Recommendations for the prevention of recurrence of medical accidents
Number 3

Analysis of deaths related to "Anaphylaxis caused by injections"

January 2018

Medical Accident Investigation and Support Center
Japan Medical Safety Research Organization

In publishing the recommendations for the prevention of recurrence of medical accidents (Number 3)

Fumimaro Takaku
Chair of the Board of Directors
Japan Medical Safety Research Organization

Based on the Medical Accident Investigation System enforced in October 2015 by the Medical Accident Investigation and Support Center（ISC）of the Japan Medical Safety Research Organization（Medsafe Japan）has been working with every effort to promote medical safety and to prevent recurrence of medical accidents. Along with the advancement and diversification of the current medical surroundings, medical institutions are supposed to have taken preventive measures against medical accidents, by accumulating reports of near-miss incident cases so as not to allow serious medical accidents to occur. However, serious events do occur in fact and at times resulting in death of the patient. Such cases have been reported to the ISC. I believe that the mission of the Medical Accident Investigation System is to accumulate and analyze each case and to provide information for preventing the recurrence of serious events.

Two years have passed since the enforcement of the Medical Accident Investigation System, and we, ISC, have published the third report of recommendations by the Expert Analysis Subcommittee to prevent recurrence of medical accidents. The total number of “In-Hospital Investigations” was 476 cases that were completed and reported to the ISC in the two years from the start of the system to September 2017. ISC decided to take up the deaths related to anaphylaxis caused by injections as the theme of analysis this time. The target cases were 12 that were reported in the Medical Accident Investigation System. Considering that similar deaths related to anaphylaxis caused by injections had occurred repeatedly in the past, and in view of the seriousness of being resulted in deaths, these recommendations were compiled.

ISC’s measures to prevent recurrence of accidents are the recommendations obtained from the “death” cases after analyzing 12 cases from the viewpoint of “avoiding accidents leading to death”. The government and the academic societies have released the guidelines that were examined from broad knowledge. We believe that our measures should be distinguished from those guidelines. With this in mind, we sincerely hope that the recommendations in this report will be widely utilized to avoid deaths related to anaphylaxis caused by injections in each medical institution.

Finally, we would like to express our sincere gratitude to the medical institutions and bereaved families who cooperated in providing in-hospital investigation reports and offering additional information, as well as to the experts of the analysis subcommittee who analyzed the 12 cases in detail to explore the measures for the recurrence prevention for their understanding and cooperation.

Recommendations for the prevention of recurrence of medical accidents (Number 3)

Analysis of deaths related to "Anaphylaxis caused by injections"

[Understanding of anaphylaxis]

Recommendation 1

It should be recognized that anaphylaxis can occur with any injected drug and that it may develop even with the injections that have been safely used multiple times previously.

[Observation at the time of the injection]

Recommendation 2

When a drug which has a high risk of anaphylaxis, such as contrast medium, antibiotics and muscle relaxants, is injected intravenously, careful observation is required for at least five minutes from the start of the administration.

[Recognition of symptoms and preparation of adrenaline]

Recommendation 3

Not limited to skin symptoms, if the patient's condition turns for the worse after the administration, anaphylaxis should be suspected. Then discontinue the injection immediately, not waiting for the full marks in diagnosis, and prepare adrenaline 0.3 mg (a dose for adult).

[Intramuscular injection of adrenaline]

Recommendation 4

If anaphylaxis is suspected, do not hesitate to inject the standard dose of adrenaline 0.3 mg (in case of adult) intramuscularly into the antero-lateral part of the thigh.

[Adrenaline deployment, instruction and rapid response system]

Recommendation 5

Adrenaline should be deployed in the places where the causative injections as a high risk of anaphylaxis are used. The instruction and communication system should be established so that the intramuscular injection can be performed without delay.

[Understanding and sharing of allergy information]

Recommendation 6

Grasping information on the allergy to drug, it should be endeavored to construct and operate the system in which the information can be shared among multiple professions.

January 2018

Expert Analysis Subcommittee for Anaphylaxis

Committee for Prevention of Recurrence, Medical Accident Investigation and Support Center

Japan Medical Safety Research Organization

Table of Contents

[Glossary]

Anaphylaxis	It is the hypersensitivity reaction where allergic symptoms occur systemically in multiple organs due to the invasion of allergens and can possibly threaten life.
Anaphylactic shock	It refers to cases where anaphylaxis is accompanied by decrease in blood pressure or disturbance of consciousness.

1. Introduction

1) Anaphylaxis

Anaphylaxis is a hypersensitivity reaction where allergic symptoms are caused systemically in multiple organs due to the invasion of allergens and can possibly threaten life, and anaphylactic shock is defined as cases where anaphylaxis is associated with decrease in blood pressure or disturbance of consciousness.[1,2] The etymological derivation of the term anaphylaxis is based on the fact that the body's defense system [phylaxis] contrarily [ana-] threatens life, and it has been known for a long time that it occurs from bee venom and food in the setting of a hypersensitive constitutional predisposition. In the past, there were no unified diagnostic criteria for anaphylaxis, but from about 2010, diagnostic criteria were developed throughout the world, and it was proposed to make a clinical diagnosis based on the course of onset and the symptoms regardless of IgE involvement. When a fatal accident of anaphylaxis caused by food occurred in Chofu-shi, Tokyo in 2012, there were no guidelines for anaphylaxis in Japan. However, a special committee for measures against anaphylaxis was launched by the Japanese Society of Allergology in 2013, and guidelines for anaphylaxis tailored to the actual conditions in Japan were developed in 2014. In the guidelines, the same diagnostic criteria as in other countries were adopted[2] (see Recommendation 1).

Recent demographic statistics show that the number of deaths due to anaphylactic shock is 50 to less than 80 per year, and the most common cause is medicines, accounting for about 20 to 40 people (Table 1).[2] The process from anaphylaxis developed after the administration of causative drugs to shock and further death involves various factors, such as the location of onset, administration route of the causative drugs, speed of the symptom progress, diagnosis by healthcare professionals and the details of the treatment. In particular, the speed of symptom progress is remarkable; in a case study of a death caused by anaphylaxis in the United Kingdom, the median time to cardiac arrest or respiratory arrest was reported as 5 minutes for drugs, 15 minutes for bee venom and 30 minutes for food.[3]

This time, the Medical Accident Investigation and Support Center (hereinafter referred to as ISC) examined the cases of deaths related to anaphylaxis caused by injections as reported to the ISC based on the Medical Accident Investigation System. After gathering additional information, such as on clinical course, we compiled measures as six recommendations.

The first line drug for treatment of anaphylaxis is the intramuscular injection of adrenaline. It is necessary to realize that antihistamines and corticosteroids are merely second line drugs and that there is no evidence that their administration contributes to the saving of lives.

We sincerely hope that the six recommendations described in this booklet will be useful in decreasing the number of deaths related to anaphylaxis caused by injections and the practice of a prompt response to anaphylaxis in the healthcare settings.

Table 1 Number of deaths due to anaphylactic shock (Numbers indicate the number of patients.)

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
Overall total	66	48	51	51	71	55	77	52	55	69	595
Medicines	29	19	26	21	32	22	37	25	23	29	263
Bee sting	19	15	13	20	16	22	24	14	23	19	185
Food	5	4	4	4	5	2	2	0	0	2	28
Serum	1	0	1	0	0	0	1	1	1	0	5
Details unknown	12	10	7	6	18	9	13	12	8	19	114

Tabulated from the dynamic of population statistics "By number of deaths, gender and cause of death (basic classification of death)". Ministry of Health, Labour and Welfare

Source: Japanese Society of Allergology Anaphylaxis Measures Special Committee/Anaphylaxis Guidelines, P3, 2014.
(Reprinted with permission, partially modified)

2) The background and significance of the establishment of the Expert Analysis Subcommittee

As for medical safety information regarding anaphylaxis, "Administration of drugs known of allergy history" from the Japan Council for Quality Health Care in May 2009, and case studies (examples) "Prevention of drug-induced anaphylaxis onset and early response" from the Japan Medical Safety Research Organization in December 2012 were issued. In addition, anaphylaxis guidelines were published by the Japanese Society of Allergology in 2014, and the first line drug for the treatment of anaphylaxis was defined as an intramuscular injection of adrenaline. However, it is said that even in severe cases many patients have still been treated only with antihistamine or corticosteriods. [4]

In the in-hospital investigation reports submitted/presented to the ISC multiple cases of deaths related to anaphylaxis have been reported. Deaths related to anaphylaxis occur at a certain frequency and are difficult to anticipate. Concerning the response to the onset of anaphylaxis, the Expert Analysis Subcommittee was established because we believed the significance of disseminating measures to prevent recurrences leading to death. The Expert Analysis Subcommittee verified and analyzed the cases of death reported to the ISC and compiled recommendations from the viewpoint of how to avoid situations leading to death.

