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Hepatic CT Enhancement: Comparison between Dimeric and Monomeric Nonionic Contrast Agents in Rabbits[1]

Gi Hyeon Kim, M.D., Byung Kook Kwak, M.D., Hyung Jin Shim, M.D., Kyo Nam Kim, M.D.[2], Wei Chiang Liu, M.D.[3], Seung Hoon Ryu, M.D., Yang Soo Kim, M.D., Jong Beum Lee, M.D., Kun Sang Kim, M.D.

Purpose: To determine the hepatic and vascular enhancement profiles with nonionic dimeric, iodixanol, contrast agent in the rabbit and to compare them with nonionic monomeric, ioversol, contrast agent.

Materials and Methods: Seven rabbits initially underwent hepatic dynamic CT scan with either iodixanol or ioversol, followed by repeated CT scan with other unused contrast agent with one week interval between scans. Pre and post contrast attenuation values of hepatic parenchyma, aorta and portal vein were measured sequentially. The mean enhancement of the hepatic parenchyma, aorta and portal vein were compared between two agents. The mean peak enhancement and peak enhancement time of the liver, aorta, and portal vein were also compared.

Results: The attenuation values of ioversol showed a greater mean hepatic enhancement than iodixanol from 18 seconds to 39 seconds after injection (from late arterial phase to early portal venous phase) with a statistical significance ($p < 0.05$). The mean peak enhancement of hepatic parenchyma, aorta and portal vein was also greater using ioversol than iodixanol, but the mean peak enhancement times of ioversol and iodixanol were nearly identical.

Conclusion: Ioversol may have the greater effects than iodixanol on hepatic tumor conspicuity, especially from late arterial phase to early portal veneous phase.

Index words : Computed tomography (CT), contrast enhancement
Computed tomography (CT), contrast media
Contrast media, comparative studies
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Liver, CT

[1]Cardiovascular Center, Department of Radiology, Yongsan Hospital, Chung-Ang University College of Medicine
[2]Department of Radiology, Sung-Ae General Hospital.
[3]Department of Radiology, Samsung Medical Center, Sungkyunkwan University School of Medicine.
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Address reprint requests to : Byung Kook Kwak, M.D., Cardiovascular Center, Department of Radiology, Yongsan Hospital, Chung-Ang University College of Medicine, 65-207 Hangangro-3-ga, Yongsan-gu, Seoul 140-757, Korea.
Tel. 82-2-748-9867 Fax. 82-2-798-4745
E-mail: kwakbk@cau.ac.kr

In hepatic CT imaging, an iodinated contrast agent is administered to achieve a high contrast of hepatic parenchyma to lesion to increase tumor conspicuity (1 - 5). It is usually considered that the increased enhancement of the normal hepatic parenchyma with contrast agent means increased conspicuity of hepatic lesions (6). Although adverse reactions have been reduced by the use of nonionic monomeric contrast agent (7), these monomeric agents are hyperosmolar to blood. Therefore, efforts have been made to generate contrast agents with an osmolarity equal to that of blood (8).

A new nonionic dimeric, iodixanol, contrast agent is isoosmotic with plasma and is reported as less toxic for the vascular administration (8 - 11), but it is increased in the molecular size and weight and viscosity of the contrast agent (Table 1) (8). This nonionic dimeric contrast agent, iodixanol, is reported to have a higher diagnostic confidence, excellent tolerance and lower overall toxicity compared to monomeric contrast media (8 - 11). Because of these reasons, nonionic dimer contrast is sometimes preferred in CT examination, especially in patients with a high risk of contrast agent-induced adverse effects (8). However, the pharmacokinetics of iodixanol has not been fully studied enough in the normal hepatic parenchyma for potential use in CT (12).

The purpose of this study is to determine the hepatic and vascular enhancement profiles with iodixanol in the rabbit and to compare them with ioversol.

