Can the lower rate of CT- or MRI- related adverse drug reactions to contrast media due to stricter limitations on patients undergoing contrast- enhanced CT or MRI?

Research Article

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Abstract

Objectives: The aim of this study was to examine whether the decreased rates of adverse drug reactions (ADRs) to contrast media in contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) are due to the relatively strict limitations on patients undergoing such imaging. A secondary aim was to elucidate safety profiles for contrast media and factors influencing the occurrence of ADRs.

Methods: Clinical data of patients who underwent contrast-enhanced CT (5576 cases) or MRI (3357 cases) were retrospectively analyzed to evaluate rates of ADRs to contrast media, symptoms of ADRs, treatments for ADRs, and differences in medical history, blood test results, and other factors between patients with and without ADRs in a dental hospital.

Results: The rate of ADRs to contrast media was 0.54% for CT and 0.09% for MRI. The most frequent ADRs in contrast-enhanced CT or MRI were nausea and vomiting as physiologic reactions. Two serious reactions were seen for CT, but none for MRI. Significant differences between patients with and without ADRs were seen in liver function according to blood tests for CT, and in digestive disorders elicited from medical interviews for MRI.

Conclusions: The lower rate of ADRs to contrast media in dental hospitals could be due to relatively strict limitations on patients undergoing enhanced CT or MRI. Complete suppression of ADRs to contrast media for CT or MRI is unrealistic, so attention is warranted for patients with decreased liver function when performing enhanced CT, and for patients with digestive disorders when performing enhanced MRI.

Key words: contrast media; dental hospital; CT; MRI; adverse drug reactions

Introduction

MRI and CT are routinely performed in dental hospitals for cases involving expanded inflammation, tumors, and cysts in the oral and maxillofacial regions.[1-3] Contrast media are frequently used for more exact qualitative diagnosis of diseases from CT or MRI. Contrast-enhanced CT or MRI tends to be evaluated positively by radiologists for suspected malignant tumors, as these modalities provide more exact and more precise information regarding the presence and site of lesions and qualitative diagnosis than imaging without contrast media.[1, 2] However, adverse drug reactions (ADRs) such as allergy can be induced by the use of contrast media in CT or MRI, and serious status has resulted from anaphylaxis as a complication in rare cases.[4-14] Of course, ADRs cannot be completely prevented even if we pay close attention to avoiding complications associated with contrast media.[4-14] Various reports have examined rates and other issues associated with ADRs from CT or MRI using contrast media.[4-14] In Japan, some large-scale investigations have been conducted.[4, 5, 11, 12] However, the majority of patients with oral-related disease in dental hospitals tend not to present with serious status such as systemic diseases, and we hypothesized that previous data from medical hospitals on ADRs for CT or MRI with contrast media might not necessarily apply to dental hospitals. In addition, we hypothesized that the occurrence rate of ADRs to contrast media for CT or MRI in dental hospitals may be lower because of the better general condition than medical hospitals, stricter criteria for performing contrast-enhanced CT or MRI propriety. However, no reports have described occurrence rates and associated data for ADRs from CT or MRI using contrast media in dental hospitals.

We therefore analyzed the occurrence rate and other data for ADRs to contrast media for CT or MRI in dental hospitals. We retrospectively evaluated and analyzed the

occurrence of ADRs to contrast media for CT or MRI, symptoms of ADRs to contrast media, and treatments for ADRs over an 18-year period in a dental hospital.

Methods and Patients

The clinical data of patients who underwent contrast-enhanced CT (5576 cases) or contrast-enhanced MRI (3357 cases) from 1 July 2000 to 31 March 2017 were retrospectively analyzed to evaluate occurrence rates of ADRs to contrast media. We performed contrast-enhanced examinations only for the diagnosis of malignant tumor or when such pathologies were suspected. Before CT or MRI using contrast media, medical interviews were conducted to elicit patient history and blood testing was performed. Patients for whom contrast-enhanced CT or MRI examinations were considered inadvisable (**Table 1**) were excluded from imaging. The specific criteria in our dental hospital were defined in reference to drug package inserts from the Japanese pharmacopoeia, guidelines from the European Society of Urogenital Radiology (ESUR) and Japan Radiological Society, and other relevant literature.[15-18] The present study was approved by the institutional review board at Kyushu Dental University (approval no. 16-15). The Human Investigations Committee of Kyushu Dental University ensures the protection of the individual rights of patients.

