Adverse reactions to iodinated contrast media: prevalence, risk factors and outcome – the results of a 3-year period

Panitan Pradubpongsa,[1] Naruemon Dhana,[2] Kowit Jongjarearnprasert,[2] Sureerat Janpanich[3] and Torpong Thongngarm[4]

Summary

Background: **Iodinated contrast media (CM) are commonly used. Hypersensitivity reactions to CM occasionally result in morbidity. Risk factors and the role of premedication remain to be investigated.**

Objective: **We sought to explore the prevalence, risk factors and outcome of CM reactions.**

Methods: The retrospective case-control study was conducted between 2008 and 2010. In total, 55,286 subjects who were exposed to iodinated CM were enrolled to determine the prevalence of CM reactions. The case-control statistical method was applied to determine the risk factors of CM reactions. 579 subjects who had CM reactions were categorised in the case group and 1,175 of the 55,286 subjects who had tolerated CM exposure were randomised for the control group.

Results: **The overall prevalence of CM reactions was 1.05%. In a multivariate analysis, the history of previous CM reactions, female gender and the history of seafood allergy were significant risk factors for CM reactions. The significant risk factors for the first episode of CM reactions were female gender, the history of seafood allergy and asthma. We found sixteen serious reactions in the immediate reaction group: ten fully recovered after hospitalisation, five fully recovered after out-patient treatment and one died after the administration of CM via an intra-arterial route during coronary angiogram. The most significant risk factor associated with serious reactions was asthma, whereas comorbid cardiovascular disease, male gender, history of seafood allergy and history of previous CM reactions were significant risk factors for mild reactions.**

Conclusions: **The prevalence of CM adverse reactions was as low as 1.05%. Risk factors consist of a history of previous CM reactions, female gender and seafood allergy. Nevertheless, serious immediate reactions could occur particularly in patients with asthma.** ***(Asian Pac J Allergy Immunol 2013;31:299-306)***

Key words: *adverse reaction, iodinated contrast media, prevalence, risk factor, seafood allergy*

Introduction

Iodinated contrast media (CM) are administered more than 75 million times per year to perform the diagnosis and treatment of several diseases.[1] Hypersensitivity reactions to CM may present immediately as anaphylaxis, which potentially results in fatality. Delayed reactions occur, such as maculopapular exanthema with or without serious reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms).

There are four classes of iodinated CM available including ionic monomers, ionic dimers, non-ionic monomers and non-ionic dimers. Since ionic iodinated CMs are associated with a higher risk of adverse reaction, non-ionic iodinated CMs have been recommended by The American College of Radiology for patients who are at increased risk of adverse reactions. Other risk factors that have been reported are female gender, asthma, β-blocker drugs use, comorbid cardiovascular diseases,[2] and elderly

From 1. Division of Allergy and Clinical Immunology, Department of Medicine, Phramongkutklao Hospital, Bangkok, Thailand
2. Department of Pharmacy, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
3. Nursing Division of Radiology, Department of Nursing, Siriraj Hospital, Mahidol University, Bangkok, Thailand
4. Division of Allergy and Clinical Immunology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
Corresponding author: Torpong Thongngarm
E-mail: torpong.tho@mahidol.ac.th
Submitted date: 6/9/2012
Accepted date: 7/12/2012

age.[3] Seafood allergy remains to be a concern in general practice as a risk factor for CM reactions. No premedication regimen has consistently been shown to decrease severe adverse events. Therefore, identifying patients who are at increased risk is of clinical significance. The present study was conducted to analyse risk factors, as well as to demonstrate prevalence and clinical outcome of CM reactions.

Methods

Patient selection and study design

This retrospective case-control study was approved by the Institutional Review Board (IRB), allowing access to the medical records of all patients exposed to iodinated CM in Siriraj Hospital, the biggest tertiary hospital in Thailand, from January 1, 2008 – December 31, 2010. CM administrations were performed by doctors (radiologists and residents) and monitored by doctors, nurses or radiology technologists who had received training in CM administration techniques. If a CM reaction occurred, the physician was notified to attend the patient immediately. Finally, the physician was required to complete a CM incident data form. Several CMs used in Siriraj Hospital include ionic CMs (high osmolarity) and non-ionic CMs (iso or low osmolarity).