Materials and Methods

Seven New Zealand white rabbits underwent two dynamic hepatic CT examinations with nonionic dimeric iodixanol (Visipaque 320, Nycomed, Oslo, Norway) and nonionic monomeric ioversol (Optiray 320, Mallincrodt medical, Quebec, Canada) on two-separate days (one week interval between CT scans). Ioversol was chosen since it had the same iodine concentration (320 mgI/ml) as iodixanol. Their physicochemical properties are listed in Table 1. Three rabbits were initially examined with the iodixanol, followed by the second examination with the ioversol, whereas the remaining four rabbits were examined in reverse order. The study was performed on either male or female rabbits weighing 2.8 to 3.8 kg (mean, 3.2 kg). Just before the first examination, blood samplings were done for sGOT, sGPT, BUN and creatinine to insure that each evaluated laboratory findings were within the normal range. The rabbits were anesthetized by an intramuscular injection of ketamine 75 mg/kg and by an intravenous infusion of pentothal sodium 20 mg/kg. A butter fly needle (21 G) with a connecting tube (0.8 ml in luminal volume) was placed in the marginal vein of rabbit 's ear. The rabbits were then placed in right lateral decubitus position for CT scan (13). After connecting the injector syringe to the intravenous access site, the connecting tube was filled with 0.8 ml of each contrast agent. The equal amounts of each contrast agent per body weight, 640 mgI/kg (2 ml/kg) were used, and the injection rate was 0.3 ml/sec in all cases. CT examinations were obtained on a SCT-7000 TH (Shimadzu, Kyoto, Japan) with 100 mA, 80 kVp, 3 mm collimation, and field of view range was 110 mm. Power injector was used for the administration of contrast agents. Scanning was done with 3-second interval during 120 seconds in the same area of the liver. Following each examination, precontrast attenuation values for the hepatic parenchyma, aorta and portal vein were determined by measuring and averaging the first two scans. Three postcontrast attenuation measurements of the hepatic parenchyma were taken in the different hepatic lobes or segments, and these were averaged for each image. Regions of interest encompassed at least 1 cm^2 and avoided blood vessels and artifacts. Postcontrast attenuation was also measured at each level in the aorta and portal vein. The attenuation values were measured and averaged by two radiologists (B.K.K., K.N.K.). Measurements for all examinations were obtained without knowledge of contrast agent used in either examination. Enhancement was defined as the difference in attenuation values between the postcontrast and precontrast images. The mean enhancement-time curves were created and compared. The statistical comparison between two CT examinations with two different contrast agents was performed using Wilcoxon-signed ranks test.

For the determination of each hepatic enhancement phase, it was regarded as an initiation of arterial phase when the aorta was enhanced more than 150 HU (Hounsfield unit) from the time of contrast injection, and as a end time of arterial phase when the hepatic enhancement reached 30% of hepatic peak enhancement. It was considered as a beginning of portal phase when the liver was enhanced to 70% of hepatic peak enhancement (13 - 15).

Results

The mean peak enhancement of the hepatic parenchy-

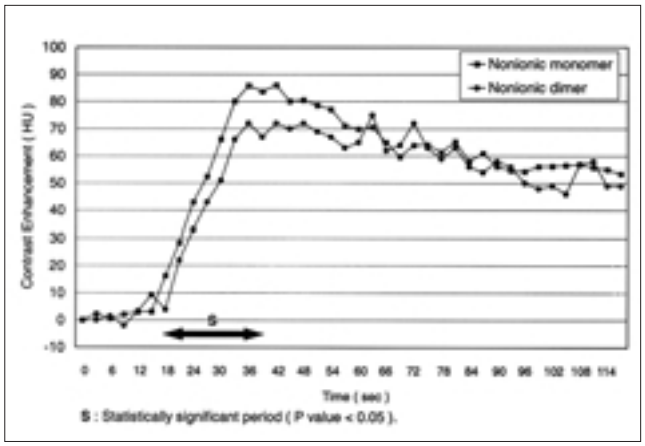

Fig. 1. The Time-density Curve of Hepatic Parenchyma.
The attenuation values of ioversol showed a greater mean hepatic enhancement than iodixanol from 18 seconds to 39 seconds after injection, which corresponded to the late arterial and early portal venous phases of dynamic hepatic enhancement with a statistical significance (↔, $p < 0.05$).

ma, aorta and portal vein was greater using ioversol than iodixanol, but the mean peak enhancement time of ioversol and iodixanol was nearly identical (Table 2). The arterial phase of CT scanning using ioversol and iodixanol was from 12 seconds to 21 seconds after contrast injection; the beginning time of portal venous phase, 30 seconds after injection. The time-density curve of hepatic parenchyma was demonstrated graphically in Figure 1. The attenuation values of ioversol showed a greater mean hepatic enhancement than iodixanol from 18 seconds to 39 seconds after injection, which corresponded to the late arterial and early portal venous phases of dynamic hepatic enhancement with a statistical significance ($p < 0.05$) (Fig. 1, Table 3).

