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ORIGINAL ARTICLE

Evaluation of the acute adverse reaction of contrast medium with high and moderate iodine concentration in patients undergoing computed tomography

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Abstract
Purpose. The aim of this prospective study was to evaluate and compare acute adverse reactions between contrast medium containing moderate and high concentrations of iodine in patients undergoing computed tomography (CT).
Materials and methods. A total of 945 patients undergoing enhanced CT were randomly assigned to receive one of two doses of contrast medium. We then prospectively investigated the incidence of adverse reactions. Iopamidol was used as the contrast medium, with a high concentration of 370 mg I/ml and a moderate concentration of 300 mg I/ml. The frequency of adverse reactions, such as pain at the injection site and heat sensation, were determined.
Results. Acute adverse reactions were observed in 2.4% (11/458) of the moderate-concentration group compared to 3.11% (15/482) of the high-concentration group; there was no significant difference in incidence between the two groups. Most adverse reactions were mild, and there was no significant difference in severity. One patient in the high-concentration group was seen to have a moderate adverse reaction. No correlation existed between the incidence of adverse reactions and patient characteristics such as sex, age, weight, flow amount, and flow rate. The incidence of pain was not significantly different between the two groups. In contrast, the incidence of heat sensation was significantly higher in the high-concentration group.
Conclusions. The incidence and severity of acute adverse reactions were not significantly different between the two groups, and there were no severe adverse reactions in either group.

Key words Contrast medium · Acute adverse reaction · CT

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Introduction

Since multidetector-row CT (MDCT) has started to be widely used in clinical practice, the acquisition time for helical CT has shortened. As a result, the concentration and total amount of contrast medium and when to start the CT imaging after administration of the contrast agent have been critical in achieving the best contrast enhancement. Contrast enhancement detectability is affected by the body weight, hemodynamics, and renal function of each patient. Among these factors, body weight probably has the greatest effect on contrast enhancement during CT, and we therefore consider body weight to be the most important measure for obtaining a clear image.[1–4] Contrast enhancement of the parenchyma of an organ generally depends on the total amount of radioactive iodine, which is directly proportional to the amount of contrast medium administered. There has been growing interest in three-dimensional (3D) intravenous MDCT; and specially designed software that can produce high-quality images of the vascular system has been developed and is available in the clinical field. An

Table 1. Summary of the cases

Parameter	300 mg I/ml group	370 mg I/ml group
No. of cases	458	482
Male/female	279/179	287/195
Age	64.7	63.5
Body weight (kg)	57.5	57.4
Presence of underlying disease	173 (44.7%)	208 (50.6%)
History of allergy	22 (5.4%)	28 (6.4%)

adequate amount of contrast medium for the body weight should be used in 3D imaging of parenchymal organs.[1–6] At that point in time, then, we must know the differences in the adverse reactions due to high-concentration contrast medium and those due to intermediate-concentration contrast medium. We therefore attempted to compare the incidence of adverse reactions in two cases using contrast medium with either a high concentration or a moderate concentration of iodine in the same volume of medium.

Patients and methods

Patient selection

A total of 945 patients undergoing enhanced CT at Ohashi Hospital, Toho University School of Medicine from October 2002 to February 2003 were prospectively investigated (Table 1). Every patient had given written informed consent, and our institutional review board approved the study. Patients who had renal failure, congestive heart failure, respiratory failure, hepatic failure, a poor general condition, or some contraindication for iodinated contrast material were excluded from this study. The patients were randomized for administration of contrast medium with either a high iodine concentration or a moderate concentration. We assigned the patients to one of the two groups every week.

Methods

Equipment and contrast medium

We used iopamidol (Nihon Schering, Osaka, Japan) as the contrast medium, with 370 mg I/ml the high concentration and 300 mg I/ml the moderate concentration. The contrast medium was administered in all patients by an automatic percutaneous injector (Auto Enhance A-50; Nemotokyorindo, Tokyo Japan). The contrast medium was stored in a warmer at 37.5°C and was removed immediately before use. The dosage was broadly determined as 100 ml for patients whose body weight was ≥45 kg and 80 ml for those weighing <45 kg.

