ORIGINAL ARTICLE

Incidence and Risk Factors of Immediate Hypersensitivity Reactions Associated With Low-Osmolar Iodinated Contrast Media: A Longitudinal Study Based on a Real-Time Monitoring System

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Abstract

Objectives: We investigated the incidence of immediate hypersensitivity reaction (HSR) caused by different types of low-osmolar contrast media (LOCM) and cumulative exposure to LOCM.
Methods: This cohort study included all consecutive patients who underwent LOCM-enhanced computed tomography from 2012 through 2014. We assessed 5 LOCM (iobitridol, iohexol, iomeprol, iopamidol, and iopromide). All patients were monitored for adverse events, and new symptoms and signs were recorded in real time using the Contrast Safety Monitoring and Management System (CoSM^{2}oS).
Results: The overall incidence of immediate HSR to LOCM was 0.97% (2004 events resulting from 205 726 exposures). Incidence differed significantly depending on whether the patient had a previous history of HSR to LOCM (0.80% in patients with no history and 16.99% in patients with a positive history of HSR to LOCM, *P*=.001). The incidence of HSR to individual LOCM ranged from 0.72% (iohexol) to 1.34% (iomeprol), although there were no significant differences across the 5 LOCM. A longitudinal analysis demonstrated that the incidence of HSR increased gradually with more frequent previous exposure to LOCM (HR=2.006 [95%CI, 1.517-2.653], *P*<.001). However, this cumulative increase in risk was observed in patients who had experienced HSR to LOCM, but not in those who had not.
Conclusion: The incidence of HSR did not differ significantly across the 5 LOCM assessed in the study. Repeated exposure to LOCM did not increase the risk of HSR among patients who had never experienced HSR to LOCM.

Key words: Contrast media. Hypersensitivity. Incidence. Risk Factors. Secondary prevention.

Resumen

Objetivos: Estudio de la incidencia de reacciones de hipersensibilidad inmediata frente a diferentes medios de contraste de baja osmolaridad, así como la incidencia global de dichas reacciones con estos contrastes yodados.
Métodos: Estudio de cohortes en el que se incluyó de forma consecutiva a todos los pacientes a los que se realizó TAC con contraste yodados de baja osmolaridad durante los años 2012 a 2014. Se emplearon 5 contrastes yodados: iobitridol, iohexol, iomeprol, iopamidol, y iopromide. En todos los pacientes se valoró la presencia de efectos adversos. La aparición de cualquier síntoma fue registrada en el mismo momento de su aparición en el *Contrast Safety Monitoring and Management System* (CoSM^{2}oS) en tiempo real.
Resultados: La incidencia global de reacciones de hipersensibilidad inmediata a medios de contraste yodados de baja osmolaridad fue de 0,97% (2.004 reacciones en 205.726 exploraciones con contraste). La incidencia fue significativamente mayor en los pacientes con historia previa de reacción adversa (16,99%) frente a tan solo 0,80% en los pacientes sin historia previa de reacción (p=.001). La incidencia de estas reacciones osciló desde el 0,72% con iohexol al 1,34% con iomeprol, sin alcanzar diferencias significativas entre los cinco contrastes. Un análisis longitudinal mostró que la incidencia de reacciones inmediatas de hipersensiblidad se incrementa de forma gradual en los pacientes con historia de reacciones previas con medios de contraste yodados (CR=2,006 (1.517-2.653), p<.001). este incremento solo se observaba en los pacientes con historia de reacciones previas, pero no en los sujetos sin historia previa de estas reacciones.
Conclusión: La incidencia de las reacciones de hipersensibilidad inmediata no fue significativamente diferente entre ninguno de los 5 contrastes utilizados en el estudio. Exposiciones repetidas a estos medios de contraste no aumentan el riesgo de este tipo de reacciones de hipersensibilidad inmediata en los pacientes que no habían presentado previamente este tipo de reacciones.

Palabras clave: Medios de contrate yodados. Hipersensibilidad. Incidencia. Factores de riesgo. Prevención secundaria.