3) About the related medical accident reports

[The Project to Collect Medical Near-miss/Adverse Event Information, Japan Council for Quality Health Care]

(http://www.med-safe.jp/mpsearch/SearchReport.action Browsed date: December 26, 2017)

We found that 23 cases of death related to anaphylaxis had been reported as a result of searching the cases reported after January 1, 2010, using "anaphylaxis", "drug product", "drug", "medicine" and "death" as keywords.

[Model Project for Survey and Analysis of Deaths Associated with Clinical Practice, Japan Medical Safety Research Organization] (from September 2005 to the closing of the project in 2015)

Three out of 224 cases (1.3%) announced during the decade from 2005 to 2015 were reported as deaths related to anaphylaxis.

2. Methods of analysis

1) Extraction of target cases

Of the 476 cases in the in-hospital investigation reports during two years from October 1, 2015 to September 30, 2017, the cases where the relevant medical institutions determined (regarded) the cause of death as anaphylaxis were 13 cases.

As the subjects of an analysis, the Expert Analysis Subcommittee selected a total of 12 cases. Regarding the cause of death, some of them were confirmed as anaphylaxis from the autopsy results, or presumed to be anaphylaxis from the clinical course and autopsy results, and in the other cases anaphylaxis was deemed undeniable.

All of the target cases were attributed to injection.

2) Collecting and sorting of information from target cases

Based on the information described in the in-hospital investigation report submitted to the ISC, the cases were analyzed in the Expert Analysis Subcommittee. With regard to the parts that require confirmation, additional information was collected with cooperation of the reporting facilities as far as possible. They were arranged according to the investigation items checklist (see 7. "Materials").

3) Meetings of the Expert Analysis Subcommittee

○ First meeting May 17, 2017
○ Second meeting July 24, 2017
○ Third meeting October 30, 2017

• In addition, opinions were exchanged through electronic media and other means.

An overview of the recommendations, the core points extracted from "Analysis of deaths related to anaphylaxis caused by injections", is carried in the following website. Please make a good use of it as training materials in each medical institution.

URL https://www.medsafe.or.jp/uploads/uploads/files/teigen-03siryou.pdf

You can download from the website.

3. Overview of target cases

The case overview was prepared by the Expert Analysis Subcommittee based on the in-hospital investigation reports and additional information. Regarding the notation of drug names, the product names（brand names）were described, and the registered trademark signs were omitted.

Case 1

- A male in his 70s who was receiving chemotherapy for lung cancer. Anaphylaxis occurred in the contrast-enhanced CT examination room. Ai absent, autopsy present.
- The causative drug was Iopamiron used as the contrast agent.
- Iopamiron had been used three times for the patient in the past, but no allergy symptoms had appeared.
- After injection of Iopamiron, redness along the blood vessel running occurred, but the redness disappeared at the time of the medical examination. In approximately 10 to 15 minutes the examination was over. The patient lost consciousness in the corridor after changing clothes. Adrenaline 1 mg was intravenously injected 16 minutes later, and emergency treatment was provided, but heart beat did not return and the patient died about one and a half hours later.

Case 2

- A male in his 50s who was receiving chemotherapy for lung cancer. A β blocker was administered orally. Anaphylaxis occurred in the contrast-enhanced CT examination room. Ai present, autopsy absent.
- The causative drug was Iopamiron used as the contrast agent.
- Iopamiron had been used two times for the patient in the past, but no allergy symptoms had appeared.
- Five minutes after injection of Iopamiron, at the same time as the CT imaging ended, snoozing, nausea/vomiting and feeling of body heat occurred. In six minutes, response to the name being called disappeared and radial artery palpation became impossible. Adrenaline 0.3 mg was intramuscularly injected in 12 minutes, but bradycardia and lowered blood pressure were observed; adrenaline 1 mg was intravenously injected in 13 minutes and emergency treatment was provided, but the patient died about four days later.

Case 3

- A female in her 50s who was suspected of having pancreatic cancer. Anaphylaxis occurred in the contrast-enhanced CT examination room. Ai present, autopsy absent.
- The causative drug was Iopamiron used as the contrast agent.
- Iopamiron had been used five times for the patient in the angiography examinations, etc. in the past, but no allergy symptoms had appeared.
- Three minutes after injection of Iopamiron, the patient complained of respiratory disturbance, feeling nausea and a feeling of itchy feet, and she lost consciousness seven minutes later. Adrenaline 1 mg was intravenously injected in 15 minutes and emergency treatment was provided, but the patient died about one and a half hours later.

Case 4

- A female in her 70s after resection of a colorectal cancer. Anaphylaxis occurred in the contrast-enhanced CT examination room. Ai present, autopsy absent.
- The causative drug was the contrast agent Omnipaque.
- Omnipaque had been used five times for the patient in the past, but no allergy symptoms had appeared.
- Five minutes after the Omnipaque injection, the examination was over and the patient complained of swaying at the same time as she stood up and lost consciousness as soon as she took a sitting position. There was flushing from the dorsum of the hands to the forearms. A corticosteroid and adrenaline 1 mg was intravenously injected in 10 minutes and emergency treatment was provided, but the patient died about two and a half hours later.

Case 5

- A female in her 80s who repeated acute cholecystitis associated with common bile duct stones/choledocholithiasis. Anaphylaxis occurred in the emergency department. Ai absent, autopsy absent.
- The causative drug was antibiotics "Bakfose" (sulbactan sodium-cefoperazone sodium).
- Cefon and Bakfose had been used for the patient in the past and allergy symptoms had appeared.
- The patient visited with the chief complaint of coughing, left chest pain with coughing, abdominal pain and fever. Five minutes after the start of drip infusion of Bakfose, rolling of eyes occurred, and gradually from rigid convulsions to clonic convulsions appeared. In 10 minutes the patient lost consciousness and blood pressure decreased, and respiratory arrest occurred in 15 minutes. Adrenaline 1 mg was intravenously injected in 25 minutes and emergency treatment was provided, but the patient died about two and a half hours later.

Case 6

- A female in her 70s with repeated cholangitis after laparoscopic cholecystectomy. Anaphylaxis occurred in the emergency department. Ai absent, autopsy present.
- The causative drug was antibiotics Wystal.
- Wystal had been used for the patient in the past and allergy symptoms had appeared.
- The patient visited with fever persisting for several days. Immediately after the start of drip infusion of Wystal, she complained of itching of the throat, hands and feet, and then lost consciousness. There were ST changes on electrocardiogram. Tracheal intubation was performed in 17 minutes, corticosteroids in 18 minutes and noradrenaline 1 mg in 20 minutes were intravenously injected; emergency treatment was provided, but the patient died about eight hours later.

Case 7

- A male in 70s after resection of lung cancer. Anaphylaxis occurred in the hospital ward. Ai absent, autopsy present.
- The causative drug was antibiotics Sulbacillin.
- Penicillin antibiotics had been used for the patient in the past and allergy symptoms had appeared.
- After the start of drip infusion of Sulbacillin for the prevention of infection, numbness of the upper extremities and dyspnea occurred, in three minutes dyspnea worsened and consciousness was lost, and there was flushing from the face to the neck. In eight minutes pulse palpation became difficult and sternal compressions were started. Adrenaline 1 mg was intravenously injected in 12 minutes, the cricothyroid ligament was dissected in 27 minutes and emergency treatment was provided, but the patient died two days later.

Case 8

- A female in her 80s who was receiving treatment for choledocholithiasis. Anaphylaxis occurred in the hospital ward. Ai present, autopsy present.
- The causative drugs were antibiotics Wystal and protease inhibitor Nafatat（nafamostat mesilate）.
- Wystal and Nafatat had been used for the patient in the past and she had experienced vomiting and loss of consciousness.
- Before ERCP（endoscopic retrograde cholangiopancreatography）, started the drip infusion of Nafatat for prevention of pancreatitis and of Wystal for prevention of infection. After 17 minutes the patient was found to have lost consciousness. Adrenaline 1 mg was intravenously injected after 29 minutes and emergency treatment was provided, but the patient died about 11 hours later.

