanced CT has been investigated only for the iodinated contrast agents (17), but not for the Gd-based contrast agents. In our study, Gd-DTPA was used as the contrast agent for CT and this resulted in satisfactory enhancement of the cerebral vasculature with minimal enhancement of the brain parenchyma. The degree of contrast enhancement was variable according to the injection rate, concentration and volume. Among these, the most important factor affecting Hmax of the vessels was concentration, and the most important factor affecting Tmax of the vessels was the volume of contrast medium. Similar previous studies have supported the close relationship between volume and concentration of the contrast medium with the Hmax and Tmax (17 - 19).

Gd-based contrast agent may be an alternative contrast agent for brain CT, especially in the cerebral vessels, and it may also be advantageous to use in the brain parenchyma of patients having BBB disfunction. Further study is needed for clinical application of the optimal injection techniques to obtain an ideal time-attenuation curve as well as to understand the effects of various parameters on the contrast enhancement. This study will be a useful baseline for the clinical application of gadolinium as an alternative CT contrast agent.

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CT 조영제로서의 gadolinium: 가토 뇌에서 조영증강에 영향을 미치는 인자에 관한 실험적 연구[1]

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목적: CT 조영제로서 gadolinium (Gd - DTPA)의 주입변수에 따른 뇌혈관 및 뇌실질의 조영증강 효과를 가토 뇌에서 실험적으로 조사하고자 하였다.

대상과 방법: 시험관 실험에서는 Gd - DTPA와 iopromide를 1배에서 0.1배까지 생리식염수를 섞어 희석하여 농도에 따른 조영증강 정도를 비교하였다. 동물 실험에서는 토끼 5마리를 대상으로 주입변수를 변화시키면서 단일주입방법으로 Gd - DTPA를 주입하여 뇌 단면의 역동적 CT를 시행하였다. 조영증강 정도의 비교를 위해 토끼 한 마리를 선택하여 iopromide를 주입하여 CT를 시행하였다. 모든 영상에서 뇌혈관과 뇌실질의 흡수감약계수를 측정하여 시간 - 흡수감약곡선을 구했으며 흡수감약계수 최고치와 최고점 도달시간을 분석하였다.

결과: 시험관 실험에서 Gd - DTPA 원액의 흡수감약계수는 2,578 HU로서 동일한 몰수의 iopromide 1,761 HU보다 높았다. 동물실험의 경우 뇌혈관에서는 Gd - DTPA의 뚜렷한 조영증강 효과를 보였으나 뇌 실질에서는 Gd - DTPA와 iopromide 두 조영제 모두 조영증강 효과가 미약했다. Gd - DTPA의 주입농도와 주입량을 일정하게 하면서 주입속도를 증가시키면 흡수감약계수 최고치는 증가되었고 최고점에 도달하는 시간이 짧아지는 결과를 보였다. 주입농도를 증가시키면 흡수감약계수 최고치 증가에만 영향을 주었다. 주입량을 증가시키면 흡수감약계수 최고치는 증가하였고 최고점에 도달하는 시간은 지연되었다.

결론: CT에서 gadolinium의 조영증강효과는 정상 뇌실질에서는 미약하나 뇌혈관에서는 뚜렷하였으며, 조영증강 최고치에는 조영제의 주입농도 그리고 최대 조영증강에 도달하는 시간에는 조영제의 주입량이 가장 큰 영향인자로 작용하였다. 임상적으로 뇌혈관이나 혈액 - 뇌 장벽이 손상된 뇌실질의 조영증강 CT에서 대체 조영제로서 gadolinium의 사용을 고려할 수 있을 것이다.