Introduction

Hypersensitivity reaction (HSR) to drugs is an important cause of morbidity and mortality. Increased use of contrast agents has resulted in an increased incidence of drug sensitivity reactions, and contrast agents have become a major cause of drug hypersensitivity [1]. Although most reactions are mild to moderate, severe immediate reactions induced by low-osmolar contrast media (LOCM) occur with a frequency of 0.02%-0.04% and an estimated mortality rate of 1 in 100 000 examinations [2]. In many studies, the most significant risk factor for an immediate HSR was a previous immediate reaction [3-5]. The osmolarity of contrast agents is another obvious risk factor for hypersensitivity. High-osmolar contrast media (HOCM) have been replaced by LOCM since the late 1980s and are no longer used worldwide [6]. The incidence of severe immediate reactions was reduced up to 10-fold in patients given LOCM after previously experiencing a reaction to HOCM [7]. The prevention strategies used in high-risk patients include changing the type of agent administered and premedication regimens, and various authors have reported on the effectiveness of these measures for reducing the incidence of hypersensitivity [8-11].

However, there is no clear evidence for differences in the risk of an immediate HSR within the same class or for the cumulative effects of repeated exposure to LOCM. Allergic-like HSRs induced by HOCM were considered to be caused by nonspecific direct histamine release [12]. The effect of repeated exposures has been overlooked, because the mechanism of contrast media hypersensitivity was believed to be a non–IgE-mediated reaction [13,14]. Growing evidence recently suggested that some reactions, especially more severe reactions, can be triggered by an IgE-dependent mechanism [14-17]. In IgE-mediated responses, repeated exposures could enhance the possibility of allergic sensitization through T-cell and IgE memory [18,19] and increase the frequency of HSR to the allergen. In this study, we investigated whether the risk of immediate hypersensitivity to LOCM is increased by repeated exposures and analyzed specific LOCM.

Methods

Study Participants and Monitoring of Contrast Media Hypersensitivity

This study included all patients who underwent an LOCM-enhanced computed tomography (CT) examination from July 2012 through June 2014 at Seoul National University Hospital, Seoul, Korea.

After administration of LOCM, patients were monitored for 1 hour to determine whether an immediate HSR occurred. Symptoms and signs indicating an immediate reaction to LOCM were monitored in real time by trained radiology nurses and recorded in the electronic medical record (EMR)–based Contrast Safety Monitoring and Management System (CoSM^{2}oS). Through this system, we recorded information such as types of agent, pretreatment, and response to re-exposure to contrast media in patients who had previously experienced an HSR to LOCM [10]. The system automatically recommends a premedication regimen in accordance with the severity of the previous response when an examination using contrast agents is ordered for a patient with a history of hypersensitivity to LOCM [10,20]. Data collected retrospectively from the EMR included comorbidities, presence of allergic diseases (including allergic asthma, rhinitis, and chronic urticaria), information regarding LOCM, previous history of exposure to LOCM, and any previous immediate HSR to contrast media.

Throughout the study period, we used 5 LOCM for enhancement of CT scans, as follows: iobitridol, iohexol, iomeprol, iopamidol, and iopamide.

The study was approved by our institutional review board. The requirement for informed consent was waived, and participant data confidentiality was assured.

Severity of Immediate HSR

Immediate HSR was defined as a reaction that occurred within 1 hour of administration of the LOCM. Symptoms and signs were classified as mild, moderate, or severe based on the American College of Radiology Manual on Contrast Media [21]. Mild reactions included limited urticaria, pruritus, cutaneous edema, nasal congestion, rhinorrhea, and conjunctivitis. Moderate reactions included diffuse urticaria, erythema, facial edema without dyspnea, laryngeal edema, and mild wheezing without hypoxia. Severe reactions included signs and symptoms that are often life-threatening, such as diffuse erythema, edema with dyspnea, hypotension (defined as systolic blood pressure <90 mmHg), laryngeal edema with hypoxia, wheezing with hypoxia, unresponsiveness, cardiopulmonary arrest, and clinical arrhythmias.

