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Case Report

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Rush Immunotherapy Using Ifn-Gamma for Cefazoline Allergy

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Abstract

Cefazolin is a first generation cephalosporin widely used for preoperative antibiotic prophylaxis. Although cefazolin hypersensitivity constitutes a potential life-threatening condition with serious consequences, correct diagnosis of cefazolin hypersensitivity is not straightforward for various reasons. A graded challenge is perhaps the most reliable in vivo test for the diagnosis of cefazolin allergy. Desensitization is performed by the cautious administration of incremental doses of the drug to the patient. In the case of intravenous drug, the challenge and desensitization has been regarded as extremely dangerous. IFN-gamma has allergen-specific tolerogenic effects, together with the administration of allergens. Moreover, IFN-gamma was introduced for desensitization for aspirin and cefaclor. In this case report, two cases were described concerning challenge test and desensitization for anaphylactic drug allergy for intravenous cefazolin using IFN-gamma.

Keywords: Cefazolin, IFN-gamma, Desensitization, Drug Allergy

Introduction

Cefazolin is a first generation cephalosporin and widely used for preoperative antibiotic prophylaxis [1, 2]. β-lactam antibiotics are a relevant cause of IgE-mediated hypersensitivity reactions and cefazolin is responsible for the majority of these reactions [3, 4]. Cephalosporin's can cause a range of hypersensitivity reactions from mild, cutaneous reactions to life-threatening anaphylaxis in patients with IgE-mediated allergy [5-9]. The estimated prevalence of hypersensitivity to cephalosporins is 1%-3% in the general population [10, 11].

Although cefazolin hypersensitivity constitutes a potential life-threatening condition with serious consequences, correct diagnosis of cefazolin hypersensitivity is not straightforward for various reasons; drug provocation tests with this parenteral cephalosporin are hazardous and time consuming and no reliable cefazolin-specific IgE antibody assay is available. Therefore, clinical suspicion of cefazolin hypersensitivity is generally confirmed with skin tests [12]. Cephalosporin hypersensitivity is not a classic hypersensitivity in a series of reports [13]. Especially regarding cefazolin, studies conducted up to now showed that IgE-mediated hypersensitivity toward cefazolin appears to be selective in the great majority of allergic subjects [13-18].

A graded challenge is perhaps the most reliable in vivo test to prove or disprove unequivocally whether an antibiotic allergy exists [19]. Desensitization is defined as the conversion of a patient with a drug allergy from a highly sensitive state to a clinically tolera¬ble state [20]. Desensitization is performed by the cautious administration of incremental doses of the drug to the patient. But, a problem to be solved is that all desensitization for drug allergy is not successful. Especially, in case of intravenous drug, the challenge and desensitization has been regarded as extremely danger.

Tolerance induction for anaphylactic food allergy has been performed effectively and safely using IFN-gamma in our group. Challenge and tolerance induction was also very dangerous in case of anaphylactic food allergy as anaphylactic drug allergy [21]. IFN-gamma has allergen-specific tolerogenic effects administrating with allergens together [22]. Recently, IFN-gamma was introduced for desensitization for cefaclor, consecutively in addition to aspirin in acute myocardial syndrome and oral antibiotic [23, 24]. In this case report, two cases was described concerning challenge test and desensitization for anaphylactic drug allergy for intravenous cefazolin using IFN-gamma.

Case Reports

Principle of desensitization of cefazolin using IFN-gamma

In case of drug allergy, drug challenge was done and the minimal provocation dose was checked with the diagnosis of cefazolin allergy. And the desensitization for cefazolin proceeded.

