Introduction

Iodine contrast agents are used in general imaging tests including coronary angiography all over the world. Allergic reactions after administering iodine contrast agents occur with a certain probability of 0.7–3.1%\textsuperscript{1}. We should keep the risk of allergic reactions in mind during coronary angiography when using iodine contrast agents. It is known that allergic reactions sometimes cause a serious reaction leading to an unstable hemodynamic status. The incidence of anaphylactic shock, which is one of the worst scenarios, has been reported to be 0.01 to 0.03%\textsuperscript{2}. When anaphylactic shock occurs, the administration of adrenaline is generally the first choice. However, some cases do not respond to adrenaline under certain conditions. We report two cases of anaphylactic shock during coronary angiography, which did not respond to adrenaline because the patients had taken beta-blockers. Instead, glucagon relieved their conditions. If patients treated with beta-blockers experience anaphylactic shock during coronary angiography, we should consider glucagon as a treatment option because the persistence of shock refractory to adrenaline leads to unfavorable outcomes.

Key words: anaphylactic shock, adrenaline, glucagon, beta-blocker, coronary angiography

Glucagon for Adrenergic Refractory Anaphylactic Shock in Patients Taking Beta-Blockers during Coronary Angiography

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Allergic reactions to iodine contrast agent rarely lead to anaphylactic shock affecting hemodynamics. We treated two cases of anaphylactic shock during coronary angiography, which did not respond to adrenaline because the patients had taken beta-blockers. Instead, glucagon relieved their conditions. If patients treated with beta-blockers experience anaphylactic shock during coronary angiography, we should consider glucagon as a treatment option because the persistence of shock refractory to adrenaline leads to unfavorable outcomes.

Key words: anaphylactic shock, adrenaline, glucagon, beta-blocker, coronary angiography

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ten minutes. Considering the possibility that adrenaline might not be effective for this anaphylactic shock because he had been taking beta-blockers, 1 mg of glucagon was administered intravenously. After a few minutes the blood pressure increased and the symptoms disappeared.

**Case 2 (Fig. 2)**

A 63-year-old man who underwent PCI for the right coronary artery for angina pectoris two years ago was admitted to our hospital for a re-evaluation after coronary treatment for suspected recurrent chest pain. His medical history included hypertension, hyperlipidemia, and an abdominal aortic aneurysm. He and his family didn’t have any allergic history. No adverse events had previously been found in the examination using iodine contrast agents (iomeprol, iopromide, and iopamidol) performed at our hospital. He had also been taking beta-blockers (carvedilol 10 mg/day) for angina for two years. He
underwent coronary angiography using about 15 mL of iopamidol and his coronary artery had no significant stenosis. Five minutes after the start of the examination, he had erythema on his face and upper limbs. He underwent rapid rehydration and we prepared to administer hydroxyzine. During this period, his SBP dropped to 60 mmHg and SpO\textsubscript{2} to 88%. He was diagnosed with anaphylactic shock, and was given a DIV of 50 mg of hydroxyzine and 500 mg of hydrocortisone. According to the previous case experience, we administered 1 mg of glucagon IV a few minutes after the injection of the 0.3 mg of adrenaline IM. After five minutes, his hemodynamics recovered.

**Discussion**

In those cases, the patients had been taking beta-blockers. In case 1, adrenaline was administered for anaphylactic shock, but the shock state was prolonged, and therefore, glucagon was additionally administered, and the shock improved. In case 2, the patient had a quick recovery of his hemodynamics by administering glucagon early following adrenaline IM, utilizing the experience from case 1.

**Anaphylactic risk factors**

It is known that illness increases the risk of anaphylaxis including a history of anaphylaxis itself, bronchial asthma, atopic dermatitis, allergic rhinitis, cardiovascular diseases, and some medications such as beta-blockers and angiotensin-converting-enzyme inhibitors. In particular, the risk of anaphylaxis is increased by an odds ratio of 4.54–8.74 times by bronchial asthma, 2.67–3.37 times by beta-blockers, and 7.71 times by cardiovascular diseases\textsuperscript{3–5}. Among those, beta-blockers are known to be prone to shock when anaphylaxis develops because it blocks the beta-stimulatory effects that suppress chemical mediators such as histamine\textsuperscript{6}. Even in these cases, the patients were taking beta-blockers, and about 70% of patients who undergo coronary stent implantations are taking beta-blockers\textsuperscript{7}. Particularly, prompt treatment is required when patients taking beta-blockers develop anaphylaxis.

**Treatment for anaphylactic shock**

The “Anaphylaxis Guidelines” advocated by The Japanese Society of Allergy recommend adrenaline as the first choice for the treatment of anaphylactic shock and consider glucagon in patients who take beta-blockers and do not respond sufficiently to adrenaline\textsuperscript{8}. Adrenaline exerts a positive inotropic and chronotropic effect by increasing the intracellular cyclic adenosine monophosphate (cAMP) concentration by binding to beta receptors in cardiomyocytes, and on the other hand glucagon is thought to be effective in adrenaline-refractory patients because it raises the myocardial cAMP concentration without intervention with beta-receptors\textsuperscript{9} (Fig. 3).

As the method of administration for glucagon, if shock status is continued in spite of adrenaline administering, glucagon is administered 1 mg IV. Without sufficient effect, it is recommended to administer repeatedly every 5 minutes\textsuperscript{10}.

In both cases, the shock improved after single 1 mg of glucagon IV.