Statistical Analysis

The incidence of immediate reaction was calculated by dividing the number of patients who experienced an immediate HSR to LOCM by the total number of cases where contrast-enhanced CT was used during the study period. The incidence of hypersensitivity to LOCM in patients with underlying diseases or previous exposure to LOCM was calculated by dividing the number of patients with hypersensitivity to LOCM by the total number of patients with these conditions. The χ^2 statistic was used to compare the incidence rate between groups. Risk factors for hypersensitivity were determined using univariate and multivariate regression models. Analyses were adjusted for age, gender, presence of allergy, previous exposure to LOCM, and previous history of hypersensitivity to LOCM. Univariate analysis was performed to investigate the relationships between underlying diseases and immediate HSR to LOCM. The regression method was used to test *P* values for the trend toward an increased cumulative effect of previous exposures on hypersensitivity to LOCM. A forward stepwise model was used, and variables with a *P* value <.05 were retained. All analyses were performed using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp).

Results

Incidence of Immediate Hypersensitivity to LOCM

Of a total of 205 726 exposures to LOCM in 86 328 patients, we detected 2004 immediate HSRs during the study period (incidence of 0.97%) (Table 1). The incidence of mild, moderate, and severe reactions was 0.85%, 0.10%, and 0.02%, respectively. Of the 2004 cases of immediate HSRs, 81.0% (1623 of 2004 events) were new cases, and the remaining 381 cases (19.0%) were recurrent cases in patients who already had a history of immediate HSR to LOCM. A previous history of hypersensitivity to LOCM significantly predisposed patients to future HSRs (P=.001 [χ^2]). While the incidence rate for the first reaction among patients with no history of previous reactions was 0.80% (1623 events from 203 483 exposures), the incidence among patients who had a history of hypersensitivity was 16.99% (381 events from 2243 exposures).

The incidence of HSR to individual LOCM ranged from 0.72% (iohexol) to 1.34% (iomeprol), although there were no significant differences across the 5 LOCMs (Table 2). Moderate to severe reactions were less frequent in patients given iopamidol than in those given other agents (8.5% vs 13.6%, P=.045 [χ^2 test], Figure 1). Although the proportion of severe reactions was highest in the iobitridol group (4.5%), the results were not statistically significant. The percentage of patients who experienced hypersensitivity following a previous immediate HSR to LOCM differed according to the type of LOCM (P<.001, χ^2 test). This percentage was highest in patients with hypersensitivity to iopromide (36.6%) and lowest in patients who reacted to iomeprol (11.1%) (data not shown).

Table 1. Incidence of Immediate Hypersensitivity to Low-Osmolar Contrast Media

	First Event (n=203 483)	Recurring Event (n=2243)	Total (N=205 726)
Mild reaction	1428 (0.70%)	320 (14.27%)	1748 (0.85%)
Moderate reaction	164 (0.08%)	46 (2.05%)	210 (0.10%)
Severe reaction	31 (0.02%)	15 (0.67%)	46 (0.02%)
Overall	1623 (0.80%)	381 (16.99%)	2004 (0.97%)

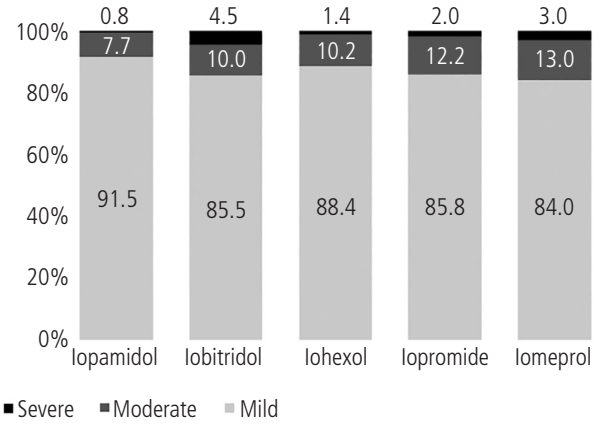

Figure 1. Severity profile according to the individual agents.