All incident data forms were reviewed and details including gender, age, information concerning CM usage (indication for CM, type of CM, timing of CM administration/reaction /reaction resolved, premedication used, characteristics of CM reactions), and subsequent patient management were obtained. Using the hospital database, the patient medical records generated on the day of the CM reaction were reviewed for any potential risks of CM reaction and any adverse sequelae.

CM reactions have been classified into 1) toxic, 2) unrelated and 3) hypersensitivity reactions according to Brockow et al.[4] The hypersensitivity reaction is defined as an immediate reaction (onset within 1 hour after CM administration) and non-immediate or delayed reaction (onset beyond 1 hour after CM administration). Immediate hypersensitivity reactions were classified by the magnitude of severity into 4 grades[5] including grade I: generalised cutaneous and/or mucocutaneous symptoms, grade II: mild systemic reactions, grade III: life threatening systemic reactions, and grade IV: cardiac and/or respiratory arrest. Non-immediate or delayed hypersensitivity reactions were graded as mild when no treatment was required, moderate when the patient responded readily to appropriate treatment without hospitalisation and severe when the reaction was life-threatening and required hospitalisation.[4,6]

Table 1. Prevalence of contrast media adverse reactions (N= 55,286)

Characteristic	Number	(%)
Contrast media adverse reaction		
Total CM adverse reaction	579	(1.05)
Repeated reactions	67	(0.12)
Breakthrough reactions*	62	(0.11)
Serious reactions	16	(0.03)
Fatal reaction	1	(0.002)
Type of CM adverse reaction		
Immediate reactions	561	(1.01)
- Grade I	365	(0.66)
- Grade II	180	(0.33)
- Grade III	14	(0.02)
- Grade IV	2	(0.004)
Non-immediate/Delayed reactions	18	(0.03)
- Mild	5	(0.009)
- Moderate	13	(0.02)
- Severe	0	(0)

* Repeated CM reactions occurred despite premedication

Statistical methods

In the first part of the study, 55,286 subjects who were exposed to iodinated CM were enrolled to determine the prevalence of CM adverse reactions. In the second part of the study, the case-control statistical method was applied to determine the risk factors of adverse reaction to CM. All of the 579 subjects who had CM reactions were categorised in the case group. A cohort of 1,175 out of the 55,286 subjects who had no CM reaction was randomised for the control group by using the simple random sampling technique. We used SPSS version 15.0 as a statistical analysis tool. The demographic data and baseline variables were presented using descriptive statistics. The risk factors of CM reaction were analysed by using Chi-square test or Fisher's exact test for categorical variables and using independent T-test or Mann-Whitney U test for continuous variables. Finally, Multiple Logistic Regression was employed for multivariate analysis.

Table 2. Co-morbid diseases of CM reactors (N= 579)

Co-morbid diseases	Number	(%)
Non allergic co-morbid diseases		
Cancer	319	(55.1)
Cardiovascular diseases	160	(27.6)
Diabetes mellitus	77	(13.3)
Chronic kidney diseases	8	(1.4)
Seizure	6	(1.0)
Psychiatric diseases	4	(0.7)
Myasthenia gravis	3	(0.5)
Allergic co-morbid diseases		
Drug allergy	76	(13.1)
Seafood allergy	41	(7.1)
Allergic rhinitis	16	(2.8)
Asthma	12	(2.1)
Chronic urticaria	5	(0.9)

Results

CM was administered 55,286 times during a 3-year period for patient diagnosis and treatment, of which 579 administrations were reported to result in CM adverse reactions. The overall prevalence was 1.05% (95% CI 0.96-1.14), of which 555 reactions (95.9%) and 24 reactions (4.1%) occurred in adult and paediatric (aged <18) patients, respectively. Individuals with reactions were aged from 4-90 years old (mean 51.5±16.5). The female to male ratio was 1.4:1. Of the 579 CM adverse reactions, 569 (98.3%) and 10 (1.7%) followed administration via intravenous and intra-arterial routes, respectively. Low osmolarity CM (non-ionic iodinated monomer), high osmolarity CM (ionic iodinated monomer and dimer), and iso-osmolarity CM (non-ionic iodinated dimer) were the culprit CMs in 567 (97.9%), 8 (1.4%), and 4 (0.7%) cases, respectively. Among the 67 patients who had repeated reactions, 24 did not receive the premedication, but none developed a serious reaction (Table 1). Among the patients who had CM reactions, 75.8% (439/579) had at least one comorbid disease, either a non-allergic or allergic comorbid disease, as shown in Table 2. Clinical manifestations of CM adverse reactions are summarised in Table 3. Skin involvement was the most frequent manifestation found in 75% of immediate reactions and 100% of non-immediate reactions. Besides cutaneous reactions, the 561 immediate CM reactors exhibited gastrointestinal reaction (16.7%), respiratory reaction (10.7%), cardiovascular reaction (5.7%) and neurological reaction (4.8%). The 18 non-immediate CM reactors had only two organs involved, including skin (pruritus/erythema: 55.6%; maculopapular exanthems: 33.3%; angioedema: 11.1%; and flushing: 5.6%) and the respiratory system (chest tightness/ dyspnoea: 5.6%.)