Contrast-enhanced CT was performed using multidetector-row CT after the patient received an intravenous dose of 50 mL iohexol (300 mgI/mL; Omnipaque 300™, Daiichi Pharmaceutical, Tokyo, Japan) at the start of scanning and an additional 50-mL intravenous infusion during scanning to allow better visualization of the vascular structures. Scanning was performed in the axial plane without angulation, in 5-mm-thick contiguous sections from the cavernous sinuses to the thoracic inlet. Images were

photographed with standard algorithms and soft-tissue windows. Contrast-enhanced MRI was performed using a 1.5-T full-body MR system (EXCELART Vantage^{TM} Powered by Atlas; Toshiba, Tokyo, Japan) with a circular polarized neck coil to visualize the level of the maxilla and mandible after the patient received an intravenous dose of gadolinium contrast agent (0.2 mL/1 kg body weight).

We retrospectively evaluated the kinds of diseases patients presented with and rates of ADRs to contrast media for contrast-enhanced CT or MRI. Symptoms and treatments for ADRs to contrast media were also analyzed. At the same time, our data were compared with ADR-related references obtained from search engines. Next, differences in medical history, blood test results, and demographic factors were compared between patients with and without ADRs to contrast media. To compare distributions of medical histories and blood data between patients with and without ADRs, we also analyzed medical histories and blood data in 60 patients without ADRs to contrast media in contrast-enhanced CT or MRI examinations by random sampling.

All statistical analyses, such as Student's *t*-test, Fisher's exact test, and the chi-square test were performed using SPSS version 11 software (SPSS, Chicago, IL). Probability values of $p < 0.05$ were considered significant.

Results

Distributions of contrast-enhanced CT and MRI examinations

Contrast-enhanced CT was performed for 5576 cases and contract-enhanced MRI was performed for 3357 cases from 1 July 2000 to 31 March 2017 in our dental hospital. Among the 5576 patients who underwent contrast-enhanced CT, 1468 patients were receiving a first examination, and 4108 were receiving a follow-up examination. First

examinations included 753 male patients and 715 female patients **(Table 2)**. Of the 3357 patients who underwent contrast-enhanced MRI, 1124 were receiving a first examination, and 2233 were undergoing follow-up examinations. The 1124 first examinations included 580 male patients and 544 female patients **(Table 2)**. The distribution of ages in patients with contrast-enhanced CT or MRI is shown in **Table 2**. Mean age of male and female patients at first contrast-enhanced CT was 64.1±14.2 years and 67.1±15.9 years, respectively. Mean age of male and female patients at first contrast-enhanced MRI was 63.5±13.9 years and 66.9±14.6 years, respectively. Most patients were over 60 years old. Few younger patients and children underwent contrast-enhanced imaging.

Occurrence of ADRs in contrast-enhanced CT

The occurrence rate of ADRs to contrast media in contrast-enhanced CT was 0.54% (30 of 5576 patients) (**Table 3**), including 10 males (mean age, 63.3±22.2 years) and 20 females (mean age, 65.3±22.2 years). This rate was significantly lower than that reported in the biggest study from Japan (3.14%), by Katayama et al. (χ^2 test, $p<0.0001$), and also lower than the lowest ADR rate previously reported (0.83%), by Fujiwara et al. (χ^2 test, $p=0.026$).[4, 5] In addition, no significant difference was found between the present data and the lowest rate reported from around the world (0.40%), by Li et al. (χ^2 test, $p=0.131$).[9] The distribution of symptoms of ADRs to contrast media in CT is shown in **Table 3**. The most frequent symptoms were nausea and vomiting as physiologic reactions, followed by dizziness and headache (**Table 3**). Hypersensitivity reactions were less frequent than physiologic reactions (**Table 3**). Two serious reactions were seen among the 30 cases of ADR to contrast media in contrast-enhanced CT. Both

patients showed lowered blood pressure due to allergic reaction. One patient was a 70-year-old woman with nausea, vomiting, and lowered blood pressure as an immediate allergic reaction. In the other case, the 56-year-old male patient reported nausea and vomiting 6 h after contrast-enhanced CT, followed by a sudden decrease in blood pressure and loss of consciousness due to delayed allergic reaction. Frequent ADRs included nausea, vomiting, and local urticaria **(Table 3)**. The distribution of ADR symptoms in the present study broadly matched previous data.[4-9]