Case 9

- A male in his 50s under appendectomy. Anaphylaxis occurred in the operating room. Ai present, autopsy present.
- The causative drug was muscle relaxant Eslax.
- The patient had taken a commercial antipyretic analgesic drug and allergy symptoms had appeared.
- Two minutes after administration of Eslax in general anesthesia, ventilation became difficult immediately after intubation. Although bronchodilator inhalation after six minutes made slight ventilation possible, decreased SpO2 and elevated ST on the electrocardiogram were observed after 10 minutes, and adrenaline 100 μg（0.1 mg）was intravenously injected 11 minutes later. Cardiac arrest occurred 13 minutes later. Adrenaline 1 mg was intravenously injected and emergency treatment was provided, but the patient died about 6 hours later.

Case 10

- A male in his 80s under resection of a malignant tumor. Anaphylaxis occurred in the operating room. Ai absent, autopsy present.
- The causative drug was muscle relaxant Eslax.
- No allergy symptoms caused by drugs had appeared in the past.
- Resistance of mask ventilation pressure appeared immediately after administration of Eslax in general anesthesia, ST elevation and severe bradycardia on ECG were observed in 2 minutes, and the skin changed to reddish black. Palpation of the brachial artery, the radial artery and the femoral artery became difficult; and sternal compressions were started. Adrenaline 1 mg was intravenously injected after 6 minutes and emergency treatment was provided, but the patient died about 13 hours later.

Case 11

- A male in his 70s who was receiving maintenance dialysis. Anaphylaxis occurred in the dialysis room. Ai absent, autopsy absent.
- The causative drug was protease inhibitor Futhan.
- Futhan's IgE-specific antibody I, II had been confirmed as negative in the past. After that, Futhan had been used four times for the patient, but no allergy symptoms had appeared.
- The patient complained of itching in the neck two minutes after the start of administration of Futhan（start of dialysis）; decreased consciousness and rolling of the eyes were observed in six minutes and bradycardia seven minutes later, therefore, antihistamine was administered eight minutes later. Adrenaline 1 mg was intravenously injected after 13 minutes, a trachea was intubated and emergency treatment was provided, but the patient died about 11 hours later.

Case 12

- A male in his 60s who was receiving treatment for decayed teeth. Anaphylaxis occurred in the dental clinic. Ai absent, autopsy present.
- Neozalocaine paste and ORA（Xylocaine）injection for dental local anesthetics could not be denied as the causative drugs.
- Neozalocaine paste and ORA injection had been used four times in the past, but no allergy symptoms had appeared.
- Neozalocaine paste ORA injection and laughter gas were used for the tooth extraction. About 15 minutes after the start of using the drugs, feeling bad was seen and consciousness disappeared immediately after gargling. Sternal compressions were started and first aid was requested. Because of cardiopulmonary arrest, adrenaline 1 mg was intravenously injected in the medical institution and emergency treatment was provided, but the patient died about 2 days later.

4. Recommendations and explanations for preventing a recurrence

[Understanding of anaphylaxis]

Recommendation 1

It should be recognized that anaphylaxis can occur with any injected drug and that it may develop even with the injections that have been safely used multiple times previously.

● Recognition of anaphylaxis

Anaphylaxis may occur with any drug, and in particular, there are many cases of onset where it was caused by contrast medium, antibiotics, or muscle relaxants. Among the 12 target cases, the used drugs were four cases of contrast medium, four cases of antibiotics（including one case of a combination with a protease inhibitor）, two cases of muscle relaxants, one case of protease inhibitors and one case of dental local anesthetics.

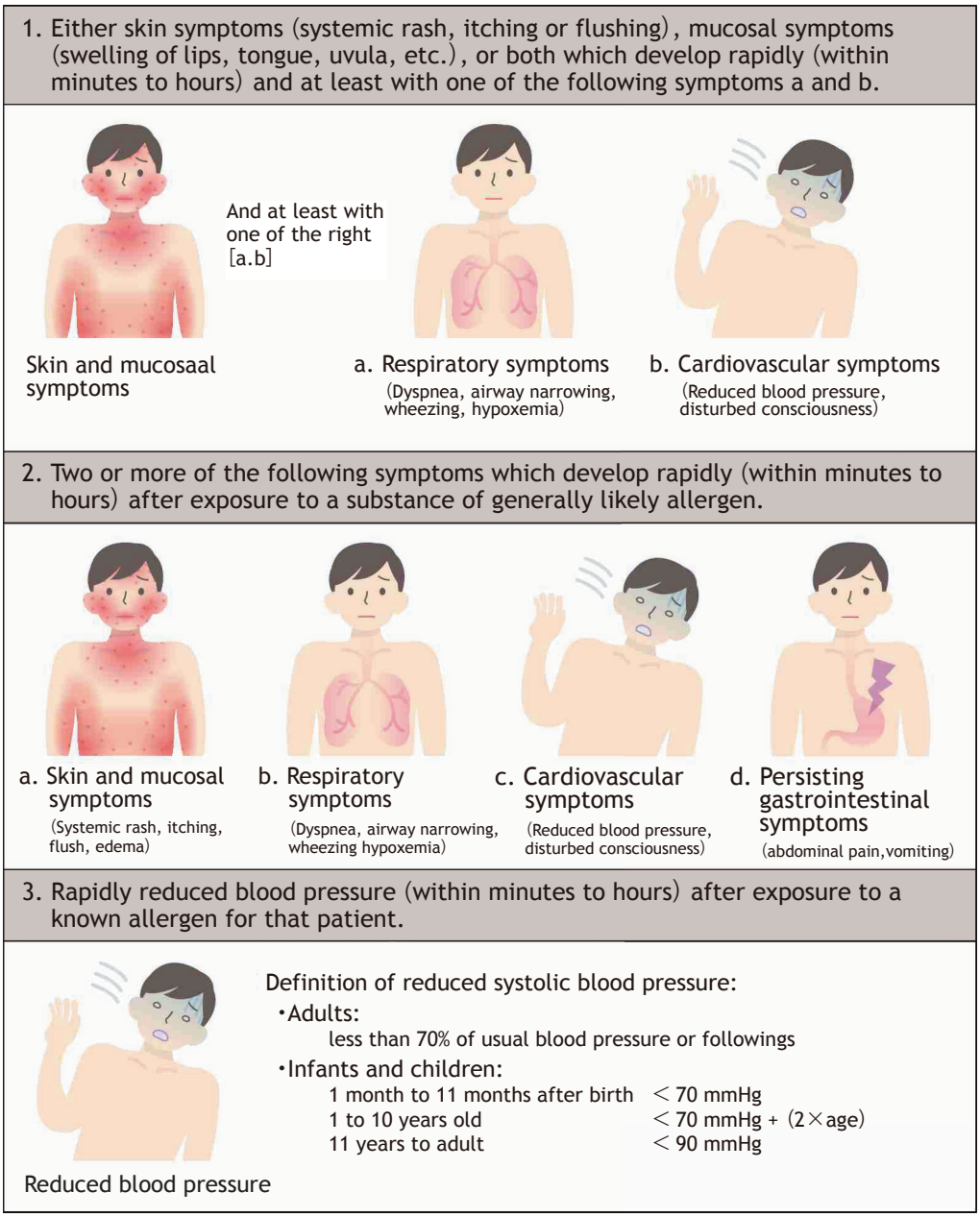
Even the drugs that were used safely multiple times in the past, caused fatal anaphylactic shock. In each of the four cases where contrast medium were used, the patient had experienced using the same contrast agent over the past two to five times for the treatment evaluation of cancer. In the case of using protease inhibitors, the IgE-specific antibody of the same drug had been confirmed negative before use and it had been used safely four times, but the fifth administration resulted in the onset of anaphylaxis.

In any case, it is difficult to predict the onset of anaphylaxis; therefore, it is important to recognize that anaphylaxis may occur even with the drugs that could be safely used multiple times in the past and whose specific antibodies were negative.

According to the diagnostic criteria in the Anaphylaxis Guidelines, if a patient's symptoms fall into one of the following three items, the patient should be diagnosed with anaphylaxis（see Fig. 1）[2]: （1）Either skin symptoms or mucosal symptoms are present, developing rapidly and accompanied by at least one of respiratory symptoms and cardiovascular symptoms; （2）following exposure to a substance that can generally become an allergen, the patient's symptoms are accompanied by two or more of rapidly developing skin/mucosal symptoms, respiratory symptoms, cardiovascular symptoms, and persisting gastrointestinal symptoms; and （3）rapidly lowered blood pressure after exposure to allergens in the patient.