Table 3. Clinical manifestations of CM immediate reactions (N=561)

Characteristic of reaction	Number	(%)
Skin reactions		
Pruritus/urticaria and erythema	416	(74.2)
Angioedema	27	(4.8)
Pruritus/numbness without rash	12	(2.1)
Maculopapular exanthems	1	(0.2)
Flushing	5	(0.9)
Gastrointestinal reactions		
Nausea/vomiting	92	(16.4)
Hematemesis	1	(0.2)
Abdominal bloating	1	(0.2)
Respiratory reactions		
Chest tightness/dyspnoea	38	(6.8)
Brochospasm/hypoxemia	22	(3.9)
Nasal congestion/sneezing	14	(2.5)
Injected conjunctiva	3	(0.5)
Laryngeal oedema	1	(0.2)
Ear tenderness	1	(0.2)
Cardiovascular reactions		
Hypotension	15	(2.7)
Tachycardia	13	(2.3)
Hypertension	11	(2.0)
Bradycardia	2	(0.4)
ECG: ventricular tachycardia	1	(0.2)
ECG: PVC, inverted T wave	1	(0.2)
Cardiac arrest	1	(0.2)
Neurological reactions		
Rigor or chill/fever	19	(3.4)
Dizziness/headache/fainting	5	(0.9)
Syncope	3	(0.5)
Convulsion	2	(0.4)
Stupor	1	(0.2)

There were differences between patients with CM reactions (N=579) and patients who tolerated CM (N=1,175) in terms of gender, history of

Table 4a. Risk factors of contrast media adverse reactions

Risk factors*	Control		CM reactor		1st episode of reaction		CM reactor vs. Control	1st episode vs. Control
	N=1,175 (%)		N=579 (%)		N=512 (%)		OR (95%CI) *p* value	OR (95%CI) *p* value
History of previous reaction	9	(0.8)	67	(11.6)	-	-	15.9 (7.8-32.3) ***p* <0.001**	-
Female gender	549	(46.7)	340	(58.7)	303	(59.2)	1.6 (1.3-2.0) ***p* <0.001**	1.6 (1.3-2.0) ***p* <0.001**
History of seafood allergy	21	(1.8)	41	(7.1)	30	(5.9)	3 (1.7-5.4) ***p* <0.001**	3.1 (1.7-5.5) ***p* <0.001**
Chronic urticaria	1	(0.1)	5	(0.9)	5	(1.0)	7.4 (0.8-66.0) *P* =0.075	7.3 (0.8-65.8) *p* =0.076
Asthma	10	(0.9)	12	(2.1)	12	(2.3)	2 (0.8-5.1) *P* =0.126	2.5 (1.02-6.0) ***p* =0.044**
History of drug allergy	104	(8.9)	76	(13.1)	65	(12.7)	1.4 (1.0-1.9) *P* =0.08	1.4 (0.9-1.9) *p*=0.078

* Adjusted for age

Table 4b. Risk factors of contrast media reactions according to severity of reactions