Table 2. Injection methods

Injection method	300 mg I/ml group	370 mg I/ml group
Dose (ml)		
100	390	399
95	1	8
90	6	0
80	48	52
70	0	2
Unknown	13	21
Injection rate (ml/s)		
<1	337	340
1.0–2.0	2	5
2.0–3.0	115	128
Unknown	4	9

Patients received an antecubital vein injection; but if this was considered inappropriate, the injection was made at the wrist joint or in the dorsal venous network of the hand. Normally, we used an indwelling 20-gauge needle or a 22-gauge Surflow flash needle (Terumo, Tokyo, Japan), but we had to use winged needles when it was difficult to secure the necessary vein. The injection speed was 0.2–3.0 ml/s, depending on the purpose of performing the CT in each patient, and the site of the injection was carefully observed during the procedure (Table 2).

Method of evaluation

Age, body weight, sex, primary disease, and the medical history of the patient were documented from medical records and by interview. In addition, the patient's history of idiosyncrasies, allergic reactions induced by contrast medium, allergic asthma, and other allergic reactions were also obtained from each patient by interview or patient charts (or both). Serum creatinine concentration was checked right before performing CT.

We carefully monitored whether the contrast medium produced adverse reactions in patients from the time of starting the infusion to 1 h after the examination. The type, intensity, and outcome of adverse reactions were

recorded. The severity of adverse reactions was classified according to three categories as per the Katayama et al. report[7]: mild, treatment unnecessary; moderate, treatment with medication; severe, hospitalization or a doctor from the anesthesiology department required. We asked all patients whether they had local pain at the injection site or heat sensation during the time of injection. Pain was classified into the following three stages: mild, no complaints of pain until asked about the presence of pain; moderate, face drawn unconsciously because of the pain; severe, face obviously drawn with pain or crying because of the pain. Heat sensation was classified into the following three stages: mild, no complaints of heat sensation until asked about it; moderate, complaints of heat sensation but without crying or clenched teeth; severe, yells about the heat sensation or moving the body because of it.

Statistical analysis

For statistical analysis of patient characteristics, Fisher's exact test (two-sided) was performed for sex, complications, and drug idiosyncrasy; and the unpaired *t*-test was used for age and body weight. The Mann-Whitney U-test was performed for examination protocols, amount of contrast medium, flow rate, and type of needle. Fisher's exact test was also performed for the incidence of adverse reactions, pain at the injection site, and heat sensation. $P < 0.05$ was considered significant.

Results

Of the total 945 patients, 940 were studied (the concentration of the contrast medium used in five cases was not recorded). Contrast medium of moderate concentration was used in 458 patients (279 males and 179 females; mean age 64.7 years, mean body weight 57.5 kg) and high-concentration medium was administered to 482 patients (287 males and 195 females; mean age 63.5 years; mean body weight 57.4 kg). There were no significant differences in age, sex, weight, complications, or idiosyncrasies between the two patient groups. Moreover, in terms of technical factors when performing CT, there were no statistically significant differences in the dose of the contrast agent, flow rate, or injection site between the two groups (Table 3).

Adverse reactions were observed in 2.4% (11/458) receiving the moderate concentration of the agent compared with 3.11% (15/482) receiving the high concentration; there was no significant difference in incidence between the two groups (Table 4). Most of the reactions were mild, and there was no significant difference in severity. Nausea ($n = 2$), urticaria ($n = 2$), eruption ($n = 2$), and other episodes ($n = 1$) were observed in the moderate-concentration group; and nausea ($n = 6$), urticaria ($n = 2$), sternutation ($n = 2$), and other episodes ($n = 1$) were observed in the high-concentration group (Table 5). One patient using the high-concentration agent showed moderately adverse reactions, such as edema palpebrarum, urticaria, and facial swelling; but the patient recovered with medication within approximately 15 minutes. No correlation existed between the