Risk Factors for Hypersensitivity to LOCM

Multivariate regression analysis showed that the most significant risk factor for development of hypersensitivity to LOCM was previous hypersensitivity (HR=40.693; 95%CI, 35.466-46.692; P<.001). This was followed by age under 50 years (HR=2.113; 95%CI, 1.912-2.336; P<.001), presence of allergies (HR=1.621; 95%CI, 1.280-2.051; P<.001) such as asthma (HR=1.476; 95%CI, 1.082-2.013), allergic rhinitis (HR=1.502, 95%CI, 1.041-2.166), and chronic urticaria (2.535, 95%CI, 1.384-4.645), as well as female gender (1.291, 95%CI, 1.117-1.417, P<.001) and previous exposure to LOCM (1.178, 95%CI 1.022-1.358, P<.001).

The incidence of immediate hypersensitivity to LOCM was higher in patients with comorbid allergic diseases (2.6%, P=.001) such as asthma (2.4%, P=.015), allergic rhinitis (2.4%, P=.036), and chronic urticaria (4.0%, P=.006), and in patients with cancer (2.1%, P=.001) and chronic liver disease (3.1%, P=.001) (Table 3). The proportion of patients who received premedication did not differ between patients with or without these underlying diseases.

Longitudinal Analysis of the Risk of HSR Based on Cumulative Exposure to LOCM

The number of previous exposures to LOCM affected the difference in the incidence of HSR to LOCM. The incidence

Table 2. Incidence of Immediate Hypersensitivity to Low-Osmolar Contrast Media According to Individual Agents

ICM				
Contrast Agent	Osmolarity, mOsm/kg	Number of Exposure	Incidence of HSR	Incidence of Severe HSR
Iopamidol	300	16 894	1.28%	0.01%
Iobitridol	350	27 363	0.88%	0.04%
Iohexol	350	78 586	0.72%	0.01%
Iopromide	370	67 590	1.00%	0.02%
Iomeprol	400	15 293	1.34%	0.04%

Abbreviations: ICM, iodinated contrast media; HSR, hypersensitivity reaction.

Table 3. Incidence of HSR to Low-Osmolar Contrast Media in Specific Comorbid Conditions

	Incidence of HSR, %[a]						
	Patients With Comorbidity	Patients Without Comorbidity	*P* Value	Exp (B)	Lower End	Upper End	*P* Value
Allergic diseases	2.6	1.6	.001	1.621	1.280	2.051	.001
Asthma	2.4	1.6	.015	1.476	1.082	2.013	.014
Allergic rhinitis	2.4	1.6	.036	1.502	1.041	2.166	.029
Chronic urticaria	4.0	1.6	.006	2.535	1.384	4.645	.003
Diabetes	1.8	1.6	.091	1.149	0.979	1.349	.088
Hypertension	1.4	1.7	.073	0.746	0.706	1.012	.067
Angina	1.3	1.7	.093	0.803	0.624	1.034	.089
Dyslipidemia	1.5	1.6	.443	0.905	0.711	1.151	.414
Chronic kidney disease	1.2	1.6	.320	0.748	0.455	1.228	.251
Cancer	2.1	1.1	.001	1.914	1.713	2.139	.001
Chronic liver disease	3.1	1.5	.001	2.064	1.769	2.408	.001

Abbreviation: HSR, hypersensitivity reactions.
[a]The incidence of hypersensitivity to LOCM according to underlying diseases was calculated by dividing the number of patients with ICM hypersensitivity by the total number of patients.

of immediate hypersensitivity to LOCM gradually increased with the number of previous exposures (*P* for trend <.001, Figure 2A). The cumulative effect of previous repeated exposures on the incidence of LOCM hypersensitivity was dependent on the presence of a history of hypersensitivity to LOCM. A sharp increase in repeated exposures was recorded in patients with a history of HSR to LOCM, although this plateaued at 6 or more exposures (Figure 2B). In patients with no previous history of hypersensitivity, the incidence did not increase in response to repeated exposures (Figure 2C).