Risk factors*	Control		Mild reactor		Serious reactor		Mild vs. Control	Serious vs. Control	Serious vs. Mild
	N=1,175 (%)		N=563 (%)		N=16 (%)		OR (95%CI) *p* value#	OR (95%CI) *p* value#	OR (95%CI) *p* value#
Asthma	10	(0.9%)	10	(1.8%)	2	(12.5%)	1.9 (0.7-4.9), *p* =0.21	14.3 (2.5-80.1), ***p* =0.003**	8.4 (1.6-45.3), ***p* =0.013**
Cardiovascular disease	453	(38.6%)	152	(27.0%)	8	(50.0%)	0.6 (0.5-0.8), ***p* <0.001**	1.8 (0.6-5.2), *p* =0.312	2.6 (0.9-7.9), *p* =0.087
Male gender	626	(53.3%)	229	(40.7%)	10	(62.5%)	0.6 (0.5-0.7), ***p* <0.001**	1.4 (0.5-3.9), *p* =0.52	2.4 (0.9-6.9), *p* =0.098
History of seafood allergy	21	(1.8%)	40	(7.1%)	1	(6.3%)	3.1 (1.8-5.6), ***p* <0.001**	1.8 (0.2-19.7), *p* =0.62	0.8 (0.1-7.4), *p* =0.85
Chronic urticaria	1	(0.1%)	5	(0.9%)	0	N/A	10 (1.04-87.5), ***p* =0.046**	N/A	N/A
History of previous reaction	9	(0.8%)	67	(11.9%)	0	N/A	16.6 (8.1-34), ***p* <0.001**	N/A	N/A

N/A = not applicable
* Adjusted for age

Statistical significant only when *p*-value ≤ 0.017 (Adjusted *p*-value with Bonferroni method: 0.05/3 = 0.017)

previous CM reaction and comorbid allergic diseases such as seafood allergy, chronic urticaria, asthma and drug allergy. In a multivariate analysis, as shown in Table 4a, a history of previous CM reaction, female gender and a history of seafood allergy were significant risk factors associated with CM reactions. Female gender, history of seafood allergy and asthma were significantly associated with the first episode of CM reactions. Subgroup analysis revealed that only the history of seafood allergy was a significant risk factor of repeated reactions (N =67) compared to patients who developed a CM reaction in the first episode of exposure (N =512) with an OR of 3.2 (1.5-6.6), *p* =0.004. In a multivariate analysis, as shown in Table 4b, the most significant risk factor associated with serious CM reactions was asthma, when compared to mild reactions (*p* =0.013) and controls (*p* =0.003). Comorbid cardiovascular disease, male gender, history of seafood allergy and a history of

Table 5. Medications used for the treatment of CM adverse reactions (N=579)

Medications	Number	of patients (%)
H_1-antihistamine	312	(53.9)
Systemic corticosteroid	213	(36.8)
Intravenous fluid	22	(3.8)
Oxygen therapy	16	(2.8)
Inhaled short acting β_2-agonist	11	(1.9)
H_2-antihistamine	11	(1.9)
Epinephrine	10	(1.7)
Dopamine	1	(0.2)
Atropine	1	(0.2)
Furosemide	1	(0.2)
Antiepileptic drug	1	(0.2)

previous reaction were significantly associated with mild CM reactions.

Regarding the management of CM adverse reactions, 331 patients (57.1%) were treated as outpatients, 7 patients (1.2%) were hospitalised and one patient (0.2%) died. No medication was given in 240 (41.5%) patients. Medications used for the treatment of CM reactions are summarised in Table 5.

The various CM reactions were classified as serious reactions if they were grade III or grade IV immediate reactions or severe non-immediate reactions. We found 16 serious reactions in the immediate reaction group. The details of serious CM adverse reactions of each patient were presented according to clinical symptoms and signs, the onset of the reaction, treatment options and outcome, as shown in Table 6. Seven of sixteen serious reactions were considered to have received inappropriately or potentially harmful management: 4 (patients 2, 5, 7 and 14) received delayed epinephrine injections 10-25 minutes following the onset of the anaphylactic reaction; 2 (patients 10 and 12) did not receive epinephrine, even though anaphylactic reactions were suspected; and 2 (patients 9 and 14) received an improper route of epinephrine administration instead of the intramuscular route. A total of 62 patients developed breakthrough reactions. One of them had a serious reaction within 3 minutes of the administration of a non-ionic iodinated monomer CM via intravenous route. Fortunately, this patient fully recovered after proper treatment and hospitalisation (Patient 2, Table 6). In summary, of the patients who suffered from serious reactions, 10 of 16 fully recovered after hospitalisation, 5 of 16 fully recovered after out-patient treatment and one died after the administration of a non-ionic iodinated monomer via intra-arterial route during coronary angiogram (Patient 11, Table 6).

