



Incidence rate of severe adverse drug reactions to nonionic contrast media at the National Hospital Organization Osaka National Hospital

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Summary

Background Severe adverse drug reactions in response to intravascular contrast media used in computed tomography, although rare, are potentially life-threatening. This retrospective cohort study aimed to estimate the incidence rate of severe adverse drug reactions to nonionic contrast media at the National Hospital Organization Osaka National Hospital and to report individually on each fatality.

Methods In total, 42,501 relevant cases were obtained from the individual case safe reports of the Ministry of Health, Labour and Welfare and the reports of code blue from our hospital database for the period of January 2013 to December 2017. The cases were studied, and the rate of adverse drug reactions was calculated from these data.

Results Severe adverse drug reactions occurred in 0.019% (8/42,501) of the patients, including two deaths. All eight of these patients presented with disturbance of consciousness. Additionally, one patient had dyspnea, five had distributive shock that recovered after treatment, and two died. However, a causal relationship to the contrast media could not be established in one death. When examining the medical histories, four patients were found to have renal dysfunction.

Discussion Although the rate of severe adverse drug reactions in this study appears to be higher than

expected, the sample size of 42,501 patients is insufficient to conclusively determine the incidence and mortality rates of adverse drug reactions, as these rates are extremely low. Further studies are required to estimate the countrywide prevalence of adverse drug reactions in response to contrast media.

Keywords Contrast media · Contrast-enhanced CT · Adverse drug reaction · Anaphylaxis · Hypersensitivity

Abbreviations

ACR	American College of Radiology
ADR	Adverse drug reaction
AIH	Autoimmune hepatitis
AS	Aortic stenosis
ASO	Arteriosclerosis obliterans
AV	Atrioventricular
CECT	Contrast-enhanced CT
CM	Contrast media
CRF	Chronic renal failure
CRP	C-reactive protein
CT	Computed tomography
DoC	Disorder of consciousness
HCC	Hepatocellular carcinoma
ICSR	Individual case safe reports
IM	Intramuscular
IRB	Institutional review board
IV	Intravenous
PCPS	Percutaneous cardiopulmonary support
RCC	Renal cell carcinoma

Introduction

Computed tomography (CT) scans are a commonly used diagnostic tool in radiology and intravascular contrast media (CM) are often used to investigate certain conditions. In the United States, it is estimated that approximately 70 million CT scans are performed

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each year [1]. Over the past decade, the number of contrast-enhanced CT (CECT) scans performed in the United States has been increasing at the rate of ~2 million per year [2]. In Japan, the number of CT scans performed each year is higher than in many other developed countries and appears to be increasing annually [3]. According to a 2004 study, around 36 million CT scans are performed in Japan each year [4].

However, there is a risk of severe adverse drug reactions (ADRs) occurring in response to the CM. These ADRs, although rare, are potentially life-threatening [5, 6]. The American College of Radiology (ACR) Manual on Contrast Media has proposed a classification that stratifies allergic reactions to CM as mild, moderate, and severe [7]. The signs and symptoms of a severe allergic reaction are similar to those of anaphylaxis. Severe ADRs are one of the most important issues faced in the practice of radiology. According to Suh et al., severe ADRs to CM seldom occur and the estimated pooled incidence of severe ADRs is 0.0141% (95% confidence interval: 0.0108–0.0183%; [8]). Moreover, death is extremely rare, and the mortality rate is estimated to be approximately 0.00025% (1/400,000; [5, 9]). However, in Japan's aging society, changes in the patient's background may influence the rate of severe ADRs.

Objectives

The objective of this study was to estimate the incidence rate of severe ADRs to nonionic CM at the National Hospital Organization Osaka National Hospital and to report individually on each fatality.

Materials and methods

This study was approved by the institutional review board (IRB) and ethical approval was obtained.

Individual case safe reports (ICSRs) from the Ministry of Health, Labour and Welfare and the reports of code blue from our hospital database were studied for the period of January 2013 to December 2017. The ICSR and reports of code blue relating to severe ADRs to CM used in CT scans were extracted from the database; these amounted to a final number of eight cases (eight patients). The data collected included the patients' sex, age, background, symptoms, manifestations of the reaction, treatment provided, and outcome. The patients' background comorbidities were analyzed by reviewing their medical records and diagnostic codes. Duplicate reports and overlapping reports were manually searched for and excluded.