The number of previous exposures to LOCM was not higher in patients with allergic diseases. However, the frequency of exposure to LOCM was higher in patients with cancer (3.7-fold, *P*=.016 [χ^2 test]) and chronic liver disease (5.8-fold, *P*=.005 [χ^2 test]) than in those without these diseases.

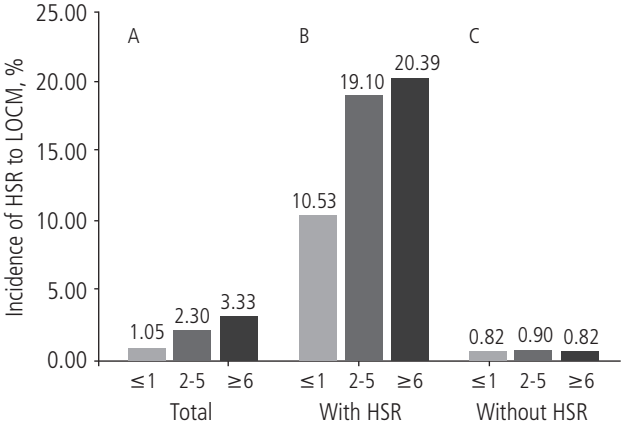

Figure 2. Gradually increasing trend in the incidence of hypersensitivity to iodinated contrast media as the number of previous exposures increased (*P*<.001). A, Total. B, Previous history of hypersensitivity to LOCM. C, No previous history of hypersensitivity to LOCM. The incidence rate was calculated by dividing the number of patients with LOCM hypersensitivity by the total number of patients. HSR indicates hypersensitivity reaction; LOCM, low-osmolar iodinated contrast media.

Discussion

We monitored 205 726 cases in which LOCM were administered for enhanced CT examination in a single institution over a 2-year period. Incidence and risk factors of HSR to LOCM were evaluated. Processing of data for large numbers of CT cases was possible through our EMR–based Contrast Safety Monitoring and Management System (CoSM^{2}oS).

The incidence of hypersensitivity to LOCM has been reported to range from 0.31 to 1.34 [22-26] and has markedly declined over time through interventions for high-risk patients. In this study, the overall incidence of hypersensitivity to LOCM was 0.97%, which is similar to results from other studies [22,23]. The incidence of hypersensitivity in patients with a history of previous reactions (ie, 1.1% of the total) was about 20 times higher than the incidence in patients without a previous history.

Several methods have been used to prevent hypersensitivity to LOCM [27-29]. A previous history of hypersensitivity to LOCM is a major risk factor for further hypersensitivity [30], and several preventive strategies have been used in at-risk patients. Accurate documentation of the contrast agent that induced the response and history of iodine allergy should be evaluated [31], because a previous history of hypersensitivity is the main risk factor. Premedication before injection of the LOCM is widely used to lower the incidence of hypersensitivity in patients with previous hypersensitivity, and some studies suggest that stratifying premedication according

to the severity of the index reaction could be effective and safe as a prophylactic measure while minimizing the use of corticosteroids [10,20]. Along with premedication, changing the LOCM administered is also an important strategy for reducing the risk of recurrence [20]. Although changing the LOCM to another agent in the same class has historically been considered to have little or no benefit, recent ACR guidelines stated that changing contrast media within the same class of LOCM may help to reduce the risk of recurrent HSRs to LOCM [32].

In the present study, the incidence of HSRs was not significantly different across the 5 LOCMs used. There is still some controversy regarding differences in the incidence of hypersensitivity between the different LOCM [7,33-38], since the results of previous studies were inconsistent. Although several studies have shown no differences in the incidence of adverse drug reactions resulting from administration of various agents [7,36-38], others reported that the incidence of hypersensitivity to LOCM was higher with specific agents [33,35]. In previous studies evaluating the incidence of hypersensitivity, risk factors such as previous use of LOCM, previous history of hypersensitivity, and comorbidities were not considered.