Table 3. Summary of adverse events

Parameter	ADR (+)	ADR (–)	*P*
Male/female	16/10	544/362	NS
Age (years), mean ± SD	63.7 ± 14.6	64.1 ± 13.3	NS
Body weight (kg), mean ± SD	58.7 ± 10.6	57.3 ± 11.4	NS
Underlying disease	8/26 (30.8%)	372/906 (41.1%)	NS
History of allergy	6/26 (23.1%)	44/799 (5.5%)	0.001047
Protocol			
IV injection	16/19	617/857	NS
Bolus injection	3	240	NS
Other	0	0	NS
Dose (ml), mean ± SD	98.1 ± 5.7	97.6 ± 6.5	NS
Injection rate (ml/s), mean ± SD	1.1 ± 0.9	1.3 ± 1.0	NS
Catheter location			
Anterior to elbow	15/18	681/844	NS
Forearm	2	144	NS
Back of hand	1	12	NS
Other	0	0	NS
Unknown	0	7	NS
sCr (mg/dl), mean ± SD	0.7 ± 0.2	0.8 ± 0.6	NS

ADR, adverse reaction; sCr, serum creatinine; IV injection, injection ratio is <1 ml/s; Bolus injection, injection ratio is ≥1 ml/s

Table 4. Adverse events with moderate and high concentrations

Parameter	300 mg I/ml group		370 mg I/ml group	
	No. of cases	Prevalence	No. of cases	Prevalence
Total no. of cases	458		482	
ADRs	11	2.40%	15	3.11%
Severity				
Mild	10		13	
Moderate	0		1	
Severe	0		0	
Unknown	1		1	

Table 5. Incidence of adverse events with moderate and high concentrations

Adverse event	300 mg I/ml group	370 mg I/ml group
Nausea	2	6
Urticaria	2	2
Itching	1	1
Itching of eye	1	
Eruption	2	
Eyelid edema		1
Facial edema		1
Laryngeal discomfort		1
Sneezing	1	2
Cough		1
Discomfort	1	
Hypertension	1	
Vascular pain	1	
Unknowns	1	1

Table 6. Incidence of vascular pain, heat sensation, and extravasation for each concentration

Complication	300 mg I/ml group	370 mg I/ml group	Total	*P*
Vascular pain				
Total	453	472	925	0.62424
Positive	16 (3.5%)	13 (2.8%)	29	
Heat sensation				
Total	456	479	935	0.00818
Positive	357 (78.3%)	408 (85.2%)	765	
Extravasation				
Total	452	478	930	0.19431
Positive	5 (1.1%)	1 (0.2%)	6	

incidence of adverse reactions and any of the characteristics of patients, such as sex, age, weight, flow amount, or flow rate. There was a significantly higher proportion of idiosyncratic patients (23.1%) among those who developed adverse reactions than among those who did not show adverse reactions (5.5%).

A high frequency of heat sensation and pain was observed in both the moderate- and high-concentration groups (Table 6). The incidence and severity of pain were not significantly different between the two groups. In contrast, both the incidence and severity of heat sensation were significantly higher in the high-concentration group than in the moderate-concentration group. No significant difference was observed between the groups with regard to the prevalence of extravasation of contrast medium.

Discussion

The introduction of MDCT has had an important effect on diagnostic imaging, with one of the most important benefits being reduced imaging acquisition time. Because the acquisition time for imaging a number of targets simultaneously can be markedly decreased, relevant imaging findings can be attained in the abdominal and thoracic organs and the cardiovascular area during just several seconds of breath-holding. The body weight, hemodynamics, and renal function of a patient are important factors in producing clear contrast enhancement using MDCT. At the same time, the concentration, flow volume, flow rate, and imaging time after administration of contrast medium are also critical variables. We believe that contrast enhancement is significantly affected by the total amount of iodine, resulting in a time–density curve in combination with the overall volume, concentration, and injection time.[1–6] Therefore, contrast media with high iodine concentration or increased iodine volume are generally used for MDCT. However, few reports have examined differences in the development of adverse reactions in relation to the various concentrations of iodine in the contrast medium.[8–10]