The decision of impediment was the most important issue during the desensitization for allergenic drug. In these aspects, the principle of desensitization was decided before challenge and desensitization. Differently from tolerance induction for food allergy, challenging allergen is intravenous drug. Challenge and desensitization was performed intravenously. Considering the principle of tolerance induction for anaphylactic food allergy, Slight numbers of allergy symptoms and/or signs and slight degree of allergic responses regarded as impediment [21]. However, more numbers of symptoms and signs were appeared and/or clinical severity was severe, the

challenging dose is decided as impediment. When clinical severity score is 0, then new lesion was evaluated for the impediment. If clinical symptoms and signs were remained in a some degree, the next dose was challenged. In this condition, both the remained symptoms and signs the appearing new lesions were evaluated. If the remained symptoms and signs were aggravated, then the challenged dose was decided as an impediment. If new symptoms and signs with over a certain degree of severity was developed in addition to remained clinical symptoms and signs, also the last challenging dose. Also, the kinds of clinical symptoms and signs were considered for the determination of an impediment.

When the impediment was met, IFN-gamma was introduced to overcome the impediment. Impediment resolution was repeated until the clinical symptoms and signs was disappeared or decreased as insignificant clinically as described above. Repetition of resolution of impediment was described as cycle.

IFN-gamma was used only once a day in the morning. If the next impediment was met, the next treatment was performed the next day for the use of IFN-gamma.

Cases

Case 1

A 48 year-old female patient who complaint allergy to multiple drugs visited Allergy & Clinical Immunology Center, Cheju Halla General Hospital. Patients wanted to get one safe antibiotics for the unexpected condition to use antibiotics and, in the previous admission, desensitization for cefaclor was successfully performed. This treatment was reported. Then, her right little toe is fractured and the surgery was needed. So, urgently and inevitably she needed a safe intravenous antibiotic which does not provoke allergic reaction. Written informed consent was obtained from each of the patients for case 1 and case 2. Patient had past histories of chilling, generalized myalgia, change of body temperature and transient paralysis on whole body after using unidentified antibiotics after delivery 25 years ago as a first episode. The second and third episode is that patients felt chilling and tremor of whole body by intramuscular injection of gentamycin in the local clinic 2 years ago. Patients tolerate without antibiotics mediation due to suspected multiple drug allergy syndrome in spites of conditions in which she should receive antibiotics due to surgery of urinary bladder in the local clinic. She had a history of transient paralysis of lower extremities after intramuscular injection of analgesics. She wanted to get one safe antibiotics for the future. Her wounds by injury or surgery have not been healed well. The erythema and eruption occurred frequently when she took unidentified foods. Also, urticarial occurred when she took place in hazy air, or was exposed to grass, or went to mountain. Also she had white dermographism. She was severely ill by flue vaccination. Cefaclor was identified as an allergenic drug and desensitization for ceclor was done successfully. Under the diagnosis of suspected multiple drug allergy, she was admitted for intravenous challenge and desensitization for cefazolin.

Blood tests and skin prick tests were performed for general allergy laboratory analysis. In complete blood count with differential count, eosinophil fractions were 1.4 %. Serum eosinophil cationic protein level and serum total IgE levels were high as 18.60 μg/L (normal range, 0.0-14.9 μg/L) and 30.1 KU/L (normal range, 350 KU/L>).

