ORIGINAL ARTICLE

A Clinical Study of Cutaneous Adverse Reactions to Nonionic Contrast Media in Korea

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Background: The use of intravenous contrast media (CM) has increased for the diagnosis of several diseases. The newly developed low osmolar nonionic contrast agents cause significantly decreased adverse reactions than the higher osmolar ones. However, adverse reactions may still occur, ranging in severity from minor side effects to severe complications. However, there have been few reports about cutaneous adverse reactions (CARs) to nonionic monomer CM. **Objective:** The purpose of this study was to evaluate clinical features of CAR to intravenous nonionic monomer CM. **Methods:** A total 47,338 examinees underwent intravenous iodinated contrast-enhanced computed tomography scan using nonionic monomer CM. Among the adverse reactions to the CM, we divided them into cutaneous or noncutaneous and immediate (< 1 hr) or late (≥ 1 hr) adverse reactions. **Results:** Adverse reactions were noted in 62 cases out of the total 47,338 cases; 50 cases (80.7%) were categorized CARs. Among them, there were 24 male and 26 female patients. There was no significant difference between the sexes, and CARs occurred in all age groups. The highest occurrence was in the age range of 50～59 years. CARs included urticaria (78%), angioedema (10%), maculopapular rash (8%), erythema (2%), and pruritus without rash (2%). Immediate reactions were 92% (46 cases), while late reactions were 8% (4 cases). **Conclusion:** CARs to nonionic monomer CM accounted for most of the adverse reactions (80.7%) and urticaria was the most common. **(Ann Dermatol 24(1) 22～25, 2012)**

-Keywords-
Contrast media, CT, Cutaneous adverse reaction

INTRODUCTION

Imaging modality using contrast media (CM) is increasing. Adverse reactions to CM range from a mild inconvenience, such as nausea, vomiting, flushing, and pruritus, to life-threatening hypotension, anaphylactoid reaction, Stevens-Johnson syndrome, and toxic epidermal necrolysis[1,2]. The adverse reactions occurring after CM administration may be divided into three different types: allergic and non-allergic hypersensitivity reactions, toxic reactions and events unrelated to CM exposure[3]. The CM maybe divided into higher osmolar, ionic agent and lower osmolar, nonionic agent. The former dissociate into ions when dissolved in water and are contained in an iodinated benzene ring[4]. As a result, ionic agents have a higher osmolarity than blood, and the latter is less likely to cause adverse reaction[5-8]. To date there has been research conducted on the adverse reactions of CM, but studies on cutaneous adverse reaction (CAR) are rare. Here, we report results for CARs due to nonionic monomer CM, and hope to provide useful data for patient care and clinical research.

Received May 18, 2011, Revised June 27, 2011, Accepted for publication June 28, 2011
*This research was supported by a grant (09182KFDA889) from Korea Food & Drug Administration for Pharmacovigilance Research in 2011.

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MATERIALS AND METHODS

Materials

We studied 50 CAR cases that were reported by patients or perceived by computed tomography (CT) radiological staff using nonionic monomer CM for CT scan between August 2005 and November 2009. We investigated adverse reactions in nature and gender difference through medical records and telephone contacts.

The CM that causes adverse reactions includes nonionic monomer including Iomeprol (Iomeron, Ilsung pharmaceuticals CO., Seoul, Korea), Iopamidol (Iopamiro, Ilsung pharmaceuticals CO.), Iopromide (Ultravist, Bayerin Korea), Ioversol (Optiray, Mallinckrodt, St. Louis, MO, USA).

Methods

1) Types and severity of adverse reactions of CM

The adverse reactions to nonionic monomer CM are classified into cutaneous, respiratory, cardiovascular, gastrointestinal symptoms[2]. We defined the immediate reactions which occur within 1 hour after CM administration, and the delayed reactions which occur more than 1 hour after injection[2,3,9]. The severity of the reaction was classified into mild and severe, and severe adverse reactions were defined as one or any combination of the following symptoms: dizziness, severe generalized urticaria, hypotension, laryngeal edema, and facial edema[10].