Discussion

In hepatic CT imaging, the main objective for injecting iodinated contrast agent is for an achievement of a high parenchyma-to-lesion contrast to optimize lesion conspicuity (1 - 5). CT number actually has two components - a true interstitial tissue contrast component and a blood pool component (depending on the relative sizes of the true interstitial contrast component and the blood pool component of enhnacement at various times and also depending on the proportion of the tissue volume occupied by those compartments themselves) (16). Therefore, hepatic enhancement after an injection of contrast agent is dependent not only on the proportional volume of blood pool and interstitium but also on the vascular permeability of the contrast agent (17, 18). The physicochemical properties of each contrast agent such as molecular weight, size, viscosity and osmolarity are important in determination of their vascular concentration and their leakage (vascular permeability) into interstitial space, ie, hepatic enhancement.

A nonionic dimer, iodixanol has a concentration of 320mgI/ml, osmolarity of 290 mOsm/kg , viscosity of 11. 4 mPa · S at 37 ℃ and 1.550 kDa. On the other hand, a nonionic monomer, ioversol, a concentration of 320 mgI/ml, osmolarity of 702 mosm/kg, viscosity of 5.8 mPa · S at 37 ℃ and 0.807 kDa (Table 1). Iodixanol is higher in viscosity and heavier in molecular weight and larger in molecular size and lower in osmolarity than ioversol. Consequently, these different physicochemical properties of both contrast agents certainly cause differ-

Table 1. The Physicochemical Properties of Contrast Agents

	Ioversol (Nonionic monomer)	Iodixanol (Nonionic dimer)
Structural formula	$C_{18}H_{24}I_3N_3O_9$	$C_{35}H_{44}I_6N_6O_{15}$
Molecular weight (kDa)	0.807	1.550
Osmolarity (mOsm/kg H2O at 37(C)	702	290
Concentration (mgI/ml)	320	320
Viscosity (mPa · S at 37 ℃)	5.8	11.4
pH value	7.2 - 7.6	7.2 - 7.6
Hydrophilicity (No. of hydroxil groups)	6	9

Table 2. Difference between Ioversol and Iodixanol in the Mean Hepatic Enhancement

Postinjection time (sec)*	Mean hepatic enhancement (HU)		*p*-value
	Ioversol	Iodixanol	
18	16.3	3.9	0.027
21	28.4	22	0.016
24	43	33	0.050
27	52.4	43	0.031
30	66.1	51	0.041
33	80.1	66	0.016
36	85.9	72	0.031
39	83.7	67	0.016

* In sequential dynamic CT scan, time recorded above is statistically significant range after an injection of each contrast agent.

Table 3. The Mean Peak Enhancement in Equivalent Time

Organ	Mean Peak Enhancement (HU/sec)	
	Ioversol	Iodixanol
Aorta	430/18	397/18
Liver	86/36	72/36
Portal vein	200/30	168/30

ent hepatic enhancement pattern from the late arterial to early portal phases in this study (6, 12).

To begin with, a smaller molecular weight and size of the monomeric nonionic contrast agent may cause better diffusion to the interstitium, which possibly increases hepatic enhancement. Secondarily, a lower osmolarity of the nonionic dimeric contrast agent plays a role in better vascular enhancement, partly because of a lesser degree of osmotic-driven self-dilution and partly because of a reduced leak through blood vessels into the interstitium. Whereas the higher osmolarity of nonionic monomeric contrast agent induces increased interstitial contrast concentration, which, in turn, increase enhancement of tissue in which interstitial component dominates (16). Thirdly, although the effect of viscosity is not clear, a higher viscosity probably reduces leak to the interstitium. Subsequently, enhancement of hepatic tissue, especially interstitium, is relatively lower in nonionic dimeric contrast agent than monomeric contrast agent. In hepatic enhancement, maybe all properties of iodixanol such as low osmolarity, high viscosity, and large size and molecular weight serve as a slow diffusion of the agent to the interstitium. Moreover, it is not clearly identified how much the physicochemical properties of contrast agent are affected by the pulmonary vascular beds (pulmonary circulation of contrast agent) and cardiac circulation.