Occurrences of ADRs in contrast-enhanced MRI

The rate of ADRs to contrast media in contrast-enhanced MRI was 0.09% (3 of 2801 patients) (**Table 3**). This rate was again significantly lower than that described in the biggest study from Japan, by Kozuka et al. (1.21%) (χ^2 test, $p<0.0001$).[12] In addition, this rate was significantly lower than that reported in the biggest study conducted globally (0.4%), by Herborn et al. (χ^2 test, $p=0.0189$).[13] Patients with ADRs to contrast media in enhanced MRI included 2 males (age, 54 and 68 years), and 1 female (age, 75 years). The distribution of symptoms of ADRs to contrast media in enhanced MRI is shown in **Table 3**. Two cases involved nausea and vomiting and one involved local urticaria (**Table 3**). No serious reactions were seen for MRI. Likewise, no cases of nephrogenic systemic fibrosis due to contrast for MRI were seen. The distribution of ADRs in the present data broadly coincided with those reported previously.[10-14]

Treatments for patients with ADRs to contrast media in contrast-enhanced CT or MRI

Treatments for various ADRs were clinically appropriate, including emergency

treatments in two serious cases of allergy. The majority of patients experienced non-serious ADRs such as nausea and headache, and had almost completely recovered by follow-up on the examination day. Patients with skin rash such as itching and urticaria were treated with intravenous injections of a glycyrrhizin, glycine, and cysteine combination drug, and their symptoms resolved within several hours. In the case of severe immediate allergy during contrast-enhanced CT, emergency treatment was performed in our dental hospital. Nausea, vomiting, and low blood pressure were treated according to standard therapy for allergy, such as infusion of epinephrine and intravenous injection of steroid hormone. As a result, the patient recovered relatively early. In the case of delayed allergy to enhanced CT, the patient had tongue cancer and leukemia as a medical history, and was followed-up in a general medical hospital. After contrast-enhanced CT, the patient showed no symptoms of ADR. After 6 h, the patient reported feeling nausea, then vomited. Blood pressure suddenly decreased and the patient lost consciousness. Luckily, the patient had visited the doctor treating the leukemia due to worry about continuing nausea and vomiting after contrast-enhanced CT, and that doctor treated the lowered blood pressure and loss of consciousness. With contrast-enhanced MRI, the two patients with nausea recovered fully and symptoms had resolved by follow-up on the examination day. The patient with itching was treated with intravenous injections of a glycyrrhizin, glycine, and cysteine combination drug, and the patient's symptoms resolved within several days.

Medical history and blood data characteristics of patients with ADRs

The distributions of medical history, blood data, and other characteristics in patients with and without ADRs in contrast-enhanced CT or MRI are shown in **Table 4**. A

significant difference was seen in liver function results from blood tests between 30 patients with ADRs and 60 patients without ADRs in CT (Fisher's exact test, p=0.041) **(Table 4)**. However, no significant differences were seen in other medical histories or blood data between patients with and without ADRs **(Table 4)**. In MRI, a significant difference was seen in digestive disorders elicited from medical interviews between the two groups (Fisher's exact test, p=0.040) **(Table 4)**. No other significant differences in medical history, blood tests, or other characteristics were found between patients with and without ADRs in MRI **(Table 4)**.

Discussion

One of the most interesting results in the present study was that the rate of ADRs to contrast media was 0.54% in CT, and 0.09% in MRI performed under the relatively strict limitations on patients undergoing contrast-enhanced imaging in dental hospitals. The present rate for enhanced CT was significantly lower than that reported in the biggest study from Japan.[12] In addition, no significant difference was found between the present data and the lowest rate reported globally.[9] Regarding enhanced-MRI, the present rate was significantly lower than in the biggest studies from Japan and around the world.[10-14] Therefore, our present result suggests that the rate of ADRs to contrast media could be decreased by relatively strict limitations on patients undergoing contrast-enhanced imaging. However, the most frequent symptoms were nausea and vomiting as physiologic reactions, followed by dizziness and headache (**Table 3**). Hypersensitivity reactions were much less frequent than physiologic reactions (**Table 3**). These rates largely matched the results of previous findings.[4-14] One possible explanation was that the exclusion criteria for patients who could undergo contrast-

enhanced CT or MRI at our dental hospital were relatively stricter than those at most medical hospitals. In concrete terms, patients with only slight asthma (besides pediatric asthma) were strictly excluded. At the same time, relatively high standards were provided for kidney, liver, and thyroid diseases based on blood tests criteria **(Table 1)**. In addition, all of the present patients, who could appropriately undergo CT or MRI enhanced using contrast media in our dental hospital, had either confirmed or suspected oral cancers. Therefore, enhanced CT or MRI was not applied for patients with various kinds of disease in the present study, such as cellulitis with systemic symptoms, and this likely means that subjects were strictly limited. Basically, if patients do not have suspected or confirmed oral and/or salivary cancers, non-enhanced CT or MRI is applied for patients in our dental hospital. One of the most important differences between the present study and previous reports was the presence or absence of diseases involving other regions. For example, use of contrast media for diagnosing liver disease involves a dilemma. Despite such patients experiencing liver dysfunction, contrast-enhanced CT is an effective modality for diagnosing liver disease.[19, 20] No such dilemma is seen for the oral and maxillofacial region. At a mental and emotional level, patients with cancers involving the oral cavity generally recognize the need for imaging, and active cooperation and participation in imaging examinations using contrast media was thus able to be obtained. We speculated that such positive cooperation might be related to the decreased rate of ADRs. Moreover, the majority of subjects were in their sixties or seventies, with few children. The complex synergistic effects mentioned above might have contributed to the low rate of ADRs to contrast media in patients undergoing contrast-enhanced CT or MRI.