Severe ADRs were defined as a disturbance of consciousness, dyspnea, or definite hypotension (following the administration of CM) that were severe enough to require the help of another physician (especially an emergency physician) and admission to the hospital. The criteria were defined according to the ACR Manual on Contrast Media version 10.3 [7]. According to

the manual, we categorized symptoms such as cardiac arrhythmias, depressed myocardial contractility, cardiogenic pulmonary edema, and seizures as "physiologic reactions." Hypotension induced by the vagal reflex was ruled out by checking the patients' heart rate, blood pressure, and oxygen saturation, and by observing them for over 15 min. Outcomes were categorized according to the medical records as "patient hospitalized but recovered and discharged" or "death".

Results

In total, 42,501 CECT scans were performed on adult patients from January 2013 to December 2017 at the National Hospital Organization Osaka National Hospital. Of these, eight patients developed severe ADRs related to the CECT scans. From these numbers, the incidence rate of severe ADRs in response to CM was calculated as 0.019% (8/42,501), including two in-hospital deaths (no. 7 and 8). All eight of these patients presented with disturbance of consciousness. Additionally, one patient had dyspnea, five had distributive shock that recovered after treatment, and two died. However, a causal relationship to the CM could not be established in case 8. All eight patients were classified as having acute hypersensitivity reactions within 1 h of nonionic CM administration, i.e., none was classified as having physiological reactions.

The characteristics of the patients with severe ADRs are presented in Table 1. Of the eight patients, six were males and two were females. One patient had a history of delayed ADR to CM (case 6)—the same patient also had asthma—while the other seven had no history of ADRs to CM or asthma. No instances of atopic diseases, urticaria, or mastocytosis were identified in any of the eight patients.

As a rule, the staff at the National Hospital Organization Osaka National Hospital administer intravenous corticosteroid (hydrocortisone 500 mg, administered intravenously over a sufficient period at least 5 h before the scan) as premedication before CECT examinations to patients with a history of ADRs to CM or asthma. Since 2019, our protocol has changed to betamethasone 6.5 mg, in accordance with the Japan Radiological Society's recommendations.

When studying medical histories, four patients were found to have renal dysfunction, of whom three underwent maintenance dialysis (cases 1, 4, and 6), and one was about to begin artificial dialysis (case 8). One patient took metoprolol (case 4) and five had a history of cancer (cases 1, 2, 3, 4, and 5).

Case presentation

The case details of the two fatalities are presented here.

Case 7 was a male patient in his 80s who underwent a CECT scan to examine the liver and pancreas. He developed cough and nausea 30 s after the administra-

Table 1 Cases with severe ADRs at the National Hospital Organization Osaka National Hospital from January 2013 to December 2017

Patient no. [sex, age]	History of ADRs to CM	Asthma	Renal dys- function	Comorbidities	Symptoms	Dose and route of adminis- tration of adrenaline	Outcome
1 [F, 80s]	–	–	Dialysis	HCC (AIH), severe AS	DoC, respiratory arrest	–	Recovery Hospitalization
2 [M, 60s]	–	–	–	Lung cancer after surgery	DoC, hypotension	0.3 ml IM	Recovery Hospitalization
3 [M, 80s]	–	–	–	Gastric cancer	DoC, dyspnea	–	Recovery Hospitalization
4 [M, 70s]	–	–	Dialysis	Sepsis, ischemic enteritis, prostate cancer, RCC, ASO	Gait disorder, DoC	0.3 ml IM twice	Recovery Hospitalization
5 [F, 70s]	–	–	–	Gastric cancer, Hypertension	DoC, finger tremor	–	Recovery Hospitalization
6 [M, 70s]	Yes ^b	Yes	Dialysis	RCC, suspected AV block	DoC, hypotension	0.3 ml IM	Recovery Hospitalization
7 [M, 80s]	–	–	–	Liver cystic lesion	Asystole, cough, nausea	0.5 ml IM 1.0 ml IV twice	Death
8 [M, 70s]	–	–	CRF	Preparing for dialysis, heart failure	Asystole, respiratory arrest	1.0 ml IV twice	Death ^a

ADRs adverse drug reactions, AIH autoimmune hepatitis, AS aortic stenosis, ASO arteriosclerosis obliterans, AV atrioventricular, CM contrast media, CRF chronic renal failure, DoC disorder of consciousness, HCC hepatocellular carcinoma, IM intramuscular, IV intravenous, RCC renal cell carcinoma

^aThe contrast agent was not directly implicated in the death of the patient

^bDelayed allergic reaction to CM

Table 2 Severe ADRs and their corresponding death rates (compilation of results previously reported in the literature and the results of the current study)