Discussion

Our study shows that the overall prevalence of CM adverse reaction was 1.05%. The prevalence of repeated reactions, breakthrough reactions, serious reactions, and fatal reactions were 0.12%, 0.11%, 0.03%, and 0.002%, respectively. Most CM adverse reactions were non-serious immediate reactions, which were significantly associated with a history of previous CM reaction, female gender, and a history of seafood allergy. The first episode of CM reaction was associated with female gender, a history of seafood allergy and asthma. However, only a history of seafood allergy was significantly linked to repeated CM reactions, compared to the first episode of reaction.

The overall prevalence of mild immediate CM reactions has been reported as 3.8% to 12.7% in patients using ionic iodinated CM and 0.7% to 3.1% for non-ionic iodinated CM,[7-9] whereas severe immediate reactions have been reported in 0.1% to 0.4% and 0.02% to 0.04% of patients for ionic iodinated CM and non-ionic iodinated CM, respectively.[7-10] The frequency of non-immediate CM reactions ranges from 0.5% to 23%,[11] which were mild and self-limited.[2] Unlike immediate CM reactions, there appears to be a higher incidence of non-immediate CM reactions associated with non-ionic iodinated dimer CM, but not with other types of CM[12]. Our prevalence rates of immediate reaction (1.01%) and severe immediate reaction grade III and grade IV (0.03%) are comparable with previous reports, whereas the frequency of non-immediate reaction in our study was only 0.03%. This is probably due to the difficulty in verifying whether symptoms that occurred days after CM exposure were, in fact, caused by the CM, and the variations in the clinical manifestations in non-immediate reactions.[13]

The main risk factor for both immediate and non-immediate hypersensitivity reaction is a history of previous CM reaction, which poses a 21% to 60% risk of a repeated reaction.[4,11,14,15] Other risk factors include female gender, asthma, and ß-blocker drug use.[2] Patients with comorbid cardiovascular

Table 6. Characteristics of 16 patients with serious contrast media adverse reactions

No.	Patient Sex	Age (y)	Onset (min)	Symptoms and signs	Treatment	Outcome
1	F	86	60	Dyspnoea, peripheral cyanosis, sweating, hypoxemia	O_2 therapy and bronchodilator nebuliser	Resolved within 120 min. and discharged
2	M	28	3	Nausea, vomiting, diffuse urticaria, facial oedema, bronchospasm, seizure, hypoxemia, refractory hypotension, atrial fibrillation	Synchronized cardioversion 100J, 0.5 mg of epinephrine IM, O_2 therapy, IV fluid, bronchodilator nebuliser, H_1-antihistamine IV, systemic steroid, H_2-antihistamine IV	Resolved within 95 min. and hospitalisation
3	F	25	10	Bronchospasm, refractory hypotension	Bronchodilator nebuliser, IV fluid	Hospitalisation
4	M	37	40	Seizure	Antiepileptic drug	Hospitalisation
5	M	72	10	Nausea, vomiting, diffuse urticaria, laryngeal oedema, bronchospasm, hypoxemia, refractory hypotension	Endotracheal intubation, 0.5 mg of epinephrine IM, H_1-antihistamine IV, systemic steroid, H_2-antihistamine IV, IV fluid, bronchodilator nebuliser	Resolved within 140 min. and hospitalisation
6	F	73	5	Dyspnoea, hypoxemia, hypertension, tachycardia, crepitation both lungs	40 mg of furosemide IV	Resolved within 310 min. and hospitalisation
7	F	72	15	Diffuse urticaria, refractory hypotension	0.5 mg of epinephrine IM, H_1-antihistamine IV, systemic steroid, O_2 therapy, IV fluid NSS	Resolved within 95 min. and hospitalisation
8	M	54	10	Refractory hypotension	H_1-antihistaime IV, systemic steroid, O_2 therapy, IV fluid NSS	Hospitalisation
9	M	49	15	Nausea, vomiting, bronchospasm, hypoxemia, refractory hypotension	0.5 mg of epinephrine IV, H_1-antihistamine IV, systemic steroid, O_2 therapy, IV fluid	Resolved within 140 min. and hospitalisation
10	M	53	40	Nausea, vomiting, tachycardia, inverted T wave with PVC, hypoxemia, refractory hypotension	H_1-antihistamine IV, systemic steroid, O_2 therapy, IV fluid, dopamine IV drip	Resolved within 24h and hospitalisation
11	M	59	5	Bradycardia, ventricular tachycardia, PEA, cardiac arrest	CPR,1 mg of epinephrine IV, 1 mg of atropine IV, endotracheal intubation, defibrillation, pacemaker, IABP, H_1-antihistamine IV, systemic steroid, H_2-antihistamine IV, IV fluid	Death
12	M	53	14	Facial oedema, injected conjunctiva, bradycardia, refractory hypotension	H_1-antihistamine IV, systemic steroid, IV fluid, H_2-antihistamine oral	Resolved within 54 min. and discharged
13	F	60	5	Nausea, vomiting, bronchospasm, hypoxemia	H_1-antihistamine IV, 5 mg of dexamethasone IV, IV fluid, bronchodilator nebuliser, H_2-antihistamine oral	Resolved within 60 min. and discharged
14	F	46	11	Diffuse urticaria, refractory hypotension	0.5 mg of epinephrine SC, H_1-antihistamine IV, systemic steroid, H_2-antihistamine IV, IV fluid	Observed clinically in emergency room until stable and discharged
15	M	38	15	Facial oedema, bronchospasm, refractory hypotension	0.5 mg of epinephrine IM, H_1-antihistamine IV, systemic steroid, H_2-antihistamine IV, bronchodilator nebuliser, IV fluid	Hospitalisation
16	M	57	10	Chest tightness, hypoxemia	O_2 therapy	Observed clinically until stable and discharged