Specific IgE levels which were tested for 40 allergens by MAST (Green Cross®, Seoul Korea). Only two allergens (Cat (1.30 IU/ml, 2+) and Dog (0.41 IU/ml, 1+)) showed positive results and other allergens (Dermatophagoides pteryonyssinus, Dermatophagoides farinae, Egg white, Milk, Soybean, Shrimp, Peach, Mackerel, Crab, Rye, Cockroach, Cladosporium, Aspergillus, Alternaria, Birch/Alder, White oak, Short ragweed, Mugwork, Japanese hop, Hazelnut, Sweet Grass, Bermuda Grass, Cocksfoot, Timothy Grass, Reed, Ox-eye daisy, Penicillium, Sycamore, Sallow willow, Cottonwood East, Ash mix, Pine, Japanese Cedar, Acacia, Dandelion, Russian thistle, Goldenrod, and Pigweed) were negative. Skin prick tests were performed and she is poly-sensitized for multiple variable allergens. Among 53 items, 25 allergens (Alternaria alternate (2+), Aspergillus fumigatus (2+), Penicilium Chrysogerium (2+), Dermatophagoides pteronyssinus (2+), Dermatophagoides farina (3+), Dog(2+), Gray Alder (Silver Birch) (3+), Grass mix (3+), Mugwort (2+), Short Ragweed (2+), Black willow pollen (3+), Orchard (1+), Bermuda grass (2+), Timothy (2+), Holm oak (2+), Japanese cedar (3+), Pork (2+), Cod (2+), Prawn (2+), Almond (2+), Peanut (2+), Walnut (2+), Peach (2+), Black pepper (3+), F acacia (2+)) showed positive results and remains (Aspergillus niger, Candida albicans, Clasdosporium, German cockroach, Cat, English plantain, English Rye grass, Cotton flock, Milk, Egg, Chicken, Beef, Oyster, Salmon, Mackerel, Tuna, Bean, Carrot, Cabbage, Maize, Tomato, Spinach, Wheat, Rabbit, Kapok, Hop, Pine and Poplar) were negative. Intradermal test for cefazolin was negative. Skin prick test for cefazoline was grade 3 positive (Cefazoline 3mmx3mm. histamine control 3mmx3mm and normal saline 0mmx0mm)(Figure 1).

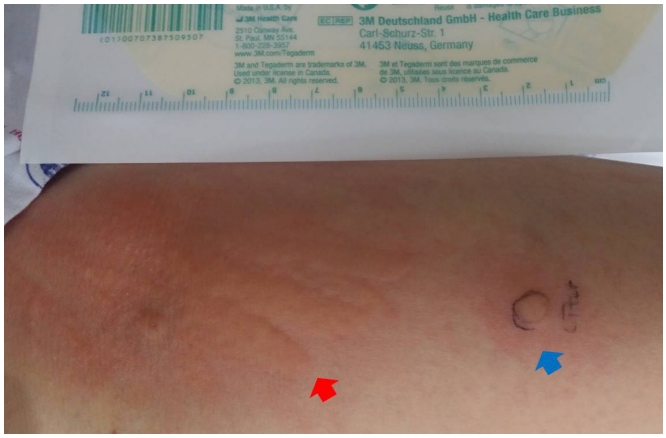

Figure 1: Positive skin prick test result for cefazolin. Urticaria and erythema was developed at the site of intradermal test (blue arrow). Patient scratch the skin due to itching and white dermographism was developed even at the near separated area (red arrow).

Intravenous drug challenge was started with dose of 1ng of cefazoline. The intravenous cefazolin challenge proceeded according to the protocol (Table 1).

Table 1: Challenge/Desensitization Protocol for cefazolin

Dosage	x1									x10								x100									
ng	1	2	3		5					10	20	30	50	60	70	80	90	100	200	300	400	500	600	700	800	900	1000
ug		2	3	4	5	6	7	8	9	10	20	30	40	50	60	70	90	100	200	300	400	500	600	700	800	900	1000
mg		2	3	4	5	6	7			10		30		50				100		300		500					1000

Patients showed variable symptoms and signs during the desensitization. The score was made by the counts of symptoms and signs by challenging as listed in (Table 2).

Table 2: List of symptoms and signs. A total of 34 symptoms and signs were listed which were developed during the challenge / desensitization processes. The severity scores were described as the counts of symptoms and signs.