In ten target cases, some sort of symptoms of anaphylaxis began to appear within five minutes after the start of administration. Especially because the time to sudden change is short once anaphylaxis caused by drugs or intravenous injections develops, it is important to always be aware of the possibility of anaphylaxis onset on the occasion of administration.

Figure 1　Clinical criteria for anaphylaxis diagnosis



Simons FE, et al. WAO Journal 2011; 4: 13-37, Simons FE. J Allergy Clin Immunol 2010:125: S161-81, Simons FE. et al. Allergy 2013; 62: 1464-500 (Cited and modified)

Source: Japanese Society of Allergology Anaphylaxis Measures Special Committee/ Anaphylaxis Guidelines, P1, 2014. (Reprinted with permission)

Figure 1 is the diagram that the Japanese Society of Allergology cited and modified as diagnostic criteria in the Anaphylaxis Guidelines from the one contained in the World Allergy Organization guidelines "Clinical Criteria for Diagnosis of Anaphylaxis." The diagnostic criteria for anaphylaxis are targeted for anaphylaxis due to various causes and are not specialized for injections. For example, since anaphylaxis with food may occur several hours after food intake, criterion is described as "rapid (within a few minutes to several hours)". However, regarding anaphylaxis caused by injections, particular attention should be paid to the fact that these symptoms often develop within five minutes (especially in such severe cases as death) as shown in the target cases in the Overview section.

[Observation at the time of the injection]

Recommendation2

When a drug which has a high risk of anaphylaxis, such as contrast medium, antibiotics, and muscle relaxants, is injected intravenously, careful observation is required for at least five minutes from the start of the administration.

● Onset and observation of anaphylaxis

The drugs used in the 12 target cases were contrast medium in four cases, antibiotics, in four cases (including one case of combination with a protease inhibitor), muscle relaxants in two cases, protease inhibitors in one case, and dental local anesthetics in one case. In ten cases, symptoms appeared during drug administration or within five minutes from the start of drug administration (see Fig. 2). They were subjective symptoms of feeling lightheaded, throat itching, numbness, nausea, feeling of dyspnea, sneezing and feeling of body heat. Furthermore, redness along the length of the blood vessels running, flushing from dorsum of both hands to the forearms and from the face to the neck, and rolling of the eyes and convulsions were observed after intravenous injection. In the cases of anesthesia, various symptoms appeared, such as rapid ventilation difficulty, skin changes to reddish black after drug administration and ST elevation on electrocardiogram. After those, the conditions resulted into irreversible within 20 minutes.

There were no cases where wheals like urticaria occurred in the target cases. Skin rash is well known as a symptom not only of anaphylaxis with drugs but also of general anaphylaxis, but anaphylaxis is not always accompanied by a skin rash. It is necessary to keep in mind that skin symptoms are not essential for the diagnosis of anaphylaxis.

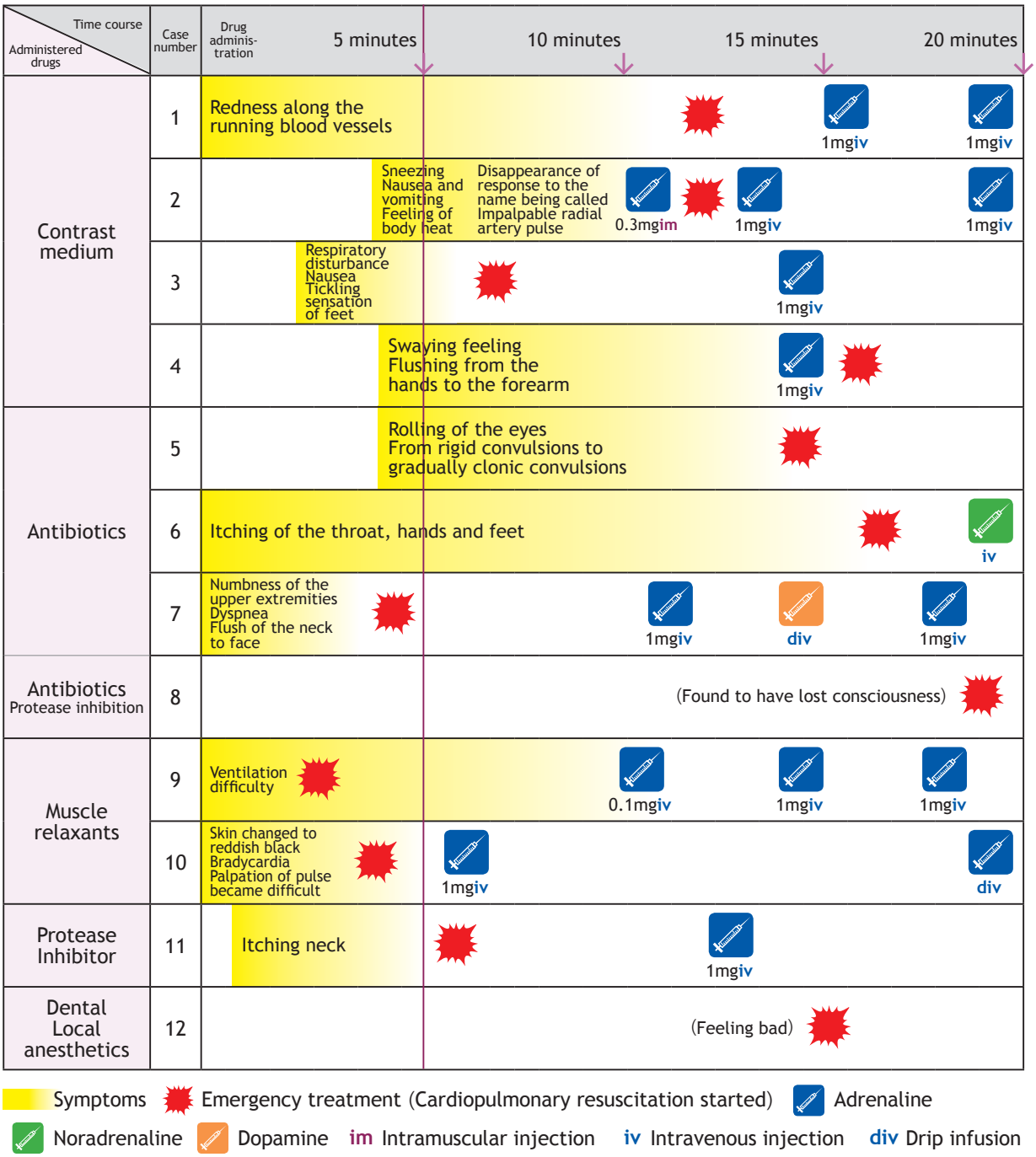
There is not a moment to lose in the treatment of anaphylaxis. If the condition of the patient changes, including but not limited to skin symptoms, within five minutes from the start of drug administration, it is necessary to suspect anaphylaxis, taking them as symptoms of anaphylaxis.

It is important to ensure observation of the patient, keeping the possibility of onset of anaphylaxis in mind from the start of drug administration. This is the result obtained from reviewing the cases of death. In reality, however, it is considered that there is also the occurrence of symptoms after five minutes. In addition, when the same antibiotics are administered for a certain period of time, especially when the administration is for the first time, it is desirable to take the system that allows observation for five minutes from the start of drug administration.

● Understanding symptoms by the participation of patients

Regarding the observation method for five minutes from the start of administration of injection, the participation of patients in accordance with the situation is also required. For the patients who can complain of symptoms, explain the possibility of the onset of anaphylaxis due to the injections and ask them to actively inform healthcare professionals when changes in mood or physical condition changes during five minutes from the start of administration of injections. To obtain patients' cooperation like this is also one way. In addition, it is desired to document the observation results after starting the administration of injections.

Figure 2　Symptoms categorized by causative drugs, appearance time and provided treatment in the target cases



Characteristics of 12 target cases

- There were 10 cases where symptoms of anaphylaxis occurred within five minutes after the start of drug administration.
- All cases resulted in an irreversible condition within 20 minutes after the start of drug administration.
- There was only one case where adrenaline 0.3 mg was intramuscularly injected as an initial response to anaphylaxis.

[Recognition of symptoms and preparation of adrenaline]

Recommendation3

Not limited to skin symptoms, if the patient's condition turns for the worse after the administration, anaphylaxis should be suspected. Then discontinue the injection immediately, not waiting for the full marks in diagnosis, and prepare adrenaline 0.3 mg (a dose for adult).