These results are differed from the study done by Graf, et al (12) in that the nonionic monomeric contrast agent shows a greater mean peak enhancement in the aorta and portal vein than the nonionic dimeric contrast agent. In Graf, et al 's study (they used iopromide instead of ioversol), the nonionic dimer (iodixanol) showed a greater mean enhancement of the aorta and portal vein than the nonionic monomer (iopromide). However, their study was done with dual-phase study on three different human groups whereas our this study was done on the dynamic sequential study on the same subjects (rabbit). Since each contrast agent has a unique time-density curve, the knowledge of time-sequential characteristics of enhancement pattern on the same subjects is more important than the degree of enhancement on different groups during a certain period of time. Consequently, it would be difficult to compare results of these two studies.

Iodixanol is isoosmotic with plasma and is reported less toxic for the vascular administration (8 - 11). In case of using iodixanol because of its tolerability, a CT scanning protocol, in which the time from the late arterial to late portal phase is avoided, is recommended for the outstanding conspicuity of hepatic lesion.

The limitations of our study included a small number of rabbits as well as the different status of each rabbit such as cardiac output, heart rate and hydration between one-week interval. Nevertheless, the time of peak enhancement of the aorta, portal vein and hepatic parenchyma was nearly identical in both contrast agents, strongly suggesting that the different status of individual rabbit did not greatly affect the results.

In conclusion, the nonionic monomeric contrast agent showed a greater enhancement of the liver of rabbits from the late arterial phase to early portal phase than nonionic dimeric contrast agent with a statistical significance. However, further studies are needed to determine whether the use of the isotonic agents effects on the lesion conspicuity in pathologic liver.

References

1. Berland LL, Lawson TL, Foley WD, Melrose BL, Chintapalli KN, Taylor AJ. Comparison of pre and postcontrast CT in hepatic masses. *AJR Am J Roentgenol* 1982;138: 853-858
2. Moss AA, Dean PB, Axel L, Goldberg HI, Glazer GM, Friedma MA. Dynamic CT of hepatic masses with intravenous and intraarterial contrast material. *AJR Am J Roentgenol* 1982;138:847-852
3. Foley WD, Berland LL, Lawson TL, Smith DF, Thorsen MK. Contrast enhancement technique for dynamic hepatic computed tomographic scanning. *Radiology* 1983;147:797-803
4. Bluemke DA, Fishman EK, Anderson JH. Effect of contrast concentration on abdominal enhancement in the rabbit: Spiral computed tomographic evaluation. *Acad Radiol* 1995;2:226-231
5. Polger M, Seltzer SE, Head BL, Savci G, Silverman SG, Adams DF. Spiral computed tomography of the liver: contrast agent pharmacokinetics and the potential for improved hepatic enhancement. *Acad Radiol* 1995;2:19-25
6. Chambers TP, Barson RL, Lush RM, Dodd GD 3rd, Miller WJ. Hepatic CT enhancement: comparison of ionic and nonionic contrast agents in the same patients. *Radiology* 1994;190:721-725
7. McClennan BL, Stolberg HO. Intravascular contrast media. Ionic versus nonionic: current status. *Radiol Clin North Am* 1991;29 :437-454
8. Jynge P, Holten T, Oksendal AN. Sodium-calcium balance and cardiac function with isotonic iodixanol. An experimental study in the isolated rat heart. *Invest Radiol* 1993;28:20-25
9. Spencer CM, Goa KL. Iodixanol. A review of its pharmacodynamic and pharmacokinetic properties and diagnostic use as an x-ray contrast medium. *Drugs* 1996;52:899-927
10. Justesen P, Downes M, Grynne BH, Lang H, Rasch W, Seim E. Injection-associated pain in femoral arteriography: An european multicenter study comparing safety, tolerability, and efficacy of iodixanol and iopromide. *Cardiovasc Intervent Radiol* 1997;20:251-256
11. Verow P, Nossen JO, Sheppick A, Kjaersgaard P. A comparison of iodixanol with iopamidol in aortofemoral angiography. *Br J Radiol* 1995;69:973-978
12. Graf O, Gazelle GS, Kreuzer S, et al. Enhancement of hepatic