Another possible explanation was that patients with oral cancers in our dental hospital

tended to have a relatively good general condition. In other words, relatively many patients in general medical hospitals need treatments under general management, but this is not the case in dental hospitals. Of course, the very small sample size for this study cannot be ruled out as a cause of this result.

As mentioned for the present results, however, perfect suppression of ADRs to contrast media is not a realistic goal. In other words, application of strict limitations on contrast media for subjects would not eliminate ADRs to contrast media. The present results for the distribution of ADR rates largely coincided with previous data, and the study design of the present examination thus seems appropriate.[4-14] This suggests that the low ADR rate in the present study was not attributable to bias, and was very significant.

Conversely, we found that patients with decreased liver functions according to blood tests in patients undergoing enhanced CT required attention, as did patients with digestive disorders elicited from medical interviews in patients undergoing enhanced MRI. In particular, even liver-related values for our criteria for blood tests might be lenient. We should therefore reconsider the criteria for liver-related values used to allow contrast-enhanced CT.

Treatments for ADRs applied in the present study largely coincided with previous reports.[9] Most patients with light ADRs such as nausea and vomiting had almost completely recovered by follow-up on the examination day. Patients with skin rash such as itching and urticaria were treated by intravenous injections of a glycyrrhizin, glycine, and cysteine combination drug, and their symptoms resolved within several days. For the two serious ADRs in the present study, both patients showed lowered blood pressure due to immediate or delayed allergy. One patient was treated in our dental hospital, and the other in a medical hospital. The two patients recovered without problems. In one

patient, the nausea, vomiting, and lowered blood pressure occurred immediately after performing contrast-enhanced CT, and common treatments for representative allergy were provided such as infusion of epinephrine and intravenous injection of steroid hormone. As a result, the patient recovered relatively early as mentioned above. Conversely, the other case involved a very particular pattern. The patient with tongue cancer had a medical history of leukemia, and had been followed-up in a general medical hospital. The patient reported feeling nausea and vomited about 6 h after contrast-enhanced CT. The patient visited the doctor treating his leukemia due to worries about the nausea and vomiting, and that doctor appropriately treated the subsequent lower blood pressure and loss of consciousness. Neither patient met any of our exclusion criteria for administration of contrast media, and both had more than one experience of CT using contrast media. We clearly cannot perfectly suppress these ADRs, and we instruct patients after CT or MRI using contrast media to pay close attention to their condition for at least several days.

Several potential limitations need to be considered in our present study. First, because the sample size in our present study was much smaller than in previous reports, our data might not necessarily be representative or accurate.[4-9] Data on the variables of sex and age might not necessarily be accurately reflected in our study sample. In the next trial, we are planning to include a larger sample size to provide more accurate results in a multicenter study of dental hospitals.

Another possible limitation was that the rates of ADRs in this study were limited to our dental hospital. The techniques for contrast-enhanced CT or MRI would be uniform, but patient ages and diseases would also be limited. Therefore, if some aspect of the techniques for CT or MRI using contrast media were incorrect, the present

data would have included clear bias. However, the distribution of ADRs in the present study basically coincided with data from previous reports, despite the very small sample size, and the present study design was thus considered appropriate.[4-14] The present data thus seem likely to be characteristic and significant for the occurrence of ADRs among relatively older patients with oral cancers and relatively good conditions under uniform techniques for contrast-enhanced CT or MRI.