● Preparation of adrenaline intramuscular injection 0.3 mg

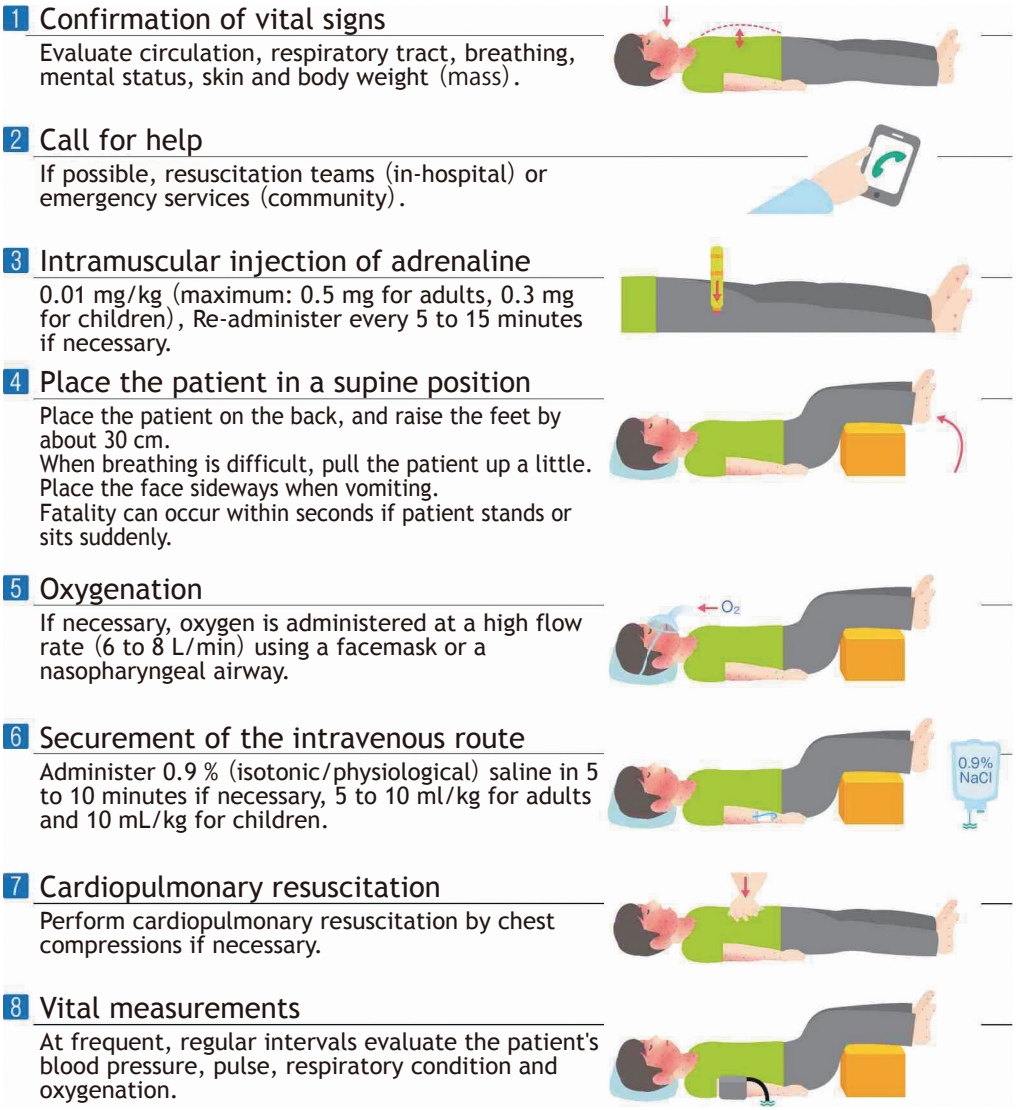
After the administration of injections, it is important to observe patient changes carefully, and if the condition of the patient changes, including but not limited to skin symptoms, within five minutes from the start of drug administration, you should suspect anaphylaxis, discontinue the drug administration immediately and prepare adrenaline intramuscular injection 0.3 mg (for adults), which is the first line drug for the treatment of anaphylaxis.

In the case study of death caused by anaphylaxis in the United Kingdom, the time (median) from administration to cardiac arrest or respiratory arrest was reported as five minutes with drugs, 15 minutes with bee venom and 30 minutes with food[3]; therefore, it can be said that in the case of drug-induced anaphylaxis patient's condition can change rapidly in a short time. It has also been reported that among the 55 people who died of drug-induced anaphylaxis, only 16% had adrenaline administered before cardiac arrest or respiratory arrest.[3]

In 10 cases out of the 12 target cases, some symptoms appeared within five minutes and within 20 minutes they were lead to the situation where emergency treatment was required (see Fig. 2). As described above, since anaphylaxis caused by injections is highly likely to change suddenly in a short time, a rapid emergency response is important.

Initial responses to anaphylaxis (see Fig. 3) should give priority to intramuscular injection of adrenaline in parallel with measuring/evaluating vital signs and calling for help, rather than emergency care, such as oxygenation and securing the intravenous route. For this purpose, it is important to observe patient changes carefully after the administration of injections, and if the condition of the patient changes, including but not limited to skin symptoms, you should suspect anaphylaxis from these symptoms and prepare adrenaline intramuscular injection 0.3 mg (for adults) while measuring blood pressure.

Figure 3　Procedures for initial response



Simons FE, et al. WAO Journal 2011; 4: 13-37 (Cited and modified)

Source: Japanese Society of Allergology Anaphylaxis Measures Special Committee/Anaphylaxis Guidelines, P13, 2014. (Reprinted with permission)

Figure 3 is the diagram that was cited and modified from the World Allergy Organization Guidelines for the basic treatment of anaphylaxis by the Japanese Society of Allergology as the procedures for the initial response in the Anaphylaxis Guidelines. The procedures for the initial response are common to various anaphylaxis onset. In particular, since anaphylaxis caused by injections is likely to change suddenly in a short time, you should prepare adrenaline concurrently with measuring / evaluating vital signs and calling for help and give priority to intramuscular injection of adrenaline over emergency care, such as oxygenation and securing the intravenous route,.

[Intramuscular injection of adrenaline]

Recommendation4

If anaphylaxis is suspected, do not hesitate to inject the standard dose of adrenaline 0.3 mg (in case of adult) intramuscularly into the antero-lateral part of the thigh.

● Do not hesitate to intramuscularly inject an adrenaline 0.3 mg.

The initial response is very important for anaphylaxis. First, immediately discontinue the injection suspected of causing anaphylaxis, and intramuscularly inject adrenaline 0.3 mg.

Guidelines on anaphylaxis in various countries of the world, such as those issued by World Allergy Organization and Japanese Society of Allergology, recommend the intramuscular injection of adrenaline up to 0.5 mg as the first line drug for the treatment of anaphylaxis. Many deaths due to anaphylaxis involve delay of adrenaline administration.[5]

Among the target cases also, it is in only one case that a patient was intramuscularly injected with 0.3 mg of adrenaline (see Fig. 2). In other cases, the timing of intramuscular injection being missed, intravenous injection of adrenaline 1 mg was performed for the purpose of resuscitation after cardiopulmonary arrest or in a situation close to it.

After using injections, when symptoms suspected of anaphylaxis are found and a shock symptom or decrease in systolic blood pressure (as a guide, less than 90 mmHg or obviously lower than normal blood pressure) is observed, adrenaline 0.3 mg should immediately be injected intramuscularly into the antero-lateral region of the thigh for adults. For children, adrenaline 0.15 mg should be intramuscularly injected.

It is necessary to realize that antihistamines and corticosteroids are merely second line drugs, and that there is no evidence that their administration contributes to the saving of lives.

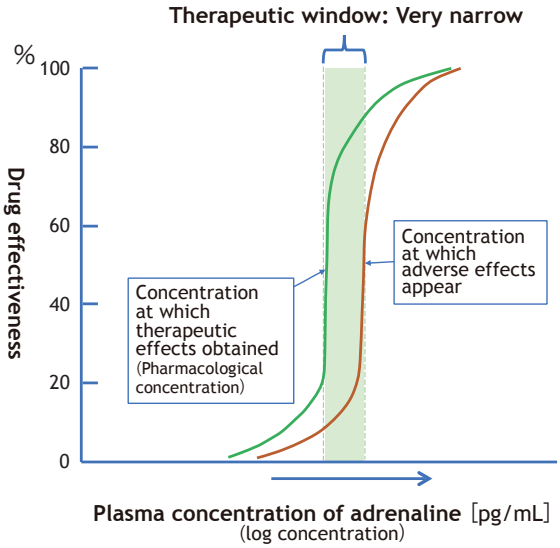
● Intramuscular injection of adrenaline 0.3 mg is unlikely to have adverse events.