parenchyma, aorta, and portal vein in helical CT: comparison of iodixanol and iopromide. *AJR Am J Roentgenol* 1997;168:213-217
13. Kwak BK, Kim SH, Liu WC, et al. Optimal scan time of dual-phase spiral CT in normal rabbit liver: effect of contrast injection rate. *J Korean Radiol Soc* 1999;40:1159-1164
14. Frederick MG, McElaney BL, Singer A, et al. Timing of parenchymal enhancement on dual-phase dynamic helical CT of the liver: how long does the hepatic arterial phase predominate? *AJR Am J Roentgenol* 1996;166:1305-1310
15. Walkey MM. Dynamic hepatic CT: How many years will it take ' til we learn? *Radiology* 1991;181:17-18
16. Dawson P, Blomley M. Opacification of blood vessels and soft tissues at CT with nonionic contrast media. *Radiology* 1994;193:284-285
17. Krause W, Schuhmann-Gampieri G. Pharmacokinetics of contrast media. In: Dawson P, Claub W, eds. Contrast media in practice. Berlin, Pa: Springer Verlag, 1994;26-34
18. Almen T. Relations between chemical structure, animal toxicity and clinical adverse effects of contrast media. In: Enge I, Edgren J, eds. Patient safety and adverse events in contrast medium examinations. Amsterdam, Pa: Elsevier Science, 1989;25-56

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비이온성 조영제의 종류에 따른 정상 가토 간의 조영 증강 정도의 비교[1]

[1]중앙대학교 의과대학 방사선과학교실, 심혈관센터
[2]성애병원 방사선과
[3]성균관대학교 의과대학 방사선과학교실

김기현 · 곽병국 · 심형진 · 김교남[2] · 유위강[3] · 유승훈 · 김양수 · 이종범 · 김건상

목적: 정상 가토에서 비이온성 이중체(dimer)인 iodixanol과 단량체(monomer)인 ioversol간의 간과 대동맥에서의 조영증강 정도를 비교하고자 하였다.

대상과 방법: 나선식 CT를 이용하여 가토 7마리에서 일주일 간격을 두고 iodixanol(Visipaque 320, Nycomed, Oslo, Norway)과 ioversol(Optiray 320, Mallincrodt medical, Quebec, Canada)로 각각 3초간격으로 120초 동안 간의 한 부위에서 역동적 CT를 시행하였다. 각 가토 체중에 따라 동일량의 조영제를 사용하였으며 (2 ml/kg), 조영증강 전,후 CT에서 간실질, 문맥과 대동맥에서 각각의 감쇠계수(HU)를 측정하였다. 이후 평균 조영 증강치, 평균 최고 조영 증강치와 최고 조영 증강치에 도달하는 평균 시간을 산출한 후 조영증강 곡선을 구하였고, 두 조영제간의 차이를 통계학적으로 비교하였다.

결과: 간실질의 평균 조영 증강치는 후기 동맥기에서 조기 문맥기(18 - 39초)에 이르는 동안 ioversol을 사용한 예에서 더 높게 관찰 되었으며 통계학적으로 의의가 있었다($p<0.05$). 또한 간실질, 문맥, 대동맥에서의 평균 최고 조영 증강치 역시 ioversol을 사용한 예에서 더 높게 관찰되었다. 그러나, 최고 조영 증강치에 도달하는 평균시간은 두 조영제 사이에 유의한 차이가 관찰되지 않았다.

결론: Ioversol은 후기 동맥기에서 조기 문맥기에 이르는 동안 간실질의 조영증강에 있어서 iodixanol보다 통계적으로 유의한 효과를 보였다.