The frequency of acute adverse reactions was 2.40% in the moderate-concentration group and 3.11% in the high-concentration group. The frequency of acute adverse reactions in the ionic contrast medium group was lower than 12.66% and was almost the same as the 3.11% of those in the nonionic monomer group that Katayama et al. reported in 1990 based on a large-scale comparative study they conducted on some 340 000 patients.[7] There was no correlation between the frequency of acute

adverse reactions and the flow amount or flow rate of the contrast medium. The incidence of adverse reactions was significantly increased in patients who had a history of allergy or a history of adverse reactions caused by contrast agents. Most adverse reactions were allergic reactions, such as urticaria or eruption. The mechanism by which contrast medium causes adverse reactions is as yet unclear, although these reactions have been thought to be caused mainly by the mechanical, chemical, and immunological components of the contrast medium. Most adverse reactions may develop by one or a combination of these components. Because high osmotic pressure affects the incidence of gastrointestinal manifestations, such as nausea, these reactions might increase in the group of patients given high-concentration contrast medium. There is consistency in the results between our study and a previous study that compared the incidence of adverse reactions with ionic and nonionic contrast medium.[8] The osmotic pressure of moderate-concentration medium is nearly three-fourths that of high-concentration medium, and it appears to be involved mainly in the development of gastrointestinal reactions. In addition, manifestations of nausea were seen in those who underwent detailed examinations for abdominal pain or vomiting due to underlying gastrointestinal disease or related cancer and in patients immediately before and after surgery for cancer. However, this was not statistically proved. It is somewhat difficult to discriminate adverse reactions from signs or symptoms of the onset of the disease itself. In this study, with the exception of one case, most adverse reactions were found to be mild.

The incidence of heat sensation at the injection site was greater in the high-concentration group. In both groups, the incidence of patients complaining of heat sensation was shown to be higher than the incidence of patients suffering from pain; and the degree of heat sensation was significantly greater in the high-concentration group than in the moderate-concentration group.[10–14] It has been reported that heat sensation induced by contrast medium is significantly increased when ionic contrast medium is used compared to nonionic contrast medium.[12] However, there is little in the literature showing a difference in the incidence of heat sensation depending on concentration of the nonionic contrast medium. Although the mechanisms of the development of pain and heat sensation have not yet been fully elucidated, it has been suggested that the direct effect of the osmotic pressure of the contrast medium on the vessel wall or the interaction of chemical substances may have an effect.[11,15,16] Masui et al.[10] reported that the score for heat sensation was significantly higher in the high-concentration group and had no correlation with pain. Our results are similar. It was believe that a different type of injection needle might cause a different result. Masui et al. mainly used winged needles in their study, whereas we mostly used nonwinged, fine needles. Even though we used different needles, we had the same results. Therefore, the incidence of pain appears to be independent from the concentration of the contrast medium. As a limitation for this point, it may be difficult to strictly differentiate pain from heat sensation based on the criteria we used in the study, which may cause patients to shift from suffering "pain" to "heat sensation" and vice versa. In addition, there was some possibility of a patient changing his or her response when the doctor took a different approach or asked the patient other questions. We might have needed to discriminate pain from heat sensation more precisely. "Pain" should be a reaction in the upper extremity where the needle is injected, whereas "heat sensation" should be considered a systemic reaction.

There were no significant differences in the incidence of extravasation of contrast medium between the two groups. It has been reported that the incidence varied from 0.04% to 1.30% according to previous reports. Some reports showed a correlation between the rapid flow rate and the incidence of extravasation, whereas others noted that no correlation has been reported between the frequency of adverse reactions and any of the rapid flow rates or the specific injection site.[6,16–20] In our study, there was also no difference between the two groups regarding extravasation of the contrast medium. It is believed that extravasation of contrast medium may occur not so much depending on osmotic pressure, concentration, and vulnerability of the vessels but, rather, on whether the connection to the vein by the inserted needle can be secured.

We investigated the incidence of acute adverse reactions between high and moderate concentrations of contrast medium. However, we have not yet evaluated the incidence of delayed adverse reactions. Previous studies reported that the incidence of delayed reactions covered a wide range (0.4%–28.2%). Some studies showed an increase in the incidence of the adverse reactions when high doses or a high osmotic pressure of the contrast medium was used. Further study is needed to investigate this possibility.

Conclusions

We investigated and evaluated the acute adverse reaction to contrast medium in patients who were randomly assigned to receive a high or moderate iodine concentration in contrast medium. There were no significant

differences in either the incidence or the severity of adverse reactions between these two groups. The proportion of idiosyncratic patients who developed adverse reactions was significantly higher than those who were not idiosyncratic. The incidence of heat sensation was significantly greater in the high-concentration group than in the moderate-concentration group.