General	Headache	Respiratory	Dyspnea
	Dizziness		Chest tightness
	Chilling		Chest pain
	Myalgia		Cough
	General weakness		Sputum
	Tremor	Throat & Neck	Dryness of tongue
	Sweating		Tingling sensation of tongue
	Heating sensation		Throat pain
	Facial flushing		Chocking
	Angioedema		Tingling sensation of throat
	Urticaria		Dryness of throat
	Skin rash	GI	Nausea
Eye	Tearing		Vomiting
	Eyeball pain		Abdominal discomfort
	Heating sensation		Abdominal pain
	Blurred vision	GU	Tingling Sensation/ Itching of urethra
Nasal	Sneezing		Feeling of residual urine
	Rhinorrhea		
	Nasal stiffness		

A first impediment was met at the dose of 30ng of cefazolin. Patients showed positive allergic reactions. A first impediment was met at the dose of 30ng of cefazolin. Patients showed positive allergic reactions (Figure 2). Initially desensitization proceeded according to the conventional protocol and 30ng of cefazolin was challenged repetitively 4 times. However, the symptoms and signs were abruptly aggravated at the 4th times (Figure 3). Further proceeding of desensitization for intravenous cefazolin was suspected at the high risk of anaphylaxis with the conventional concepts and protocols, and in this point introduction of IFN-gamma was decided as an allergen-specific tolerogenic cytokine.

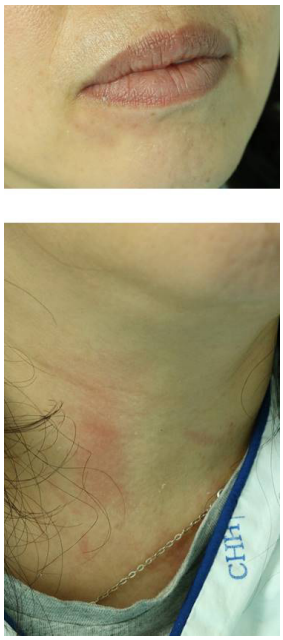

Figure 2: Skin manifestations by cefazolin challenge. Patient of case 1 showed skin rashes on whole body including perioral area (upper photo) and necks (lower photo) by challenging cefazolin with the dose of 30ng. The cefazolin allergy was confirmed.

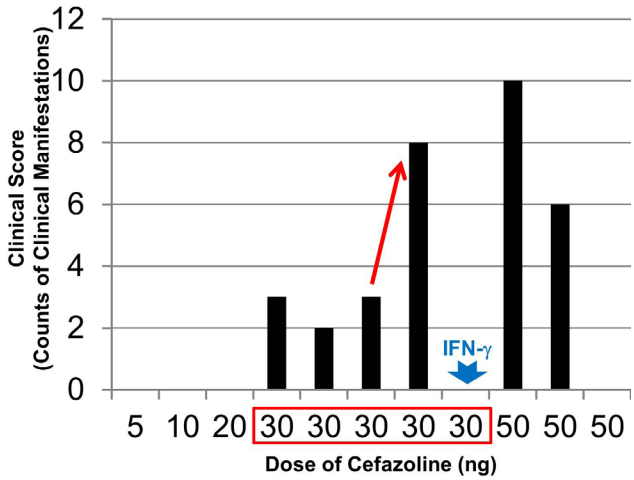

Figure 3: 1st Impediment and overcome of impediment using IFN-gamma. Patients showed the 1st allergic reaction at 30ng cefazolin 4th times. Even at the 4th times of challenge with the dose of 30ng cefazolin, the symptoms and signs became more exaggerated (red arrow). Aggravation of symptoms and signs with anaphylaxis was expected at the next challenge. IFN-γ was introduced at the 5th challenge and allergic symptoms and signs were not appeared no more (blue arrow). The 1st impediment at the dose of 30 ng cefazolin was overcome using IFN-gamma (red box at the horizontal axis).

IFN-gamma (Intermax gamma, LG Chemistry®, Seoul, Korea) was introduced to overcome the impediment. It was administrated at a dose of 2,000,000 Unit (50 μg) by subcutaneously on the arm 15 minutes before the challenge of impediment dose. Acetaminophen 650mg was prescribed 15 minutes before IFN-gamma injection to avoid untoward side reactions of IFN-gamma including headache, myalgia, abdominal pain. IFN-gamma was administrated early in the morning.