Conclusion

We analyzed ADRs to contrast media for enhanced CT or MRI in a dental hospital, not a general medical hospital, and elucidated safety profiles for contrast media and factors influencing the occurrence of ADRs. The methods involved retrospective analysis of clinical data from patients who underwent contrast-enhanced CT or MRI to evaluate rates and symptoms of ADRs to contrast media, symptoms and differences in medical history, blood tests, and other characteristics between patients with and without ADRs in dental hospitals. As a result, the rate of ADRs to contrast media was 0.54% in enhanced CT, and 0.09% in enhanced MRI. Distribution rates largely coincided with previous data. A significant difference was seen in liver function from blood tests between patients with and without ADRs in contrast-enhanced CT. A significant difference was also seen in digestive disorders elicited from medical interviews between patients with and without ADRs in contrast-enhanced MRI. The present results suggest that the rate of ADRs to contrast media could be low due to relatively strict limitations on patients undergoing contrast-enhanced CT or MRI. While complete suppression of ADRs to contrast media is unrealistic, we should pay attention to patients with decreased liver functions in blood tests for enhanced CT, and to patients with digestive disorders elicited from medical interviews for enhanced MRI.

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Table 1. Criteria for examination using contrast-enhanced CT or MRI

	Enhanced CT	Enhanced MRI
Inadvisable		
	General poor condition	General poor condition
	Previous history of ADRs caused by iodine contrast media	Previous history of ADRs caused by iodine or gadolinium contrast media
	Asthma, except pediatric asthma	Asthma, except pediatric asthma
	Kidney diseases (estimated glomerular filtration rate <40 ml/min/1.73 m^2)	Kidney diseases (estimated glomerular filtration rate <40 ml/min/1.73 m^2)
	Hypersensitivity to iodine	
	Hyperthyroidism	
	Macroglobulinemia	
	Multiple myeloma	
	Pheochromocytoma	
	Tetany	
After consultation with medical doctor		
	Liver disease (AST>80 U/L or ALT>80 U/L or γGTP>100 U/L)	Liver disease (AST>80 U/L or ALT>80 U/L or γGTP>100 U/L)
Conditional		
	Diabetes mellitus taking biguanide (biguanide withdrawal before and after 48 h)	

Table 2. Distribution of sex and age at first performance of contrast-enhanced CT or MRI

	Enhanced CT			Enhanced MRI		
Age	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**
10-19	6	2	8	4	1	5
20-29	12	18	30	10	11	21
30-39	32	32	64	28	18	46
40-49	62	40	102	50	30	80
50-59	119	102	221	95	84	179
60-69	210	154	364	170	126	296
70-79	228	202	430	170	167	337
80-89	80	143	223	51	94	145
>90	4	22	26	2	13	15
Total	753	715	1468	580	544	1124

Table 3. Distribution of symptoms for ADRs to contrast media in contrast-enhanced CT or MRI

	Number of patients (%)	
	Enhanced CT	**Enhanced MRI**
Hypersensitivity reaction	**13 (0.233)**	**1 (0.030)**
Local urticaria	4 (0.072)	1 (0.030)
Itching	3 (0.054)	0 (0)
Generalized urticaria	3 (0.054)	0 (0)
Dyspnea	1 (0.018)	0 (0)
Anaphylactic shock reaction with loss of consciousness	1 (0.018)	0 (0)
Anaphylactic shock reaction with convulsions	1 (0.018)	0 (0)
Physiologic reaction	**17 (0.305)**	**2 (0.060)**
Nausea, vomiting	8 (0.143)	2 (0.060)
Dizziness	4 (0.072)	0 (0)
Headache	3 (0.054)	0 (0)
Sneezing	1 (0.018)	0 (0)
Coughing	1 (0.018)	0 (0)
Total number of ADRs	**30 (0.538)**	**3 (0.089)**

Table 4. Distributions of risk factors in patients with and without ADRs to contrast media in contrast-enhanced CT or MRI

	Enhanced CT			Enhanced MRI		
	ADR group (n=30)	**Control group (n=60)**	**P value (Fisher's exact test)**	**ADR group (n=3)**	**Control group (n=60)**	**P value (Fisher's exact test)**
Risk factor for contrast media (some overlap)						
Allergy-like rashes or urticaria	5	7	0.525	0	6	1
History of drug hypersensitivity	0	1	1	0	2	1
Dehydration	0	0	-	0	0	-
Hypertension	11	23	1	1	25	1
Arteriosclerosis	0	0	-	0	1	1
Diabetes mellitus	5	10	1	0	10	1
Disease of thyroid gland	2	5	1	0	1	1
Decreased liver function	4	1	**0.041***	0	9	1
Decreased renal function	1	1	1	0	3	1
Acute pancreatitis	0	0	-	0	0	-
Elderly people	16	34	0.824	2	35	1
Young children	1	0	0.333	0	0	-
Nervous system disease (dizziness)	1	0	0.333	1	2	0.138
Digestive disturbance	2	5	1	2	6	**0.040***
Number of patients with ≥1 risk factor	24	48		3	46	
Percentage of patients with ≥1 risk factor (%)	80	80		100	76.7	

*p<0.05