References

1. Yamashita Y, Komohara Y, Takahashi M, Uchida M, Hayabuchi N, Shimizu T, et al. Abdominal helical CT: evaluation of optimal doses of intravenous contrast material—a prospective randomized study. Radiology 2000;216:718–23.
2. Sultana S, Morishita S, Awai K, Kawanaka K, Ohyama Y, Nakayama Y, et al. Evaluation of hypervascular hepatocellular carcinoma in cirrhotic liver by means of helical CT: comparison of different contrast medium concentrations within the same patients. Radiat Med 2003;21:239–45.
3. Fenchel S, Fleiter TR, Aschoff AJ, van Gessel R, Brambs HJ, Merkle EM. Effect of iodine concentration of contrast medium on contrast enhancement in multislice CT of the pancreas. Br J Radiol 2004;77:821–30.
4. Yamamoto K, Narabayashi I, Nambu T, Iwata Y, Moriyama N, Fukuda Y, et al. Hepatic and vascular enhancement at helical CT: comparison of 2.5 ml/kg and a fixed dose (100 ml) of iopamidol (300 mgI/ml) in a prospective randomized study. Nichidoku Iho 2002;47:549–62.
5. Haman S. Computed tomography contrast enhancement principles and the use of high-concentration contrast medium. J Comput Assist Tomogr 2004;28:S7–11.
6. Shuman WP, Adam JL, Schoenecker SA, Tazioli PR, Moss AA. Use of a power injector during computed tomography. J Comput Assist Tomogr 1986;10:1000–2.
7. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast medium. Radiology 1990;175:621–8.
8. Rouviere O, Ecochard R, Berger P, Pangaud C, Fontaine B, Lyonnet D. Low-versus high-osmolality contrast medium. Acta Radiol 2000;41:508–13.
9. Saku M, Murakami S, Nakamura J, Yamaguchi Y, Komori T, Kimura M, et al. A prospective study about an imaging quality of low dosage of contrast medium with single-detector CT. Fukuoka Igaku Zasshi 2004;95:118–23.
10. Masui T, Katayama M, Kobayashi S, Sakahara H. Intravenous injection of high- and medium-concentration of computed tomography contrast medium and relation to heat sensation, local pain, and adverse reactions. J Comput Assist Tomogr 2005;29:704–8.
11. Jacobs JE, Birnbaum BA, Langlotz CP. Contrast medium reactions and extravasation: relationship to intravenous injection rates. Radiology 1998;209:411–6.
12. Federoe MP, Willis LL, Swanson DP. Ionic versus nonionic contrast medium: a prospective study of the effect of rapid bolus injection on nausea and anaphylactoid reactions. J Comput Assist Tomogr 1998;22:341–5.
13. Carro JJ, Trindoade E, McGregor M. The risk of death and severe nonfatal reactions with high vs low-osmolality contrast media: a meta-analysis. AJR Am Roentgenol 1991;156:825–32.
14. Choan RH, Bomyea, Sayre JW. Trend in adverse events after IV administration of contrast media. AJR 2001;176:1385–8.
15. Davis P, Roberts MB, Roylance J. Acute reactions to urographic contrast medium. BMJ 1975;2:434–7.
16. Alguacil LF, Gonzalez C, Bohle F, Jimenez I, Alamo C, Martin JL. Contrast medium algogenic potential in peripheral arteriography: potentiation of bradykinin-induced pain in the rat. Invest Radiol 1994;29:294–300.
17. Sistrom CL, Gay SB, Peffley L. Extravasation of Iopamidol and Iohexol during contrast-enhanced CT: report of 28 cases. Radiology 1991;180:707–10.
18. Cohan RH, Dunnick NR, Leder RA, Baker ME. Extravasation of nonionic radiologic contrast media: Efficacy of conservative treatment. Radiology 1990;176:65–7.
19. Miles SG, Rasmussen JF, Litwiller T, Osik A. Safe use of an intravenous power injector for CT: experience and protocol. Radiology 1990;176:69–70.
20. Cohan RH, Bullard MA, Ellis JH, Jan SC, Francis IR, Garner WL, et al. Local reactions after injection of iodinated contrast material: detection, management, and outcome. Acad Radiol 1997;4:711–8.