By pretreatment of IFN-gamma, the 5th challenge of 30ng cefazolin showed no symptoms and signs and impediment at the dose of 30ng was overcome. The desensitization proceeded according to the protocol and IFN-gamma was used when impediments were met. Patient met the impediment 8 times (Figure 4).

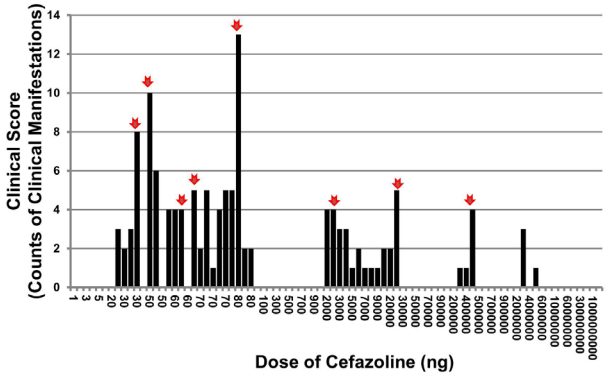

Figure 4: Total Progress of Challenge/Desensitization Process. At the dose of cefazolin 30ng, patient showed allergic reaction for the 1st time during the challenge. The desensitization could not precede at this dose (30ng) and this dose was decided as 1st impediment. A total of 8 impediments were met and IFN-γ was used for the overcome of impediment (red arrow).

The characteristics of impediments during the desensitization for intravenous cefazolin were that the severity of allergic reactions was severe at the low dose range and decreased with the increasing challenge dose (Figure 5 Right). The cycles of impediment overcome (repetitive challenge numbers with same dose using IFN-gamma to overcome the impediment) were high at the low dose area and decreased further with increasing challenge dose (Figure 5 Left).

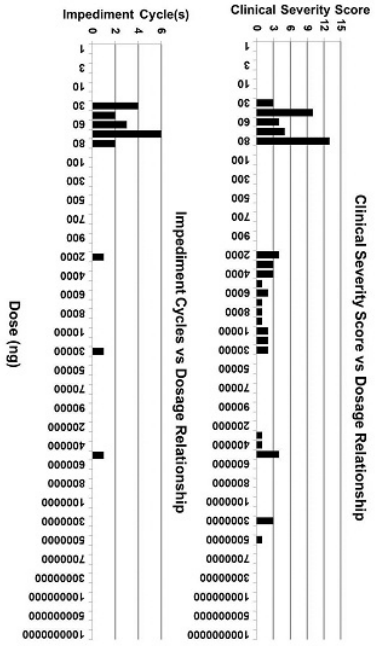

Figure 5: Relationship of dose with clinical severity score and impediment cycle. The clinical severity of allergy provocation was more severe in the extremely low dose range and the impediment cycles were more in the extremely low dose range than those in the high dose range.

Patients finished desensitization for cefazolin successfully at the dose from 1ng to 1g using IFN-gamma. The next day of finishing desensitization, patient received cefazolin 1g without any symptoms and signs. Several months later, patients received operation for little toe fracture with using intravenous cefaozolin in other hospital.

Case 2

A 43 year-old female patient visited Allergy & Clinical Immunology Center, Cheju Halla General Hospital because of drug allergy. Patients had history of emergency treatment due to severe allergic reaction after taking oral medications for upper respiration infection 7 years ago. Patient showed vomiting, diarrhea, abdominal pain. Blood pressures were decreased and she experience transient loss of vision and it is suspected to be loss of consciousness. Patient took oral medication of cefaclor, tyrenol and streptokinase just before the development of anaphylaxis. She was diagnosed that she had allergy to aspirin but not to tyrenol. She visited emergency room more three times due to severe angioedema including face 20 months ago, anaphylaxis 16 months ago and anaphylaxis after intake of medications for upper respiratory infection 1 month ago. In the previous admission, the diagnosis of cefaclor allergy was made by oral drug challenge and desensitization was performed successfully. Patient wanted to confirm the allergy to intravenous cephalosporin and keep at least a safe intravenous cephalosporin for the emergency use. So, she was admitted for the diagnosis of allergy and desensitization for intravenous cefazolin.