The intramuscular injection of adrenaline 0.3 mg is very unlikely to cause adverse events. In a study implemented in the United States, a total of 316 intramuscular injections of adrenaline (a dose of 0.5 mg or less) were conducted in the 573 patients who were treated for anaphylaxis in the emergency department, and minor adverse reactions appeared only four times (1.3%) among them.[6] When the dose of adrenaline is 0.5 mg or less, it is believed that life-threatening complications do not occur. Perform intramuscular injection without hesitation because anaphylaxis means a lethal emergency.

● Reason why the intramuscular injection is recommended over intravenous injection

When adrenaline is intravenously injected, the blood concentration rises dramatically, which may cause severe myocardial ischemia, cardiac arrhythmia and pulmonary edema.[7] It has been pointed out that there is a small difference between the blood concentration of adrenaline at which an effect is obtained and the blood concentration at which adverse reactions appear, and that a therapeutic range is very narrow[7]; therefore, the intramuscular injection of adrenaline 0.3 mg is recommended (See Fig. 4).

Figure 4　Therapeutic window of adrenaline (Imaged diagram)



Source: Simons FE: Anaphylaxis, killer allergy: long-term management in the community. Journal of Allergy and Clinical Immunology 2006; 117 (2) : 367-377. (Reprinted with permission, partially modified)

Adrenaline administration by intravenous injection is not recommended for the initial treatment of anaphylaxis. Intravenous injection of adrenaline should be limited to cases where the effects are not observed despite the repeated intramuscular injections of adrenaline or in a state close to cardiac arrest or cardiac arrest. The intramuscular injection of adrenaline should not be confused with the intravenous injection because its indication is different from that of the intravenous injection of adrenaline 1 mg used for cardiopulmonary resuscitation.

≪ Reference: Intravenous injection of adrenaline responding to anaphylaxis ≫

When adrenaline is intravenously injected as an initial treatment of anaphylaxis, you should pay close attention to the dose and administration speed. Adrenaline intravenous injection becomes possible in a limited place such as an operating room where continuous observation by physicians and monitoring by biological monitors, etc. are available

The dose of adrenaline intravenously injected varies depending on the guidelines, but 50 to 100 μg (0.05 to 0.1 mg) is regarded as an absolute amount. Dilute 1 mg/1 mL of adrenaline with 19 mL of physiological saline and slowly administer intravenously 1 mL (0.05 mg) of them.

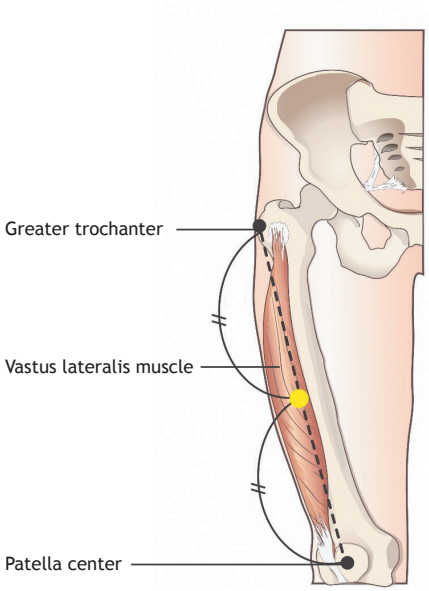
Site of intramuscular injection

Generally skeletal muscle has a rich blood flow, and an increase in blood concentration of the drug injected is relatively fast. In the case study in the past regarding the site of intramuscular injection of adrenaline 0.3 mg, a subcutaneous injection and an intramuscular injection into the upper arm and an intramuscular injection into the thigh were compared. As a result, the optimal blood concentration of adrenaline was immediately obtained after the intramuscular injection into the thigh and it has been reported to be suitable for the initial treatment of anaphylaxis. [8]

Intramuscular injections into the thigh have been avoided since the relationship with the quadriceps contracture in the children was pointed out. However, when anaphylaxis is suspected and an intramuscular injection of adrenaline 0.3 mg is required, an intramuscular injection into the middle of antero-lateral region of the thigh is recommended as it is a fatal emergency [1,2] (see Fig. 5).

> As a site for intramuscular injection into the antero-lateral region of the thigh (vastus lateralis muscle), near the middle of the line connecting the greater trochanter and the patella center has been proposed.

Figure 5
Site of intramuscular injection



Treatment procedure for anaphylaxis

If anaphylaxis left untreated, the risk of death due to circulatory collapse and airway obstruction may be inevitable. As an initial treatment when anaphylaxis is suspected, intramuscularly inject adrenaline 0.3 mg, and if the symptoms do not improve after the intramuscular injection, re-administer every 5 to 15 minutes as necessary. When shock symptoms appear, open the airway, administer high-flow oxygen, replace sufficient fluids and raise the lower extremities (see Fig. 3). If it comes to cardiac arrest, perform treatment according to the algorithms of the cardiopulmonary resuscitation guidelines.

As for securing intravenous routes, stop using the intravenous route for administration of causative drugs and secure a new intravenous route. When using an existing intravenous route, exchange the infusion kits, aspirate and discard the drug remaining in the injection needle, then use it.

[Adrenaline deployment, instruction and communication system]

Recommendation5

Adrenaline should be deployed in the places where the causative injections as a high risk of anaphylaxis are used. The instruction and communication system should be established so that intramuscular injection can be performed without delay.

● Deployment of adrenaline

In the places where the drugs, such as contrast medium, antibiotics and muscle relaxants which are likely to cause anaphylaxis, are used, adrenaline should be deployed so that it is available at any time.

Among the target cases, in the eight medical institutions adrenaline was deployed in the places where drugs were used. However, in the three medical institutions adrenaline was not deployed in the places where drugs were used at that time. As an emergency drug, adrenaline is necessary to be deployed in a fixed quantity and in a fixed position like an emergency cart from which adrenaline is easy to take out.

Currently, 0.3 mg/0.3 mL is used from an ampule containing 1 mg/1 mL adrenaline. For fast and reliable implementation in an emergency, we expect "Prefilled syringe preparations for intramuscular injection of adrenaline 0.3 mg" which are dedicated to the treatment of anaphylaxis will be developed.

According to the situation of medical institutions and dental clinics, it is necessary to deploy 0.3 mg of adrenaline (or 0.3 mg of an EpiPen injection solution in some cases) and for the staff to perform training of intramuscular injection of adrenaline.

● Development of the immediate direction and communication systems

Onset of anaphylaxis is a life-threatening emergency situation. Radiological technologists and nurses who respond to examinations and treatments at the risk of developing anaphylaxis are expected to be familiar with the initial response to anaphylaxis and are hoped to prepare instructional learning program for practice and have trainings in advance. It is required to develop an in-hospital direction and communication system in order to inform the physicians promptly so that they can respond to the anaphylaxis onset smoothly, if symptoms associated with anaphylaxis appears after administering the injection.

In dental clinics, when the onset of anaphylaxis is suspected, the dentist should immediately injects adrenaline 0.3 mg intramuscularly, determining it as an emergency response. At the same time, it is important to prepare a system to notify emergency and transport the patient to the medical institution.

[Understanding and sharing of allergy information]

Recommendation6

Grasping information on the allergy to drug, it should be endeavored to construct and operate the system in which the information can be shared among multiple professions.

● Understanding and sharing of allergy information

Anaphylaxis caused by injection is difficult to predict in advance. Therefore, understanding patient's allergy information leads to prevention of the onset of anaphylaxis as much as possible. It is extremely important for healthcare professionals to carefully listen to allergy information from the patient multiple times prior to administration of injections, to list the obtained allergy information in the medical chart and to share the information among multiple professions.

The following is the actual cases:

In one case, where antibiotics was used, although allergy information had been obtained, the information was not shared among multiple professions.

In some case, the site of the list was not fixed on the medical record, where the patient's allergy information should be expressed.

In some case, the risk of developing anaphylaxis could not be noticed because patient's allergy information did not indicated that of the related generic drug.

In another case, the warning system of the electronic medical record did not work when contraindicated drugs were entered manually.

As for generic drugs whose amount of use has increased in recent years, they may not be recognized as having the same components as the precedent ones, because their trade names are not the same.

In medical institutions, when and who confirms patients' allergy information based on what information should be arranged and that allergy information should be shared thoroughly.