	Study design	Number of patients ^a	Severe ADRs	Rate of severe ADRs (%)	Deaths	Death rate (%)	Study period
Katayama H et al. [5]	Retrospective	168,363	6–70	0.0036–0.042	1 ^b	0.00059 ^b	1986–1988
Lasser EC et al. [9]	Retrospective	Per 1,000,000	10.52	0.0011	2.07	0.00021	1990–1994
Cochran ST et al. [10]	Retrospective	68,701	10	0.015	2 ^c	0.0029 ^c	1991–1999
Mortel�� KJ et al. [11]	Prospective	29,508	4	0.014	1	0.0034	2001–2003
Wang CL et al. [12]	Retrospective	84,928	11	0.013	0	0	1999–2005
Hunt CH et al. [13]	Retrospective	298,491	15	0.0050	1 ^b	0.00034 ^b	2002–2006
Kobayashi [14]	Retrospective	36,472	23	0.063	0	0	2004–2011
Suh YJ et al. [8]	Meta-analysis (30 stud- ies)	1,360,488	–	0.014	–	–	–
Our report	Retrospective	42,501	8	0.019	2 ^b	0.0047 ^b	2013–2017

ADRs adverse drug reactions, CM contrast media

^aNumber of patients who underwent examination using nonionic CM

^bThe contrast agent was not directly implicated in the death of the patient

^cBoth cases were considered to be physiological reactions

tion of the CM and was soon unconscious. Although intramuscular adrenaline was immediately administered, he suffered a cardiac arrest. Spontaneous circulation was restored following cardiopulmonary resuscitation, intravenous injection of adrenaline, intubation, and introduction of percutaneous cardiopulmonary support (PCPS); however, the increased vascular permeability could not be controlled. He died of pulmonary edema and circulatory failure 4 h later.

Case 8 was a male patient in his 70s. He presented to the hospital with hypothermia, hypotension, lactic acidosis, high levels of C-reactive protein (CRP), pancytopenia, and fulminant hepatitis. Contrast medium was administered in the course of further examination

and 2 min later, he suffered a cardiopulmonary arrest. He died of bowel necrosis, sepsis, and hemophagocytic syndrome on the 14th day of hospitalization.

Discussion

Many previous studies have researched risk factors that predispose to ADRs to CM, such as asthma or history of hypersensitivity reactions to CM [5]. These risk factors are well known to physicians, and the indications for CM have been clearly defined, which seems to have reduced the incidence of severe ADRs in response to CM. In Table 2, we have summarized the previously reported data on ADRs and the associated

mortality rates following the administration of non-ionic CM. Since it is not appropriate to compare the numbers and rates with those of previous studies, it is difficult to conclude whether the rate of ADRs is increasing or decreasing; however, the rate of severe ADRs in this study is somewhat higher than expected. This can be explained by the fact that our sample size of 42,501 patients is insufficient to conclusively determine the incidence and mortality rates of ADRs, because these rates are extremely low. The ADR rates have been sporadically reported in several publications, but the definitions of severe ADRs are ambiguous and different from those in other papers.

As Japan's population is rapidly aging, the average age of those who undergo CT scans is also increasing [15]. The elderly commonly experience decreased cardiac reserve and multimorbidity, and in the event of cardiac arrest, this might result in difficulty in resuscitation. Although the results of Katayama et al. and Motosugi et al. revealed that the incidence of ADRs to nonionic CM is lower in elderly patients than in younger adults, most of the ADRs in these papers were classified as mild or moderate [5, 16].

According to the results of the present study, the rate of severe ADRs was 0.019% (8/42,501), including two deaths. Four of these eight patients had renal dysfunction. Although these rates appear to be higher than expected, this could be due to the insufficient sample size of 42,501 patients. Our hospital has a dialysis center and we did not attempt to restrict CT scans in patients on dialysis, which may have led to selection bias. Further studies are required to address this issue. Another limitation is the potential bias in choosing the study period and patient population needing CT scans at the National Hospital Organization Osaka National Hospital.

Conclusion

Severe ADRs occurred in 0.019% of the patients in this study (8/42,501), including two deaths. Four of these eight patients had renal dysfunction. Although the rate of severe ADRs in this study is higher than expected, the sample size of 42,501 patients is insufficient to determine conclusively the incidence and mortality rates of ADRs, as these rates are extremely low. If the rate of severe ADRs is truly higher than previously estimated, physicians should be more cautious regarding the use of CM, i.e., they should prefer to perform CT without CM wherever possible. Further studies are required to estimate the countrywide prevalence of ADRs to CM.

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Compliance with ethical guidelines

Conflict of interest T. Honda, K. Kuriyama, K. Kiso, K. Kishimoto, T. Tsuboyama, A. Inoue and M. Higashi declare that they have no competing interests.

Ethical standards The study was approved by the appropriate institutional ethics committee and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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