In complete blood count with differential count, eosinophil fractions were 4.7% (normal range, 0-5%), serum eosinophil cationic protein level was 2 μg/L> (normal range, 0.0-14.9 μg/L) and serum total IgE levels were 133.0 KU/L (normal range, 350 KU/L>). Specific IgE levels which were tested for 40 allergens by MAST (Green Cross®, Seoul Korea). Cat (2.00 IU/ml, 3+), Rye (4.80 IU/ml, 3+) Sweet Grass (4.31 IU/ml, 3+), Bermuda Grass (1+), Cocksfoot (2+), Timothy Grass (2+), Reed (1+) were positive and other allergens (Dermatophagoides pteryonyssinus), Dermatophagoides farinae, Dog, Egg white, Milk, Soybean, Shrimp, Crab, Peach, Mackerel, Cockroach, Cladosporium, Aspergillus, Alternaria, Birch/Alder, White oak, Short ragweed, Mug work, Japanese hop, Hazelnut, Penicillium, Sycamore, Sallow willow, Cottonwood East, Ash mix, Pine, Japanese Cedar, Acacia, Dandelion, Russian thistle, Goldenrod, Ox-eye daisy and Pigweed) were negative.

Skin prick test was conducted for 53 allergens. 11 items (Dermatophagoides pteronyssinus (3+), Dog (2+), Cat (3+), Gray Alder (Silver Birch) (3+), Grass mix (3+), Mugwort (2+), Orchard (6+), Bermuda grass (2+), Timothy (3+), English Rye grass (3+), Japanese cedar (2+)) were positive and remains (Alternaria alternate, Aspergillus fumigatus, Aspergillus niger, Candida albicans, Clasdosporium, Penicilium Chrysogerium, German cockroach, Dermatophagoides pteronyssinus, Dermatophagoides farina, Short Ragweed, Black willow pollen, English plantain, Holm oak, Cotton flock, Milk, Egg, Chicken, Beef, Pork, Cod, Oyster, Salmon, Prawn, Mackerel, Tuna, Almond, Peanut, Bean, Carrot, Cabbage, Walnut, Maize, Peach, Tomato, Black pepper, Spinach, Wheat, Rabbit, Kapok, Hop, F acacia, Pine and Poplar) were negative.

Intradermal test and skin prick test for cefazoline were negative in this case. Intravenous cefazolin was challenged according to the protocol. Initial dose was 1ng. Patient showed allergic reaction at the dose of 50ug. Patient showed respiratory difficulty with dyspnea,

severe chest tightness, skin rash, generalized itching. Challenge test was stopped at the dose of cefazolin 50ug and the anaphylactic drug allergy for cefazolin was made. IFN-gamma was given 2,000,000 IU (50 μg) subcutaneously 15minutes before the second challenge of the impediment dose, cefazolin 5mg. Acetaminophen 650mg was prescribed 15 minutes before IFN-gamma injection to avoid untoward side reactions. With premedication of IFN-gamma, patient did not show any allergic symptoms and signs. Moreover, patient did not showed any symptoms and signs no more with increasing doses of cefazolin according to the protocol until 900 ug. Patient wanted to finish desensitization and in hospital day 2, she was discharged.

Discussion

Intravenous desensitization for cefazolin was successfully achieved using IFN-gamma as an immunomodulatory drug. This is the first report to desensitize intravenous drug using IFN-gamma.

Successful desensitization using IFN-gamma for patients who had aspirin allergy with acute myocardial syndrome who was not treated with conventional method was reported [23]. Subsequently, desensitization using IFN-gamma for oral cephalosporin, cefaclor was also succeeded in patients who showed impediment to a certain dose and was not overcome this impediment with conventional method [24]. Surprisingly, the impediments during desensitization of intravenous cefazolin were overcome dramatically just administration of IFN-gamma. IFN-gamma was effective for the resolving impediment during desensitization of intravenous antibiotics as well as oral antibiotic and aspirin. With using IFN-gamma, desensitization for drug allergy was further effective and this concept of desensitization is innovative for the treatment of drug allergy solving the previous difficulties for desensitization.