● Registering and sharing of drug allergy information

The proper utilization of the electronic medical record makes it possible in drowing the attention, using its system or warning function, not to prescribe contraindicated drugs which has a history of allergies. However, contraindicated drug information may sometimes past through the system because of system defects or malfunctions, non-entry of allergy information and careless oversight of warning information of contraindicated drugs, etc.

As a countermeasure, regarding the notation of the allergy information in the electronic medical record, it is desirable to make the color, size and font type of the letters noticeable. Whenever entering data to the "Contraindicated drugs column" of the electronic medical record, the information should be reliably reflected with the correct input method. Also, if allergies are suspected with multiple drugs, list and register all used drugs.

Healthcare professionals who use electronic medical record should make use of them and be familiar with the specifications of the warning function of the electronic medical record. On the

other hand, when using paper medical charts, it is useful to specifically describe allergy information on the cover of the medical chart, or to create a page dedicated to allergy and to confirm it without fail, etc.

Multilayered measures of precaution

It is necessary to recognize that it is not perfect to grasp information on contraindicated drugs with the current electronic medical record system alone. Meanwhile, even paper charts have possibilities that contraindicated drugs will be administered if you cannot confirm and share allergy information reliably. In the cases where contraindicated drugs have already been clarified, it is also effective to take multilayered measures of precaution, including rechecking the presence or absence of allergy in patients before the administration of injections, having patients wear wristband and labeling allergy information on the bedside.

5. What we expect of (or what we want to propose to) academic societies and companies

Although it is difficult to predict the onset of anaphylaxis, in medical institutions in order to make every effort to prevent and to respond promptly and reliably in the case of onset, we expect that academic societies and companies will support and lead the efforts of individual medical institutions.

(1) Dissemination of correct knowledge on drug-induced anaphylaxis

In response to injection-induced anaphylaxis, healthcare professionals such as physicians, dentists, pharmacists, nurses, radiological technologists and dental hygienists play an important role in every institution involved in administration of injections, and accurate response and dissemination of correct knowledge among them are indispensable when anaphylaxis occurs. It is expected that these healthcare prolessionals will have the opportunity for training to aquire the basic knowsledge.

We hope that each academic society will provide educational opportunities for the onset of and the response to injection-induced anaphylaxis.

(2)Development of "Prebilled syringe preparations for intramuscular injection of adrenaline 0.3 mg"

Prefilled syringe preparations of adrenaline 1 mg which are usually used as an intravenous injection during resuscitation procedures against cardiac arrest have an important role in an emergency response.

Meanwhile, intramuscular injection of adrenaline 0.3 mg also plays an important role as a first line drug at the stage where life-threatening anaphylaxis is suspected. For anaphylaxis treatment, development of "Prefilled syringe preparations for intramuscular injection of adrenaline 0.3 mg" is expected in order to quickly inject 0.3 mg intramuscularly without mistaking how to use adrenaline.

(3) Improvement of drug registration/warning system of electronic medical record

Regarding the registration of drugs in electronic medical record, we expect that standardization of systems in which generic drug names including trade names and ingredient names (common names) are all displayed in a list so that anyone can understand them easily.

Furthermore, there are the cases where the warning system sometimes does not work correctly, because of the difference among the respective registration methods of contraindicated drugs. For the companies that provide electronic medical record, the improvement and standardization of the warning system on complicated drug allergy are desired (including display method of antibiotics of the same family and addition of common names of generic drugs).

6. Conclusion

In this subcommittee, ten experts from each relevant field examined the information on the cases of deaths related to anaphylaxis caused by injections reported to the ISC and then created this booklet. Although the most common cause of death due to anaphylactic shock is "medicinal drug", its mechanism is often unknown unlike anaphylactic shocks caused by bee venom and food whose causes are mostly limited to reactions via IgE antibodies. The process from anaphylaxis onset after the administration of causative injections to shock and further death involves a variety of factors, such as the location of onset, the route of administration of the causative drugs, the speed of progress of the symptoms, judgment by the healthcare professionals (medical staffs) and the treatment.

In the target cases there were also the cases where multiple injections were used, so it was not easy to identify the causative drugs. Therefore, it was necessary to comprehensively consider the involvement of different factors and the background. In addition to discussing in the three times of meetings of the Expert Analysis Subcommittee, the members exchanged opinions among them via electronic media and the subcommittee made six recommendations, giving priority to disseminating information that is easy to understand.

In Recommendation 1, we emphasized that anaphylaxis caused by injections can occur with any drug, and we described the need to usually recognize injections as a basic item in response to anaphylaxis. In Recommendation 2, the necessity of observation at the time of using injections was described because in many cases some symptoms appeared within five minutes from the start of administration of injection. In Recommendation 3, preparing 0.3 mg of adrenaline as the first line drug was recommended at the stage of suspecting anaphylaxis. In Recommendation 4, we dared to mention 0.3 mg intramuscular injection (for adults) in order to emphasize the necessity of intramuscular injection of adrenaline without hesitation. In Recommendation 5, the importance of adrenaline deployment was explained. In Recommendation 6, measures to grasp and share allergy information were presented.

Although it is impossible to completely reduce the risk of anaphylaxis caused by injections to zero, we will continue to accumulate and analyze the cases, aiming to reduce the cases of anaphylaxis and deaths since new study results on anaphylaxis caused by injections have been successively reported.

Finally, we would like to express our deepest condolences to the patients who died due to the anaphylaxis and to the bereaved families, as well as to express our sincere gratitude to the medical institutions that contributed to the investigation of the causes of accidents and to the prevention of recurrence, and cooperated in sharing the in-hospital investigation reports. We hope that this report will be useful to healthcare professionals (medical staffs) as a step towards improving medical safety.

≪ Reference ≫

1）Simons FER, Ardusso LRF, Bilò MB, et al: World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis. Allergy 2013; 62（11）: 1464-1500.（Translated from World Allergy Organization Journal 2011;4:2, pp13-37 into Japanese by the Special Committee for Measures against Anaphylaxis）

2）Japanese Society of Allergology Anaphylaxis Measures Special Committee: Anaphylaxis Guidelines, 2014.

3）Pumphrey RSH: Lessons for management of anaphylaxis from a study of fatal reactions. Clinical & Experimental Allergy 2000; 30（8）：1144-1150.

4）Motohiro Ebizawa: Anaphylaxis Guidelines - Importance of initial response and prevention of recurrence. Allergy 2015; 64（1）: 24-31.

5）Xu YS, Kastner M, Harada L, et al: Anaphylaxis-related deaths in Ontario: a retrospective review of cases from 1986 to 2011. Allergy, Asthma & Clinical Immunology 2014; 10（1）:38.

6）Campbell RL, Bellolio MF, Knutson BD, et al: Epinephrine in anaphylaxis: higher risk of cardiovascular complications and overdose after administration of intravenous bolus epinephrine compared with intramuscular epinephrine. The Journal of Allergy and Clinical Immunology. In Practice 2015; 3（1）:76-80.

7）Simons FER: Anaphylaxis, killer allergy: long-term management in the community. The Journal of Allergy and Clinical Immunology 2006; 117（2）: 367-377.

8）Simons FER, Gu X, Simons KJ: Epinephrine absorption in adults: intramuscular versus subcutaneous injection. The Journal of Allergy and Clinical Immunology 2001; 108（5）:871-873.