2) Statistics

The results of the study were analyzed statistically by chi square test using Statistical Package for the Social Sciences (SPSS) version 12.0 for Windows (SPSS Inc., Chicago, IL, USA). All statistical significance levels of differences were less than 0.05.

RESULTS

Adverse reactions and clinical manifestation

From August 2005 to November 2009, a total 47,338 examinees (27,733 male, 19,615 female) underwent intravenous iodinated contrast-enhanced CT scans using nonionic monomer CM. Age distribution varied from 0 to over 80 years. Of the total 47,338 examinees, 62 experienced adverse hypersensitivity reactions. Among them, 50 cases (80.7%) were categorized into CARs. Other symptoms included dizziness (n=10), hypotension (n=6), vomiting (n=6), dyspnea (n=4), chest pain (n=3), headache (n=2), perspiration (n=2), rhinorrhea (n=1), nasal congestion (n=1), cough (n=1), palpitation (n=1), anxiety (n=1), chill (n=1), and nausea (n=1). Severe adverse reactions such as dizziness, severe generalized urticaria, hypotension, and facial edema occurred in 16 cases, which accounted for 25.8% of all 62 cases of adverse reactions.

General characteristics of CARs

CARs occurred in 24 men and 26 women, wth an age range from 18 to 81 and the 50's showed highest incidence, making the average age 51.5 (Table 1). On past medical history, a total of 17 cases of CAR combined with malignant neoplasm: colon cancer (n=6), stomach cancer (n=3), kidney cancer (n=3) and other cancer. Five allergic history including atopic dermatitis (n=2), food allergy (n=1), drug allergy (n=1) and chronic urticaria (n=1) was accompanied by CARs. Three of CAR patients had past previous history of contrast adverse reaction. Other than that, hypertension (n=13), diabetes mellitus (n=6), kidney disease (n=5), tuberculosis (n=3), liver cirrhosis (n=3), hepatitis (n=2) combined with CARs, and asthma

Table 1. Age distribution of CARs to nonionic CM

Age (yr)	Cutaneous adverse reactions by sex		Overall rage (No)
	Male (No)	Female (No)	
10~19	0	1	1
20~29	1	3	4
30~39	4	1	5
40~49	2	6	8
50~59	7	10	17
60~69	4	4	8
70~79	5	1	6
>80	1	0	1
Total	24	26	50

CARs: cutaneous adverse reactions, CM: contrast media, No: number.

Table 2. Past medical history of the 50 patients with CARs to nonionic monomer CM

Past medical history	Number
Malignant neoplasm	17
Hypertension	13
Diabetus Mellitus	6
Allergic history	5
Atopic dermatitis	2
Food reaction	1
Drug reaction	1
Chronic urticaria	1
Renal disease	5
Past adverse reactions to CM	3
Tuberculosis	3
Hepatitis	2
Asthma	0

CARs: cutaneous adverse reactions, CM: contrast media.

Table 3. Immediate and delayed CARs to nonionic monomer CM

Immedeate	No (%)	Delayed	No (%)
Urticaria	39 (78)	Maculopapular rash	4 (8)
Angioedema	5 (10)		
Erythema	1 (2)		
Pruritus without rash	1 (2)		
Total	46 (92)		4 (8)

CARs: cutaneous adverse reactions, CM: contrast media, No: number.

was not included in those cases (Table 2).

CARs and clinical manifestation

Forty-six cases (92%) of CAR were immediate hypersensitivity reactions including 39 cases (78%) of urticaria, 5 cases (10%) of angioedema, 1 case (2%) of erythema, 1 case (2%) of pruritus without rash. Delayed type hypersensitivity accounted for 4 cases (8%), presenting maculopapular rash (Table 3).

Treatment and progress

Seven cases were resolved spontaneously, and some were resolved after oxygen infusion (n=1), hydration (n=10), oxygen and hydration (n=1), Pheniramine injection (n=16), oral antihistamine (n=2), Pheniramine and dexamethasone or dexamethasone alone (n=23), combining epinephrine (n=2).