Although this is the case reports including just 2 cases, this report imply very important clues for the nature of intravenous drug allergy and desensitization. Also according to the process and results of desensitization, the understanding and principles for the optimal protocol of challenge and desensitization for intravenous drug allergy was deduced.

A thorough history is an essential component of the evaluation of patients with suspected cephalosporin allergy [19]. However, these two patients had allergy for cefaclor and had no history of allergy to cefazolin. However, both patients was suspected to have multiple drug allergies and faced to fix a safe antibiotic. Case 1 had an inevitable condition to need intravenous antibiotics due to the bone fracture.

Cephalosporin skin testing is usually performed by skin prick testing followed by intradermal testing. Intradermal test for cefazolin was negative in both cases. However, skin prick test for cephazolin was positive in case 1 (Figure 1). Cephalosporin skin tests are not standardized and have a limited clinical value [19]. However, a positive skin test result to a cephalosporin suggests that drug-specific IgE antibodies may be present.

The dosage range of allergy provocation by cefazolin is estimated as 30ng to 50ug. Basically, the approximate dosage unit was ng. The dosage range of minimal allergy provocation is very important to make the challenge protocol for intravenous drug. Until now, a graded challenge is perhaps the most reliable in vivo test to prove or disprove unequivocally whether an antibiotic allergy exists [19]. First of all, the minimal provocation dose is not expected due to the lack of document or concept about the minimal dose which provoking allergy in case of intravenous drugs including cefazolin. It is because, currently, it is not clarified that whether intravenous drug provoke allergic response at least minimal dose above a certain dose range similarly or the range of minimal provocation dose is completely different according to the kinds of drug. Provocation testing protocols for the implicated cephalosporin was recommended by both the American and European guidelines [25, 26]. A graded challenge typ¬ically involves 2 or 3 steps. The starting dose for a graded chal¬lenge is usually 1/100 of the full dose, and 10-fold increasing doses are administered every 30 to 60 minutes until the full therapeutic dose is reached [25]. A lower starting dose should be used in patients with a history of severe reactions. However, this protocol is crude and obscure to perform challenge tests for intravenous cefazolin. With this concept, the starting dose range is different according to the drug just by usual 1/100 of the full dose. The calibration of the minimal provocation dose is very crude and there is a high risk of sudden anaphylactic reaction by 10 fold increasing dose. Namely, with this conventional protocol, there was no concept to clarify the fix the minimal provocation dose during the challenge test. This is also lack of concept for desensitization according to the minimal provocation dose. So, they describe that a graded challenge can be dangerous and resuscitative equipment and well-trained physicians must be in attendance throughout the procedure [19].

In this case report, the more precise and dense dosage protocol for challenge test is established for the safe calibration of the minimal provocation dose from 1ng to 1g as decade unit. Patients started to response to drug challenge at the dose of 30ng and 50ug. This is very important clinical date to challenge for other patient with same drug and other intravenous drug to establish dosage protocol of intravenous drug. The challenge test for intravenous drug should be started at least below 30ng.

Patients, who develop symptoms consistent with an IgE-mediated reaction during the graded challenge, should not receive further drug [19]. The drug should be avoided or administered via desensitization. In our cases, the diagnosis for cefazolin allergy was made by challenge in this point and challenge was stopped.

Desensitization is performed by the cautious administration of incremental doses of the drug to the patient. A typical starting dose is often 1/10,000th of the final dose or twice the dose used in the skin testing, 44 followed by doubling of previous dose at regular intervals until the final therapeutic dose is achieved [19]. However, in this case report, one patient showed allergic reaction to cefazolin 30ng and the other, 50ug. So, it is not proper that 1/10,000 of 1g (100ug) was a starting dose. So, the exact calibration of minimal provocation dose seems to be very important for performing desensitization. Here, the concept of the minimal provocation dose and calibration was suggested. Protocols of desensitization for cefazolin were set according to the minimal allergy provocation dose and the severity of allergic reactions.