Abbreviation: PEA, Pulseless electrical activity; IABP, Intra-aortic balloon pump; CPR, Cardiopulmonary resuscitation; IM, Intramuscular; IV, Intravenous

diseases[2] and the elderly[3] were at increased risk of serious or fatal reaction. The most striking risk factor in our study was a history of seafood allergy which was significantly associated with both the first episode of reactions and repeated CM reactions. A systematic review from 7 prospective studies (75,616 CM injections) showed that allergies to shellfish were associated with the same minimal increased risk of reaction to CM injection as other forms of atopy such as asthma and other food allergies.[16] This indicates that a general atopic disposition, rather than an iodine-specific reactivity, accounts for the increased incidence of CM reactions in this sub-group. Thus, reactions to CM should not be considered to be associated with an IgE-mediated iodine allergy, and allergy to shellfish does not change the risk of CM reaction compared to other allergies.[17] Nevertheless, further studies are needed to clarify whether the history of seafood allergy in our patients is truly an allergy; some patients may require skin testing and/or food challenge.

Repeated CM reactions occasionally develop despite premedication so-called breakthrough reactions.[18-22] Sixty-two breakthrough reactions occurred (0.11%) in our study, of which one serious reaction was noted. Evidence from a systematic review suggests that 100-150 of unselected patients required an oral double dose of methylprednisolone to prevent a one potentially life threatening CM reaction.[22] There is no valid data supporting the efficacy of steroid and/or antihistamine administration in patients with a history of allergic reactions.[22] Other strategies to prevent CM hypersensitivity reactions according to the guidelines of the American College of Radiology include the use of non-ionic iodinated CM in patients who are at increased risk of reaction, such as patients with previous CM reactions, asthma, multiple true allergies or diseases that increase the risk of adverse reactions, e.g. pheochromocytoma, hyperthyroidism, thyroid cancer, renal failure.[23]

One patient with coronary artery disease in this study died during a coronary angiogram procedure that used CM via an intra-arterial route; the cause of death, due to either coronary artery disease or CM hypersensitivity, remained inconclusive. Nevertheless, previous studies have reported a significant difference between the intra-arterial and intravenous administration of CMs, with higher rates of reaction associated with an intra-arterial application.[24-26]

Taken together, the prevalence of CM reactions in our study was 1.05%. A previous history of CM reaction and female gender were the main risk factors for CM reactions, whereas asthma was shown to be a significant risk factor for serious reactions. Whether seafood allergy is a risk factor remains to be investigated. More studies are required to reduce the morbidity and mortality of such reactions.

Acknowledgements

This study was supported by the research grant from Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. The authors would like to thank Miss Pimrapat Tengtrakuljareon for statistical analysis.

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