The frequency of anaphylactic shock is very low. In case 1, adrenaline was administered immediately after the anaphylactic shock occurred, however, we could not administer glucagon immediately because the cause of the prolonged shock had not been suspected to be an adrenaline refractory status due to the effect of the beta-blockers. After experiencing this case, we always perform coronary artery angiography after confirming the presence or absence of beta-blockers. We also prepare for the preservation method, preservation place, and administration method of glucagon, and make an effort to educate not only the doctors but also all of the medical staff. We could administer glucagon to the patient in case 2 more quickly than case 1.

**Anaphylaxis prevention**

Case 1 presented with anaphylactic shock despite the prior administration of steroids (100 mg hydrocortisone) as a pre-medication. It was reported that oral premedication with steroids reduces the mild side effects of allergic reactions caused by iodine contrast agents in the American College of Radiology Contrast Administration Manual “American College of Radiology Manual on Contrast Media” (ACR manual)\textsuperscript{11}. According to a past
survey in Japan, steroids were often given intravenously before catheterization procedures, and 20.7% of hospitals that premedicated used intravenous steroids\(^\text{13}\). In case 1, the infusion of hydrocortisone was performed several hours before the start of the catheterization. The ACR manual states that it is effective to administer steroids in multiple doses. Specifically, the ACR manual recommends the oral administration of 50mg of prednisolone 13 hours, 7 hours, and 1 hour, or oral administration of 32 mg methylprednisolone 12 hours and 2 hours, before the administration of contrast agents. Accordingly, the Japanese Society of Medical Radiology for the use of steroids in June 2017 stated that steroids should be administered after giving sufficient informed consent referring to the above American guidelines\(^\text{13}\). In the present cases, it might have been possible to have prevented the anaphylactic shock if an oral administration had been given rather than an intravenous injection 12 hours prior as in the American guidelines, however, it remains unclear whether an oral administration is effective or not. Therefore, if we must use a contrast agent in patients who have had anaphylactic shock, alternatives to contrast agents should be selected as much as possible, and prednisolone should be pre-administered orally to prevent the disease. It is also necessary to prepare glucagon for use in the contingency of an adrenaline refractory situation, especially in patients taking beta-blockers.

**Conclusion**

Glucagon is used for patients with anaphylactic shock who is non responder of adrenaline because of taking beta-blockers. However, it is difficult to respond to the situation quickly for us like case 1 because this event is very rare. It would be important to check how to handle glucagon for adrenaline refractory situation.

**Author’s disclosure of potential Conflicts of Interest**

Daisuke Fukamachi belongs to the endowed department of Boston Scientific Japan. Yasuo Okumura belongs to the endowed departments of Boston Scientific Japan, Abbott Medical Japan, Japan Lifeline, Medtronic Japan, and Nihon Kohden. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

**References**

1. Kvedariene V, Martins P, Rouanet L, et.al. Diagnosis of iodinated contrast media hypersensitivity: results of a 6-year period. *Clin Exp Allergy* 2006; 36: 1072–1077.
2. Moneret-Vautrin DA, Morisset M, Flabbee J, et al. Epidemiology of life-threatening and lethal anaphylaxis: a review. *Allergy* 2005; 60: 443–451.
3. Muñoz-Cano R, Pascal M, Araujo G, et al. Mechanisms, Cofactors, and Augmenting Factors Involved in Anaphylaxis. *Front Immunol* 2017; 8: 1193.
4. Lang DM, Alpern MB, Visintainer PF, et al. Increased risk for anaphylactoid reaction from contrast media in patients on beta-adrenergic blockers or with asthma. *Ann Intern Med* 1991; 115: 270–276.
5. Lang DM, Alpern MB, Visintainer PF, et al. Elevated risk of anaphylactoid reaction from radiographic contrast media is associated with both beta-blocker exposure and cardiovascular disorders. *Arch Intern Med* 1993; 153: 2033–2040.
6. Goddet NS, Descatha A, Liberge O, et al. Paradoxical reaction to epinephrine induced by beta-blockers in an anaphylactic shock induced by penicillin. *Eur J Emerg Med* 2006; 13: 358–360.
7. Roovink V, Ibáñez B, Ottervanger JP, et al. Early Intravenous Beta-Blockers in Patients With ST-Segment Elevation Myocardial Infarction Before Primary Percutaneous Coronary Intervention. *J Am Coll Cardiol* 2016; 67: 2705–2715.
8. Simons FE, Arduso LR, Bilò MB, et al. World allergy organization guidelines for the assessment and management of anaphylaxis. *World Allergy Organ J* 2011; 4: 13–37.
9. Nagano T, Iseki K, Niki T, et al. A case of anaphylaxis with cardiopulmonary arrest in a patient receiving \(\beta\)-blocker. *Nihon Syuchuchiryo Igakukai Zasshi (Journal of the Japanese Society of Intensive Care Medicine)* 2010; 17: 207–210 (in Japanese).
10. Brown AF. Anaphylactic shock: mechanisms and treatment. *J Accid Emerg Med* 1995; 12: 89–100.
11. O’Malley RB, Cohan RH, Ellis JH, et al. A survey on the use of premedication prior to iodinated and gadolinium-based contrast material administration. *J Am Coll Radiol* 2011; 8: 345–354.
12. Tsushima Y, Ishiguchi T, Murakami T, et al. Safe use of iodinated and gadolinium-based contrast media in current practice in Japan: a questionnaire survey. *Jpn J Radiol* 2016; 34: 130–139.
13. Japan Radiological Society. 2018. Anzen ni kansuru Zyoho (Safety information) http://www.radiology.jp/member_info/safety/20181115.html accessed 2020-05-02 (in Japanese).