Our study showed an increased risk of hypersensitivity with repeated exposures to LOCM. The incidence of hypersensitivity increased linearly with the number of previous exposures that resulted in HSRs. Few studies describing the cumulative effect of repeated exposures to LOCM on drug hypersensitivity have been undertaken. Repeated exposures increased the risk of adverse reactions in patients with hepatocellular carcinoma [39], although in a nested case-control study, the number of exposures to LOCM was lower in patients with hypersensitivity than in controls [4]. The increased incidence of HSR with repeated exposure may be the result of IgE-mediated sensitization. Growing evidence demonstrates that IgE-mediated allergic reactions may be at least partly involved in immediate hypersensitivity to LOCM [17,40]. However, it is still unclear whether immediate HSR to LOCM is IgE-dependent or IgE-independent (eg, direct mast cell activation or complement activation). In the current study, immunological mechanisms were not determined by allergy tests; therefore, the mechanism involved in hypersensitivity remains unclear. As HSRs were more frequent and more severe with repeated exposure to the same LOCM than to a different one [10,20], the possibility of immunologic memory in cases of hypersensitivity is substantial. Despite the sharp increase in the incidence of hypersensitivity with increased previous exposures in patients with a history of HSR, incidence did not increase in patients who did not have a history of hypersensitivity to LOCM. A previous study reported that patients who have previously been exposed to LOCM without a reaction have a lower risk of hypersensitivity [23]. These results suggest that repeated exposure itself may be not a significant risk factor for hypersensitivity to LOCM if there is no history of hypersensitivity, although there is a possibility that IgE-mediated sensitization increases the risk of hypersensitivity in susceptible patients. Further investigations are necessary to determine whether exposure to all kinds of LOCM can increase sensitization and which patients are susceptible to sensitization to LOCM.

Several other risk factors for hypersensitivity to LOCM have been identified [23,30,41,42]. In addition to past history of hypersensitivity, the presence of allergic disease, female gender, and younger age are associated with an increased risk of HSRs. In the present study, chronic urticaria, which was not previously identified as a risk factor for hypersensitivity, was associated with an increased incidence of hypersensitivity to LOCM, with a high HR. However, HSRs in patients with chronic urticaria were exacerbations of preexisting urticaria, and none of these patients had systemic reactions. The correlation between underlying diseases other than allergic diseases and hypersensitivity to LOCM has not been studied extensively. Heart disease [43], renal insufficiency, and hyperthyroidism [44] are possible risk factors. However, a recent study reported a low incidence of adverse drug reactions independently of underlying diseases, except for allergic diseases [23]. In the present study, the incidence of hypersensitivity to LOCM was higher in patients with cancer and chronic liver disease. Although evidence is lacking for the association between these underlying diseases and hypersensitivity to LOCM, repeated exposure to LOCM in patients with cancer or chronic liver disease may have increased the risk of hypersensitivity because of more frequent exposure.

The main findings of the present study are that repeated exposure to LOCM can increase the risk of hypersensitivity and that the differences in the incidence of hypersensitivity between different LOCM remain controversial. Our study is subject to a series of limitations. First, contrast agents were not selected at random. Rather, a single contrast agent was preselected for each organ-specific CT scan by the corresponding radiology subspecialist to be used for a specific period. The contrast agent was changed if the patient experienced a previous HSR to an LOCM. Therefore, selection of the LOCM was not random and varied depending on patient characteristics. Second, when a patient had experienced an HSR at another center in the past, the agent responsible was sometimes unknown; therefore, some patients may have been re-exposed to the agent responsible for the adverse effect. A larger, prospective, controlled follow-up study to evaluate the mechanisms underlying hypersensitivity to LOCM will be of great value in improving the safety of these agents.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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