DISCUSSION

In the past, we had frequent adverse reactions and poor radiographic imaging due to using hyperosmolar ionic CM. However, the adverse reaction decreased following the introduction of low osmolar CM, which was achieved by converting tri-iodinated benzoic acid into a nonionic molecule by replacing the carboxylic acid radical with an amide in the 1970s[11].

Skin eruption was known as the most common adverse reaction of nonionic CM. In studies of Mortelé et al.[7], among 545 hypersensitivity cases, 286 were urticaria, 131 were pruritus, 114 were rash, 7 were associated with severe responses. Therefore a total of 538 CARs (98.7% of all hypersensitivity reactions) were reported, which was higher than the result of current study (80.7%; 50 out of 62 cases).

There was no gender difference for CARs in this study, which was similar to the Wendt-Nordahl et al.[12] result where they investigated CARs after using nonionic CM for intravenous urography.

Adverse hypersensitivity reactions mainly occurred in 20 to 50 year old patients, as like drug hypersensitivity reactions for they have vigorous immune function. In our study, incidence of CARs was higher for 20 to 50 year old patients than for other age groups ($p<0.05$).

Delayed-type hypersensitivity reactions have been reported ranging from 0.52% to 9%[13-15], because it is difficult to correlate the relationship between the symptoms and usage of CM after a certain amount of time has passed. More than 50% of the delayed type hypersensitivity reaction includes maculopapular rash, but because some include lethal responses such as Stevens-Johnson syndrome and toxic epidermal necrolysis, careful attention of the delayed type reaction is necessary after the use of CM even if there is no immediate hypersensitivity reaction. This study included 4 cases of maculopapular rash out of 47,338 cases which did not show immediate symptoms, therefore the patient may not have recognized it as a hypersensitivity reaction caused by CM, and because the mild symptoms resolved spontaneously it may have been missed from the record.

The pathogenesis of hypersensitivity caused by CM is known to be related to drug reactions or non-immunologic mechanisms. Immediate type was proved to be related to histamines from mast cells by Laroche et al.[16], and that IgE related responses may explain the pathogenesis of contrast hypersensitivity[17,18]. The delayed type is clinically similar to the T-cell mediated drug eruption, and by looking at lymphocytic infiltrations after the biopsy of skin lesions, skin reaction tests and patch tests, the relationship between the reaction and T-cell is now recognized[19-21]. Still, the exact pathogenesis of hypersensitivity caused by CM is not known, and therefore further study is needed to prove it.

There is a report that shows the hypersensitivity caused by CM can be reduced by using corticosteroid prior to the use of CM by Lasser et al.[22] and Greenberger et al.[23]. On the other hand, Wolf et al.[24] suggested that the use of corticosteroid to reduce the rate of hypersensitivity caused by CM is not yet proven. However, when the patient has prior history of systemic hypersensitivity to CM and when it is not in a very urgent state, using the steroid before CM infusion may help in reducing the hypersensitivity of CM, provided the patient is not in a contraindication state of using the steroid[25-27].

In Conclusion, Based on 50 cases of CARs to nonionic CM from August 2005 to November 2009, we have come to the following conclusion: there was no difference between the sexes. The incidence of CARs was higher among people in their 20's to 50's than for other ages, because their immune system function is more active than at other ages, and among them the 50's showed highest incidence of hypersensitivity. Three among 50 people

who showed CAR had previous adverse reaction to contrast material. CARs included 39 cases of urticaria (78%), 5 cases of angioedema (10%), 4 cases of maculopapular rash (8%), 1 case of erythema (2%), 1 case of pruritus (2%). A total of 46 cases (92%) showed immediate type reaction, while 4 cases (8%) showed delayed type reactions, presenting as maculopapular rash. Because the study is retrograded in finding CARs among all hypersensitivity reactions due to nonionic CM, and because the result was reported via patients themselves and medical team in CT room, some patients such as those who had mild symptoms may have been excluded from the study. Therefore, in order to measure and analyze CAR due to CM more accurately, an anterograde study at a large scale is mandatory.

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