The management when impediment was met during desensitization was different by using IFN-gamma. Dosage should be reduced or modulated when impediment was met during desensitization without IFN-gamma. However, Impediment was overcome just by repetition in desensitization with IFN-gamma. This is the great conceptual

difference between desensitization with and without IFN-gamma.

There was the most definite difference in the use of IFN-gamma between food allergy and drug allergy. IFN-gamma was used in every challenges of allergenic food with increasing dose during tolerance induction [21]. However, in desensitization of drug allergy, IFN-gamma was used just to overcome the impediment in which patients showed allergic reactions at a certain dose. The application of IFN-gamma also should be revised concerning this point.

In case 1, patients showed 8 impediments during the treatment. As compared to patient of case 1, patient of case 2 showed just an impediment which was solved by the use of IFN-gamma just once.

From the cases, drug allergy is the allergy to extremely low dose of drug allergen as anaphylactic food allergy [27]. So, considering the minimum provocation dose, the provocation test should be started from 1ng and the protocol which used in this report seemed to be appropriate. The severity curve during the desensitization showed the similar to that during the tolerance induction of anaphylactic food allergy [21].

Differently from expected allergic responses, the dense and precise dosage protocol for desensitization for cefazolin allergy mad the relatively safe and tolerable severity for allergy provocation as in tolerance induction of anaphylactic food allergy.

Until now, the relation between the anaphylactic allergy and allergy provocation dose has been recognized vague and abstractly. From this report and the study from the tolerance induction for food allergy, it is because the minimal provocation dose is extremely low [21]. In this report, the extremely low dosage range of 1 ng to 1ug is expanded and the challenge process proceeded. Indeedly, the minimal provocation was confirmed. The important thing is that allergy provocation was rapid but not explosive by minimal provocation dose if we set the protocols as dense and precise. By 10-fold increasing doses, the precise calibration of the minimal provocation dose by detecting the initiation of allergy at a certain dose is difficult or impossible. Rather, just rapid and explosive allergy provocation may be expected which result in the risky anaphylaxis.

Minimal allergy provocation dose of intravenous drug showed extremely low as compared with that of oral drug. The impediment is also more frequent in the desensitization for intravenous drug as compared to the desensitization for oral drug. Desensitization for intravenous drug seems to be more difficult than desensitization for oral drug [23, 24]. However, with success of desensitization for intravenous cefazolin of this report, the new insight and concept for the causative treatment of drug allergy by desensitization using IFN-gamma may be arising. This therapy may be applied in other drug allergy including anti-cancer drug of which is the sole choice for the cancer therapy.

In the past, drug desensitization was considered an approach to the acute management of IgE sensitivity only. Modified forms of desensitization can be used to manage drug induced reactions that are thought to be immunologic in nature but that are not IgE-mediated. A more prolonged, slow type of desensitization has been reported to be successful in AIDS patients with drug allergy [28]. This procedure is performed over several days. Here, the desensitization method using IFN-gamma was successful as an effective advanced therapeutic concept, expecting allergen-specific tolerogenic effects. The term induction of drug tolerance encompasses both IgE-mediated desensitization, as well as non-IgE-mediated mechanisms, and has replaced the term drug desensitization [25]. IFN-gamma actually reported for the tolerance induction for food allergy of non-IgE-mediated type. Tolerance induction for allergenic drug of non-IgE-mediated type is also expected.

Acknowledgement

I declare that there is no conflict of interest regarding the publication of this paper. Also, this treatment was approved by Institutional Review Board of Cheju Halla General Hostpital (Jeju-si, Republic of Korea). During the study and writing the manuscript, I always think my son Chanyong Noh and my daughters, Yonseo Noh and Damseo Noh.

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