7. Materials

Anaphylaxis caused by injections [Investigation items checklist]

Items		Viewpoints	Concrete items
Basic information	Patient information	Current medical history (primary disease)	
		Medical history	☐ Present ( ) ☐ Absent ☐ Unknown
		Allergy history	☐ Present ( ) ☐ Absent ☐ Unknown
		Oral medicine	☐ Present ( ) ☐ Absent ☐ Unknown
		Smoking	☐ Present (pieces / day) ☐ Absent ☐ Unknown
		Alcohol use	☐ Present (every day / every week / sometimes) ☐ volume ( ) kinds ( ) ☐ Absent ☐ Unknown
		Important notice	☐ Present ( ) ☐ Absent
	Data information	Data on hospitaladmission	☐ Age : years old ☐ Height : cm ☐ Body weight : kg ☐ Male ☐ Female
Cause of death	Ai & Autopsy	Ai results	
		Autopsy results	
	Other	Imaging findings	☐ Electrocardiogram ( ) ☐ X-ray image ( ) ☐ CT image ( ) ☐ Other ( )
		Result of examination	☐ Tryptase value 1st (ng/mL) Collection date / time ( ) ☐ Tryptase value 2nd (ng/mL) Collection date / time ( ) ☐ Tryptase value 3rd (ng/mL) Collection date / time ( )
			☐ Urine histamine, pooled urine (ng/mL) Collection date / time : from to ☐ Urine histamine 1st (ng/mL) Collection date / time ( ) ☐ Urine histamine 2nd (ng/mL) Collection date / time ( )
			☐ Specific IgE (RAST) (ng/mL) Collection date / time ( ) ☐ Other ( ) Collection date / time ( )
Informed Consent	Timings	Timing of explanation	☐ At hospitalization ☐ Examination/pre-treatment ☐ Sudden change ☐ Other ( )
	Contents	Details of explanation	☐ Side effects in treatment/examination ☐ Possible side effects ☐ Possible anaphylaxis ☐ Possible death ☐ Response at the onset of side effects ☐ Other ( )
	Methods	Explanation method	☐ Explanation sheet ☐ Verbal ☐ Other ( )
Patient care	Causative drugs	Drugs used	☐ Ingredient/Common name ( ) Product/Trade name ( ) ☐ Ingredient/Common name ( ) Product/Trade name ( )
		Usage amount / Route of administration	☐ Usage amount ( ) ☐ Route of administration ( )
		Administration start time	☐ Start of drug administration (Time :)
	Course	Symptoms and findings Treatment course	☐ Time course record from the time of administration of injection (including treatment details)

Items		Viewpoints	Concrete items
Patient care	Response to anaphylaxis	Cancellation/ discontinuation of the injection	☐ Present (Time :) ☐ Cancellation time unknown ☐ Absent
		Confirmation of vital signs	☐ Understanding of breathing, circulation and state of consciousness ☐ State of Consciousness ( ) ☐ Breathing ( ) times/min ☐ Pulse ( ) times/min ☐ Blood pressure ( ) mmHg
		Observed details	☐ Swaying feeling ☐ Itching ☐ Numbness ☐ Nausea ☐ Difficulty in breathing ☐ Sneezing ☐ Feeling of body heat ☐ Redness ☐ Flush ☐ Rolling of eyes ☐ Convulsion ☐ Loss of consciousness ☐ Other ( )
		Aid request	☐ Present (Time :) ☐ Absent
		Intramuscular injection of Adrenaline 0.3 mg	☐ Present Administration time (1) : (2) : (3) : ☐ Absent (reason :)
		Oxygenation	☐ Present (details:) ☐ Absent ☐ Airway securing (details : Time :)
		Intravenous route securing	☐ New intravenous route securing (site:) ☐ Use existing intravenous route
		Cardiopulmonary resuscitation	☐ Sternal compression (start time :)
		Use of other drugs	☐ Present:Ingredient /Common name ( ) Product/Trade name ( ) ☐ Usage amount/method ( )
		Reason for diagnosis	☐ Side effect history of drugs/estimated from allergy history ☐ Extremely high possibility determined from clinical course and findings ☐ Other ( )
		Timing of in-hospital team's response	☐ Onset of symptoms ☐ Start of cardiopulmonary resuscitation ☐ Other ( ) ☐ Absent
Management system of medical institution	Information sharing	Examinations / treatments received in the past	☐ Contrast-enhanced CT examination Present ( ) times ☐ Absent ☐ Angiography examination Present ( ) times ☐ Absent
		Presence or absence of abnormalities due to examinations / treatments received in the past	☐ Present (Date :) Examination and treatment details ( ) ☐ Absent ☐ Unknown
		Confirmation of allergy information	☐ Inquiries ☐ Drug prescription ☐ Drug administration ☐ Absent ☐ Other ( )
		Confirmer of allergy information	☐ Physician ☐ Dentist ☐ Pharmacist ☐ Nurse ☐ Radiological technologist ☐ Dental hygienist ☐ Other ( )
		Registration of allergy information	☐ Present ☐ Absent
		Allergy presentation in medical records	☐ Present (location :) ☐ Absent
		Target of allergy information check	☐ Patient ☐ Family ☐ Attendant ☐ Absent ☐ Other ( )
		Medical record/ medicationprescription media	☐ Paper medical chart ☐ Electronic medical record ☐ Other ( )
	In-hospital system	Deployment of adrenaline	☐ Adrenaline ☐ EpiPen injection solution 0.3 mg ☐ Other ( )
		Preparation for emergency response	☐ Emergency cart ☐ AED ☐ Other ( )
		Response system in the event of a sudden change	☐ Present ☐ Absent
		Manuals for anaphylaxis response	☐ Present ☐ Absent
		Development of direction and communication system for intramuscular injection of adrenaline 0.3 mg	☐ Present ☐ Absent

Members of the Expert Analysis Subcommittee for Anaphylaxis

Subcommittee chairman	Hirohisa Saito	Japanese Society of Allergology
Subcommittee members	Emiko Asaka	Japanese Association for Emergency Nursing
	Takekazu Okado	The Japanese Society for Dialysis Therapy
	Tomonori Takazawa	Japanese Society of Anesthesiologists
	Toru Naito	The Japanese Society of Periodontology
	Kenji Nishizawa	Japanese Society of Pharmaceutical Health Care and Sciences
	Hitoshi Niwa	Japanese Association for Dental Science
	Hiromitsu Hayashi	Japan Radiological Society
	Katsuyuki Miyasaka	The Japanese Society of Pediatric Anesthesiology
	Masao Yamaguchi	The Japanese Respiratory Society

Conflict of interests
Medical Accident Investigation and Support Center confirmed the status of conflicts of interest on the contents of this report that was self-declared by the members of Expert Analysis Subcommittee for Anaphylaxis.

Members of the Committee for Prevention of Recurrence

Chairman	Hisahiro Matsubara	Professor, Department of Frontier Surgery, Graduate School of Medicine, Chiba University
Vice chairman	Shin Ushiro	Director/Professor, Medical Safety Management Division, Kyushu University Hospital
Committee members	Yumi Arai	Medical Safety Manager/Vice Director, Medical Quality/ Safety Promotion Office, Kitasato University Hospital
	Sadaomi Imamura	Executive Director, Japan Medical Association
	Yukihide Iwamoto	Hospital Director, Japan Organization of Occupational Health and Safety Kyushu Rosai Hospital
	Kiyomi Ueno	Director, Office of Safety I, Pharmaceuticals and Medical Devices Agency
	Michio Ueno	Hospital Director, National Hospital Organization Fukuoka-Higashi Medical Center Vice President, Fukuoka Prefecture Medical Association
	Keiko Kasai	Executive Director, Japanese Midwives Association
	Hamako Katsumata	Executive Director, Japanese Nursing Association
	Yoshio Kato	Lawyer, Sakae Legal Affairs Office
	Yasushi Kodama	Attorney at Law(JPN and NY), Shinsei Sogo Law Offices
	Kazunori Sugai	Division Chief, Medical Management Division, National Center for Global Health and Medicine
	Ryo Suzuki	Lecturer, Department of Diabetes and Metabolic Diseases, Faculty of Medicine, the University of Tokyo
	Fumito Tsuchiya	Vice President, Japanese Society of Hospital Pharmacists
	Hiroshi Matsuda	Hospital Director, Kashiwazaki Welfare Hospital, Tachikawa Medical Center
	Hiroaki Mitsui	Managing Director, Japan Dental Association
	Hiroaki Miyata	Professor, Department of Health Policy and Management, School of Medicine, Keio University
	Makoto Yano	Deputy General Manager, Healthcare Service Headquarters, Japanese Red Cross Society
	Ikuko Yamaguchi	President, Authorized NPO Sasaeai Center for Health Care and Human Rights COML

The list of Members of the Committee for Prevention of Recurrence is as of the time when the "Recommendations for the Prevention of Recurrence of Medical Accidents" (Number 3) was approved.

Executives of the Japan Medical Safety Organization

Chair of the board	Fumimaro Takaku	Japan Medical Safety Research Organization
Senior Executive Director	Keiji Tanaka	Japan Medical Safety Research Organization
Executive Director	Sosuke Kimura	Japan Medical Safety Research Organization

Recommendation for the prevention of recurrence of medical accidents (Number 3)

Analysis of deaths related to anaphylaxis caused by injections

Issued in January 2018
Edited and published by Japan Medical Safety Research Organization
World Trade Center Building 5th Floor
2-4-1 Hamamatsucho, Minato-ku, Tokyo 105-6105, Japan
TEL: +81-(0)3-5401-3021 (Main number)
Contact: Sosuke Kimura, MD.PhD.
Kimura.s@medsafe.or.jp